PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-006742- -00000-0000
Fecha: 2008-01-24 16:40:54 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYI Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 131

ación

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

[X] Patente de Invención [ ] Patente de Modelo de Utilidad
[X] Capítulo I. [ ] Capítulo II.

(2) SOLICITANTE (71)

Nombre: WYETH
Dirección: Five Giralda Farms, Madison, New Jersey 07940, Estados Unidos de América
Nacionalidad o Domicilio: Nueva Jersey, Estados Unidos de América
Lugar de Constitución: Delaware, Estados Unidos de América
Teléfono: Fax:
E-Mail

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ
Dirección: Avenida 82 No.10-62 Piso 6
Teléfono: 634 1500 Fax: 376 2211
E-Mail: office.bogota@bakernet.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.143.366 de Usaquén TP 20.281

(4) INVENTOR (ES) (72)

Nombre: MEGATI, Sreenivasulu; CHAN, Anita, Wai-yin y FEIGELSON, Gregg, B.
Dirección: 1 Hearth Court, New City, NY 10956, Estados Unidos de América; 1600 CENTER AVE., Apt. 6d, Fort Lee, NJ 07024, Estados Unidos de América y 173 Bull Mill Road, Chester, NY 10918, Estados Unidos de América, respectivamente
Nacionalidad o Domicilio: Hindú, Estadounidense y Estadounidense, respectivamente.

(5) PCT (85)

Solicitud Internacional No. PCT/US2006/028655 Fecha 24-JUL-06
Publicación Internacional No. WO/2007/016029 Fecha 08-FEB-07

(6) Título (54) DIAZEPINOQUINOLINAS, SU SÍNTESIS, E INTERMEDIOS DE ESTA

(7) Clasificación Internacional (51) C07D 471/06, C07D 221/16 A61K 31/4709. A61K 31/551. A61P 25/18

(8) Prioridad

SI [X] NO [ ]

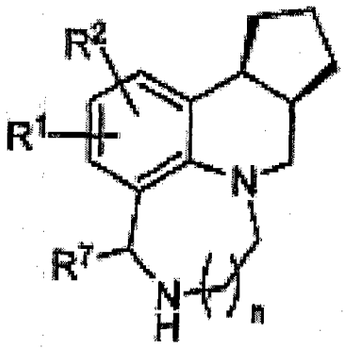
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	26-JUL-05	60/702,509

(9) Comprobante de pago No. 07-53105, 08-978 y 07-102597 Fecha 29-jun-7, 3-ene-8 y 18-dic-7

(10) **ANEXOS**

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

(11) **FIGURA CARATERISTICA**



II

(12) Solicito la concesión de la patente.

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 07 - 53,135
FECHA : JUNIO 29 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-006742- -00000-0000

Fecha. 2008-01-24 16:40:54 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 131

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	49375877	29/06/2007	$4,444,000.00

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

CANT.	CONCEPTO		TOTAL CONCEPTO
1	99005-01-07 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS	9,000.00
		TOTAL : $	9,000.00

SON: NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

55

00000025

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 102,597
FECHA : DICIEMBRE 18 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-006742- -00000-0000
Fecha: 2008-01-24 16:40:54 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 131

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO POPULAR	050-00110-6	72421434	17/12/2007	68,183,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

TRADUCCIÓN OFICIAL No. 030/08 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 22 de enero de 2008 por la Sra. María Teresa Lara, c.c. 41.568.055 de Bogotá, Traductora Oficial según Resolución No. 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia.

= =

Poder otorgado por WYETH respecto de la solicitud de patente titulada "DIAZEPINOQUINOLINAS, SU SÍNTESIS E INTERMEDIOS DE ESTA". Certificación notarial suscrita por Michelle McGowan, Notario Público del estado de Nueva Jersey, y legalizaciones subsiguientes.

EL PODER Y LA CERTIFICACIÓN NOTARIAL NO SE TRADUCEN POR ENCONTRARSE EN INGLÉS Y ESPAÑOL EN EL DOCUMENTO ORIGINAL.

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINJUSTICIA

MICHELLE L. McGOWAN
Notario Público, Estado de Nueva Jersey
No. 2108903
Habilitada en el Condado de Morris
La comisión expira el 9 de febrero de 2011

(Sello notarial
en relieve)

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: Estados Unidos de América
2. Este documento público ha sido firmado por: Michelle L. McGowan
3. actuando en calidad de: Notario Público de Nueva Jersey
4. lleva el sello/timbre de: Michelle L. McGowan, Notario

7

CERTIFICADO

5. en Trenton, Nueva Jersey

6. el día 6 de diciembre de 2007

7. por Michellene Davis, TESORERO DE NUEVA JERSEY

8. No. A311094

9. Sello/Timbre: 10. Firma

(Sello del Estado de Nueva Jersey) (Fdo.) Michellene Davis

= =

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.

MARIA TERESA LARA R. TRADUCTORA OFICIAL RESOLUCION No. 01016 DE MINJUSTICIA

María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MICHELLE L MC GOWAN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MICHELLE L MC GOWAN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

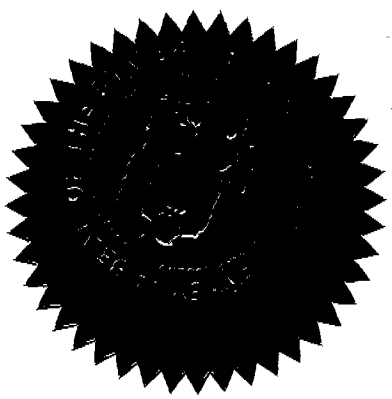
6. THE 6TH DAY OF DECEMBER 2007

7. BY: Michellene Davis, NEW JERSEY TREASURER

8. NO. A311094

9. SEAL/STAMP:

10. SIGNATURE



MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 0030
DE MINJUSTICIA

030/08

BAKER & McKENZIE

AM102000 Colombia

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.068.840-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

9
9

POWER OF ATTORNEY

The undersigned.

WYETH

with offices at

Five Giralda Farms, Madison, NJ 07940,
United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

all members of the law firm Raisbeck, Lara, Rodriguez & Rueda, with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, and for so long as they remain members of the law firm, a full and sufficient power of attorney with respect to Colombian patent application(s) based on PCT/US2006/028655 and entitled "DIAZEPINOQUINOLINES, SYNTHESIS THEREOF, AND INTERMEDIATES THERETO" and to obtain patent protection thereof, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of a patent(s) based upon said patent application(s), including filing of assignments, change of name or address, voluntary cancellation; and defending oppositions, cancellations, nullity, writ mandamus, and in general the civil, penal, an administrative processes relating to those rights.

I hereby ratify all lawful actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 5th day of December 2007

Signature of the person issuing the Power

WYETH

William H. Calnan
Assistant Secretary

PODER DE ABOGADO

La abajo firmada,

WYETH

con oficinas en

Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

Todos miembros de la firma de abogados Raisbeck, Lara, Rodríguez & Rueda, con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, y hasta tanto ellos continúen siendo miembros de la firma, poder especial amplio y suficiente con respecto a la solicitud(es) de patente en Colombia basada(s) en PCT/US2006/028655 y titulada "DIAZEPINOQUINOLINAS, SU SINTESIS, E INTERMEDIOS DE ESTA",

y para obtener la protección de patente de la misma, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de la(s) patente(s) de invención basada(s) en la mencionada solicitud de patente, incluyendo presentación de traspasos, cambio de nombre o dirección, cancelación voluntaria; y defensa en oposiciones, cancelaciones, nulidades, la tutela, y en general procesos civiles, penales, administrativos relacionados con estos derechos.

Igualmente, ratifico todo lo actuado en derecho hasta el momento en nombre de esta compañía por cualquiera de los mencionados apoderados en los casos mencionados.

Dado y firmado en

A los 5 días del mes de Diciembre de 2007

Firma de la persona que firma el Poder

NOTARIAL CERTIFICATION

On this 5th day of December 2007, the undersigned Notary

CERTIFIES

1. That **William H. Calnan** [illegible] his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has [illegible]egal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as

Assistant Secretary

of the judicial person **WYETH**

4. That the judicial person **WYETH** having its home office in
Five Giralda Farms, Madison, NJ 07940,
United States of America

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
Minutes of the Board of Directors Meeting held on April 26, 2007.

Michelle L. McGowan
Notary Public
MICHELLE L. McGOWAN
Notary Public, State of **New Jersey**
No. 2108903
Qualified in Morris County
Commission Expires Feb. 9, 2011

CERTIFICACION NOTARIAL

A los 5 días del mes de diciembre de 2007, el suscrito Notario

DA FE

1 Que William H. Calnan suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de

de la persona jurídica **WYETH**

4 Que la persona jurídica **WYETH** con sede en
Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
Minutas de la reunión del comité ejecutivo del 26 de abril, 2007.

El Notario Público

TRADUCCIÓN OFICIAL No. 031/08 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 22 de enero de 2008 por la Sra. María Teresa Lara, c.c. 41.568.055 de Bogotá, Traductora Oficial según Resolución No. 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia.

= =

Cesión a WYETH del invento titulado "DIAZEPINOQUINOLINAS, SU SÍNTESIS E INTERMEDIOS DE ESTA". Certificación notarial suscrita por Barbara A. Kiely, Notario Público del estado de Nueva Jersey, y legalizaciones subsiguientes.

AM102000 L1

DECLARACIÓN JURAMENTADA

MARIA TERESA LARA R. TRADUCTORA OFICIAL RESOLUCION ... DE ...

Yo, Michelle L. McGowan, Asociada para Legalizaciones, Wyeth, certifico por la presente que la copia adjunta ha sido comparada con la Cesión original (para nuestro Expediente Número AM102000, el cual corresponde al U.S.S.N. 60/702,509 y cualquier equivalente legal del mismo en un país extranjero, para el invento titulado: "DIAZEPINOQUINOLINAS, SU SÍNTESIS E INTERMEDIOS DE ESTA"), fechada el 28 de octubre de 2005 de Sreenivasulu Megati, Anita Wai-Yin Chan y Gregg B. Feigelson a Wyeth y que la citada copia es fiel copia del original.

Dado a los 29 días del mes de noviembre de 2007, en Madison, Nueva Jersey, Estados Unidos de América.

Wyeth

(Fdo.) Michelle L. McGowan

Michelle L. McGowan
Asociada para Legalizaciones

PARA USO EN COLOMBIA

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RECONOCIMIENTO

Estado de Nueva Jersey)
)
Condado de Morris)

A los 29 días del mes de noviembre de 2007, ante mi personalmente compareció Michelle L. McGowan, Asociada para Legalizaciones de Wyeth, a quien conozco y de quien me consta que es la persona descrita en el instrumento anterior y quien lo suscribió, y reconoció ante mi haber suscrito el mismo.

(Fdo.) Barbara A. Kiely
Notario Público

(Sello notarial
en relieve)

[Sello] Barbara A. Kiely ID. 33893
Notario Público de Nueva Jersey
Mi comisión expira el 20 de junio de 2009

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 0181
DE MINJUSTICIA

Cesión de Invento

En virtud del pago por la CESIONARIA al CEDENTE de contraprestación válida y valiosa, el recibo de la cual se reconoce por la presente, el CEDENTE:

(1) Nombre Completo del Inventor: Sreenivasulu Megati
Residencia: 1 Hearth Court, Nueva York, NY 10956
Ciudadanía: India

---

(2) Nombre Completo del Inventor: Anita Wai-Yin Chan
Residencia: 1600 Center Avenue, Apt. 6D, Fort Lee, NJ 07024
Ciudadanía: Estados Unidos

---

(3) Nombre Completo del Inventor: Gregg B. Feigelson
Residencia: 173 Bull Mill Road, Chester, NY 10918
Ciudadanía: Estados Unidos

---

por la presente vende, cede y traspasa a la CESIONARIA:

Wyeth
Five Giralda Farms
Madison, NJ 07940

y a los sucesores, cesionarios y representantes legales de la CESIONARIA, todo derecho, título e interés para los Estados Unidos y sus posesiones territoriales y en todos los países extranjeros, incluidos todos los derechos a reclamar prioridad, en y sobre el invento titulado:

DIAZEPINOQUINOLINAS, SU SÍNTESIS E INTERMEDIOS DE ESTA

e inventado por el CEDENTE y los siguientes inventores adicionales, en caso de haberlos:

y el cual se encuentra en la Solicitud Provisional de los E.U. No. 60/702,509 presentada el: 26 de julio de 2005

[ ] Yo, el suscrito CEDENTE, por la presente autorizo y solicito la inserción anterior del número de solicitud y la fecha de presentación, una vez se conozcan,

[marcar también si se están cediendo solicitud(es) extranjera(s)]

[X] y cualquier equivalente legal de las mismas en un país extranjero,

incluyendo el derecho a reclamar prioridad, incluidas todas y cada una de las mejoras allí divulgadas, y en y sobre todas las Patentes que hayan de obtenerse para dicho invento en virtud de la solicitud anterior o cualquier solicitud provisional, no provisional, de continuación, divisional, de renovación

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 0181
DE MINUSTERIO

o sustituta de la misma posteriormente presentada, y respecto de Patentes, cualquier reemisión o reexamen de las mismas.

El CEDENTE pacta por el presente que no se ha hecho ni se hará ni se realizará ninguna cesión, venta, acuerdo o gravamen que pudiese entrar en conflicto con esta cesión.

El CEDENTE autoriza a la CESIONARIA a presentar solicitudes y recibir Patentes para dicho invento en cualquiera de dichos países en su propio nombre, o en nombre del CEDENTE, a su elección.

El CEDENTE pacta y acuerda suscribir u obtener cualquier garantía adicional necesaria del título sobre dicho invento y cualquier Patente que pueda expedirse para el mismo y, en cualquier momento, a solicitud y por cuenta de la CESIONARIA, entregar cualquier testimonio en cualquier interferencia, litigio o proceso relacionado con el mismo y otorgar todos los documentos que puedan ser necesarios o convenientes para perfeccionar el título sobre dicho invento o cualquier Patente que pueda otorgarse para el mismo a la CESIONARIA, sus sucesores, cesionarios u otros representantes legales y, en cualquier momento, a solicitud y por cuenta de la CESIONARIA, suscribir cualquier continuación, continuación en parte, solicitud divisional, de renovación o sustituta de la misma, y en cuanto a Patentes y reemisión o reexamen de las mismas, o cualquier otra solicitud adicional de Patente para dicho invento o cualquier parte del mismo, todas las cuales solicitudes y cualesquiera Patentes que se expidan sobre las mismas son por la presente cedidas a la CESIONARIA, y hará todos los juramentos o declaraciones lícitos, y realizará todo los actos lícitos requeridos para adquirir las mismas, sin otra

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compensación, pero por cuenta de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales.

El CEDENTE autoriza y solicita al Comisionado de Patentes expedir todas y cada una de las Patentes de los Estados Unidos para dicho invento, resultantes de cualquiera de las anteriores solicitudes a su CESIONARIA.

(Fdo.) Sreenivasulu Megati — 28-Oct-2005
Sreenivasulu Megati — Fecha

RECONOCIMIENTO

Estado de Nueva York }
ss:
Condado de Rockland }

A los 28 días del mes de octubre de 2005, compareció personalmente ante mí Sreenivasulu Megati, a quien conozco como la misma persona descrita en el instrumento anterior y quien lo otorgó, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH6052604
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

MARÍA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCIÓN No. 0189
DE MINJUSTICIA

(Fdo.) Anita Wai-Yin Chan — 28-Oct-2005
Anita Wai-Yin Chan — Fecha

Estado de Nueva York }
ss:
Condado de Rockland }

16/16

RECONOCIMIENTO

A los 28 días del mes de octubre de 2005, compareció personalmente ante mí Anita Wai-Yin Chan, a quien conozco como la misma persona descrita en el instrumento anterior y quien lo otorgó, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH6052604
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

(Fdo.) Gregg B. Feigelson 28-Oct-2005
Gregg B. Feigelson Fecha

RECONOCIMIENTO

Estado de Nueva York }
ss:
Condado de Rockland }

A los 28 días del mes de octubre de 2005, compareció personalmente ante mí Gregg B. Feigelson, a quien conozco como la misma persona descrita en el instrumento anterior y quien lo otorgó, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH6052604
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

17

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: Estados Unidos de América
2. Este documento público ha sido firmado por: Barbara A. Kiely
3. actuando en calidad de: Notario Público de Nueva Jersey
4. lleva el sello/timbre de: Barbara A. Kiely, Notario

CERTIFICADO

5. en Trenton, Nueva Jersey
6. el día 6 de diciembre de 2007
7. por Michellene Davis, TESORERO DE NUEVA JERSEY
8. No. A311106
9. Sello/Timbre: 10. Firma

(Sello del Estado de Nueva Jersey) (Fdo.) Michellene Davis

MARIA TERESA LARA R. TRADUCTORA OFICIAL RESOLUCION ... DE MINJUSTICIA

= =

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.

María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA A KIELY

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
BARBARA A KIELY, NOTARY

CERTIFIED

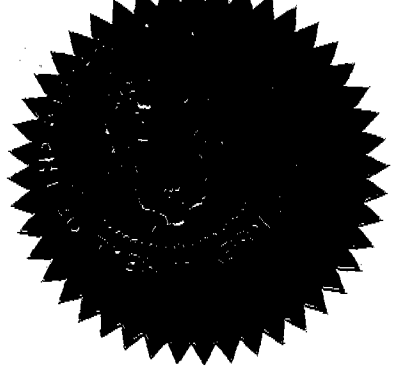
5. AT TRENTON, NEW JERSEY

6. THE 6TH DAY OF DECEMBER 2007

7. BY: Michellene Davis, NEW JERSEY TREASURER

8. NO. A311106

9. SEAL/STAMP:



10. SIGNATURE

Michellene Davis

Teresa Lara R.

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
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DE RELACIONES

19

AM102000 L1

AFFIDAVIT

I, Michelle L. McGowan, Legalization Associate, Wyeth, do hereby certify that the attached copy has been compared with the original Assignment (for our Docket Number AM102000) which correspondence to U.S.S.N. 60/702,509 and any legal equivalent thereof in a foreign country, for the invention entitled: "DIAZEPINOQUINOLINES, SYNTHESIS THEREOF, AND INTERMEDIATES THERETO") dated October 28, 2005 from Sreenivasulu Megati, Anita Wai-Yin Chan and Gregg B. Feigelson to Wyeth and that the said copy is a true copy of the original.

Dated this 29th day of November, 2007, at Madison, New Jersey, United States of America.

Wyeth

Michelle L. McGowan
Legalization Associate

TO BE USED IN COLOMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 29th day of November, 2007, before me personally appeared Michelle L. McGowan, Legalization Associate of Wyeth, to me known and known to me to be the individual described in and who executed the foregoing instrument, and she acknowledged to me that she executed the same.

Notary Public

Barbara A. Kiely ID. 33893
Notary Public of New Jersey
My Commission Expires June 20, 2009

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Assignment of Invention

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration, the receipt of which is hereby acknowledged, ASSIGNOR:

(1) Full Name of Inventor: Sreenivasulu Megati
Residence: 1 Hearth Court, New York, NY 10956
Citizenship: India

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(2) Full Name of Inventor: Anita Wai-Yin Chan
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Citizenship: United States

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(3) Full Name of Inventor: Gregg B. Feigelson
Residence: 173 Bull Mill Road, Chester, NY 10918
Citizenship: United States

---

hereby sells, assigns and transfers to ASSIGNEE:

Wyeth
Five Giralda Farms
Madison, NJ 07940

and the successors, assigns and legal representatives of the ASSIGNEE the entire right, title and interest for the United States and its territorial possessions and in all foreign countries, including all rights to claim priority, in and to the invention entitled:

DIAZEPINOQUINOLINES, SYNTHESIS THEREOF, AND INTERMEDIATES THERETO

and invented by ASSIGNOR and the following additional inventors, if any:

and which is found in U.S. Provisional Application No. 60/702,509 filed on: July 26, 2005

☐ I/we the ASSIGNOR signing below, hereby authorize and request insertion above of the application number and filing date, when they become known,

[also check if foreign application(s) is(are) also being assigned]

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including the right to claim priority, including any and all improvements disclosed therein, and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional, nonprovisional, continuation, divisional, renewal, or substitute thereof, and as to Letters Patent any reissue or re-examination thereof.

