

u.f.



Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No. 05-72452

54. TITULO PROCEDIMIENTOS E INTERMEDIOS PARA PREPARAR INHIBIDORES
DE TRANSCRIPTASA INVERSA DE HIV-1 NO NUCLEÓSIDOS

51. CLASIFICACION INTERNACIONAL _____

71. SOLICITANTE BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

DOMICILIO Ridgefield, Connecticut, Estados Unidos de América.

74. APODERADO EMILIO FERRERO
C.C. 438.019 de Usaquén.

22. BOGOTA, D.C., _____

P

GA

V


Industria y Comercio

SUPERINTENDENCIA

PETITORIO

SUPERINDUSTRIA Y COMERCIO

Radicación : 05067452 00000000

Folios: 99 ón

Fecha (RDD): 2003-01-28 17:09:38

Trámite : 011 PCT-PATENT 379 FASE NACT 411 PRESENTA

Dependencia: 2829 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT
ENTRADA EN FASE NACIONAL 28-01-2003
SOLICITUD DE:

1

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

2

**SOLICITANTE
(71)**

 Nombre: **BOEHRINGER INGELHEIM
PHARMACEUTICALS, INC**

 sociedad constituida y existente bajo las
leyes del estado de Delaware, Estados
Unidos.

 Dirección: 900 Ridgebury Road,
P.O. Box 368, Ridgefield,
Connecticut 06877-0368,
Estados Unidos de América

 Domicilio: Ridgefield, Connecticut,
Estados Unidos de América

IDENTIFICACIÓN

 C.C. ☐ NIT ☐

 C.E. ☐ Otro ☐

Cual _____

Número _____

3

**REPRESENTANTE
O APODERADO**

 Nombre: **EMILIO FERRERO**

Dirección: Carrera 4ª. No. 72-35

Teléfono: 347 36 11

Fax: 211 86 50

 E-mail: clientes@camyp.com.

Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

 C.C. ☒ NIT ☐

 C.E. ☐ Otro ☐

Cual _____

 Número 438.019 T.P 31.929

4

**INVENTOR (ES)
(72)**
1. Carl A. BUSACCA

 Boehringer Ingelheim Pharmaceuticals,
Inc.

 900 Ridgebury Road,
P.O. Box 368, Ridgefield,
Connecticut 06877-0368,
Estados Unidos de América

2. Magnus C. ERIKSSON

 Boehringer Ingelheim Pharmaceuticals,
Inc.

 900 Ridgebury Road,
P.O. Box 368, Ridgefield,
Connecticut 06877-0368,
Estados Unidos de América

3. Ji-Young KIM

 5903 Rollingwood Drive,
Ann Arbor, Michigan 48103,
Estados Unidos de América

5

PCT (86)

 Solicitud Internacional No. PCT/US2003/019415

 Fecha: 20 de Junio de 2003

 Publicación Internacional No. WO 2004/002989 A1

 Fecha: 8 de Enero de 2004

6

Título (54)
**PROCEDIMIENTOS E INTERMEDIOS PARA PREPARAR INHIBIDORES
DE TRANSCRIPTASA INVERSA DE HIV-1 NO NUCLEÓSIDOS**

7

Clasificación Internacional (51) C07D 471/14

8

Prioridad

 SI ☒ NO ☐

(33) País de Origen

US
US

(32) Fecha

28 de Junio de 2002
17 de Diciembre de 2002

(31) Número de Solicitud

60/391.979
60/434.052

9

G mprobante de pago N .: 05 - 3.506
Fecha: 17 de enero de 2005

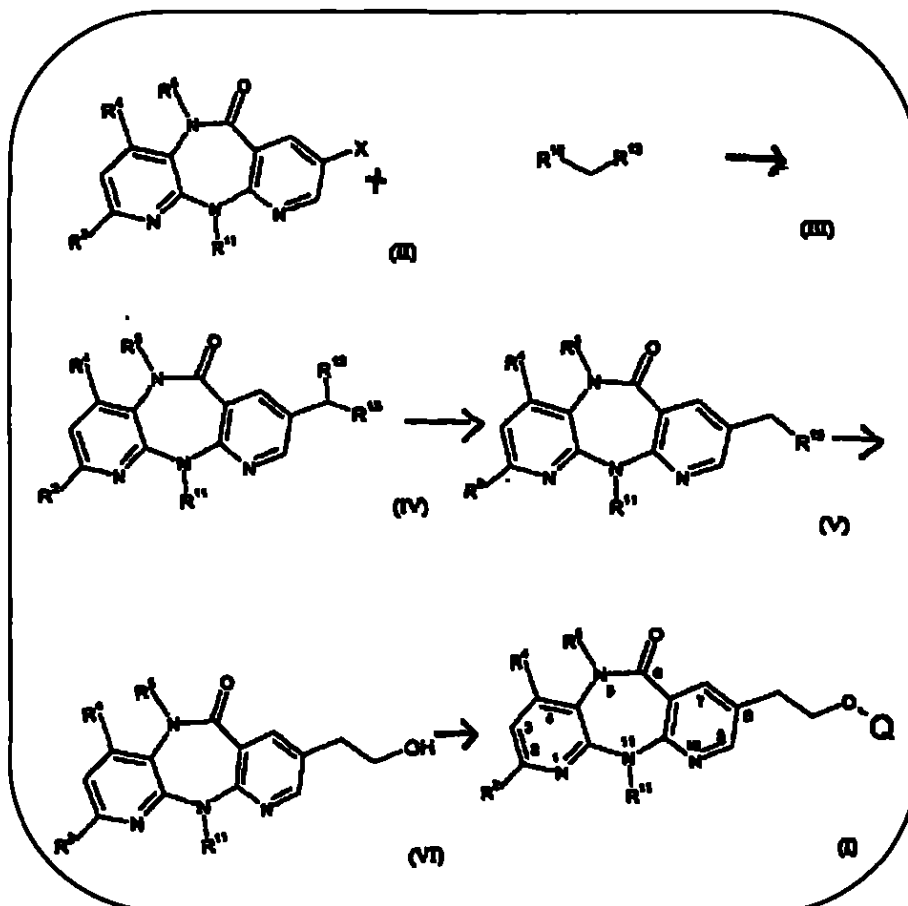
10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar 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 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11