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ASSIGNOR authorizes and requests the Commissioner of Patents to issue any and all Letters Patent of the United States for said invention, resulting from any of the aforesaid applications to its ASSIGNEE.

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Sreenivasulu Megati — 28-Oct-2005

Sreenivasulu Megati — Date

ACKNOWLEDGMENT

State of New York }
ss:
County of Rockland }

On the 28 day of October 2005, Sreenivasulu Megati personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 01-WH6052604
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-26-20 06

Janice A. White
Notary Public

Anita Wai-Yin Chan — 28-Oct-2005

Anita Wai-Yin Chan — Date

ACKNOWLEDGMENT

State of New York }
ss:
County of Rockland }

On the 28 day of October 2005, Anita Wai-Yin Chan personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

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23
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Gregg B. Feigelson

28-OCT-2005
Date

ACKNOWLEDGMENT

State of New York }
ss:
County of Rockland }

On the 28 day of October 2005, Gregg B. Feigelson personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

Janice A. White
Notary Public

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(72) Inventors; and

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

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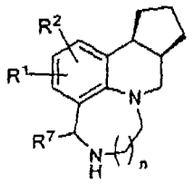

II

(57) Abstract: The present invention relates to methods for synthesizing compounds useful as $5HT_{2C}$ agonists or partial agonists, derivatives thereof, and to intermediates thereto.

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(54) Title: DIAZEPINOQUINOLINES, SYNTHESIS THEREOF, AND INTERMEDIATES THERETO

(57) Abstract: The present invention relates to methods for synthesizing compounds useful as 5HT2c agonists or partial agonists, derivatives thereof, and to intermediates thereto.

DIAZEPINOQUINOLINES, SYNTHESIS THEREOF, AND INTERMEDIATES THERETO

FIELD OF THE INVENTION

[0001] The present invention relates to methods for synthesizing compounds useful as $5HT_{2C}$ agonists or partial agonists, derivatives thereof, and to intermediates thereto.

BACKGROUND OF THE INVENTION

[0002] Schizophrenia affects approximately 5 million people. The most prevalent treatments for schizophrenia are currently the 'atypical' antipsychotics, which combine dopamine (D_2) and serotonin ($5\text{-}HT_{2A}$) receptor antagonism. Despite the reported improvements in efficacy and side-effect liability of atypical antipsychotics relative to typical antipsychotics, these compounds do not appear to adequately treat all the symptoms of schizophrenia and are accompanied by problematic side effects, such as weight gain (Allison, D. B., et. al., Am. J. Psychiatry, 156: 1686-1696, 1999; Masand, P. S., Exp. Opin. Pharmacother. I: 377-389, 2000; Whitaker, R., Spectrum Life Sciences. Decision Resources. 2:1-9, 2000).

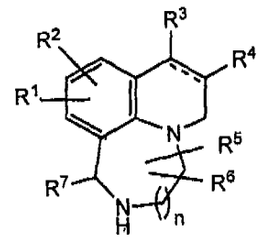
[0003] Atypical antipsychotics also bind with high affinity to $5\text{-}HT_{2C}$ receptors and function as $5\text{-}HT_{2C}$ receptor antagonists or inverse agonists. Weight gain is a problematic side effect associated with atypical antipsychotics such as clozapine and olanzapine, and it has been suggested that $5\text{-}HT_{2C}$ antagonism is responsible for the increased weight gain. Conversely, stimulation of the $5\text{-}HT_{2C}$ receptor is known to result in decreased food intake and body weight (Walsh et. al., Psychopharmacology 124: 57-73, 1996; Cowen, P. J., et. al., Human Psychopharmacology 10: 385-391, 1995; Rosenzweig-Lipson, S., et. al., ASPET abstract, 2000).

[0004] Several lines of evidence support a role for $5\text{-}HT_{2C}$ receptor agonism or partial agonism as a treatment for schizophrenia. Studies suggest that $5\text{-}HT_{2C}$ antagonists increase synaptic levels of dopamine and may be effective in animal models of Parkinson's disease (Di Matteo, V., et. al., Neuropharmacology 37: 265-272, 1998; Fox, S. H., et. al., Experimental Neurology 151: 35-49, 1998). Since the positive symptoms of schizophrenia are associated with increased levels of dopamine, compounds with actions opposite to those of $5\text{-}HT_{2C}$ antagonists, such as $5\text{-}HT_{2C}$ agonists and partial agonists, should reduce levels of

synaptic dopamine. Recent studies have demonstrated that 5-HT_{2C} agonists decrease levels of dopamine in the prefrontal cortex and nucleus accumbens (Millan, M. J., et. al., Neuropharmacology 37: 953-955, 1998; Di Matteo, V., et. al., Neuropharmacology 38: 1195-1205, 1999; Di Giovanni, G., et. al., Synapse 35: 53-61, 2000), brain regions that are thought to mediate critical antipsychotic effects of drugs like clozapine. However, 5-HT_{2C} agonists do not decrease dopamine levels in the striatum, the brain region most closely associated with extrapyramidal side effects. In addition, a recent study demonstrates that 5-HT_{2C} agonists decrease firing in the ventral tegmental area (VTA), but not in the substantia nigra. The differential effects of 5-HT_{2C} agonists in the mesolimbic pathway relative to the nigrostriatal pathway suggest that 5-HT_{2C} agonists have limbic selectivity, and will be less likely to produce extrapyramidal side effects associated with typical antipsychotics.

SUMMARY OF THE INVENTION

As described herein, the present invention provides methods for preparing compounds having activity as $5HT_{2C}$ agonists or partial agonists. These compounds are useful for treating schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, substance-induced psychotic disorder, L-DOPA-induced psychosis, psychosis associated with Alzheimer's dementia, psychosis associated with Parkinson's disease, psychosis associated with Lewy body disease, dementia, memory deficit, intellectual deficit associated with Alzheimer's disease, bipolar disorders, depressive disorders, mood episodes, anxiety disorders, adjustment disorders, eating disorders, epilepsy, sleep disorders, migraines, sexual dysfunction, gastrointestinal disorders, obesity, or a central nervous system deficiency associated with trauma, stroke, or spinal cord injury. Such compounds include those of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

==== designates a single or double bond;

n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group;

R^3 and R^4 are taken together to form a saturated or unsaturated 4-8 membered ring, wherein said ring is optionally substituted with 1-3 groups independently selected from halogen, -R, or OR;

R^5 and R^6 are each independently -R; and

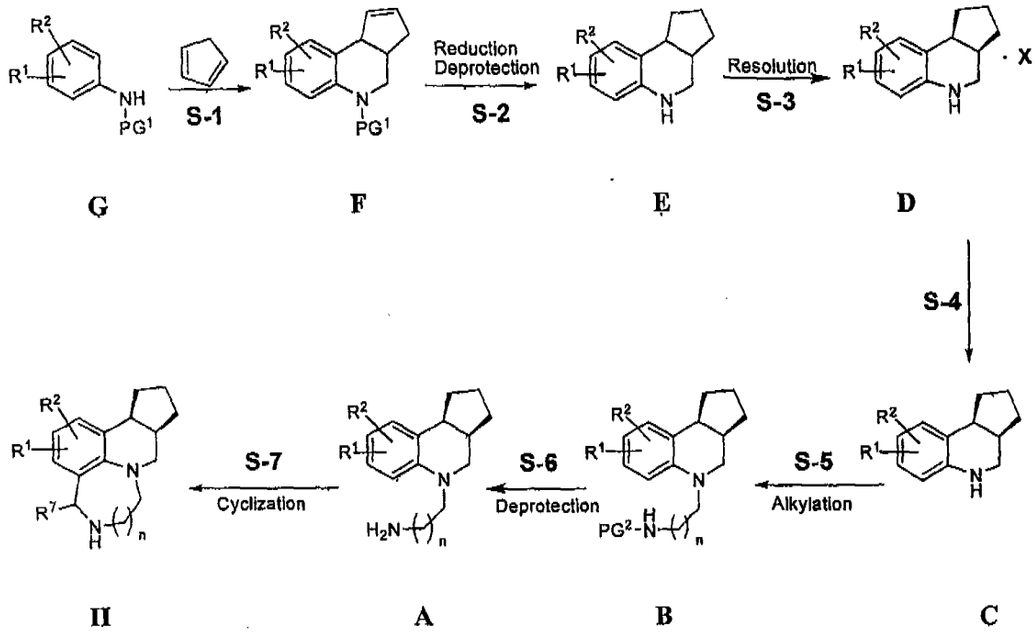
R^7 is hydrogen or C_{1-6} alkyl.

[0005] The present invention also provides synthetic intermediates useful for preparing such compounds.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0006] The methods and intermediates of the present invention are useful for preparing compounds as described in, e.g. International Patent Application WO 03/091250, in the name of Ramamoorthy, the entirety of which is incorporated herein by reference. In certain embodiments, the present compounds are generally prepared according to Scheme I set forth below:

Scheme I



G F E D

C B A II

[0007] In Scheme I above, each of n, PG^1, R^1, R^2, R^7, and PG^2 is as defined below and in classes and subclasses as described herein.

[0008] In one aspect, the present invention provides methods for preparing chiral quinoline compounds of formula **D** according to the steps depicted in Scheme 1, above. At step **S-1**, an aniline of formula **G** is reacted with formaldehyde, or an equivalent thereof, and cyclopentadiene in the presence of a mineral acid. In certain embodiments, the Diels-Alder reaction of N-benzylaniline and cyclopentadiene in the presence of concentrated HCl provides the cyclopentenyltetrahydroquinoline **F**, wherein PG^1 is benzyl. In other embodiments, step **S-1** is performed in a manner substantially similar to that described by Posson, *et al*, "Imino Diels-Alder Reaction: Application to the Synthesis of Diverse Cyclopenta[c]Quinoline Derivatives" *Synlett* 2000, No. 2, 209-212.

[0009] The PG^1 group of formulae **G** and **F** is a suitable amino protecting group. Suitable amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Suitable amino protecting groups, taken with the -NH- moiety to which it is attached, include, but are not limited to, aralkylamines, carbamates, allyl amines, amides, and the like. Examples of PG^1 groups of formulae **G** and **F** include t-butyloxycarbonyl (BOC),

ethyloxycarbonyl, methyloxycarbonyl, trichloroethyloxycarbonyl, allyloxycarbonyl (Alloc), benzyloxocarbonyl (CBZ), allyl, benzyl (Bn), fluorenylmethylcarbonyl (Fmoc), acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, trifluoroacetyl, benzoyl, and the like. In other embodiments, the PG^1 group of formulae **G** and **F** is benzyl.

[0010] At step **S-2**, the olefin of compound **F** is reduced and the amino group deprotected by removal of PG^1. One of ordinary skill in the art would recognize that, depending on the choice of PG^1, deprotection and olefin reduction may be performed in the same step. For example, when the PG^1 group of formula **F** is benzyl, reduction of the olefin would simultaneously deprotect the amine group. Accordingly, in certain embodiments, the present invention provides a method of forming a compound of formula **E** comprising the step of simultaneously reducing the olefin and deprotecting the amino group of formula **F**. Thus, in certain embodiments, the PG^1 group of formula **F** is an amino protecting group that is removed by reduction, e.g. hydrogenation. For example, reduction of the double bond and deprotection of a benzyl group is achieved in the same reaction by catalytic reduction with Pd-C under a hydrogen atmosphere. In an alternate method, the removal of PG^1 and olefin reduction at step **S-2** may be performed in a stepwise fashion using methods known to one of ordinary skill in the art.

[0011] At step **S-3**, the racemic compound **E** is treated with a chiral agent to form a diastereomeric mixture thereof. In certain embodiments, the racemic compound **E** is treated with a chiral acid to form a diastereomeric salt thereof. The resulting diastereomeric mixture is then separated by suitable means to obtain a compound of formula **D**. Such suitable means for separating diastereomeric mixtures are well known to one of ordinary skill in the art and include, but are not limited to, those methods described herein. It will be appreciated that, depending upon the chiral acid used, there may be one or more carboxylate moieties present. In certain embodiments, the chiral acid has two carboxylate moieties as with, for example, tartaric acid or a derivative thereof.

[0012] Accordingly, one of ordinary skill in the art would appreciate that a compound of formula **E** may form a hemi salt with said bi-functional chiral acid. As used herein, the term "hemi salt" refers to an adduct having two molecules of a compound of formula **E** to each molecule of chiral acid. Alternatively, the resulting salt may have a one-to-one mixture chiral acid to a compound of formula **E**. In certain embodiments, the present invention provides a compound of formula **D** wherein said compound of formula **D** comprises equal molar amounts of the chiral acid to an amine of formula **E**.

[0013] In certain embodiments, each of the aforementioned synthetic steps may be performed sequentially with isolation of each intermediate **F**, **E**, and **D** performed after each step. Alternatively, each of steps **S-1**, **S-2**, and **S-3**, as depicted in Scheme I above, may be performed in a manner whereby no isolation of intermediates **F** and **E** is performed.

[0014] When X is a chiral acid, the compound of formula **D**, at step **S-4**, is treated with a suitable base to form the free base compound **C**. Free bases according to the invention are also prepared, for example, by contacting a compound of formula **D** with a suitable base in the presence of a solvent suitable for free base formation. Such suitable bases include strong inorganic bases, *i.e.*, those that completely dissociate in water under formation of hydroxide anion. In certain embodiments, the base is added in an amount of at least about 1 mol. eq. and, in other embodiments, in an amount of at least about 1 mol. eq. to about 10 mol. eq. relative to the compound of formula **D**. Examples of such bases include alkaline metals, alkaline earth metal hydroxides, and combinations thereof. In other embodiments, the suitable base is sodium hydroxide.

[0015] Examples of solvents suitable for use during free base formation at step **S-4** include polar solvents such as alkyl alcohols, such as C_1 to C_4 alcohols (*e.g.* ethanol, methanol, 2-propanol), water, dioxane, or THF (tetrahydrofuran) or combinations thereof. In certain embodiments, the suitable solvent is a C_1 to C_4 alcohol such as methanol, ethanol, 2-propanol, water, or combination thereof. According to one aspect of the present invention, aqueous sodium hydroxide is used at step **S-4**. According to another aspect of the present invention, the free base formation at step **S-4** is performed in a bi-phasic mixture of solvents whereby the compound of formula **C**, as it is formed, is extracted into an organic layer. Thus, a suitable bi-phasic mixture of solvents includes an aqueous solvent and a non-miscible organic solvent. Such non-miscible organic solvents are well known to one of ordinary skill in the art and include halogenated hydrocarbon solvents (e.g. methylene chloride and chloroform), benzene and derivatives thereof (e.g. toluene), esters (e.g. ethyl acetate and isopropyl acetate), and ethers (e.g. MTBE, THF and derivatives thereof, glyme, and diglyme) and the like. In certain embodiments, the free base formation at step **S-4** is performed in a bi-phasic mixture comprising water and toluene. In other embodiments, the suitable base is water soluble such that the reaction is performed in a mixture of toluene and a suitable aqueous base, such as aqueous sodium hydroxide.

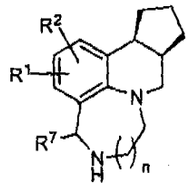
[0016] At step **S-5**, N-alkylation of the chiral compound **C** affords a compound of formula **B**. In certain embodiments, this N-alkylation is performed with 2-methyl-2-

oxazoline in the presence of catalytic amount of acid to afford the N-acetyl-N-ethylenediamine compound **B**, wherein n is 1 and PG^2 is acetyl.

[0017] Removal of the PG^2 protecting group of formula **B**, at step **S-6**, affords the diamine compound of formula **A**. In certain embodiments, the PG^2 group of formula **B** is removed by acid hydrolysis. It will be appreciated that upon acid hydrolysis of the PG^2 group of formula **B**, a salt thereof is formed. For example, where the PG^2 group of formula **B** is removed by treatment with an acid such as trifluoroacetic acid, then the resulting diamine compound would be formed as its trifluoroacetic acid salt. One of ordinary skill in the art would recognize that a wide variety of acids are useful for removing amino protecting groups that are acid-labile and therefore a wide variety of salt forms of a compound of formula **A** are contemplated.

[0018] In other embodiments, the PG^2 group of formula **B** is removed by base hydrolysis. One of ordinary skill in the art would recognize that a wide variety of bases are useful for removing amino protecting groups that are base-labile.

[0019] At step **S-7**, a compound of formula **A** is treated with formaldehyde, or an equivalent thereof, to provide a compound of formula **II**. In certain embodiments, a compound of formula **A** is treated with aqueous formaldehyde to provide a compound of formula **II**. One or ordinary skill in the art would appreciate that substituted formaldehydes may be used at step **S-7** to afford a compound of formula **IIa**:



IIa

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

R^7 is hydrogen or a C_{1-6} alkyl group.

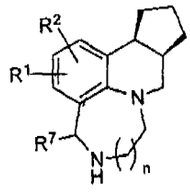
[0020] One of ordinary skill in the art will appreciate that a compound of formula **II**, as prepared by the methods of the present invention, may be treated with a suitable acid to form

a salt thereof. In certain embodiments, a compound of formula **II** is treated with HCl to form the hydrochloride salt thereof.

[0021] As used herein, the term "diastereomeric salt" refers to the adduct of a chiral compound of formula **E** with a chiral acid.

[0022] As used herein, the term "enantiomeric salt" refers to the salt of the resolved chiral compound of formula **D**, wherein said compound of formula **D** is enriched in one enantiomer. As used herein, the term "enantiomerically enriched", as used herein signifies that one enantiomer makes up at least 80% or 85% of the preparation. In certain embodiments, the term enantiomerically enriched signifies that at least 90% of the preparation is one of the enantiomers. In other embodiments, the term signifies that at least 95% of the preparation is one of the enantiomers.

[0023] According to one aspect, the present invention provides a method for preparing a compound of formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein:

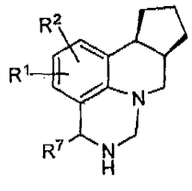
n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

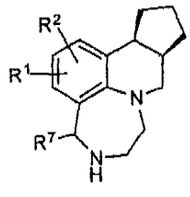
each R is independently hydrogen or a C_{1-6} alkyl group; and

R^7 is hydrogen or C_{1-6} alkyl.

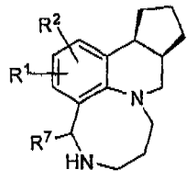
[0024] As defined generally above, the n group of formula **II** is 0, 1, or 2. Accordingly, the present invention provides a method for preparing a compound of any of formulae **IIa**, **IIb**, or **IIc**:



IIa



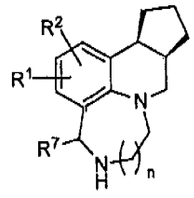
IIb



IIc

wherein each of R^1, R^2, R^7, and n is as defined above and herein.

[0025] According to another aspect, the present invention provides a method for preparing a compound of formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

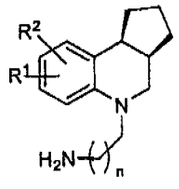
R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

R^7 is hydrogen or C_{1-6} alkyl,

comprising the steps of:

(a) providing a compound of formula **A**:



A

wherein:

n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group,

and

(b) reacting said compound of formula **A** with formaldehyde, or an equivalent thereof, to form a compound of formula **II**.

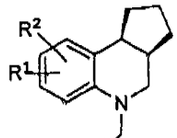
[0026] According to one embodiment, step (b) above is performed using aqueous formaldehyde. In certain embodiments, aqueous formaldehyde is added in an amount sufficient to consume the compound of formula **A**. In certain embodiments, aqueous

formaldehyde is added in amounts of at least about 0.90 mole equivalents, in amounts of about 0.90 mole equivalents to about 1.10 mole equivalents, or in amounts of from about 1.0 mole equivalents to about 1.05 mole equivalents relative to the compound of formula **A**.