FIGURA CARACTERÍSTICA



CAVELIER

ABOGADOS

DE INTELIGENCIA INDUSTRIAL

CARRERA 4ª N° 72-35

BOGOTÁ, D.C. - COLOMBIA

01612

0569

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

I (we), the undersigned / Yo (nosotros), abajo firmado (s)
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

of / domiciliado (s) en 900 Ridgebury Road,
Ridgefield, Connecticut 06877, United
States of America,

por el presente nombramos a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; y LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como nros (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo; después, la misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplente, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades 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 patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas (de fábrica) colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistír, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; and LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Cónsul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact of its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, 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, when necessary, including the following: a) Obtainment of patents of invention, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; their renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative and judicial cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general, the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this / Dado y firmado hoy 29th

day of August, 1996

In/en Ridgefield, Connecticut USA

Signature

Dr. Robert P. Raymond
Chief Patent Counsel

Firma

Boehringer Ingelheim Pharmaceuticals, Inc.

96912
ANA MARIA SALVETTI
PRODUCTORA Y REPRESENTANTE
DE INTELIGENCIA INDUSTRIAL
ITALIANO - ESPAÑOL
TEL. No. 188-MINUTERIA

CAVELIER ABOGADOS
W/PODERE-3 (MINUTA N° 12.1.1.2.6 USA)

CERTIFICADO NOTARIAL (INDIVIDUO)

A los 29 días del mes de AGOSTO de 19 96
ante mí, Notario Público de Connecticut, EE.UU.
compareció(eron) personalmente Dr. Robert P. Raymond

a quien(es) doy fe de conocer y me consta que es(son)-la(n) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

MARY ELLEN M. DEVLIN
NOTARY PUBLIC
MY COMMISSION EXPIRES OCT. 31, 2000

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy, 29 de Agosto de 19 96
compareció(eron) ante mí
Dr. Robert P. Raymond

a quien(es) conozco personalmente y que firma(n) este documento en representación de la Sociedad/compañía,

denominada BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Certifico:

1. Que he visto los siguientes documentos:

ESCRITURA DE LA SOCIEDAD, ESTATUTOS Y VARIOS
RESOLUCIONES DE LA JUNTA DIRECTIVA, BIL-071
de fecha 29 de noviembre de 1984.

25 ENE 2000

2. Que dichos documentos prueban lo siguiente:

2.1. Que BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
es una Sociedad/Compañía legalmente constituida y existente
de acuerdo con las leyes de Estado de Delaware,
Estados Unidos de América

2.2. Que el domicilio de dicha Sociedad/Compañía es
900 Ridgebury Road, Ridgefield, Connecticut
06877, Estados Unidos de América

2.3. Que el objeto u objeto para los cuales se otorga el presente
poder están comprendidos dentro del objeto social de la
mencionada Sociedad/Compañía.

2.4. Que el(las) Sr.(Sras.) DR. ROBERT P. RAYMOND

está(n) autorizado(s) para otorgar el presente Poder.

Ciudad Ridgefield
Estado Connecticut, EE.UU.

Hoy 29 Agosto de 19 96

Notario Público — Notary Public

* Los documentos deben identificarse con fecha y origen.

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 29 day of August 19 96
before me, a Notary Public of Connecticut, USA
personally appeared Dr. Robert P. Raymond

to me-known, and-known-to-me-to-be-the person(s) who
executed that foregoing document, and who has(have) legal
capacity to execute it.

MARY ELLEN M. DEVLIN
NOTARY PUBLIC
MY COMMISSION EXPIRES OCT. 31, 2000

NOTARIAL CERTIFICATE (CORPORATION)

On this 29 day of August 19 96
appeared before me
Dr. Robert P. Raymond

who(m) I know personally and who(m) signed this document as
representative(s) of the Corporation/Company

named BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

I Certify:

1. That I have seen the following documents:

Corporate Charter, By-Laws and various, board
resolutions, BIL-071 dated November 29, 1984.

2. That the above documents duly prove the following:

2.1. That BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
is a Corporation/Company legally constituted and in existence
in accordance with the laws of the State of Delaware,
United States of America

2.2. That the domicile of said Corporation/Company is
900 Ridgebury Road, Ridgefield, Connecticut
06877, United States of America

2.3. That the purpose of purposes for which the present Power of
Attorney is granted are comprised within the corporation
purposes set forth in the charter of the mentioned
Corporation/Company.

2.4. That Mr.(Messrs.) Dr. Robert P. Raymond

is(are) authorized to grant the present Power of Attorney.

City Ridgefield
State Connecticut, USA

This 29th day of August 19 96

Notary Public — Notary Public

MARY ELLEN M. DEVLIN
NOTARY PUBLIC
MY COMMISSION EXPIRES OCT. 31, 2000

* Documents must be identified with date and origin.

STATE OF CONNECTICUT
OFFICE OF THE SECRETARY OF THE STATE

I, MILES S. RAPOPORT, Secretary of the State of Connecticut,
and keeper of the seal thereof,

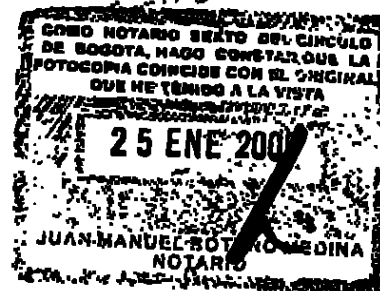
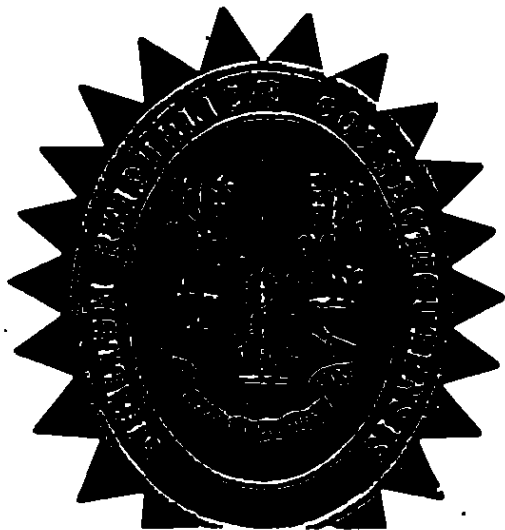
DO HEREBY CERTIFY: that BARBARA SERFILIPPI was duly elected or
appointed to the office of TOWN CLERK for the town of RIDGEFIELD in
the County of FAIRFIELD in said State, for the term of JANUARY 1,
1996 to JANUARY 5, 1998;

and that to his/her acts and
attestations as such, full faith and
credit are and ought to be given in and
out of Court.

In Testimony Whereof, I have hereunto
set my hand and affixed the Great Seal
of the State of Connecticut, at
Hartford, on August 30, 1996.

Miles S. Rapoport

Secretary of the State





STATE OF CONNECTICUT
COUNTY OF FAIRFIELD

RIDGEFIELD

5

I, Barbara Serfilippi, Clerk of the Town of Ridgefield

in said County, do hereby certify that Mary Ellen M. Devlin
by and before whom the foregoing (or annexed) acknowledgment was taken, was at the time of taking the same
a notary public (or other officer) residing (or authorized to act) in said County, and was authorized by the laws
of said State to take and certify acknowledgments in said State, and, further, that I believe that the signature to
the certificate of acknowledgment is genuine.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the seal of the State and Town this

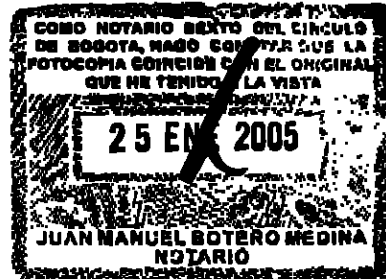
29th day of August 19 96.

96912

ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
SEA. No. 188 MINJUSTICIA

Barbara Serfilippi
Town Clerk

AD-18 FORM 22



6

CONSULADO DE COLOMBIA

535 Boylston Street 11th Floor Boston, MA 02116 Tel: (617) 536-6222 Fax: (617) 536-9372

No HS6

El suscrito Cónsul de Colombia en Boston, MA, Estados Unidos vistos los documentos presentados

CERTIFICA:

Que el señor(a) **MILES S RAPOPORT**, quien autenticó la firma de **BARBARA SERFILIPPI**, secretario de la ciudad de Ridgefield, Connecticut, en el documento adjunto ejercía en la fecha allí indicada las funciones de **SECRETARIO DE ESTADO DEL ESTADO DE CONNECTICUT, USA** y su firma y sello son los que acostumbra a usar en sus actos oficiales. Que la compañía **BOEHRINGER INGELHEIM FARMACEUTICALS INC.**, con domicilio principal en la ciudad de **RIDGEFIELD, CONNECTICUT**, es sociedad constituida bajo las leyes del estado de **DELAWARE**, Estados Unidos y tienen y ejerce su objeto social conforme a las leyes de ese país. Que el señor **ROBERT P RAYMOND**, en su calidad de **CONSEJERO JEFE DE PATENTES** de dicha compañía está debidamente autorizado para otorgar este poder a nombre de estas compañías y, para los fines y propósitos allí expresados.

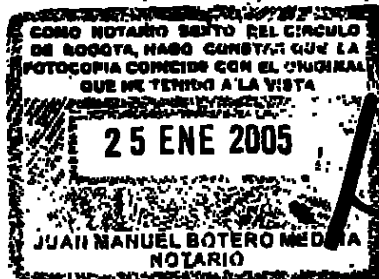
La presente certificación se expide en cumplimiento del artículo 480 del Código de Comercio.

El Cónsul no asume responsabilidad por el contenido del documento.

Esta certificación se expide en Boston a los 13 días del mes de Septiembre de 1996

Pagado Impuesto de Timbre US\$56.00

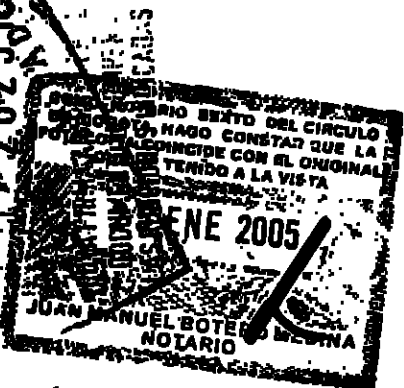

LUIS FERNANDO LEMAITRE
VICECONSUL



76912
ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
DCA No. 158 MINJUSTICIA

MINISTERIO DE RELACIONES
EXTERIORES
NO SE ASUME
RESPONSABILIDAD DEL TEXTO
1996 SET 25 A 11:45

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.



MINISTERIO DE RELACIONES
EXTERIORES
CUYA FIDELIDAD
DOCUMENTO DESEMPLEA
LAS FUNCIONES INDICADAS
1996 SET 24 A 11:46

NO SE ASUME
RESPONSABILIDAD DEL TEXTO
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

3

CERTIFICACION NOTARIAL Y AUTENTICACION CONSULAR

1. Es necesaria la legalización con certificado notarial. El Notario Público debe certificar:

- 1.1. Que la compañía está legalmente constituida y actualmente existente.
- 1.2. Su domicilio.
- 1.3. Que el propósito del poder está incluido en el objeto social de la compañía.
- 1.4. Que el poderdante está autorizado para dar el poder en nombre de la compañía.

2. Los documentos que hay que mostrarle al Notario Público para probar los puntos anteriores, deben estar expresados en el Certificado Notarial con fecha y origen:

- 2.1. Respecto a los puntos 1.1, 1.2 y 1.3 sugerimos referirse a los artículos de constitución con fecha y lugar de otorgamiento; y
- 2.2. Para el punto 1.4 sugerimos mencionar la resolución de la Junta Directiva o los estatutos, según los cuales la persona que otorga el poder está autorizada para ello.

3. Enseguida el Señor Cónsul de Colombia debe autenticar la firma del Notario Público.

NOTA PARA EL SEÑOR CONSUL COLOMBIANO: Según el artículo 259 del T5 de NEC 2005, el Señor Cónsul debe autenticar la última precedente autenticación.