[0027] According to another embodiment, step (b) is performed using a formaldehyde equivalent. Such formaldehyde equivalents are well known to one of ordinary skill in the art. In some embodiments, the formaldehyde equivalent is added in solid form to the reaction solvent to form a reaction suspension or the solid formaldehyde equivalent may be suspended in a reaction solvent and added to the reaction mixture. In other embodiments, paraformaldehyde is used as the formaldehyde equivalent, and is added in amounts sufficient to consume the compound of formula **A**. In some embodiments, paraformaldehyde is added in amounts of at least about 0.90 mole equivalents, in amounts of about 0.90 mole equivalents to about 1.10 mole equivalents, or in amounts of from about 1.0 mole equivalents to about 1.05 mole equivalents relative to the compound of formula **A**.

[0028] In certain embodiments, paraformaldehyde is in a solid form. Paraformaldehyde suitable for the reaction is commercially available in prills (or other granulated forms) and powders from a variety of suppliers such as Aldrich, Fluka, Celanese Chemicals, J.T. Baker, Mallinckrodt Laboratory Chemicals, Miljac Inc., Sego Int. Corp., Spectrum Chemicals Mfg., Total Specialty Chemicals Inc., US Chemicals Inc., Riedel- de Haen, Acros Organics, Pfaltz & Bauer Chemicals, Derivados, Lancaster Synthesis and EM Science. Certain suitable powder forms have at least about 10% particles retained on a 200 mesh screen.

[0029] According to another embodiment, the present invention provides a method for preparing a compound of formula **A**:



A

wherein:

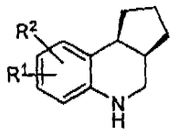
n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group,

comprising the steps of:

(a) providing a compound of formula **C**:



C

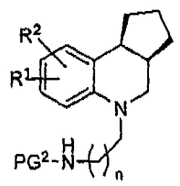
wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group,

and

(b) alkylating said compound of formula **C** to form a compound of formula **B**:



B

wherein:

n is 0, 1, or 2;

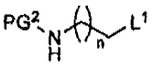
R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

PG^2 is a suitable amino protecting group,

and

(c) deprotecting said compound of formula **B** to form said compound of formula **A**.

[0030] In certain embodiments, the alkylation at step (b) above is achieved by reacting said compound of formula **C** with a compound of formula  wherein said reaction is performed in a suitable medium and wherein:

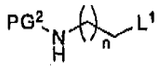
n is 0, 1, or 2;

PG^2 is a suitable amino protecting group; and

L^1 is a suitable leaving group.

[0031] As defined above, L^1 is a suitable leaving group. Suitable leaving groups are well known in the art, e.g., see, "Advanced Organic Chemistry," Jerry March, 5th Ed., pp. 351-357,

John Wiley and Sons, N.Y. Such leaving groups include, but are not limited to, halogen, alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy, optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, and diazonium moieties. Examples of suitable leaving groups include chloro, iodo, bromo, fluoro, methanesulfonyl (mesyl), tosyl, triflate, nitro-phenylsulfonyl (nosyl), and bromo-phenylsulfonyl (brosyl). In certain embodiments, L^1 is halogen. In other embodiment, L^1 is an optionally substituted alkylsulphonyloxy, optionally substituted alkenylsulfonyloxy, or optionally substituted arylsulfonyloxy group.

[0032] According to an alternate embodiment, the suitable leaving group may be generated *in situ* within the reaction medium. For example, the L^1 moiety may be generated *in situ* from a precursor of that compound of formula  wherein said precursor contains a group readily replaced by L^1 *in situ*. Such an *in situ* generation of a suitable leaving group is well known in the art, e.g., see, "Advanced Organic Chemistry," Jerry March, pp. 430-431, 5th Ed., John Wiley and Sons, N. Y.

[0033] In certain embodiments, said alkylation reaction is optionally performed in the presence of a suitable base. One of ordinary skill would recognize that the displacement of a leaving group by an amino moiety is achieved either with or without the presence of a suitable base. Such suitable bases are well known in the art and include organic and inorganic bases.

[0034] A suitable medium is a solvent or a solvent mixture that, in combination with the combined compounds, may facilitate the progress of the reaction therebetween. The suitable solvent may solubilize one or more of the reaction components, or, alternatively, the suitable solvent may facilitate the agitation of a suspension of one or more of the reaction components. Examples of suitable solvents useful in the present invention are a protic solvent, a halogenated hydrocarbon, an ether, an ester, an aromatic hydrocarbon, a polar or a non-polar aprotic solvent, or any mixtures thereof. Such mixtures include, for example, mixtures of protic and non-protic solvents such as benzene/methanol/water; benzene/water; DME/water, and the like.

[0035] These and other such suitable solvents are well known in the art, e.g., see, "Advanced Organic Chemistry", Jerry March, 5th edition, John Wiley and Sons, N.Y.

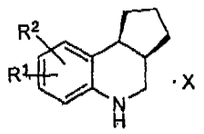
[0036] As defined generally above, the PG^2 group of formula **B** is a suitable amino protecting group. Suitable amino protecting groups are well known in the art and include

those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Suitable amino protecting groups, taken with the -NH- moiety to which it is attached, include, but are not limited to, aralkylamines, carbamates, allyl amines, amides, and the like. Examples of PG^2 groups include t-butyloxycarbonyl (BOC), ethyloxycarbonyl, methyloxycarbonyl, trichloroethyloxycarbonyl, allyloxycarbonyl (Alloc), benzyloxocarbonyl (CBZ), allyl, benzyl (Bn), fluorenylmethylcarbonyl (Fmoc), acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, trifluoroacetyl, benzoyl, and the like. In other embodiments, PG^2 group is acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, or trifluoroacetyl. In still other embodiments, the amino protecting group is acetyl.

[0037] According to yet another embodiment, one or more reagents may perform as the suitable solvent. For example, an organic base such as triethylamine or diisopropylethylamine, if utilized in said reaction, may serve as the solvent in addition to its role as a basifying reagent.

[0038] In other embodiments, the alkylation at step (b) above is achieved by reacting said compound of formula **C** with  in the presence of a suitable acid to form a compound of formula **B** wherein n is 1 and PG^2 is acetyl. Such suitable acids are well known in the art and include inorganic acids, e.g. hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid or perchloric acid, or organic acids, e.g. acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, malonic acid, lower alkyl sulfonic acids or aryl sulfonic acids. In certain embodiments, the alkylation at step (b) above is achieved by reacting said compound of formula **C** with  in the presence of toluenesulfonic acid.

[0039] Yet another aspect of the present invention provides a method for preparing a compound of formula **D**:



D

wherein:

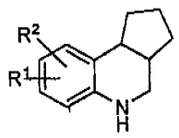
R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

comprising the steps of:

(a) providing a compound of formula **E**:



E

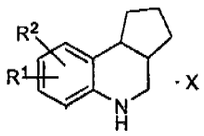
wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group,

and

(b) treating said compound of formula **E** with a chiral agent to form a compound of formula **D-1**:



D-1

wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

and

(c) obtaining said compound of formula **D** by suitable physical means.

[0040] The term "chiral agent" refers to an enantiomerically enriched group which may be ionically or covalently bonded to the nitrogen of a compound of formula **E**. As used herein, the term "enantiomerically enriched", as used herein signifies that one enantiomer makes up at least 85% of the preparation. In certain embodiments, the term enantiomerically enriched signifies that at least 90% of the preparation is one of the enantiomers. In other embodiments, the term signifies that at least 95% of the preparation is one of the enantiomers.

[0041] Chiral agents which are ionically bonded to said nitrogen include chiral acids. When the chiral agent is a chiral acid, the acid forms a diastereomeric salt with the nitrogen. The resulting diastereomers are then separated by suitable physical means. Examples of chiral acids include, but are not limited to, tartaric acid and tartaric acid derivatives, mandelic acid, malic acid, camphorsulfonic acid, and Mosher's acid, among others. In certain embodiments, the chiral acid is ditoluoyl-D-tartaric acid. In other embodiments, the chiral acid is ditoluoyl-L-tartaric acid. Chiral agents which may be covalently bonded to the nitrogen are known in the art.

[0042] The term "separated by suitable physical means" refers to methods of separating enantiomeric or diastereomeric mixtures. Such methods are well known in the art and include preferential crystallization, distillation, and trituration, among others. Chiral agents and separation methods are described in detail in Stereochemistry of Organic Compounds, Eliel, E. L. and Wilen, S. H., 1994, published by John Wiley and Sons.

[0043] In certain embodiments, a chiral salt of formula **D** is obtained *via* preferential crystallization of a diastereomeric salt formed at step (b) above. In other embodiments, the crystallization is achieved from a protic solvent. In still other embodiments, the protic solvent is an alcohol. It will be appreciated that the crystallization may be achieved using a single protic solvent or a combination of one or more protic solvents. Such solvents and solvent mixtures are well known to one of ordinary skill in the art and include one or more straight or branched alkyl alcohols. In certain embodiments, the crystallization is achieved from isopropyl alcohol.

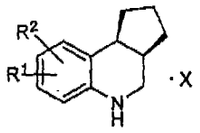
[0044] In certain embodiments, the chiral salt of formula **D** comprises an equimolar amount of chiral acid and amine. In other embodiments, the chiral salt of formula **D** comprises a substoichiometric amount of chiral acid. As used herein, the term "substoichiometric amount" denotes that the chiral acid is used in less than 1 mole equivalent relative to the compound of formula **E**. In certain embodiments the chiral acid is employed in less than 0.98 mole equivalents. In other embodiments the amine base is employed in less than 0.95 mole equivalents.

[0045] It should be readily apparent to those skilled in the art that enantiomeric enrichment of one enantiomer in the crystallized compound **D** causes an enantiomeric enrichment in the mother liquor of the other enantiomeric form. Therefore, according to another embodiment, the invention relates to a method of enhancing the %ee of a racemic or enantiomerically enriched compound of formula **D** as compared with a compound of formula

D-1. As used herein, the term "%ee" refers to the percent enantiomeric excess as would be understood by one of ordinary skill in the art.

[0046] In another preferred embodiment, the crystallized compound **D** is optionally subjected to an additional crystallization step to cause crystallization and further enrichment of the depicted enantiomer.

[0047] According to another embodiment, the present invention provides a method of obtaining an enantiomerically enriched compound of formula **D**:



D

wherein:

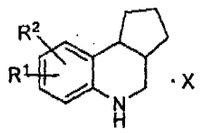
R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

comprising the steps of:

(a) combining a compound of formula **D-1**:



D-1

wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

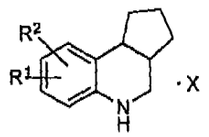
with a suitable solvent and heating to form a solution thereof; and

(b) allowing said solution to cool to cause crystallization of an enantiomerically enriched compound of formula **D**.

[0048] In certain embodiments, the suitable solvent utilized in step (a) above is a protic solvent. In still other embodiments, the protic solvent is an alcohol. It will be appreciated that the crystallization may be achieved using a single protic solvent or a combination of one

or more protic solvents. Such solvents and solvent mixtures are well known to one of ordinary skill in the art and include one or more straight or branched alkyl alcohols. In certain embodiments, the crystallization is achieved using a mixture of methanol and isopropyl alcohol.

[0049] In certain embodiments, the present invention provides a compound of formula **D-1**:



D-1

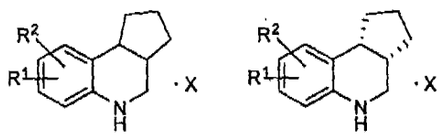
wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent.

[0050] According to another embodiment, the present invention provides a compound of either of formulae **D-1** and **D-2**:



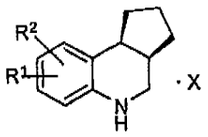
D-1 **D-2**

wherein each R^1, R^2 and X is as defined above and in classes and subclasses defined above and herein.

[0051] According to one embodiment, the R^1 and R^2 groups of formulae **D-1** and **D-2** are each independently an R group. According to another embodiment, one of R^1 and R^2 is hydrogen. According to yet another embodiment, both of R^1 and R^2 are hydrogen.

[0052] In certain embodiments, the X group of formulae **D-1** and **D-2** is a chiral acid, thus forming a chiral salt. In other embodiments, the X group of formulae **D-1** and **D-2** is a tartaric acid derivative. In still other embodiments, the X group of formulae **D-1** and **D-2** is ditoluoyl-D-tartaric acid.

[0053] Yet another embodiment provides a compound of formula **D**:



D

wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

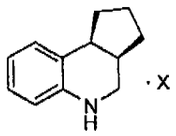
each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent.

[0054] According to one embodiment, the R^1 and R^2 groups of formula **D** are each independently an R group. According to another embodiment, one of R^1 and R^2 is hydrogen. According to yet another embodiment, both of R^1 and R^2 are hydrogen.

[0055] In certain embodiments, the X group of formula **D** is a chiral acid, thus forming a chiral salt. In other embodiments, the X group of formula **D** is a tartaric acid derivative. In still other embodiments, the X group of formula **D** is ditoluoyl-D-tartaric acid.

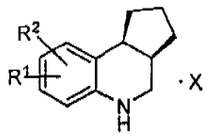
[0056] According to another embodiment, the present invention provides a compound of formula **D**, wherein R^1 and R^2 are both hydrogen and said compound is of formula **D-3**:



D-3.

[0057] In certain embodiments, a compound of formula **D-3** is provided substantially free of the corresponding enantiomer. "Substantially free," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In other embodiments, at least about 95% by weight of a desired enantiomer is present. In still other embodiments of the invention, at least about 99% by weight of a desired enantiomer is present. Such enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and chiral salt resolution, or prepared by methods described herein.

[0058] Yet another aspect of the present invention provides a method for preparing a compound of formula **D**:



D

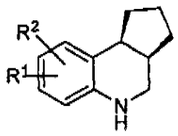
wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

as described above and herein, wherein said method further comprises the step of treating said compound of formula **D** with a suitable base to form the free-base compound of formula **C**:



C

wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group.

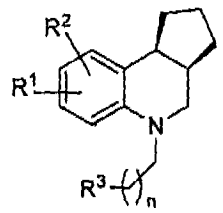
[0059] As used herein, the suitable base is an organic or inorganic base. Such suitable bases include strong inorganic bases, *i.e.*, those that completely dissociate in water under formation of hydroxide anion. In certain embodiments, the base is added in an amount of at least about 1 mol. eq. and, in other embodiments, in an amount of at least about 1 mol. eq. to about 10 mol. eq. relative to the compound of formula **D**. Examples of such bases include alkaline metals, alkaline earth metal hydroxides, and combinations thereof. In other embodiments, the suitable base is sodium hydroxide.

[0060] According to one embodiment, the free base formation is performed in the presence of a suitable solvent. Examples of solvents suitable for use during the free base formation include polar solvents such as alkyl alcohols, such as C_1 to C_4 alcohols (*e.g.* ethanol, methanol, 2-propanol), water, dioxane, or THF (tetrahydrofuran) or combinations thereof. In certain embodiments, the suitable solvent is a C_1 to C_4 alcohol such as methanol,

ethanol, 2-propanol, water, or combination thereof. According to one aspect of the present invention, the suitable base is aqueous sodium hydroxide and, thus, the solvent is water.

[0061] According to another aspect of the present invention, the free base formation is performed in a bi-phasic mixture of solvents whereby the compound of formula C, as it is formed, is extracted into an organic layer. Thus, a suitable bi-phasic mixture of solvents includes an aqueous solvent and a non-miscible organic solvent. Such non-miscible organic solvents are well known to one of ordinary skill in the art and include halogenated hydrocarbon solvents (e.g. methylene chloride and chloroform), benzene and derivatives thereof (e.g. toluene), esters (e.g. ethyl acetate and isopropyl acetate), ethers (e.g. MTBE, THF and derivatives thereof, glyme, and diglyme), and the like. In certain embodiments, the free base formation is performed in a bi-phasic mixture comprising water and toluene. In other embodiments, the suitable base is water soluble such that the reaction is performed in a mixture of toluene and a suitable aqueous base, such as aqueous sodium hydroxide.

[0062] In certain embodiments, the present invention provides a compound of formula III:



III

or a salt thereof, wherein:

n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

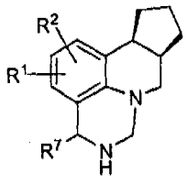
R^3 is NH_2 or a suitably protected amino group.

[0063] In certain embodiments, the R^1 and R^2 groups of formula I are each R. In other embodiments, one of R^1 and R^2 is hydrogen. In still other embodiments, both of R^1 and R^2 are hydrogen.

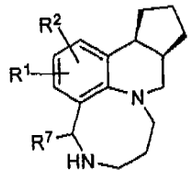
[0064] Suitable amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Suitably protected amino groups of R^3 include, but are not limited to,

aralkylamines, carbamates, allyl amines, amides, and the like. Examples of such groups include t-butyloxycarbonyl (BOC), ethyloxycarbonyl, methyloxycarbonyl, trichloroethyloxycarbonyl, allyloxycarbonyl (Alloc), benzyloxocarbonyl (CBZ), allyl, benzyl (Bn), fluorenylmethylcarbonyl (Fmoc), acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, trifluoroacetyl, benzoyl, and the like. In other embodiments, the amino protecting group is acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, or trifluoroacetyl. In still other embodiments, the amino protecting group is acetyl.

[0065] In certain embodiments, the present invention provides a compound of formula **IIa** or **IIc**, or a pharmaceutically acceptable salt thereof:



IIa



IIc

wherein each of R^1, R^2, and R^7 is defined above and herein.

[0066] In certain embodiments, the present invention provides a compound of formula **IIa** wherein R^1, R^2, and R^7 are all hydrogen.

[0067] In other embodiments, the present invention provides a compound of formula **IIc** wherein R^1, R^2, and R^7 are all hydrogen.

[0068] Pharmaceutically acceptable salts, including mono- and bi- salts, are those derived from such organic and inorganic acids such as, but not limited to acetic, lactic, citric, cinnamic, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, oxalic, propionic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, glycolic, pyruvic, methanesulfonic, ethanesulfonic, toluenesulfonic, salicylic, benzoic, and similarly known acceptable acids.

[0069] A used herein, the term halogen refers to chloride, fluorine, bromine or iodine. The C_{1-6} alkyl group may be a straight or branched chain alkyl. Suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t–butyl. The C_{1-6} perfluoroalkyl group may include a straight or branched chain alkyl. Suitable perfluoroalkyl groups include trifluoromethyl and pentafluoroethyl.