NOTARIAL CERTIFICATION AND CONSULAR AUTENTIFICATION

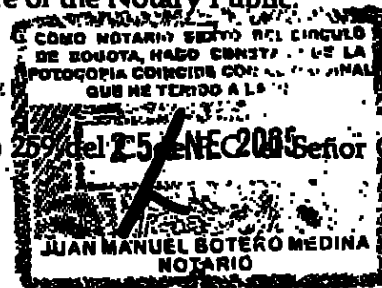
1. Notarial legalization is necessary. The Notary Public must certify:

- 1.1. That the company is legally constituted and presently existent.
- 1.2. Its place of business.
- 1.3. That the purpose of the Power-of-Attorney is included in the activities of the company.
- 1.4. That the grantor is empowered to give the Power of Attorney in the name of the company he represents.

2. The documents which the Notary Public had before him to prove the above points must be listed by him in the Notarial Certificate with dated and origin:

- 2.1. In connection with points 1.1., 1.2. and 1.3 we suggest referring to the articles of incorporation with date and place of execution.
- 2.2. For point 1.4 we suggest to mention the resolution of the Board of Directors and/or the by-laws whereby the person who grants the Power of Attorney has been authorized to give it.

3. Then the Colombian Consul must legalize the signature of the Notary Public.



8

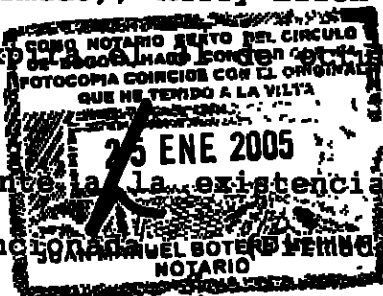
TRADUCCION OFICIAL No.96912 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor al mismo tiempo que la presente. Esta Traducción ha sido preparada por Ana María Salvetti, Traductora Oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y aprobada por el Ministerio de Justicia colombiano mediante Resolución No.158 de 1991.

(Se traducen sellos y legalizaciones que aparecen a continuación de un poder escrito en inglés y español, otorgado por la sociedad **BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**, a favor de Germán CAVELIER, Gonzalo PERDOMO, Emilio FERRERO, y Luz Clemencia de PAEZ.)

Dado y firmado el 29 de agosto de 1996 en Ridgefield, Connecticut EE.UU. (Firmado), ilegible, Robert P. Raymond, Principal Asesor de Patentes. Boehringer Ingelheim Pharmaceuticals, Inc.

(en inglés y español): CERTIFICACION NOTARIAL (INDIVIDUO) referente a la firma que antecede. (Firmado), Marry-Ellen M. Devlin, Notario Público. Mi comisión expira el 31 de octubre del 2000. Sello seco del Notario.

CERTIFICACION NOTARIAL (SOCIEDAD) referente a la existencia y representación de la sociedad mencionada (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.), Mary-Ellen M. Devlin, Notario Público. Mi comisión expira el 31 de octubre del 2000. Sello seco del Notario.



ESTADO DE CONNECTICUT

CONDADO DE FAIRFIELD, ss. RIDGEFIELD

Yo, Barbara Serfilippi, Escribano de la Población de

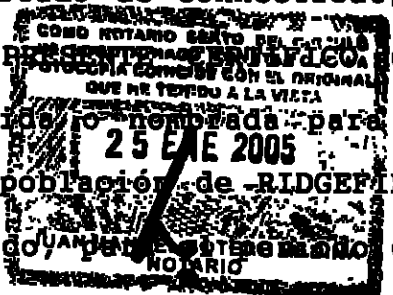
Ridgefield, en dicho Condado, por medio del presente certificado que Mary Ellen M. Devlin, por y ante quien el anterior reconocimiento (o adjunto) fue tomado, era al momento de tomarlo, un Notario Público (u otro funcionario) domiciliado (o autorizado para actuar) en dicho Condado, y que estaba autorizado por las leyes de dicho Estado para tomar y certificar reconocimientos en dicho Estado, y además, que creo que la firma que aparece en el certificado de reconocimiento es auténtica.

En Testimonio de lo Cual, he firmado y estampado del sello del Esado y Población hoy, 29 de agosto de 1996. (Firmado), Barbara Serfilippi, Escribano.

(0404/07/T/Rev.11-92)

ESTADO DE CONNECTICUT

OFICINA DEL SECRETARIO DEL ESTADO

Yo, Miles S. Rapoport, Secretario del Estado de Connecticut, y guardián de su Sello, POR MEDIO DEL  que BARBARA SERFILIPPI fue debidamente elegida o nombrada para el cargo de ESCRIBANO DEL CONDADO para la población de RIDGEFIELD en el Condado de FAIRFIELD en dicho Estado, para el periodo que va del 1o. de enero de 1996 al 5 de enero de 1998;

y que sus actos oficiales en calidad de tal merecen completa fe y crédito dentro y fuera de la Corte. En testimonio de lo cual, he firmado y estampado el Gran Sello del Estado de Connecticut, en Hartford, el 30 de agosto de 1996. (Firma facsimilar), Miles S. Rapoport, Secretario del Estado. Adherido se encuentra sello de oblea del Estado de Connecticut. Sello seco del Consulado de Colombia en Boston,

EE.UU.

(en español): Certificación No.1156 del 13 de septiembre de 1996, de la firma que antecede por el Consulado de Colombia en Boston. Pagados impuesto de timbre y derechos de fondo rotatorio. (Firmado), Luis Fernando Lemaitre, Cónsul., Sello consular en tinta. Certificación No.213241 del 24 de septiembre de 1996 de la firma que antecede por el Ministerio de Relaciones Exteriores. (Firmado), Jefe Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

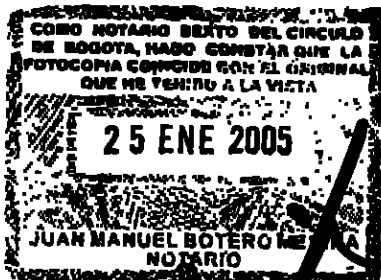
Santa fe de Bogotá, 30 de septiembre de 1996.

COLO-7612-801-005-5

ams/59-60

Ana María Salvetti

ANA MARIA SALVETTI
TRADUCCIONES Y SERVICIOS LEGALES
BOGOTÁ - COLOMBIA
CALLE 100 No. 123 MINISTRIA



MINISTERIO DE RELACIONES
EXTERIORES
Ana María
263981
Jefa Firmas y Archivos
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE
DE BOGOTA HAGO CONSTAR QUE LA FIRMA DE

Juan Manuel Botero
C.C.
COINCIDE CON LA REGISTRADA POR EL (CEN) EN ESTA NOTARIA.

30 SET. 1996
SANTAFE DE BOGOTA, D.C.



NO SE ASUME
RESPONSABILIDAD DEL TEXTO
1996 SET 30 12:07
Jefe de Legalizaciones
SANTAFE DE BOGOTA D.C.

CAVELIER

ABOGADOS

TELEFAX: (57) (1) 2388880
CABLES CAVELEYES
TELEX: 48479

EDIFICIO SISKI
CARRERA 49, No. 72-38
BOGOTÁ 8, COLOMBIA

CORREO ELECTRÓNICO MUNDIAL: CAVE
TELÉFONO: (57) (1) 2120100

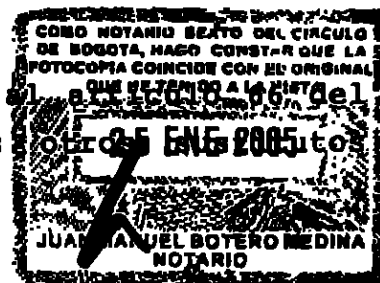
Señor Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Poderdante: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Poder conferido el: 29-08-96

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado, atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No. 31.929, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al Código de Procedimiento Civil ya que los otros faltan en este momento.



Señor Jefe,


GERMAN CAVELIER

T.P.A. No. 832

C.C. No. 2.877.924 de Bogotá

Acepto:



EMILIO FERRERO

T.P.A. N° 31.929

C.C. No. 438.019 de Usaquén.

2e-780-2

NOTARIA SEXTA DE BOGOTÁ

RECONOCIMIENTO Y PRESENTACIÓN PERSONAL

Santafé de Bogotá D. C.

06 SET 1998

Ante Mí JUAN MANUEL BOTERO MEDINA

NOTARIO SEXTO DEL CIRCULO DE BOGOTÁ

Compareció(eron) personalmente,

[Signature] *[Signature]*

[Signature] *[Signature]*

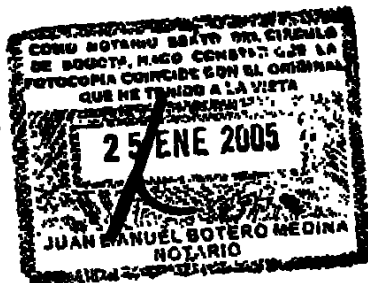
quien(es) exhibió(eron) la(s) c. c. *478018*

y la(s) Libreta(s) Minuteros. *2677964*

77802 *7771920*

identificado(s) en el momento y al momento que a(s) firma(s) que aparece(n) en el presente documento, la(s) suya(s), y que el contenido del mismo es verídico.
En constancia se firma esta diligencia.

[Signature]



[Signature]



ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTÁ, 8 - COLOMBIA

CESION

Yo, (nosotros) abajo firmado (s)

1. Carl A. BUSACCA
2. Magnus C. ERIKSSON
3. Ji-Young KIM

domiciliado(s) en

1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368,
Ridgefield, CT 06877-0368/USA
2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368,
Ridgefield, CT 06877-0368/USA
3. 523 Waymarket Drive, Ann Arbor,
MI 48103, USA

declaro(amos) bajo juramento ser único(s) y verdadero(s)
inventor(es) de la invención:

PROCEDIMIENTOS E INTEREDIOS PARA PREPARAR
INHIBIDORES DE TRANSCRIPTASA INVERSA DE
HIV-1 NO NUCLEOSIDOS

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin
limitación, a favor de la sociedad

Boehringer Ingelheim Pharmaceuticals, Inc.

constituida y existente de conformidad con las leyes de
USAdomiciliada en 900 Ridgebury Road, Ridgefield,
CT 06877todos los derechos inherentes a dicha invención y que la citada
compañía queda facultada para solicitar en su nombre la patente de
invención correspondiente en la República de Colombia.

ASSIGNMENT

I (we), the undersigned

1. Carl A. BUSACCA
2. Magnus C. ERIKSSON
3. Ji-Young KIM

of

1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368,
Ridgefield, CT 06877-0368/USA
2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368,
Ridgefield, CT 06877-0368/USA
4. 5903 Rollingwood Drive, Ann Arbor,
MI 48103, USA

state(s) under oath to be sole and true inventor(s) of the invention:

„Process and intermediates for making non-nucleoside
HIV-1 reverse transcriptase inhibitors”

state as well, that assign, without reservations or limitations in favour
of Boehringer Ingelheim Pharmaceuticals, Inc.a corporation constituted and existing in conformity with the laws of
USAdomiciled in 900 Ridgebury Road, Ridgefield,
CT 06877all rights inherent to said invention and that the above mentioned
company hereby is enabled to apply, in its name, for the corresponding
patent invention, in the Republic of ColombiaDado y firmado hoy/Given and signed this 3rd of November, 2004
en/in Ridgefield, Connecticut USA

Firma/Signature


1. Carl A. BUSACCA

3. Ji-Young KIM


2. Magnus C. ERIKSSON

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

THIS PUBLIC DOCUMENT

2. has been signed by **JEANNE E. ROGERS**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **November 26, 2001 to November 30, 2006**