EXAMPLES

[0070] As indicated herein, the %ee data was obtained *via* the following chiral HPLC method:

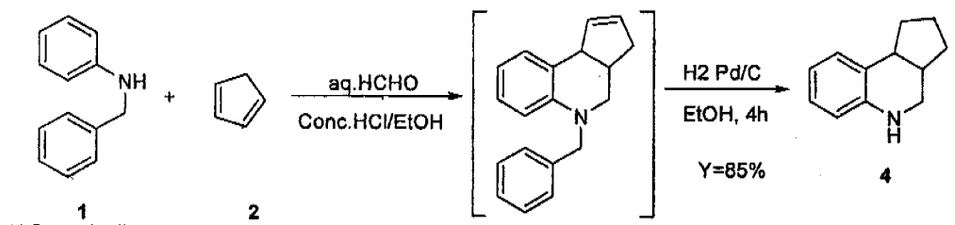
Column: Chiralcel OD 4.6 x 250
Mobile Phase: Hexane:IPA:MeOH:TEA 800:10:10:0.5
Flow rate: 1 mL/minute
Temperature: Ambient
Time: 12 minutes
Wavelength: 210 nm

[0071] As indicated herein, the % purity data was obtained *via* the following chiral HPLC method:

Column: Chromolith Performance RP-18e (100 x 4.6 mm)
Mobile Phase: A = 95:5:0.1 water:CH_3CN:H_3PO_4
B = 95:5:0.1 CH_3CN:water:H_3PO_4
Gradient: 5% B to 95% B over 8 minutes
Flow rate: 1 mL/minute
Temperature: Ambient
Time: 10 minutes
Wavelength: 210 nm

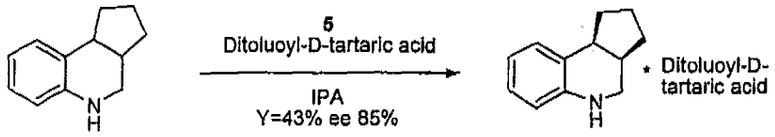
Example 1 (Method A)

2,3,3a,4,5,9b-Hexahydro-1H-cyclopenta(c)quinoline:



[0072] N-phenylbenzylamine hydrochloride (2.0 g) in 20 mL MeOH was cooled to ~5°C. Freshly cracked cyclopentadiene (1.2 g, from atmospheric heating/distillation of dicyclopentadiene) was added to the solution followed by aqueous formaldehyde (37%, 1.04 g). The reaction temperature was maintained at 5-10 °C overnight (ca. 18 hrs). No starting material was observed by TLC (10% ethyl acetate in hexanes). The reaction was then allowed to warm to RT. The reaction was diluted with EtOAc and washed with 0.5N NaOH solution, and then brine. Concentration of the organics gave 2.32 g of crude tricyclic product as an oil. The crude oil from above in 20 mL 1:1 EtOH:EtOAc was treated with 0.175 mL 1N HCl in EtOH and then 5% Pd-C (0.250 g, 50% wet). The mixture was shaken under 40-45 psi H_2 overnight. The solids were removed by filtration through celite and the pad is rinsed with EtOAc. The filtrate was concentrated to give a peach colored oil which crystallized under vacuum to give 1.38 g (87%) debenzylated product.

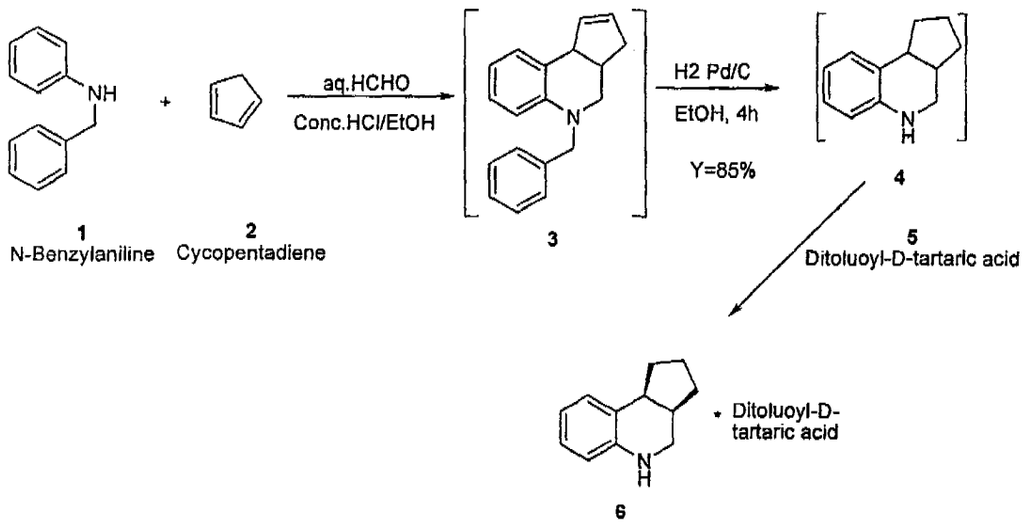
(-) 2,3,3a,4,5,9b-Hexahydro-1H-cyclopenta(c)quinoline di-p-toluoyl-D-tartaric acid (6):



[0073] A mixture of the racemic amine (16.0 g, 92.3 mmol), di-p-toluoyl-D-tartaric acid (23.3 g, 60.3 mmol) in IPA (160 mL) was heated to 70 °C for 10-15 minutes. The solids dissolved during this time. The solution was cooled to 0-5 °C over 3 hours. The resulting solids were filtered, washed with cold IPA (60 mL), and dried at 40 °C to give 21.0 g (40%) of the salt as an off-white solid. Chiral HPLC: 85%ee; ^{1}H NMR (d6-DMSO) δ 7.91 (d, J=6 Hz, 4H), 7.40 (d, J=6 Hz, 4H), 6.97 (d, J=6 Hz, 1H), 6.84 (t, J=6 Hz, 1H), 6.4-6.6 (m, 2H), 5.83 (s, 2H), 2.9-3.1 (m, 2H), 2.8-3.1 (m, 1H), 2.8-2.9 (m, 1H), 2.5-2.7 (m, 1H), 2.5 (m, 1H), 2.3-2.5 (s, 6H), 2.0-2.2 (m, 3H), 1.8-2.0 (m, 1H), 1.2-1.7 (m, 4H); ^{13}C NMR (d6-DMSO) δ 167.6, 165.0, 145.7, 144.9, 129.9, 129.8, 129.7, 126.2, 125.2, 116.4, 114.4, 71.7, 43.6, 40.7, 35.8, 35.4, 29.3, 23.0, 21.6.

Example 2 (Method B)

(-) 2,3,3a,4,5,9b-Hexahydro-1H-cyclopenta(c)quinoline di-p-toluoyl-D-tartaric acid (6:

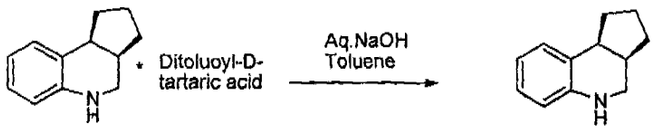


[0074] In an alternative method, N-phenylbenzylamine (50 g) in 250 mL MeOH was stirred mechanically until dissolved. 29 mL conc. HCl was added in a single portion. The mixture was allowed to cool to RT. The amine HCl salt gradually came out of solution. The

suspension was cooled in ice to about 15 °C and the freshly distilled cyclopentadiene [29.4 g, cyclopentadiene is obtained by thermal cracking of dicyclopentadiene *via* atmospheric short path distillation (pot temperature 165-170 °C, distillate ca. 60-70 °C). The cyclopentadiene was collected into an ice-cooled receiver] was added in a single portion. The temperature was allowed to drop back to 15 °C before proceeding, if necessary. Formaldehyde solution (37% aqueous) in 150 mL MeOH was added dropwise so as to maintain an internal temperature of 15-25 °C (15 mins addition time). A yellow solution resulted. Once the addition was complete, the reaction was allowed to stir at RT overnight under nitrogen (12-18h). The solution was clear, but greenish. The solution was transferred to a 2L Parr bottle and treated with 1.5 g 10% Pd/C (50% wet) and shaken under 45 psi hydrogen until uptake ceased. Once complete, the mixture was purged with nitrogen and treated with sodium bicarbonate (58 g). The slurry was stirred until the solution was neutral to slightly basic by damp pH paper. The mixture was then filtered through 1 cm celite and the pad rinsed with MeOH (50 mL). The filtrate was concentrated *in vacuo* and 450 mL IPA added. The mixture was stirred overnight and the resulting solids filtered and rinsed with 50 ml IPA. To the filtrate obtained above was added di-p-toluoyl-D-tartaric acid (63.3 g) in a single portion. The slurry was heated to ca. 80°C to dissolve all solids. The mixture was then allowed to gradually cool to RT and stir for 3 or more hours. The mixture was then cooled to 0-5°C in ice and stirred at this temperature for 1-2 hours. The solids were filtered and washed with 100 mL of cold IPA. The faintly blue-green solids were dried *in vacuo* to afford the title compound. Yield: 46.7 g (31%) Chiral purity (HPLC): 95:5%ee.

Example 3

(-) 2,3,3a,4,5,9b-Hexahydro-1H-cyclopenta(c)quinoline (7):



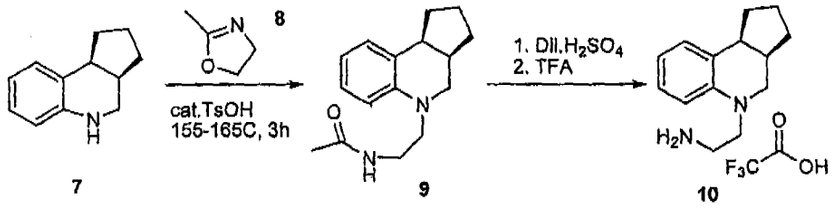
6 7

[0075] To a suspension of the ditoluoyl-D-tartrate salt (20.67 g, 37 mmol) in toluene (93 mL), aq. NaOH (12 mL of 30% NaOH diluted to 100 mL with water) was added over 5 min. The two-phase mixture was stirred vigorously and the solids slowly dissolved. The two layers were separated. The aqueous layer was extracted with toluene (46 mL). The combined organic layers were concentrated to give 6.4 g (100% yield) of the free base as

yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.09 (d, J=7.5 Hz, 1H), 6.9-7.0 (m, 1H), 6.6-6.7 (m, 1H), 6.4-6.5 (m, 1H), 3.85 (bs, 1NH), 2.9-3.2 (m, 2H), 2.8-3.1 (m, 1H), 2.80 (t, J=10.3 Hz, 1H), 2.3-2.4 (m, 1H), 2.0-2.2 (m, 1H), 1.8-2.1 (m, 1H), 1.3-1.8 (m, 4H).

Example 4

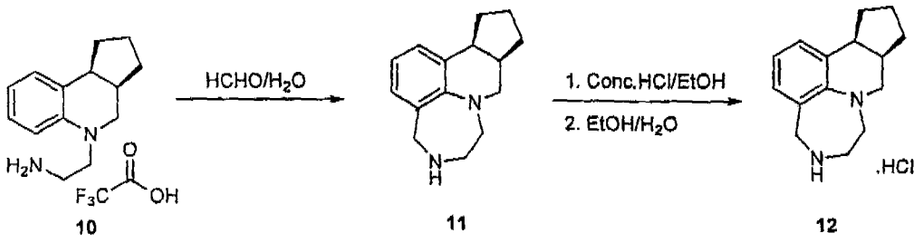
(-)[2-(1,2,3,3a,4,9b-Hexahydro-cyclopenta[c]quinolin-5-yl)-ethylamine trifluoroacetic acid salt (10):



[0076] A mixture of amine (6.4g, 36.9 mmol) and a catalytic amount of p-toluenesulfonic acid (0.07g, 0.37 mmol) was heated to 165 °C. Added 2-methyl-2-oxazoline slowly over 2 h to the reaction mixture at 165 °C. Cooled the reaction mixture to 60 °C and then added dil. H_2SO_4 (6 ml of conc. H_2SO_4 and 26 mL of water). Stirred for 1h at 60 °C. Cooled to RT, added toluene (40 mL) and 30% NaOH (30 mL). Filter off the solids and wash it with toluene (2 x 10 mL). Each wash was used to extract the aqueous layer. Washed the combined organic extracts with water (25 mL). Concentrate the toluene layer to 20 mL volume and cooled to 10 °C. Added a solution of trifluoroacetic acid (2.4 mL, 31.2 mmol) in toluene (7.5 mL) over 15 min. Stirred for 2 h at 10 °C. It was filtered and washed with toluene (10 mL). Dried the TFA salt at 55 °C in a vacuum oven. 7.7 g (yield 63%) HPLC 97.6% Chiral Purity 92.2 : 7.8.

Example 5

(-)-4,5,6,7,9,9a,10,11,12,12a-decahydrocyclopenta[c][l,4]diazepino[6,7,l-*ij*]quinoline hydrochloride (12):



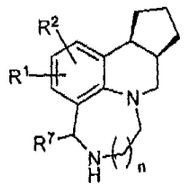
[0077] To a solution of N-ethylenediamine TFA salt (2.3 g, 7.0 mmol) in water 120 mL) at 60 C was added aqueous formaldehyde (0.72 g, 37% wt in water, 8.8 mmol, 1.26 equivs)

over a period of 2.0 h. After 19 h at 60 °C, it was cooled to ambient temperature. To the reaction mixture sodium hydroxide (0.38 g) and isopropyl acetate (20 mL) was added. The layers were separated and the aqueous layer was extracted with isopropyl acetate (10 mL). The organic layers were combined and washed with water (10 mL). To the organic layer was added conc.HCl (0.82 g) drop wise. The solids were filtered and washed with isopropyl acetate (5 mL). The crude product (2.44 g) was heated to 70 °C in ethanol (14 ml, 200 proof, denatured with 4% ethyl acetate) and then water (1.0 ml) was added. The solution was cooled to 5 °C over 3 hours. The product was filtered and washed with cold ethanol (2.4 mL). The wet product (1.4 g) was dried in a vacuum oven for 20 hours at 40 °C to afford the title compound (1.1 g, yield 60%) as a white solid. A second crop of 0.34 g (18%) was isolated from the mother liquor. HPLC (area%): 96.5%; Chiral purity (HPLC): 99.87 : 0.13

CLAIMS

We claim:

1. A method for preparing a compound of formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

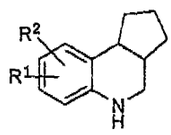
R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

R^7 is hydrogen or C_{1-6} alkyl,

comprising the steps of:

(a) providing a compound of formula **E**



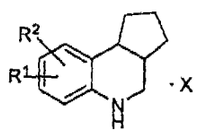
E

wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group,

(b) treating said compound of formula **E** with a chiral agent to form a compound of formula **D-1**:



D-1

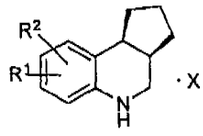
wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

(c) obtaining a compound of formula **D** by suitable physical means:



D

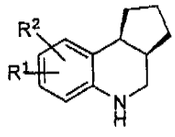
wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

(d) treating said compound of formula **D** with a suitable base to provide a compound of formula **C**:



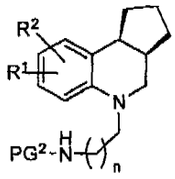
C

wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group,

(e) alkylating said compound of formula **C** to form a compound of formula **B**:



B

54

wherein:

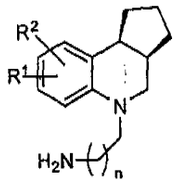
n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

PG^2 is a suitable amino protecting group,

(f) deprotecting said compound of formula **B** to form a compound of formula **A**.



A

wherein:

n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group,

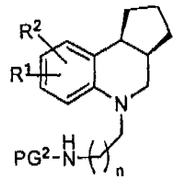
and

(g) reacting said compound of formula **A** with formaldehyde, or an equivalent thereof, to form a compound of formula **II**.

2. The method according to claim 1, wherein each n is 1 and R^1 and R^2 are both hydrogen.

3. The method according to claim 1 or 2, wherein said formaldehyde is aqueous formaldehyde.

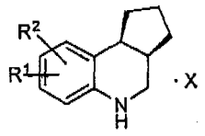
4. The method according to any one of claims 1, 2, or 3, wherein the alkylation at step (e) is achieved by reacting said compound of formula **C** with  in the presence of a suitable acid to form a compound of formula **B**:



B

wherein n is 1 and PG^2 is acetyl.

5. A method for preparing a compound of formula **D**:



D

wherein:

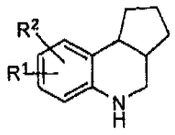
R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

comprising the steps of:

(a) providing a compound of formula **E**:



E

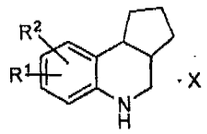
wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group,

and

(b) treating said compound of formula **E** with a chiral agent to form a compound of formula **D-1**:



D-1

wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

and

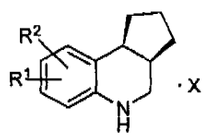
(c) obtaining said compound of formula **D** by suitable physical means.

6. The method according to claim 5, wherein X is a chiral acid.

7. The method according to claim 6, wherein the chiral acid is ditoluoyl-D-tartaric acid and the compound of formula **D** is obtained by crystallization from a protic solvent.

8. The method according to claim 7, wherein the compound of formula **D** is enantiomerically enriched.

9. The method according to claim 6, comprising obtaining an enantiomerically enriched compound of formula **D**:



D

wherein:

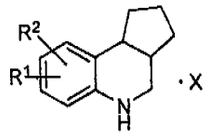
R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

comprising the steps of:

(a) combining a compound of formula **D-1**:



D-1

wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

X is a chiral agent,

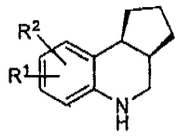
with a suitable solvent and heating to form a solution thereof; and

(b) allowing said solution to cool to cause crystallization of an enantiomerically enriched compound of formula **D**.

10. The method according to claim 9, wherein X is ditoluoyl-D-tartaric acid and said suitable solvent is a protic solvent.

11. The method according to claim 10, wherein said suitable solvent comprises a mixture of methanol and isopropyl alcohol.

12. The method according to claim 9, further comprising the step of treating said compound of formula **D** with a suitable base to form the free-base compound of formula **C**:



C

wherein:

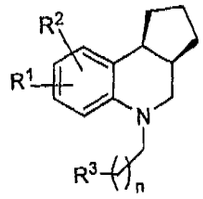
R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl; and

each R is independently hydrogen or a C_{1-6} alkyl group.

13. The method according to claim 12, wherein said method is performed in a bi-phasic mixture of solvents.

14. The method according to claim 13, wherein said method is performed in a mixture of toluene and aqueous sodium hydroxide.

15. A compound of formula **III**:



III

or a salt thereof, wherein:

n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

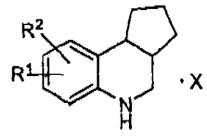
R^3 is NH_2 or a suitably protected amino group.

16. The compound according to claim 15, wherein R^3 is hydrogen or acetyl.

17. The compound according to claim 16, wherein R^1 and R^2 are each R.

18. The compound according to claim 17, wherein both of R^1 and R^2 are hydrogen.

19. A compound of formula **D-1**:



D-1

wherein:

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

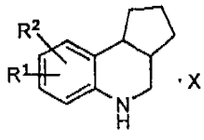
X is a chiral agent.

20. The compound according to claim 19, wherein X is a chiral acid and each of R^1 and R^2 is hydrogen.

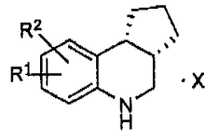
21. The compound according to claim 20, wherein X is ditoluoyl-D-tartaric acid.

22. The compound according to claim 21, wherein said compound comprises an equimolar amount of X.

23. The compound according to claim 22, wherein said compound is of either of formulae **D-1** or **D-2**:

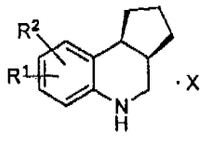


D-1



D-2.

24. The compound according to claim 19, wherein said compound is of formula **D**:



D.

25. The compound according to claim 24, wherein R^1 and R^2 are each independently an R group and X is a chiral acid.

26. The compound according to claim 25, wherein both of R^1 and R^2 are hydrogen and X is ditoluoyl-D-tartaric acid.

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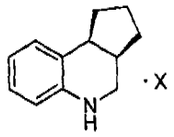
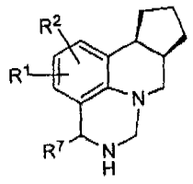
27. The compound according to claim 19, wherein said compound is of formula **D-3**:



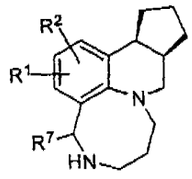
D-3.

28. The compound according to claim 27, wherein said compound is provided substantially free of the corresponding enantiomer.

29. A compound of formula **IIa** or **IIc**:



IIa



IIc

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

R^1 and R^2 are each independently halogen, -CN, phenyl, -R, -OR, -C_{1-6} perfluoroalkyl, or -OC_{1-6} perfluoroalkyl;

each R is independently hydrogen or a C_{1-6} alkyl group; and

R^7 is hydrogen or C_{1-6} alkyl.