CERTIFIED

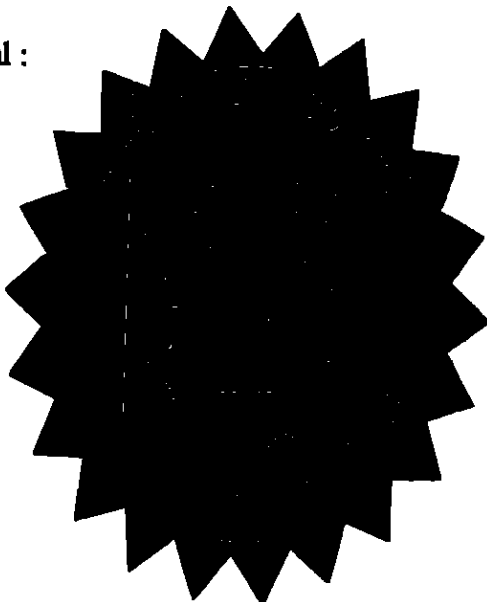
5. at Hartford, Connecticut

6. on **November 10, 2004**

7. by **SUSAN BYSIEWICZ** Secretary of the State of Connecticut

8. Number : **2004-12923**

9. Seal :



10. Signature


Secretary of the State

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____
de 200 ____ Ante mí, Notario Público de _____

compareció(eron)
personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede, y quien(es)
tiene(n) capacidad legal para otorgarlo

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this 3rd day of November
2004 _____ before me, a Notary Public of

The State of Connecticut USA

personally appeared Carl A. BUSACCA and
Magnus C. ERIKSSON

to me known, and known to me to be the person(s) who executed
that foregoing document, and who has(have) legal capacity to
execute it.

NOTARIO PÚBLICO-NOTARY PUBLIC

Jeanne E. Rogers
Jeanne E. Rogers
Notary Public
My Comisión Expires:
November 30, 2006

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country:
This public document
2. has been signed by
3. acting in the capacity of
4. bears the seal/stamp of

Certified

5. at 6. the
7. by
8. No.
9. Seal/stamp 10. Signature

.....

TRADUCCIÓN OFICIAL No. 22.12/04 preparada por María Elvira Martelo, traductora oficial aprobada por el Ministerio de Justicia mediante resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

A continuación se traducen los sellos y legalizaciones de un documento de Cesión escrito en inglés y español, por el cual:

1. Carl A. BUSACCA
2. Magnus C. ERIKSSON
3. Ji-Young KIM

de

1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877- 0368/EUA
Estados Unidos de América

2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877- 0368/EUA
Estados Unidos de América

3. 5903 Rollingwood Drive, Ann Arbor
MI 48103, USA

inventores de la invención "Procedimientos e intermedios para preparar Inhibidores de transcriptasa Inversa de HIV-1 no nucleosidos", ceden los derechos inherentes a dicha invención a **BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**, sociedad domiciliada en 900 Ridgebury Road, P.O. Box 368, Estados Unidos de América,.

Dado y firmado hoy 3 de noviembre de 2004

En Ridgefield, Connecticut, E.U.A.

(Firma)

Carl A. BUSACCA

(Firma)

Magnus C. ERIKSSON

Ji-Young KIM

CERTIFICADO NOTARIAL (INDIVIDUO)

Hoy 3 de noviembre de 2004 ante mí, un Notario Público del Estado de Connecticut EUA, comparecieron personalmente Carl A. BUSACCA y Maguns C. ERIKSS N, a

16

quienes doy fe de conocer y me consta que son las personas firmantes del documento que precede y quienes tienen capacidad legal para otorgarlo.

(Firma ilegible)

Jeanne E. Rogers

Notario Público

Mi comisión expira: 30 de noviembre de 2006.

APOSTILLA

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

1. País: Estados Unidos de América

ESTE DOCUMENTO PÚBLICO

2. ha sido firmado por **JEANNE E. ROGERS**

3. actuando en su capacidad de **NOTARIO PÚBLICO**

4. del estado de Connecticut por el término **26 de noviembre de 2001 a 30 de noviembre de 2006**

CERTIFICADO

5. en Hartford, Connecticut

6. el **2 de junio de 2004**

7. por **SUSAN BYSIEWICZ**, Secretario de Estado de Connecticut

8. Número: **2004-12923** ✓

9. Sello: sello del Estado de Connecticut

10. Firma (firma ilegible), Secretario de Estado

Es traducción fiel y completa de la cual se deja copia para su confrontación.

COLO 07612-841-008-1

WPCL 7612 - ID 235

DIC 24/04

Maria E. Martelo
TRADUCCION No: 27.12.04
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE SANTA
 EGGOTA, HAGO CONSTAR QUE LA FIRMA
[Firma manuscrita]
 COINCIDE(N) CON LA FIRMA REGISTRADA POR
 EL (ELLOS) EN ESTA NOTARIA
 SANTA FE DE BOGOTA. 29 DIC 2004



NO SE ASUME
 RESPONSABILIDAD DEL TEXTO
 2004 DIC 29 P 1:57
 JEFE DE REALIZACIONES
 BOGOTA D.C.

MINISTERIO DE
 RELACIONES EXTERIORES
 302388
 María Pardo
 CUYA FIRMA APARECE EN EL
 DOCUMENTO DESEMPENA
 LAS FUNCIONES INDICADAS

AB GAD S
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTÁ, 8 - COLOMBIA

CESION

Yo, (nosotros) abajo firmado (s)

1. Carl A. BUSACCA
2. Magnus C. ERIKSSON
3. Ji-Young KIM

domiciliado(s) en

1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368,
Ridgefield, CT 06877-0368/USA
2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368,
Ridgefield, CT 06877-0368/USA
3. 5903 Rollingwood Drive, Ann Arbor,
MI 48103, USA

declaro(amos) bajo juramento ser único(s) y verdadero(s)
inventor(es) de la invención:

PROCEDIMIENTOS E INTERMEDIOS PARA PREPARAR
INHIBIDORES DE TRANSCRIPTASA INVERSA DE
HIV-1 NO NUCLEOSIDOS

declaro(amos) así mismo que cedo(emos) y transfiero(remos), sin
limitación, a favor de la sociedad

Boehringer Ingelheim Pharmaceuticals, Inc.

constituida y existente de conformidad con las leyes de

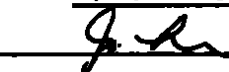
USA

domiciliada en 900 Ridgebury Road, Ridgefield,
CT 06877

todos los derechos inherentes a dicha invención y que la citada
Compañía queda facultada para solicitar en su nombre la patente de
invención correspondiente en la República de Colombia.

Dado y firmado hoy/Given and signed this 11-17-04

en/in Ann Arbor, MI, USA



Firma/Signature

1. Carl A. BUSACCA



3. Ji-Young KIM

ASSIGNMENT

I (we), the undersigned

1. Carl A. BUSACCA
2. Magnus C. ERIKSSON
3. Ji-Young KIM

of

1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368,
Ridgefield, CT 06877-0368/USA
2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368,
Ridgefield, CT 06877-0368/USA
4. 5903 Rollingwood Drive, Ann Arbor,
MI 48103, USA

state(s) under oath to be sole and true inventor(s) of the invention:

„Process and intermediates for making non-nucleoside
HIV-1 reverse transcriptase inhibitors”

state as well, that assign, without reservations or limitations in favour
of Boehringer Ingelheim Pharmaceuticals, Inc.

a corporation constituted and existing in conformity with the laws of

USA

domiciled in 900 Ridgebury Road, Ridgefield,
CT 06877

all rights inherent to said invention and that the above mentioned
company hereby is enabled to apply, in its name, for the corresponding
patent invention, in the Republic of Colombia

2. Magnus C. ERIKSSON

State of Michigan



DEPARTMENT OF STATE

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. Country: **UNITED STATES OF AMERICA**

This public document

2. has been signed by: **Regenia Richards**

3. acting in the capacity of: **Michigan Notary Public**

4. bears the seal of: **Regenia Richards**
Wayne County, Michigan

CERTIFIED:

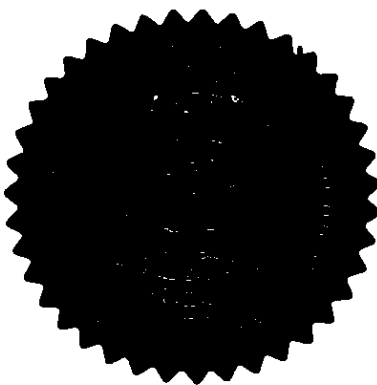
5. at Lansing, Michigan

6. the 6th of December, 2004

7. by Secretary of State, State of Michigan

8. NO. 49462F-04

9. Seal/Stamp:



10. Signature:

A handwritten signature in cursive script, reading "Terri Lynn Land".

Terri Lynn Land

This certification attests only to the authenticity of the signature of the official who signed the official document, the capacity in which that official acted, and where appropriate, the identity of the seal or stamp which the document bears. This certification is not intended to imply that the contents of the document are correct, nor that they have the approval of the State of Michigan.

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____
de 200 ____ Ante mí, Notario Público de _____
compareció(eron)
personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede, y quien(es)
tiene(n) capacidad legal para otorgarlo

NOTARIO PÚBLICO-NOTARY PUBLIC

NOTARIAL CERTIFICATION (INDIVIDUAL) 19

On this 17th day of _____ November
2004 _____ before me, a Notary Public of
Wayne County
personally appeared Ji-Young KIM

to me known, and known to me to be the person(s) who executed
that foregoing document, and who has(have) legal capacity to
execute it.

Regina Richards

REGINA RICHARDS public
NOTARY PUBLIC, STATE OF MICHIGAN
WAYNE COUNTY, MICHIGAN
ACTING IN THE COUNTY OF Wayne
MY COMMISSION EXPIRES SEPT 23, 2008

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country:
This public document
2. has been signed by
3. acting in the capacity of
4. bears the seal/stamp of

Certified

5. at 6. the
7. by
8. No.
9. Seal/stamp 10. Signature

.....

TRADUCCIÓN OFICIAL No. 22.12/04 preparada por María Elvira Martelo, traductora oficial aprobada por el Ministerio de Justicia mediante resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

A continuación se traducen los sellos y legalizaciones de un documento de Cesión escrito en inglés y español, por el cual:

- 1. Carl A. BUSACCA
- 2. Magnus C. ERIKSSON
- 3. Ji-Young KIM

de

- 1. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877- 0368/EUA
Estados Unidos de América

- 2. Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877- 0368/EUA
Estados Unidos de América

- 3. 5903 Rollingwood Drive, Ann Arbor
MI 48103, USA

inventores de la invención **"Procedimientos e intermedios para preparar inhibidores de transcriptasa inversa de HIV-1 no nucleosidos"**, ceden los derechos inherentes a dicha invención a **BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**, sociedad domiciliada en 900 Ridgebury Road, P.O. Box 368, Estados Unidos de América,.

Dado y firmado hoy 17 de noviembre de 2004

En Ann Arbor MI, E.U.A.

(Firma ilegible)

Carl A. BUSACCA

Magnus C. ERIKSSON

(Firma ilegible)
Ji-Young KIM

CERTIFICADO NOTARIAL (INDIVIDUO)

Hoy 3 de noviembre de 2004 ante mí, un Notario Público del Estado de Connecticut EUA, comparecieron personalmente Ji-Young KIM, a quien doy fe de conocer y me

consta que es la persona firmante del documento que precede y tiene capacidad legal para otorgarlo.

(Firma ilegible), NOTARIO PÚBLICO

(Sello) REGENIA RICHARDS, Notario Público, Estado de Michigan, Condado de Wayne, Michigan. Para el Condado de (ilegible). Mi comisión expira del 23 de septiembre de 2008

ESTADO DE MICHIGAN

DEPARTAMENTO DE ESTADO

APOSTILLA

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

1. País: ESTADOS UNIDOS DE AMÉRICA

Este documento público

2. ha sido firmado por: Regenia Richards
3. Actuando en su capacidad de: Notario Público de Michigan
4. lleva el sello/timbre de: Regenia Richards, Condado de Wayne

CERTIFICADO

5. En Lansing, Michigan 6. el 6 de diciembre de 2004

7. Por el Secretario de Estado, Estado de Michigan

8. No. 49462F-04

9. Sello/Timbre:

10. Firma:

El Gran Sello del Estado de Michigan

(Firmado) Terri Lynn Land

Esta certificación sólo testifica la autenticidad de la firma del funcionario que firmó el documento adjunto, la capacidad en la cual actuó dicho funcionario, y cuando así se requiere, la identidad del sello o timbre que lleva el documento. Esta certificación no implica que el contenido del documento sea correcto ni que esté aprobado por el Estado de Michigan.