DIAZEPINOQUINOLINAS, SU SÍNTESIS, E INTERMEDIOS DE ESTA

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con métodos para sintetizar compuestos útiles como agonistas o agonistas parciales de $5HT_{2C}$, sus derivados, y con sus intermedios.

ANTECEDENTE DE LA INVENCIÓN

La esquizofrenia afecta aproximadamente a 5 millones de personas. Los tratamientos más prevalentes para la esquizofrenia son actualmente los antipsicóticos 'atípicos', que combinan el antagonismo de receptor de serotonina ($5\text{-}HT_{2A}$) y dopamina (D_2). A pesar de las mejoras reportadas en la eficacia y la desventaja de efectos colaterales de los antipsicóticos atípicos relacionados con antipsicóticos típicos, estos compuestos no parecen tratar adecuadamente todos los síntomas de la esquizofrenia y están acompañados por efectos colaterales problemáticos, tal como ganancia de peso (Allison, D. B., et. al., Am. J. Psychiatry, 156: 1686-1696, 1999; Masand, P. S., Exp. Opin. Pharmacother. I: 377-389, 2000; Whitaker, R., Spectrum Life Sciences. Decision Resources. 2:1-9, 2000).

Los antipsicóticos atípicos también se unen con alta afinidad a los receptores $5\text{-}HT_{2C}$ y funcionan como antagonistas del receptor $5\text{-}HT_{2C}$ o agonistas inversos. La ganancia de peso es un efecto colateral problemático asociado con antipsicóticos

atípicos tales como clozapina y olanzapina, y se ha sugerido que el antagonismo 5-HT_{2C} es responsable de la ganancia de peso. Al contrario, la estimulación del receptor 5-HT_{2C} se conoce por resultar en toma de alimento y peso corporal reducidos. (Walsh et. al., Psychopharmacology 124: 57-73, 1996; Cowen, P. J., et. al., Human Psychopharmacology 10: 385-391, 1995; Rosenzweig-Lipson, S., et. al., ASPET abstract, 2000).

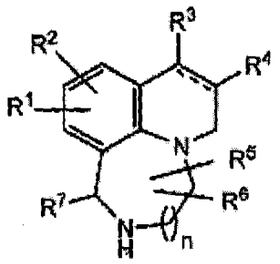
Varias líneas de evidencia soportan un papel para el agonismo parcial o agonismo del receptor 5-HT_{2C} como un tratamiento para la esquizofrenia. Los estudios sugieren que los antagonistas 5-HT_{2C} incrementan los niveles sinápticos de la dopamina y pueden ser efectivos en modelos animales de enfermedad de Parkinson (Di Matteo, V., et. al., Neuropharmacology 37: 265-272, 1998; Fox, S. H., et. al., Experimental Neurology 151: 35-49, 1998). En razón a que los síntomas positivos de la esquizofrenia se asocian con niveles incrementados de dopamina, los compuestos con acciones opuestas a aquellas de los antagonistas 5-HT_{2C}, tal como agonistas parciales y agonistas del 5-HT_{2C}, deben reducir los niveles de dopamina sináptica. Estudios recientes han demostrado que los agonistas 5-HT_{2C} reducen los niveles de dopamina en la corteza prefrontal y el nucleus accumbens (Millan, M. J., et. al., Neuropharmacology 37: 953-955, 1998; Di Matteo, V., et. al., Neuropharmacology 38: 1195- 1205, 1999; Di Giovanni, G., et. al., Synapse 35: 53-61, 2000), regiones del cerebro que se consideran median los efectos antipsicóticos críticos de drogas similares a clozapina. Sin

embargo, los agonistas del 5-HT_{2C} no reducen los niveles de dopamina en el cuerpo estriado, la región del cerebro más cercanamente asociada con los efectos colaterales extrapiramidales. Adicionalmente, un estudio reciente demuestra que los agonistas 5-HT_{2C} reducen la descarga en el área ventrotegmentaria (VTA), pero no en la sustancia nigra. Los efectos diferenciales de los agonistas 5-HT_{2C} en la ruta mesolímbica relacionada con la ruta nigroestriatal sugiere que los agonistas 5-HT_{2C} tienen selectividad límbica, y probablemente producirá menos efectos colaterales extrapiramidales asociados con antipsicóticos típicos.

RESUMEN DE LA INVENCIÓN

Como se describe aquí, la presente invención proporciona métodos para preparar compuestos que tienen actividad como agonistas parciales o agonistas del $5HT_{2C}$. Estos compuestos son útiles para tratar esquizofrenia, trastorno esquisofreniforme, trastorno esquisoafectivo, trastorno delirante, trastorno sicótico inducido por sustancias, psicosis inducida por L-DOPA, psicosis asociada con demencia por Alzheimer, psicosis asociada con enfermedad de Parkinson, psicosis asociada con enfermedad de cuerpo de Lewy, demencia, déficit de memoria, déficit intelectual asociado con enfermedad de Alzheimer, trastornos bipolares, trastornos depresivos, episodios de mal humor, trastornos de ansiedad, trastornos de adaptación, trastornos alimenticios, epilepsia, trastornos del sueño, migrañas, disfunción sexual, trastornos gastrointestinales, obesidad, o una deficiencia del sistema

nervioso central asociada con trauma, apoplejía, o lesión de la médula espinal. Tales compuestos incluyen aquellos de fórmula **I**:



I

o una sal farmacéuticamente aceptable de estos, en donde:

==== designa un enlace doble o sencillo;

n es 0, 1, o 2;

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6};

R^3 y R^4 se toman juntos para formar un anillo de 4-8 miembros saturado o insaturado, en donde dicho anillo se sustituye opcionalmente con 1-3 grupos independientemente seleccionados de halógeno, -R, o OR;

R^5 y R^6 son cada uno independientemente -R; y

R^7 es hidrógeno o alquilo C_{1-6}.

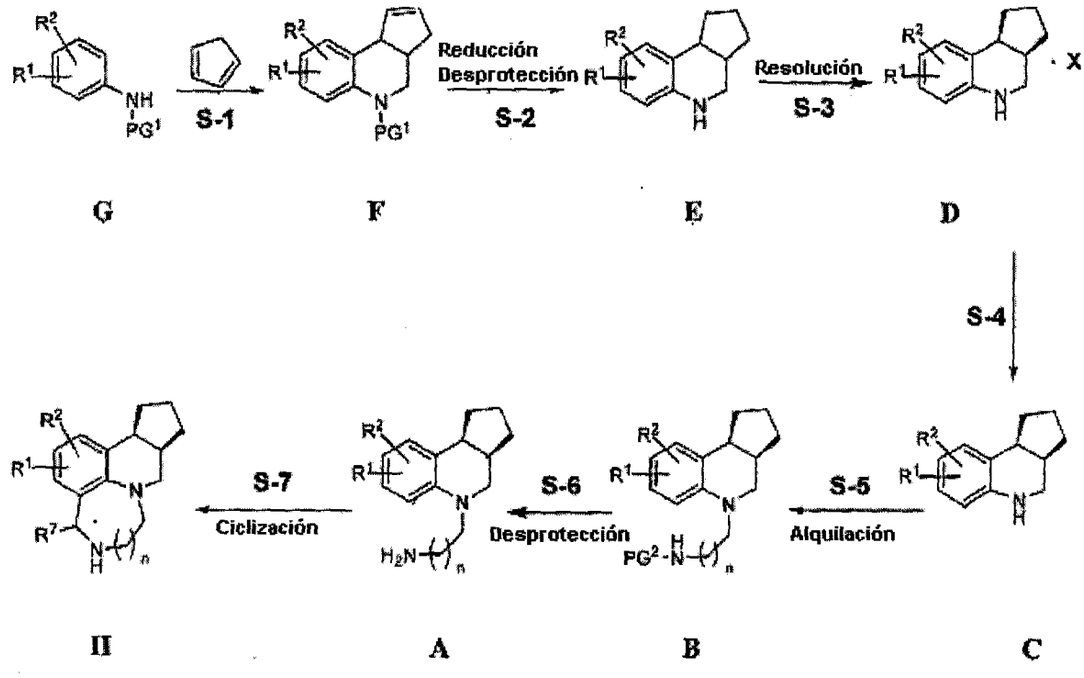
La presente invención también proporciona intermedios sintéticos útiles para preparar tales compuestos.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Los métodos e intermedios de la presente invención son útiles para preparar compuestos como se describe en, por ejemplo

Solicitud de Patente Internacional WO 03/091250, en el nombre de Ramamoorthy, la totalidad de la cual se incorpora aquí como referencia. En ciertas modalidades, los presentes compuestos se preparan generalmente de acuerdo con el Esquema I establecido adelante:

Esquema I



En el Esquema I anterior, cada uno de n, PG^1, R^1, R^2, R^7, y PG^2 es como se define adelante y en clases y subclases como se describe aquí.

En un aspecto, la presente invención proporciona métodos para preparar compuestos de quinolina quiral de fórmula **D** de acuerdo con las etapas representadas en el Esquema 1, anterior. En la etapa **S-1**, una anilina de fórmula **G** se hace reaccionar con formaldehído, o un equivalente de este, y ciclopentadieno en la presencia de un ácido mineral. En

ciertas modalidades, la reacción Diels-Alder de N-bencilanilina y ciclopentadieno en la presencia de HCl concentrado proporciona la ciclopenteniltetrahidroquinolina **F**, en donde PG^1 es bencilo. En otras modalidades, la etapa **S-1** se desarrolla en una forma sustancialmente similar a aquellas descrita por Posson, *et al,* "Imino Diels-Alder Reaction: Application to the Synthesis of Diverse Ciclopenta[c] Quinoline Derivatives" *Synlett* 2000, No. 2, 209-212.

El grupo PG^1 de las fórmulas **G** y **F** es un grupo protector amino adecuado. Los grupos protectores amino adecuados se conocen bien en la técnica e incluyen aquellos descritos en detalle en *Protecting Groups in Organic Synthesis,* T. W. Greene and P. G. M. Wuts, 3ra edición, John Wiley & Sons, 1999, la totalidad de la cual se incorpora aquí como referencia. Los grupos protectores amino adecuados, tomados con la porción -NH- a la que se adhieren, incluyen, pero no se limitan a, aralquilaminas, carbamatos, alil aminas, amidas, y similares. Ejemplos de grupos PG^1 de las fórmulas **G** y **F** incluyen t-butiloxicarbonilo (BOC), etiloxicarbonilo, metiloxicarbonilo, tricloroetiloxicarbonilo, aliloxicarbonilo (Alloc), benciloxocarbonilo (CBZ), alilo, bencilo (Bn), fluorenilmetilcarbonilo (Fmoc), acetilo, cloroacetilo, dicloroacetilo, tricloroacetilo, fenilacetilo, trifluoroacetilo, benzoilo, y similares. En otras modalidades, el grupo PG^1 de las fórmulas **G** y **F** es bencilo.

En la etapa **S-2**, la olefina del compuesto **F** se reduce y el grupo amino desprotegido por remoción de PG^1. Un experto en la técnica reconocería que, dependiendo de la elección de PG^1, que la desprotección y la reducción de olefina se pueden desarrollar en la misma etapa. Por ejemplo, cuando el grupo PG^1 de fórmula **F** es bencilo, la reducción de la olefina podría desproteger simultáneamente el grupo amina. De acuerdo con esto, en ciertas modalidades, la presente invención proporciona un método para formar un compuesto de fórmula **E** que comprende la etapa de reducir simultáneamente la olefina y desproteger el grupo amino de fórmula **F**. Así, en ciertas modalidades, el grupo PG^1 de fórmula **F** es un grupo protector amino que se remueve por reducción, por ejemplo hidrogenación. Por ejemplo, la reducción del enlace doble y la desprotección de un grupo bencilo se logra en la misma reacción por reducción catalítica con Pd-C bajo una atmósfera de hidrógeno. En un método alterno, la remoción de PG^1 y la reducción de olefina en la etapa **S-2** se pueden desarrollar en forma de etapas utilizando métodos conocidos por el experto en la técnica.

En la etapa **S-3**, el compuesto racémico **E** se trata con un agente quiral para formar una mezcla diastereómerica de este. En ciertas modalidades, el compuesto racémico **E** se trata con un ácido quiral para formar una sal diastereómerica de este. Luego se separa la mezcla diastereómerica resultante por medios adecuados para obtener un compuesto de fórmula **D**. Tales medios adecuados para separar mezclas diastereómericas se conocen bien por el experto en la técnica e incluyen, pero

no se limitan a, aquellos métodos descritos aquí. Se apreciará que, dependiendo del ácido quiral utilizado, puede haber una o más porciones carboxilato. En ciertas modalidades, el ácido quiral tiene dos porciones carboxilato con, por ejemplo, ácido tartárico o un derivado de este.

De acuerdo con esto, un experto en la técnica apreciaría que un compuesto de fórmula **E** puede formar una hemi sal con dicho ácido quiral bi-funcional. Como se utiliza aquí, el término "hemi sal" se refiere a un aducto que tiene dos moléculas de un compuesto de fórmula **E** a cada molécula de ácido quiral. Alternativamente, la sal resultante puede tener una mezcla de uno-a-uno ácidos quirales a un compuesto de fórmula **E**. En ciertas modalidades, la presente invención proporciona un compuesto de fórmula **D** en donde dicho compuesto de fórmula **D** comprende cantidades molares iguales de ácido quiral a una amina de fórmula **E**.

En ciertas modalidades, cada uno de las etapas sintéticas mencionadas anteriormente se pueden desarrollar secuencialmente con aislamiento de cada intermedio **F**, **E**, y **D** desarrollado después de cada etapa. Alternativamente, cada una de las etapas **S-1**, **S-2**, y **S-3**, como se describió en el Esquema I anterior, se puede desarrollar en una forma con la cual no hay aislamiento de los intermedios **F** y **E**.

Cuando X es un ácido quiral, el compuesto de fórmula **D**, en la etapa **S-4**, se trata con una base adecuada para formar el compuesto de base libre **C**. Las bases libres de acuerdo con la

invención también se preparan, por ejemplo, al poner en contacto un compuesto de fórmula **D** con una base adecuada en la presencia de un disolvente adecuado para la formación de base libre. Tales bases adecuadas incluyen bases inorgánicas fuertes, es decir, aquellas que se disocian completamente en agua bajo formación de anión hidróxido. En ciertas modalidades, la base se agrega en una cantidad de por lo menos aproximadamente 1 mol. eq. y, en otras modalidades, en una cantidad de por lo menos aproximadamente 1 mol. eq. a aproximadamente 10 mol. eq. con relación al compuesto de fórmula **D**. Ejemplos de tales bases incluyen metales alcalinos, hidróxidos de metales alcalinotérreos, y combinaciones de estos. En otras modalidades, la base adecuada es hidróxido de sodio.

Ejemplos de disolventes adecuados para uso durante la formación de base libre en la etapa **S-4** incluyen disolventes polares tales como alcoholes alquilo, tales como alcoholes C_1 a C_4 (por ejemplo etanol, metanol, 2-propanol), agua, dioxano, o THF (tetrahidrofurano) o combinaciones de estos. En ciertas modalidades, el disolvente adecuado es un alcohol C_1 a C_4 tal como metanol, etanol, 2-propanol, agua, o combinación de estos. De acuerdo con un aspecto de la presente invención, se utiliza hidróxido de sodio acuoso en la etapa **S-4**. De acuerdo con otro aspecto de la presente invención, la formación de base libre en la etapa **S-4** se desarrolla en una mezcla bifásica de disolvente con el cual el compuesto de fórmula **C**, como se forma, se extrae en una capa orgánica. Así, una mezcla adecuada bifásica de

disolventes incluye un disolvente acuoso y un disolvente orgánico no miscible. Tales disolventes orgánicos no miscibles se conocen bien por el experto en la técnica e incluyen disolventes de hidrocarburo halogenados (por ejemplo cloruro de metileno y cloroformo), benceno y derivados de estos (por ejemplo tolueno), ésteres (por ejemplo acetato de etilo y acetato de isopropilo), y éteres (por ejemplo MTBE, THF y derivados de estos, glimo, y diglimo) y similares. En ciertas modalidades, la formación de base libre en la etapa **S-4** se desarrolla en una mezcla bifásica que comprende agua y tolueno. En otras modalidades, la base adecuada es soluble en agua de tal manera que la reacción se desarrolla en una mezcla de tolueno y una base acuosa adecuada, tal como hidróxido de sodio acuoso.

En la etapa **S-5**, la N-alquilación del compuesto quiral **C** proporciona un compuesto de fórmula **B**. En ciertas modalidades, esta N-alquilación se desarrolla con 2-metil-2-oxazolina en la presencia de cantidad catalítica de ácido para proporcionar el compuesto N-acetil-N-etilenodiamina **B**, en donde n es 1 y PG^2 es acetilo.

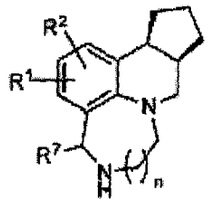
La remoción del grupo protector PG^2 de fórmula **B**, en la etapa S-6, proporciona el compuesto diamina de fórmula A. En ciertas modalidades, el grupo PG^2 de fórmula B se remueve mediante hidrólisis de ácido. Se apreciará que luego de la hidrólisis del ácido del grupo PG^2 de fórmula B, se forma una sal de este. Por ejemplo, en donde el grupo PG^2 de fórmula B se remueve por tratamiento con un ácido tal como ácido

trifuoroacético, luego el compuesto diamina resultante podría ser formado como su sal de ácido trifuoroacético. Un experto en la técnica reconocería que una amplia variedad de ácidos son útiles para remover los grupos protegidos amino que son ácido-lábiles y por lo tanto se contempla una amplia variedad de formas de sal de un compuesto de fórmula **A**.

En otras modalidades, el grupo PG^2 de fórmula B se remueve por hidrólisis de base.

Un experto en la técnica reconocería que una amplia variedad de bases son útiles para remover los grupos protegidos amino que son base-lábiles.

En la etapa **S-7**, un compuesto de fórmula **A** se trata con formaldehído, o un equivalente de este, para proporcionar un compuesto de fórmula **II**. En ciertas modalidades, un compuesto de fórmula **A** se trata con formaldehído acuoso para proporcionar un compuesto de fórmula **II**. Un experto en la técnica podría apreciar que se pueden utilizar formaldehídos sustituidos en la etapa **S-7** para proporcionar un compuesto de fórmula **IIa**:



IIa

o una sal farmacéuticamente aceptable de estos, en donde:

n es 0, 1, o 2;

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

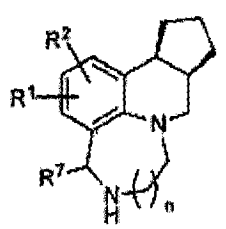
R^7 es hidrógeno o un grupo alquilo C_{1-6}.

Un experto en la técnica apreciará que un compuesto de fórmula II, según se prepara por los métodos de la presente invención, se pueden tratar con un ácido adecuado para formar una sal de este. En ciertas modalidades, un compuesto de fórmula II se trata con HCl para formar la sal de clorhidrato de este.

Como se utiliza aquí, el término "sal diastereomérica" se refiere al aducto de un compuesto quiral de fórmula **E** con un ácido quiral.

Como se utiliza aquí, el término "sal enantiomérica" se refiere a la sal del compuesto quiral resuelto de fórmula **D**, en donde dicho compuesto de fórmula D se enriquece en un enantiómero. Como se utiliza aquí, el término "enantioméricamente enriquecido", como se utiliza aquí significa que un enantiómero hace por lo menos 80% o 85% de la preparación. En ciertas modalidades, el término enantioméricamente enriquecido significa que por lo menos 90% de la preparación es uno de los enantiómeros. En otras modalidades, el término significa que por lo menos 95% de la preparación es uno de los enantiómeros.

De acuerdo con un aspecto, la presente invención proporciona un método para preparar un compuesto de fórmula **II**:



II

o una sal farmacéuticamente aceptable de este, en donde:

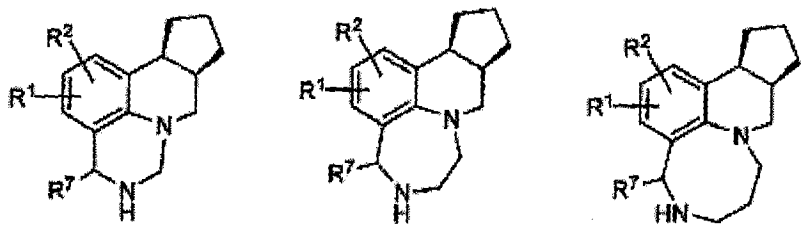
n es 0, 1, o 2;

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

R^7 es hidrógeno o alquilo C_{1-6}.

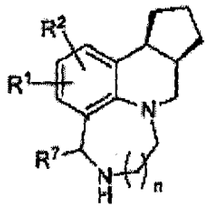
Como se definió anteriormente de manera general, el grupo n de fórmula **II** es 0, 1, o 2. De acuerdo con esto, la presente invención proporciona un método para preparar un compuesto de cualquiera de las fórmulas **IIa**, **IIb**, o **IIc**:



IIa **IIb** **IIc**

en donde cada uno de R^1, R^2, R^7, y n es como se definió anteriormente y aquí.

De acuerdo con otro aspecto, la presente invención proporciona un método para preparar un compuesto de fórmula **II**:



II

o una sal farmacéuticamente aceptable de estos, en donde:

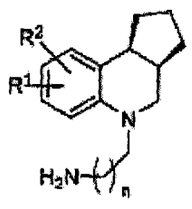
n es 0, 1, o 2;

R^1 y R^2 son cada uno independientemente halógeno, $-CN_5$ fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y_1

R^7 es hidrógeno o alquilo C_{1-6},

que comprende las etapas de:

(a) suministrar un compuesto de fórmula **A**:



A

en donde:

n es 0, 1, o 2;

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}, y

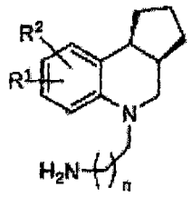
(b) hacer reaccionar dicho compuesto de fórmula **A** con formaldehído, o un equivalente de este, para formar un compuesto de fórmula **II**.

De acuerdo con una modalidad, la etapa (b) anterior se desarrolla utilizando formaldehído acuoso. En ciertas modalidades, se agrega formaldehído acuoso en una cantidad suficiente para consumir el compuesto de fórmula **A**. En ciertas modalidades, se agrega formaldehído acuoso en cantidades de por lo menos aproximadamente 0.90 mol equivalentes, en cantidades de aproximadamente 0.90 mol equivalentes a aproximadamente 1.10 mol equivalentes, o en cantidades de aproximadamente 1.0 mol equivalentes a aproximadamente 1.05 mol equivalentes con relación al compuesto de fórmula **A**.

De acuerdo con otra modalidad, la etapa (b) se desarrolla utilizando un equivalente de formaldehído. Tales equivalentes de formaldehído se conocen bien por el experto en la técnica. En algunas modalidades, se agrega el equivalente de formaldehído en forma sólida al disolvente de reacción para formar una suspensión de reacción o el equivalente de formaldehído sólido se puede suspender en un disolvente de reacción y se agrega a la mezcla de reacción. En otras modalidades, se utiliza paraformaldehído como el equivalente de formaldehído, y se agrega en cantidades suficientes para consumir el compuesto de fórmula **A**. En algunas modalidades, se agrega paraformaldehído en cantidades de por lo menos aproximadamente 0.90 mol equivalentes, en cantidades de

aproximadamente 0.90 mol equivalentes a aproximadamente 1.10 mol equivalentes, o en cantidades de aproximadamente 1.0 mol equivalentes a aproximadamente 1.05 mol equivalentes con relación al compuesto de fórmula **A**.

En ciertas modalidades, el paraformaldehído está en una forma sólida. El paraformaldehído adecuado para la reacción está disponible comercialmente en gránulos pequeños (u otras formas granuladas) y polvos de una variedad de proveedores tales como Aldrich, Fluka, Celanese Chemicals, J.T. Baker, Mallinckrodt Laboratory Chemicals, Miljac Inc., Sego Int. Corp., Spectrum Chemicals Mfg., Total Specialty Chemicals Inc., US Chemicals Inc., Riedel- de Haen, Acros Organics, Pfaltz & Bauer Chemicals, Derivados, Lancaster Synthesis and EM Science. Ciertas formas en polvo adecuadas tienen por lo menos aproximadamente 10% de partículas retenidas en un tamiz de malla de 200. De acuerdo con otra modalidad, la presente invención proporciona un método para preparar un compuesto de fórmula **A**:



A

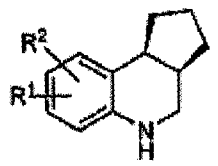
en donde:

n es 0, 1, o 2;

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y cada R es independientemente hidrógeno o un grupo alquilo C_{1-6},

que comprende las etapas de:

(a) suministrar un compuesto de fórmula **C**:

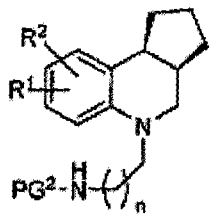


C

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}, y

(b) alquilatar dicho compuesto de fórmula **C** para formar un compuesto de fórmula **B**:



B

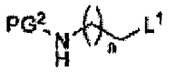
en donde:

n es 0, 1, o 2;

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

PG^2 es un grupo protector amino adecuado, y

(c) desproteger dicho compuesto de fórmula B para formar dicho compuesto de fórmula **A**.

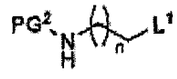
En ciertas modalidades, la alquilación en la etapa (b) anterior se logra al hacer reaccionar dicho compuesto de fórmula **C** con un compuesto de fórmula  en donde dicha reacción se desarrolla en un medio adecuado y en donde:

n es 0, 1, o 2;

PG^2 es un grupo protector amino adecuado; y

L^1 es un grupo saliente adecuado.

Como se definió anteriormente, L^1 es un grupo saliente adecuado. Grupos salientes adecuados se conocen bien en la técnica, por ejemplo, *ver*, "Advanced Organic Chemistry," Jerry March, 5^{th} Ed., pp. 351-357, John Wiley and Sons, N.Y. Tales grupos salientes incluyen, pero no se limitan a, halógeno, alcoxi, sulfoniloxi, alquilsulfoniloxi opcionalmente sustituido, alquilsulfiniloxi opcionalmente sustituido, arilsulfoniloxi opcionalmente sustituido, y porciones diazonio. Ejemplos de grupos salientes adecuados incluyen cloro, yodo, bromo, flúor, metanosulfonilo (mesilo), tosilo, triflato, nitro-fenilsulfonilo (nosilo), y bromo-fenilsulfonilo (brosilo). En ciertas modalidades, L^1 es halógeno. En otra modalidad, L^1 es un grupo alquilsulfoniloxi opcionalmente sustituido, alquilsulfiniloxi opcionalmente sustituido, o arilsulfoniloxi opcionalmente sustituido.

De acuerdo con una modalidad alterna, el grupo saliente adecuado se puede generar *in situ* dentro del medio de reacción. Por ejemplo, la porción L^1 se puede generar *in situ* a partir de un precursor de tal compuesto de fórmula  en donde dicho precursor contiene un grupo fácilmente reemplazado por L^1 *in situ*. Tal una generación *in situ* de un grupo saliente adecuado es bien conocida en la técnica, por ejemplo, ver, "Advanced Organic Chemistry," Jerry March, pp. 430-431, 5th Ed., John Wiley y Sons, N. Y.

En ciertas modalidades, dicha reacción de alquilación se desarrolla opcionalmente en la presencia de una base adecuada. Un experto reconocería que el desplazamiento de un grupo saliente por una porción amino se logra con o sin la presencia de una base adecuada. Tales bases adecuadas son bien conocidas en la técnica e incluyen bases orgánicas e inorgánicas.

Un medio adecuado es un disolvente o una mezcla de disolvente que, en combinación con los compuestos combinados, pueden facilitar el progreso de la reacción entre ellos. El disolvente adecuado puede solubilizar uno o más de los componentes de reacción, o, alternativamente, el disolvente adecuado puede facilitar la agitación de una suspensión de uno o más componentes de la reacción. Ejemplos de disolventes adecuados útiles en la presente invención son un disolvente prótico, un hidrocarburo halogenado, un éter, un éster, un hidrocarburo aromático, un disolvente prótico polar o no

polar, o cualquier mezclas de estos. Tales mezclas incluye, mezclas de disolventes próticos y no próticos tales como benceno/metanol/agua; benceno/agua; DME/agua, y similares.

Estos y otros de tales disolventes adecuados se conocen bien en la técnica, por ejemplo, ver, "Advanced Organic Chemistry", Jerry March, 5th edición, John Wiley y Sons, N.Y.

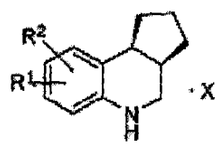
Como se definió anteriormente de manera general, el grupo PG^2 de fórmula **B** es un grupo protector amino adecuado. Los grupos protectores amino adecuados se conocen bien en la técnica e incluyen aquellos descritos en detalle en *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edición, John Wiley & Sons, 1999, la totalidad de la cual se incorpora aquí como referencia. Los grupos protectores amino adecuados, tomados con la porción -NH- a la que está adherida, incluyen, pero no se limitan a, aralquilaminas, carbamatos, alil aminas, amidas, y similares. Ejemplos de grupos PG^2 incluyen t-butiloxicarbonilo (BOC), etiloxicarbonilo, metiloxicarbonilo, tricloroetiloxicarbonilo, aliloxicarbonilo (Alloc), benciloxocarbonilo (CBZ), alilo, bencilo (Bn), fluorenilmetilcarbonilo (Fmoc), acetilo, cloroacetilo, dicloroacetilo, tricloroacetilo, fenilacetilo, trifluoroacetilo, benzoilo, y similares. En otras modalidades, el grupo PG^2 es acetilo, cloroacetilo, dicloroacetilo, tricloroacetilo, fenilacetilo, o trifluoroacetilo. En aún otras modalidades, el grupo protector amino es acetilo.

De acuerdo con todavía otra modalidad, uno o más reactivos se pueden desempeñar como el disolvente adecuado. Por ejemplo, una base orgánica tal como trietilamina o diisopropiletilamina, si se utiliza en dicha reacción, puede servir como el disolvente en adición a su papel como un reactivo de basificación.

En otras modalidades, la alquilación en la etapa (b) anterior se logra al hacer reaccionar dicho compuesto de fórmula **C** con

en la presencia de un ácido adecuado para formar un compuesto de fórmula **B** en donde n es 1 y PG^2 es acetilo. Tales ácidos adecuados se conocen bien en la técnica e incluyen ácidos inorgánicos, por ejemplo ácido clorhídrico, ácido bromhídrico, ácido fosfórico, ácido nítrico, ácido sulfúrico o ácido perclórico, o ácidos orgánicos, por ejemplo ácido acético, ácido oxálico, ácido maléico, ácido tartárico, ácido cítrico, ácido succínico, ácido malónico, ácidos sulfónicos de alquilo inferior o ácidos aril sulfónicos. En ciertas modalidades, la alquilación en la etapa (b) anterior se logra al hacer reaccionar dicho compuesto de fórmula **C** con

en la presencia de ácido toluenosulfónico. Todavía otro aspecto de la presente invención proporciona un método para preparar un compuesto de fórmula **D**:



D

en donde:

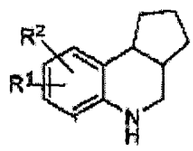
R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral,

que comprende las etapas de:

(a) suministrar un compuesto de fórmula **E**:



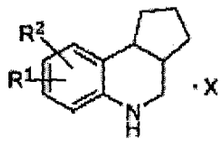
E

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}, y

(b) tratar dicho compuesto de fórmula **E** con un agente quiral para formar un compuesto de fórmula **D-1**:



D-1

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral, y

(c) obtener dicho compuesto de fórmula **D** por medios físicos adecuados.

El término "agente quiral" se refiere a un grupo enantioméricamente enriquecido que puede ser iónicamente o covalentemente ligado al nitrógeno de un compuesto de fórmula **E**. Como se utiliza aquí, el término "enantioméricamente enriquecido", como se utiliza aquí significa que un enantiómero hace por lo menos 85% de la preparación. En ciertas modalidades, el término enantioméricamente enriquecido significa que por lo menos 90% de la preparación es uno de los enantiómeros. En otras modalidades, el término significa que por lo menos 95% de la preparación es uno de los enantiómeros.

Los agentes quirales que se unen iónicamente a dicho nitrógeno incluyen ácidos quirales. Cuando el agente quiral es un ácido quiral, el ácido forma una sal diastereómerica con el nitrógeno. Los diastereómeros resultantes luego se separan por medios físicos adecuados. Ejemplos de ácidos quirales incluyen, pero no se limitan a, ácido tartárico y derivados de ácido tartárico, ácido mandélico, ácido málico, ácido camforsulfónico, y ácido de Mosher, entre otros. En ciertas modalidades, el ácido quiral es ácido ditoluoil-D-

tartárico. En otras modalidades, el ácido quiral es ácido ditoluoil-L-tartárico. Los aqentes quirales que se pueden unir covalentemente al nitrógeno se conocen en la técnica.

El término "separados por medios físicos adecuados" se refiere a métodos para separar las mezclas enantiomérica o diastereoméricas. Tales métodos se conocen bien en la técnica e incluyen cristalización preferencial, destilación, y trituración, entre otros. Los agentes quirales y los métodos de separación se describen en detalle en Stereochemistry of Organic Compounds, Eliel, E. L. and Wilen, S. H., 1994, published by John Wiley y Sons.

En ciertas modalidades, una sal quiral de fórmula **D** se obtiene por vía de cristalización preferencial de una sal diastereómerica formada en la etapa (b) anterior. En otras modalidades, la cristalización se alcanza a partir de un disolvente prótico. En aún otras modalidades, el disolvente prótico es un alcohol. Se apreciará que la cristalización se puede lograr utilizando un disolvente prótico único o una combinación de uno o más disolventes próticos. Tales disolventes y mezclas disolventes se conocen bien por el experto en la técnica e incluyen uno o más alcoholes alquilo rectos o ramificados. En ciertas modalidades, la cristalización se alcanza a partir de alcohol isopropílico.

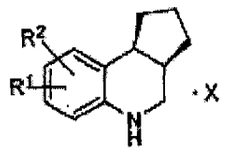
En ciertas modalidades, la sal quiral de fórmula **D** comprende una cantidad equimolar de ácido quiral y amina. En otras modalidades, la sal quiral de fórmula **D** comprende una

cantidad subestequiométrica de ácido quiral. Como se utiliza aquí, el término "cantidad subestequiométrica" denota que el ácido quiral que se utiliza es menor de 1 mol equivalente con relación al compuesto de fórmula **E**. En ciertas modalidades el ácido quiral que se emplea es menor de 0.98 mol equivalentes. En otras modalidades la base amina que se emplea es menor de 0.95 mol equivalentes.

Será fácilmente evidente para aquellos expertos en la técnica que el enriquecimiento enantiómerico de un enantiómero en el compuesto cristalizado **D** origina un enriquecimiento enantiómerico en el licor madre de la otra forma enantiomérica. Por lo tanto, de acuerdo con otra modalidad, la invención se relaciona con un método para mejorar el %ee de un compuesto enantioméricamente enriquecido o racémico de fórmula **D** como se compara con un compuesto de fórmula **D-1**. Como se utiliza aquí, el término "%ee" se refiere al porcentaje de exceso enantiomérico como lo podría entender el experto en la técnica.

En otra modalidad preferida, el compuesto cristalizado **D** se somete opcionalmente a una etapa de cristalización adicional para originar cristalización y adicionalmente el enriquecimiento del enantiómero descrito.

De acuerdo con otra modalidad, la presente invención proporciona un método para obtener un compuesto enantioméricamente enriquecido de fórmula **D**:



D

en donde:

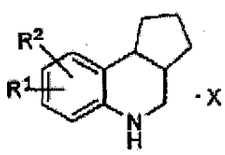
R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral,

que comprende las etapas de:

(a) combinar un compuesto de fórmula **D-1**:



D-1

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

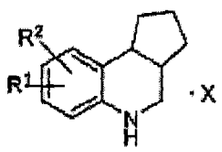
X es un agente quiral,

con un disolvente adecuado y calentar para formar una solución de este; y

(b) permitir a dicha solución enfriar para originar cristalización de un compuesto enantioméricamente enriquecido de fórmula **D**.

En ciertas modalidades, el disolvente adecuado utilizado en la etapa (a) anterior es un disolvente prótico. En aún otras modalidades, el disolvente prótico es un alcohol. Se apreciará que la cristalización se puede lograr utilizando un único disolvente prótico o una combinación de uno o más disolventes próticos. Tales disolventes y mezclas disolventes se conocen bien por el experto en la técnica e incluyen uno o más alquil alcoholes rectos o ramificados. En ciertas modalidades, la cristalización se logra utilizando una mezcla de metanol y alcohol isopropílico.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula **D-1**:



D-1

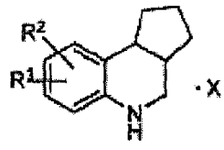
en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

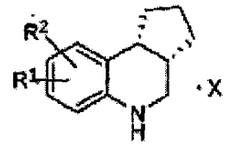
cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral.

De acuerdo con otra modalidad, la presente invención proporciona un compuesto de cualquiera de las fórmulas **D-1** y **D-2**:



D-1



D-2

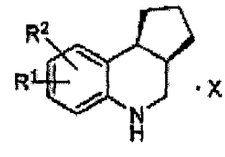
en donde cada R^1, R^2 y

X es como se definió anteriormente y en las clases y subclases definidas anteriormente y aquí.

De acuerdo con una modalidad, los grupos R^1 y R^2 de las fórmulas **D-1** y **D-2** son cada uno independientemente un grupo R. De acuerdo con otra modalidad, uno de R^1 y R^2 es hidrógeno. De acuerdo con todavía otra modalidad, ambos de R^1 y R^2 son hidrógeno.

En ciertas modalidades, el grupo X de las fórmulas **D-1** y **D-2** es un ácido quiral, formando así una sal quiral. En otras modalidades, el grupo X de las fórmulas **D-1** y **D-2** es un derivado de ácido tartárico. En aún otras modalidades, el grupo X de las fórmulas **D-1** y **D-2** es ácido ditoluoil-D-tartárico.

Todavía otra modalidad proporciona un compuesto de fórmula **D**:



D

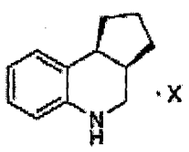
en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, $-OR_5$ -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral.

De acuerdo con una modalidad, los grupos R^1 y R^2 de fórmula **D** son cada uno independientemente un grupo R. De acuerdo con otra modalidad, uno de R^1 y R^2 es hidrógeno. De acuerdo con todavía otra modalidad, ambos de R^1 y R^2 son hidrógeno. En ciertas modalidades, el grupo X de fórmula **D** es un ácido quiral, formando así una sal quiral. En otras modalidades, el grupo X de fórmula **D** es un derivado de ácido tartárico. En aún otras modalidades, el grupo X de fórmula **D** es ácido ditoluoil-D-tartárico. De acuerdo con otra modalidad, la presente invención proporciona un compuesto de fórmula **D**, en donde R^1 y R^2 son ambos hidrógeno y dicho compuesto es de fórmula **D-3**:

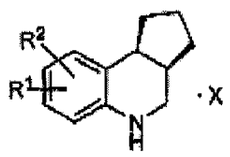


D-3.

En ciertas modalidades, un compuesto de fórmula **D-3** se suministra sustancialmente libre del enantiómero correspondiente. "Sustancialmente libre," como se utiliza aquí, significa que el compuesto se hace de una porción significativamente grande de un enantiómero. En otras modalidades, por lo menos aproximadamente 95% en peso de un

enantiómero deseado está presente. En aún otras modalidades de la invención, por lo menos aproximadamente 99% en peso de un enantiómero deseado está presente. Tales enantiómeros se pueden aislar a partir de mezclas racémicas por cualquier método conocido por aquellos expertos en la técnica, que incluye cromatografía líquida de alta resolución (HPLC) y resolución de sal quiral, o se prepara por métodos descritos aquí.

Todavía otro aspecto de la presente invención proporciona un método para preparar un compuesto de fórmula **D**:



D

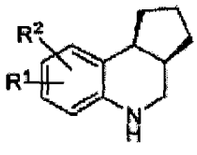
en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral,

como se describió anteriormente y aquí, en donde dicho método adicional comprende la etapa de tratar dicho compuesto de fórmula **D** con una base adecuada para formar el compuesto de base libre de fórmula **C**:



C

en donde:

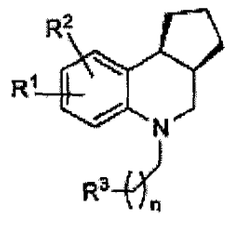
R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}.

Como se utiliza aquí, la base adecuada es una base orgánica e inorgánica. Tales bases adecuadas incluyen bases inorgánicas fuertes, es decir, aquellas que se disocian completamente en agua bajo formación de anión hidróxido. En ciertas modalidades, la base se agrega en una cantidad de por lo menos aproximadamente 1 mol. eq. y, en otras modalidades, en una cantidad de por lo menos aproximadamente 1 mol. eq. a aproximadamente 10 mol. eq. con relación al compuesto de fórmula **D**. Ejemplos de tales bases incluyen metales alcalinos, hidróxidos de metales alcalinotérreos, y combinaciones de estos. En otras modalidades, la base adecuada es hidróxido de sodio.

De acuerdo con una modalidad, la formación de base libre se desarrolla en la presencia de un disolvente adecuado. Ejemplos de disolventes adecuados para uso durante la formación de base libre incluyen disolventes polares tales como alquil alcoholes, tales como alcoholes C_1 a C_4 (por ejemplo etanol, metanol, 2-propanol), agua, dioxano, o THF (tetrahidrofurano) o combinaciones de estos. En ciertas modalidades, el disolvente adecuado es un alcohol C_1 a C_4 tal como metanol, etanol, 2-propanol, agua, o combinación de estos. De acuerdo con un aspecto de la presente invención, la

base adecuada es hidróxido de sodio acuoso y, así, el disolvente es agua.

De acuerdo con otro aspecto de la presente invención, la formación de base libre se desarrolla en una mezcla bifásica de disolventes por eso el compuesto de fórmula **C**, como este se forma, se extrae en una capa orgánica. Así, una mezcla adecuada bifásica de disolventes incluye un disolvente acuoso y un disolvente orgánico no miscible. Tales disolventes orgánicos no miscibles se conocen bien por el experto en la técnica e incluyen disolventes de hidrocarburo halogenados (por ejemplo cloruro de metileno y cloroformo), benceno y derivados de estos (por ejemplo tolueno), ésteres (por ejemplo acetato de etilo y acetato de isopropilo), éteres (por ejemplo MTBE, THF y derivados de estos, glimo, y diglimo), y similares. En ciertas modalidades, la formación de base libre se desarrolla en una mezcla bifásica que comprende agua y tolueno. En otras modalidades, la base adecuada es soluble en agua tal que la reacción se desarrolla en una mezcla de tolueno y una base acuosa adecuada, tal como hidróxido de sodio acuoso. En ciertas modalidades, la presente invención proporciona un compuesto de fórmula **III**:



III

o una sal de este, en donde:

n es 0, 1, o 2;

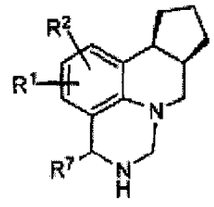
R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

R^3 es NH_2 o un grupo amino protegido adecuadamente.

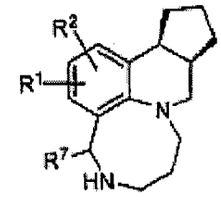
En ciertas modalidades, los grupos R^1 y R^2 de fórmula **I** son cada uno R. En otras modalidades, uno de R^1 y R^2 es hidrógeno. En aún otras modalidades, ambos de R^1 y R^2 son hidrógeno.

Los grupos protectores amino adecuados se conocen bien en la técnica e incluyen aquellos descritos en detalle en *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edición, John Wiley & Sons, 1999, la totalidad de la cual se incorpora aquí como referencia. los grupos amino protegidos adecuados de R^3 incluyen, pero no se limitan a, aralquilaminas, carbamatos, alil aminas, amidas, y similares. Ejemplos de tales grupos incluyen t-butiloxicarbonilo (BOC), etiloxicarbonilo, metiloxicarbonilo, tricloroetiloxicarbonilo, aliloxicarbonilo (Alloc), benciloxocarbonilo (CBZ), alilo, bencilo (Bn), fluorenilmetilcarbonilo (Fmoc), acetilo, cloroacetilo, dicloroacetilo, tricloroacetilo, fenilacetilo, trifluoroacetilo, benzoilo, y similares. En otras modalidades, el grupo protector amino es acetilo, cloroacetilo, dicloroacetilo, tricloroacetilo, fenilacetilo, o trifluoroacetilo. En aún otras modalidades, el grupo protector amino es acetilo.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula **IIa** o **IIc**, o una sal farmacéuticamente aceptable de estos:



IIa



IIc

en donde cada uno de R^1, R^2, y R^7 se definió anteriormente y aquí.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula **IIa** en donde R^1, R^2, y R^7 son todos hidrógeno.

En otras modalidades, la presente invención proporciona un compuesto de fórmula **IIc** en donde R^1, R^2, y R^7 son todos hidrógeno.

Sales farmacéuticamente aceptables, que incluyen mono- y bi-sales, son aquellas derivadas a partir de tales ácidos orgánicos e inorgánicos tale como, pero no limitados a acético, láctico, cítrico, cinámico, tartárico, succínico, fumárico, maláico, malónico, mandélico, málico, oxálico, propiónico, clorhídrico, bromhídrico, fosfórico, nítrico, sulfúrico, glicólico, pirúvico, metanosulfónico, etanosulfónico, toluenosulfónico, salicílico, benzoico, y ácidos similarmente aceptables conocidos.

96
96

Índice de Flujo: 1 mL/minuto

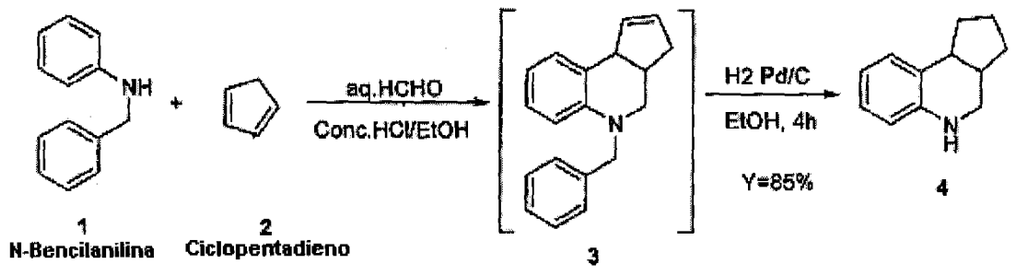
Temperatura: Ambiente

Tiempo: 10 minutos

Longitud de onda: 210 nm

Ejemplo 1 (Método A)

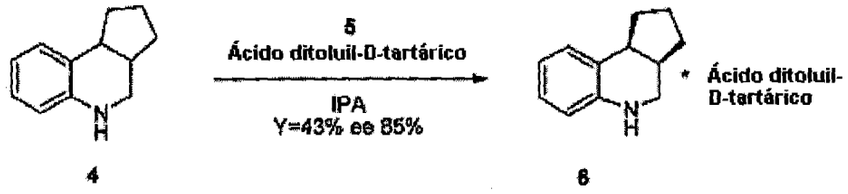
2,3,3a,4,5,9b-Hexahidro-1H-ciclopenta(c)quinolina:



Se enfría clorhidrato de N-fenilbencilamina (2.0 g) en 20 mL de MeOH a ~5°C. Se agrega ciclopentadieno craqueado rápidamente (1.2 g, de calor atmosférico/destilación de diciclopentadieno) a la solución seguido por formaldehído acuoso (37%, 1.04 g). La temperatura de reacción se mantiene a 5-10° C durante la noche (ca. 18 hrs). No se observa material de partida mediante TLC (10% de acetato de etilo en hexanos). La reacción se le permite calentar a TA. La reacción se diluye con EtOAc y se lava con solución de NaOH 0.5N, y luego con solución salina. La concentración de los orgánicos da 2.32 g de producto tricíclico crudo como un aceite. El aceite crudo del anterior se trata en 20 mL 1:1 EtOH:EtOAc con 0.175 mL de HCl 1N en EtOH y luego 5% de Pd-C (0.250 g, 50% húmedo). La mezcla se agita bajo 40-45 psi de H_2 durante la noche. Los sólidos se remueven por filtración a través de celita y la almohadilla se enjuaga con EtOAc. El

filtrado se concentra para dar un aceite de color durazno que se cristaliza bajo vacío para dar 1.38 g (87%) de producto desbencilado.

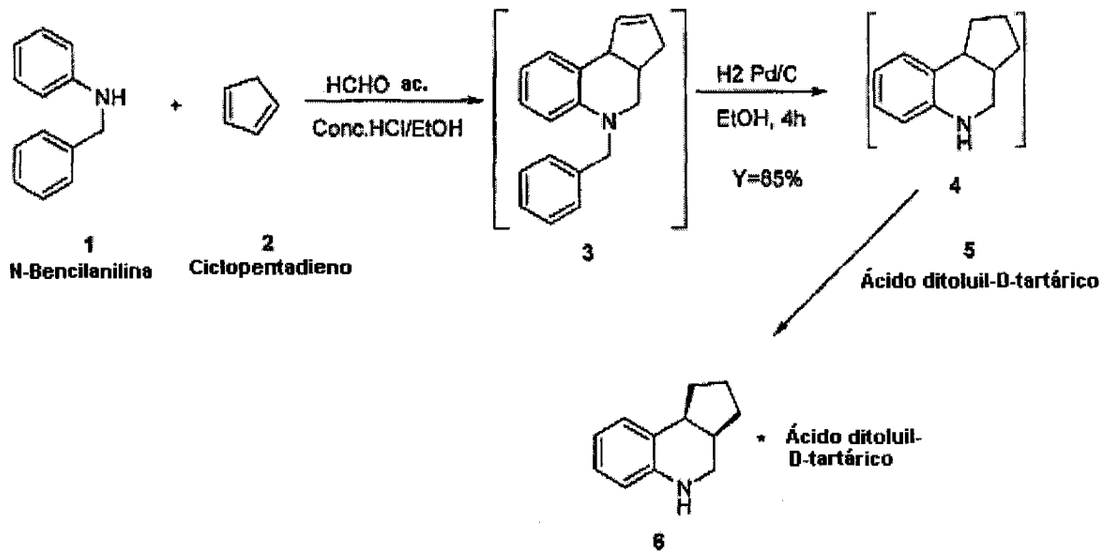
(-)2,3,3a,4,5,9b-Hexahidro-1H-ciclopenta(c)quinolina ácido di-p-toluoil-D-tartárico (6):



Una mezcla de la amina racémica (16.0 g, 92.3 mmol), ácido di-p-toluoil-D-tartárico (23.3 g, 60.3 mmol) en IPA (160 mL) se calienta a 70° C durante 10-15 minutos. Los sólidos se disuelven durante este tiempo. La solución se enfría a 0-5° C durante 3 horas. Los sólidos resultantes se filtran, se lavan con IPA frío (60 mL), y se secan a 40° C para dar 21.0 g (40%) de la sal como un sólido blancuzco. HPLC quiral: 85%ee; ^{1}H RMN (d6-DMSO) δ 7.91 (d, J=6 Hz, 4H), 7.40 (d, J=6 Hz, 4H), 6.97 (d, J=6 Hz, 1H), 6.84 (t, J=6 Hz, 1H), 6.4-6.6 (m, 2H), 5.83 (s, 2H), 2.9-3.1 (m, 2H), 2.8-3.1 (m, 1H), 2.8-2.9 (m, 1H), 2.5-2.7 (m, 1H), 2.5 (m, 1H), 2.3-2.5 (s, 6H), 2.0-2.2 (m, 3H), 1.8-2.0 (m, 1H), 1.2-1.7 (m, 4H); ^{13}C RMN (d6-DMSO) δ 167.6, 165.0, 145.7, 144.9, 129.9, 129.8, 129.7, 126.2, 125.2, 116.4, 114.4, 71.7, 43.6, 40.7, 35.8, 35.4, 29.3, 23.0, 21.6.

Ejemplo 2 (Método B)

(-)2,3,3a,4,5,9b-Hexahidro-1H-ciclopenta(c)quinolina ácido di-p-toluoil-D-tartárico (6:

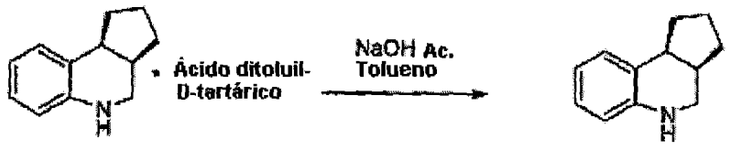


En un método alternativo, se agita mecánicamente N-fenilbencilamina (50 g) en 250 mL de MeOH hasta disolver. Se agrega 29 mL de HCl conc. en una porción única. La mezcla se le permite enfriar a TA. La sal HCl amina gradualmente llega a ser de solución. La suspensión se enfría en hielo a aproximadamente 15° C se agrega en una porción única y el ciclopentadieno destilado rápidamente [29.4 g, ciclopentadieno se obtiene por craqueo térmico de diciclopentadieno por vía de destilación de ruta corta atmosférica (temperatura de crisol 165-170° C, destilado ca. 60-70° C). El ciclopentadieno se recolecta en recipiente enfriado con hielo]. La temperatura se le permite caer a 15° C después de proceder, si es necesario. La solución de formaldehído (37% acuosa) en 150 mL de MeOH se agrega en forma de gota sucesivamente para mantener una temperatura interna de 15-25° C (15 mins tiempo adicional). Resulta una solución amarilla. Una vez la adición se completa, la reacción se le permite agitar a TA durante la noche bajo nitrógeno (12- 18h). La solución se aclara, pero es verdosa. La solución se transfiere a una botella Parr de 2L y se trata

con 1.5 g 10% de Pd/C (50% húmedo) y se agita bajo 45 psi de hidrógeno hasta que cesa la retoma. Una vez completa, la mezcla se purga con nitrógeno y se trata con bicarbonato de sodio (58 g). La suspensión se agita hasta que la solución es neutra a ligeramente básica por papel de pH damp. La mezcla luego se filtra a través de 1 cm celita y la almohadilla se enjuaga con MeOH (50 mL). El filtrado se concentra *in vacuo* y se agrega 450 mL de IPA. La mezcla se agita durante la noche y los sólidos resultantes se filtran y se enjuaga con 50 ml de IPA. Al filtrado obtenido anteriormente se agrega ácido di-p-toluoil-D-tartárico (63.3 g) en una porción única. La suspensión se calienta a ca. 80° C para disolver tolos los sólidos. La mezcla se le permite luego enfriar gradualmente a TA y se agita durante 3 o más horas. La mezcla luego se enfría a 0-5° C en hielo y se agita a esta temperatura durante 1-2 horas. Los sólidos se filtran y se lavan con 100 mL de IPA frio. Los sólidos verde-azules se debilitan y se secan *in vacuo* para proporcionar el compuesto del título. Rendimiento: 46.7 g (31%) Pureza quiral (HPLC): 95:5%ee.

Ejemplo 3

(-)2,3,3a,4,5,9b-Hexahidro-1H-ciclopenta(c)quinolina (7):



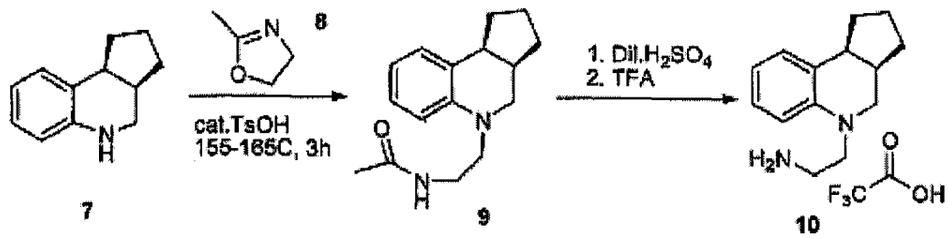
6 7

A una suspensión de la sal de ditoluil-D-tartrato (20.67 g, 37 mmol) en tolueno (93 mL), se agrega NaOH ac. (12 mL de 30% de NaOH diluido a 100 mL con agua) durante 5 min. La mezcla

de dos fases se agita vigorosamente y los sólidos se disuelven lentamente. Las dos capas se separan. La capa acuosa se extrae con tolueno (46 mL). Las capas orgánicas combinadas se concentran para dar 6.4 g (100% de rendimiento) de la base libre como aceite amarillo. ^{1}H RMN ($CDCl_3$) δ 7.09 (d, J=1.5 Hz, 1H), 6.9-7.0 (m, 1H), 6.6-6.7 (m, 1H), 6.4- 6.5 (m, 1H), 3.85 (bs, 1NH), 2.9-3.2 (m, 2H), 2.8-3.1 (m, 1H), 2.80 (t, J=10.3 Hz, 1H), 2.3- 2.4 (m, 1H), 2.0-2.2 (m, 1H), 1.8-2.1 (m, 1H), 1.3-1.8 (m, 4H).

Ejemplo 4

Sal de ácido (-)[2-(1,2,3,3a,4,9b-Hexahidro-ciclopenta[c] quinolin-5-il)-etilamina trifuoroacético (10):



Una mezcla de amina (6.4 g, 36.9 mmol) y una cantidad catalítica de ácido p-toluenosulfónico (0.07g, 0.37 mmol) se calienta a 165° C. Se agrega 2-metil-2-oxazolina lentamente durante 2 h a la mezcla de reacción a 165° C. La mezcla de reacción se enfría a 60° C y luego se agrega H_2SO_4 dil. (6 ml de H_2SO_4 conc. y 26 mL de agua). se agita durante 1h a 60° C. se enfría a TA, se agrega tolueno (40 mL) y 30% NaOH (30 mL). Se filtran los sólidos y se lavan con tolueno (2 x 10 mL). Cada lavado se utiliza para extraer la capa acuosa. Se lavan los extractos orgánicos combinados con agua (25 mL). Se concentra la capa de tolueno a 20 mL de volumen y se enfría a 10° C. Se agrega una solución de ácido trifluoroacético (2.4

mL, 31.2 mmol) en tolueno (7.5 mL) durante 15 min. Se agita durante 2 h a 10° C. Esta se filtra y se lava con tolueno (10 mL). Se seca la sal de TFA a 55° C en un horno de vacío. 7.7 g (rendimiento 63%) HPLC 97.6% Pureza quiral 92.2: 7.8.

Ejemplo 5

Clorhidrato de (-)-4,5,6,7,9,9a,10,11,12,12a-decahidrociclopenta[c][1,4]diazepino[6,7,1-*ij*]quinolina (12):

A una solución de sal N-etilenodiamina TFA (2.3 g, 7.0 mmol) en agua 120 mL) a 60 C se agrega formaldehído acuoso (0.72 g, 37% en peso en agua, 8.8 mmol, 1.26 equivs) durante un periodo de 2.0 h. Después de 19 h a 60° C, se enfría a temperatura ambiente. A la mezcla de reacción se agrega hidróxido de sodio (0.38 g) y acetato de isopropilo (20 mL). Las capas se separan y la capa acuosa se extrae con acetato de isopropilo (10 mL). Las capas orgánicas se combinan y se lavan con agua (10 mL). A la capa orgánica se agrega HCl conc. (0.82 g) en forma de gota. Los sólidos se filtran y se lavan con acetato de isopropilo (5 mL). El producto crudo (2.44 g) se calienta a 70° C en etanol (14 ml, 200 proof, desnaturalizado con 4% acetato de etilo) y luego se agrega agua (1.0 ml). La solución se enfría a 5° C durante 3 horas. el producto se filtra y se lava con etanol frío (2.4 mL). El producto húmedo (1.4 g) se seca en un horno de vacío durante 20 horas a 40° C para proporcionar el compuesto del título (1.1 g, rendimiento 60%) como un sólido blanco. Un segundo cultivo de 0.34 g (18%) se aísla a partir del licor madre. HPLC (% de área): 96.5%; Pureza quiral (HPLC): 99.87 : 0.13

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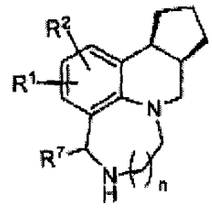
REIVINDICACIONES

Reivindicamos:

1. Un método para preparar un compuesto de fórmula **II**:



II

o una sal farmacéuticamente aceptable de este, en donde:

n es 0, 1, o 2;

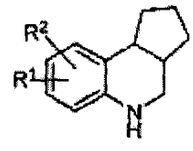
R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

R^7 es hidrógeno o alquilo C_{1-6},

que comprende las etapas de:

(a) suministrar un compuesto de fórmula **E**



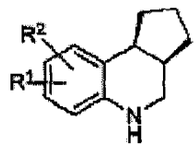
E

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y

X es un agente quiral,

(d) tratar dicho compuesto de fórmula **D** con una base adecuada para proporcionar un compuesto de fórmula **C**:



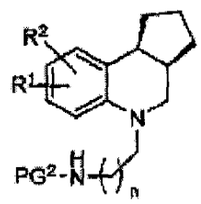
C

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6},

(e) alquilatar dicho compuesto de fórmula **C** para formar un compuesto de fórmula **B**:



B

en donde:

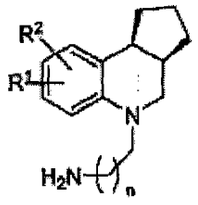
n es 0, 1, o 2;

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

PG^2 es un grupo protector amino adecuado,

(f) desproteger dicho compuesto de fórmula **B** para formar un compuesto de fórmula **A**.



A

en donde:

n es 0, 1, o 2;

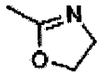
R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y

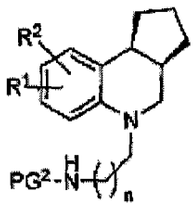
cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}, y

(g) hacer reaccionar dicho compuesto de fórmula **A** con formaldehído, o un equivalente de este, para formar un compuesto de fórmula **II**.

2. El método de acuerdo con la reivindicación 1, en donde cada n es 1 y R^1 y R^2 son ambos hidrógeno.

3. El método de acuerdo con la reivindicación 1 o 2, en donde dicho formaldehído es formaldehído acuoso.

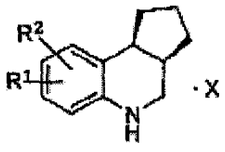
4. El método de acuerdo con una cualquiera de las reivindicaciones 1, 2, o 3, en donde la alquilación en la etapa (e) se logra al hacer reaccionar dicho compuesto de fórmula **C** con  en la presencia de un ácido adecuado para formar un compuesto de fórmula **B**:



B

en donde n es 1 y PG^2 es acetilo.

5. U n método para preparar un compuesto de fórmula **D**:



D

en donde:

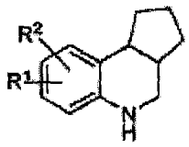
R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral,

que comprende las etapas de:

(a) suministrar un compuesto de fórmula **E**:



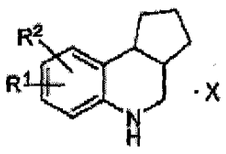
E

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}, y

(b) tratar dicho compuesto de fórmula **E** con un agente quiral para formar un compuesto de fórmula **D-1**:



D-1

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral,

Y

(c) obtener dicho compuesto de fórmula **D** por medios físicos adecuados.

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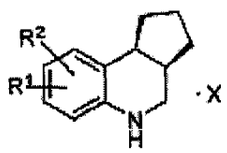
6. El método de acuerdo con la reivindicación 5, en donde X es un ácido quiral.

7. El método de acuerdo con la reivindicación 6, en donde el ácido quiral es ácido ditoluoil-D- tartárico y el compuesto de fórmula **D** se obtiene por cristalización a partir de un disolvente prótico.

8. El método de acuerdo con la reivindicación 7, en donde el compuesto de fórmula **D** se enriquece enantioméricamente.

9. El método de acuerdo con la reivindicación 6, que comprende obtener un compuesto enantioméricamente enriquecido de fórmula **D**:



D

en donde:

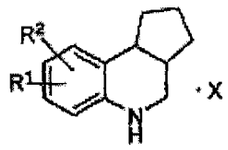
R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral,

que comprende las etapas de:

(a) combinar un compuesto de fórmula **D-1**:



D-1

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

X es un agente quiral,

con un disolvente adecuado y calentar para formar una solución de este; y

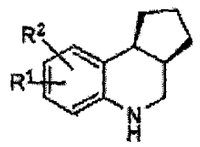
(b) permitir que dicha solución se enfríe para originar la cristalización de un compuesto enantioméricamente enriquecido de fórmula **D**.

10. El método de acuerdo con la reivindicación 9, en donde X es ácido ditoluoil-D-tartárico y dicho disolvente adecuado es un disolvente prótico.

11. El método de acuerdo con la reivindicación 10, en donde dicho disolvente adecuado comprende una mezcla de metanol y alcohol isopropílico.

12. El método de acuerdo con la reivindicación 9, que comprende adicionalmente la etapa de tratar dicho

compuesto de fórmula **D** con una base adecuada para formar el compuesto de base libre de fórmula **C**:



C

en donde:

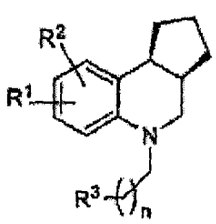
R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6}; y

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}.

13. El método de acuerdo con la reivindicación 12, en donde dicho método se desarrolla en una mezcla bifásica de disolventes. Ç

14. El método de acuerdo con la reivindicación 13, en donde dicho método se desarrolla en una mezcla de tolueno y hidróxido de sodio acuoso.

15. Un compuesto de fórmula **III**:



III

una sal de este, en donde:

n es 0, 1, o 2;

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o Operfluoroalquilo C_{1-6}; cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

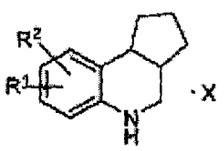
R^3 es NH_2 o un grupo amino protegido adecuadamente.

16. El compuesto de acuerdo con la reivindicación 15, en donde R^3 es hidrógeno o acetilo.

17. El compuesto de acuerdo con la reivindicación 16, en donde R^1 y R^2 son cada uno R.

18. El compuesto de acuerdo con la reivindicación 17, en donde R^1 y R^2 son hidrógeno.

19. Un compuesto de fórmula **D-1**:



D-I

en donde:

R^1 y R^2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C_{1-6}, o -Operfluoroalquilo C_{1-6};

cada R es independientemente hidrógeno o un grupo alquilo C_{1-6}; y

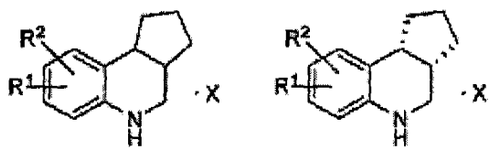
X es un agente quiral.

20. El compuesto de acuerdo con la reivindicación 19, en donde X es un ácido quiral y cada uno de R^1 y R^2 es hidrógeno.

21. El compuesto de acuerdo con la reivindicación 20, en donde X es ácido ditoluoil-D-tartárico.

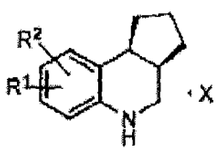
22. El compuesto de acuerdo con la reivindicación 21, en donde dicho compuesto comprende una cantidad equimolar de X.

23. El compuesto de acuerdo con la reivindicación 22, en donde dicho compuesto es de cualquiera de las fórmulas **D-1** o **D-2**:



D-1 **D-2.**

24. El compuesto de acuerdo con la reivindicación 19, en donde dicho compuesto es de fórmula **D**:



D.

25. El compuesto de acuerdo con la reivindicación 24, en donde R^1 y R^2 son cada uno independientemente un grupo R y X es un ácido quiral.

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DIAZEPINOQUINOLINAS, SU SÍNTESIS, E INTERMEDIOS DE ESTA

La presente invención se relaciona con métodos para sintetizar compuestos útiles como agonistas o agonistas parciales de $5HT_{2C}$, sus derivados, y con sus intermedios.

PATENT COOPERATION TREATY

WO 2007/016029
PCT/US2006/028655

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HS

From the INTERNATIONAL BUREAU BHJ | ACR | Law

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:

ROBIDOUX, Andrea, L.c.
Choate, Hall & Stewart
Two International Place
Boston, MA 02110
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 29 November 2007 (29.11.2007)	
Applicant's or agent's file reference 2004658-0390 ✓	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2006/028655	24 July 2006 (24.07.2006)	26 July 2005 (26.07.2005)

Applicant: WYETH et al

1. **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.

2. 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 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
08 February 2007 (08.02.2007)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, 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).

3. 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 93*bis*.1 :

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, ID, IL, IN, IS, JP, KE, KM, KN, KZ, LA, LC, LK, LR, LS, LT, LV, LY, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, RS, SC, SD, SE, SG, SK, SL, SM, 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

Facsimile No. +41 22 338 82 70

Authorized officer
Masashi Honda

e-mail: pt08.pct@wipo.int

BHJ/PCR Laws

P & Written Opinion

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W/T H

PATENT COOPERATION TREATY

Comments on Abstracts

From the INTERNATIONAL SEARCHING AUTHORITY

2·28·07

PCT

5·26·07

To:

CHOATE, HALL & STEWART
Attn. Robidoux, Andrea L.C.
Two International Place
Boston, Massachusetts 02110
ETATS-UNIS D'AMERIQUE

Amend Claims

3·30·07

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

(PCT Rule 44.1)

Applicant's or agent's file reference 2004658-0390 ✓	Date of mailing *(day/month/year)* 30/01/2007
International application No. PCT/US2006/028655	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant WYETH	International filing date *(day/month/year)* 24/07/2006

1. [x] 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, Fascimile 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 90*bis*.1 and 90*bis*.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	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Saskia Stark

Form PCT/ISA/220 (October 2005)

(See notes on accompanying sheet)

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.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
2004658-0390		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2006/028655	24/07/2006	26/07/2005
Applicant		
WYETH		

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 5 sheets.

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

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

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

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

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

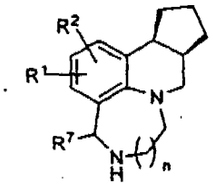
5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, 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

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

ABSTRACT

The present invention relates to methods for synthesizing compounds useful as $5HT_{2C}$ agonists or partial agonists, derivatives thereof, and to intermediates thereto.



II

INTERN IONAL SEARCH REPORT

International application No
PCT/US2006/028655

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/06 C07D221/16

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/009970 A1 (RAMAMOORTHY P SIVARAMAKRISHNAN [US]) 15 January 2004 (2004-01-15) paragraphs [0028], [0086], [0090] - paragraph [0092]	1-29
A	WO 2004/072046 A2 (CAREX S A [FR]; KOUTNIKOVA HANA [FR]; SIERRA MICHAEL [FR]; BRAUN-EGLES) 26 August 2004 (2004-08-26) page 98 - page 102; compound CRX000961 page 129, line 4 - line 5	1-14, 19-28
A	JACQUES J ET AL: "DISSOCIABLE COMPOUNDS AND COMPLEXES" ENANTIOMERS, RACEMATES, AND RESOLUTIONS, MALABAR, KRIEGER, US, 1991, pages 257-259,378, XP002029762 page 259, last paragraph; compound 25	1-14, 19-28

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2007	30/01/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Härtinger, Stefan

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

International application No
PCT/US2006/028655

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 2006/052768 A2 (WYETH CORP [US]; DEHNHARDT CHRISTOPH [US]; MEGATI SREENIVASULU [US]; S) 18 May 2006 (2006-05-18) page 29, paragraph 72 - page 30; example 3	1-29

INTERN IONAL SEARCH REPORT

Information on patent family members

Inter...onal application No
PCT/US2006/028655

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004009970 A1	15-01-2004	US 2007004707 A1	04-01-2007
WO 2004072046 A2	26-08-2004	NONE	
WO 2006052768 A2	18-05-2006	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2006/028655	24.07.2006	26.07.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/06 C07D221/16

Applicant
WYETH

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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

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

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

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

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Härtinger, Stefan Telephone No. +49 89 2399-8289

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/028655

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

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

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

~~125~~ 127

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/028655

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

1. Statement

Novelty (N)	Yes:	Claims	1-29
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-28
	No:	Claims	29
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

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

and / or

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

see form 210

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2006/028655

Re Item V

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

a) The application relates to cyclopentaquinoline derivatives and a multi-step synthesis thereof. The relevant prior art is given by the following documents.

D1 (= US 2004/009970 A1); D2 (= WO 2004/072046 A2)
D3 (= JACQUES J ET AL: "DISSOCIABLE COMPOUNDS AND COMPLEXES" ENANTIOMERS, RACEMATES, AND RESOLUTIONS, MALABAR, KRIEGER, US, 1991, pages 257-259,378, XP002029762)

b) Scheme II of D1 teaches the overall synthesis strategy currently proposed in the present application for the synthesis of tetracyclic compounds (II). In contrast to the present invention, however, a chiral resolution is performed at the stage of a fused benzodiazepine, such that racemic forms of the present intermediates A to D are pulled through the whole synthesis. The present method and intermediate related product claims are therefore novel over D1. As compounds (II) with n=1 are excluded from claim 29, this claim is likewise novel over D1.

Compound CRX000961 is the racemic form of present intermediate E. Chiral resolution of cyclopentaquinoline derivatives is performed only at a later stage of a multi-step synthesis procedure. Hence, the present claims are also novel over D2.

Chapter 5.1.2 of D3 is concerned with the chiral resolution of bases in general. Cyclopentaquinoline derivatives are not mentioned.

In view of the prior art D1-D3, the present claims appear to have met the novelty requirement of Art. 33(2) PCT.

c) The technical problem underlying the invention is regarded to be the provision of an improved process for the synthesis of fused cyclopentaquinoline derivatives (II). The problem has been solved by the novel features of the chiral resolution step S-3 involving the novel intermediate D. Compared with the alternative process of D1, which is

considered as the closest prior art, the early chiral separation allows a more efficient synthesis of the desired compounds (II), because the amount of undesired enantiomers is reduced. Since there is no incentive to perform the resolution step prior to the final ring closure step, the solution is not obvious. Hence, the claimed process together with the key-intermediate products appear to have involved an inventive step in the sense of Art. 33(3) PCT.

d) As to the final products according to claim 29, however, it would appear that the above described novel and inventive process feature does not contribute to the inventive step of the final product. The reason is that also in the prior art (D1) a chiral resolution is performed, and that the excluded final products (II) with n=2 (these are known inter alia from D1) are obvious equivalents to those claimed. Since the present application does not contain evidence that the claimed compounds would behave differently than the already known 5-HT2c antagonists of D1, the compounds of claim 29 appear to solve in an obvious manner the problem of providing further 5-HT2c antagonists.

Re Item VI
Certain documents cited

The international patent application D4 (= WO 2006/052768 A2, WYETH CORP [US]; DEHNHARDT CHRISTOPH [US]; MEGATI SREENIVASULU [US]; S, 2006-05-18) discloses benzodiazepine compounds relating to the present products (II) wherein the parameter n = 1. It also teaches a multi-step synthesis wherein the chiral resolution with ditoloyl tartaric acid is performed at a later stage than in the present application. Since D4 has been made available to the public only between the priority and filing date of the present application, it does not belong to the sate of the art as defined in the PCT. By consequence, D4 has been disregarded from further consideration.

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X

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

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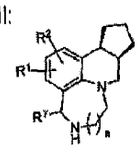
(21) N° de solicitud:	(51) Int Cl: **C07D 471/06, C07D 221/16**
22) Fecha de solicitud:	(71)Solicitante(s) **WYETH**
(30) Prioridad (31) ***No.*** **60/702,509** 32) ***Fecha*** **26/07/05** (33) ***País*** **US**	(72) Inventor(es) **MEGATI, Sreenivasulu** **CHAN, Anita, Wai-yin y** **FEIGELSON, Gregg, B.**
	(74) Apoderado: **ALVARO CORREA ORDOÑEZ**
(85) Fecha limite inicio fase nacional: **26/02/08** (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: ***24/07/06*** No. de solicitud **PCT/US2006/028655**	(87) Publicación internacional Fecha: ***08/02/07*** N° publicación: **WO/2007/016029**

(54) Titulo: **DIAZEPINOQUINOLINAS, SU SÍNTESIS, E INTERMEDIOS DE ESTA**

Reivindicación(es):

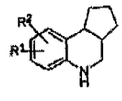
1. Un método para preparar un compuesto de fórmula II:



II

o una sal farmacéuticamente aceptable de este, en donde:
n es 0, 1, o 2;
R1 y R2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C1-6, o -Operfluoroalquilo C1-6;
cada R es independientemente hidrógeno o un grupo alquilo C1-6; y
R7 es hidrógeno o alquilo C1-6,
que comprende las etapas de:

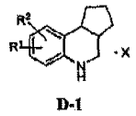
(a) suministrar un compuesto de fórmula E



E

en donde:
R1 y R2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C1-6, o -Operfluoroalquilo C1-6; y
cada R es independientemente hidrógeno o un grupo alquilo C1-6,

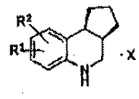
(b) tratar dicho compuesto de fórmula E con un agente quiral para formar un compuesto de fórmula D-1:



D-1

en donde:
R1 y R2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C1-6, o -Operfluoroalquilo C1-6;
cada R es independientemente hidrógeno o un grupo alquilo C1-6; y
X es un agente quiral,

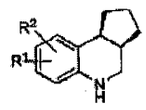
(c) obtener un compuesto de fórmula D por medios físicos adecuados:



D

en donde:
R1 y R2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C1-6, o -Operfluoroalquilo C1-6;
cada R es independientemente hidrógeno o un grupo alquilo C1-6; y
X es un agente quiral,

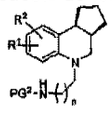
(d) tratar dicho compuesto de fórmula D con una base adecuada para proporcionar un compuesto de fórmula C:



C

en donde:
R1 y R2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C1-6, o -Operfluoroalquilo C1-6; y
cada R es independientemente hidrógeno o un grupo alquilo C1-6,

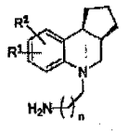
(e) alquilatar dicho compuesto de fórmula C para formar un compuesto de fórmula B:



B

en donde:
n es 0, 1, o 2;
R1 y R2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C1-6, o -Operfluoroalquilo C1-6;
cada R es independientemente hidrógeno o un grupo alquilo C1-6; y
PG2 es un grupo protector amino adecuado,

(f) desproteger dicho compuesto de fórmula B para formar un compuesto de fórmula A.



A

en donde:
n es 0, 1, o 2;
R1 y R2 son cada uno independientemente halógeno, -CN, fenilo, -R, -OR, -perfluoroalquilo C1-6, o -Operfluoroalquilo C1-6; y
cada R es independientemente hidrógeno o un grupo alquilo C1-6, y

(g) hacer reaccionar dicho compuesto de fórmula A con formaldehído, o un equivalente de este, para formar un compuesto de fórmula II.

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Industria y Comercio
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

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(71)Solicitante(s) **WYETH**

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(74) Apoderado: ALVARO CORREA ORDOÑEZ

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WYETH

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Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

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

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