Es traducción fiel y completa de la cual se deja copia para su confrontación.

COLO 07612-841-008-1

WPCL 7612 - ID 235, DIC 24/04

Maria Elvira Martelo
TRADUCCION No. 22.12.04
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE

Pedro Pablo Arango

CORRINCIDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA. 29 DIC 2004



NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2004 DIC 29 P 1:58

JEFE DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE
RELACIONES EXTERIORES

302389

Pedro Pablo Arango

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES INDICADAS

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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
8 January 2004 (08.01.2004)

PCT

(10) International Publication Number
WO 2004/002989 A1

(51) International Patent Classification⁷: C07D 471/14 //
(C07D 471/14, 243:00, 221:00, 221:00)

(74) Agents: RAYMOND, Robert, P. et al.; Boehringer In-
gelheim Corporation, 900 Ridgebury Road, P.O. Box 368,
Ridgefield, CT 06877-0368 (US).

(21) International Application Number:
PCT/US2003/019415

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

(22) International Filing Date: 20 June 2003 (20.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/391,979 28 June 2002 (28.06.2002) US
60/434,052 17 December 2002 (17.12.2002) US

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

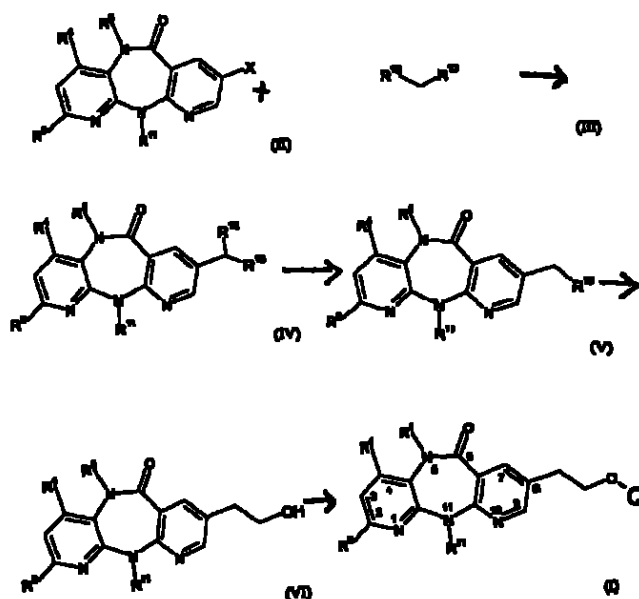
(71) Applicant: BOEHRINGER INGELHEIM PHARMA-
CEUTICALS, INC. [US/US]; 900 Ridgebury Road, P.O.
Box 368, Ridgefield, CT 06877-0368 (US).

(72) Inventors: BUSACCA, Carl, A.; Boehringer Ingelheim
Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box
368, Ridgefield, CT 06877-0368 (US). ERIKSSON,
Magnus, C.; Boehringer Ingelheim Pharmaceuticals,
Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT
06877-0368 (US). KIM, Ji-Young; 523 Waymarket Drive,
Ann Arbor, MI 48103 (US).

Published:
— with international search report

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

(54) Title: PROCESS AND INTERMEDIATES FOR MAKING NON-NUCLEOSIDE HIV-1 REVERSE TRANSCRIPTASE IN-
HIBITORS



(57) Abstract: A process and novel intermediates for making HIV reverse transcriptase inhibitors. Formula (I, II, III, IV, V, VI).

WO 2004/002989 A1

**PROCESS AND INTERMEDIATES FOR MAKING NON-NUCLEOSIDE HIV-1
REVERSE TRANSCRIPTASE INHIBITORS**

5 *TECHNICAL FIELD OF THE INVENTION*

The invention relates to a novel process and novel intermediates for the synthesis of certain non-nucleoside reverse transcriptase inhibitors.

BACKGROUND OF THE INVENTION

10 The disease known as acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), particularly the strain known as HIV-1. In order for HIV to be replicated by a host cell, the information of the viral genome must be integrated into the host cell's DNA. However, HIV is a retrovirus, meaning that its genetic information is in the form of RNA. The HIV replication cycle, therefore, requires a step of
15 transcription of the viral genome (RNA) into DNA. The transcription of the viral RNA into DNA is accomplished by an enzyme that has been aptly dubbed reverse transcriptase (RT). The HIV virion includes a copy of RT along with the viral RNA.

Reverse transcriptase has three known enzymatic functions. It acts as an RNA-dependent
20 DNA polymerase, as a ribonuclease, and as a DNA-dependent DNA polymerase. Acting as an RNA-dependent DNA polymerase, RT transcribes a single-stranded DNA copy of the viral RNA. Acting as a ribonuclease, RT destroys the original viral RNA, and frees the DNA just produced from the original RNA. Finally, acting as a DNA-dependent DNA
25 polymerase, RT makes a second, complementary DNA strand, using the first DNA strand as a template. The two strands form double-stranded DNA, which is integrated into the host cell's genome by another enzyme called integrase.

Compounds that inhibit the enzymatic functions of HIV-1 reverse transcriptase will inhibit replication of HIV-1 in infected cells. Such compounds are useful in the prevention or
30 treatment of HIV-1 infection in human subjects, as demonstrated by known RT inhibitors such as 3'-azido-2'-deoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'-

dideoxycytidine (ddC), d4T, 3TC, nevirapine, delavirdine, efavirenz and abacavir, the RT inhibitors thus far approved as drugs for use in the treatment of HIV infection.

As with any antiviral therapy, use of RT inhibitors in the treatment of HIV infection eventually leads to a virus that is less sensitive to the given drug. Resistance (reduced sensitivity) to these drugs is the result of mutations that occur in the reverse transcriptase segment of the *pol* gene. Several mutant strains of HIV have been characterised, and resistance to known therapeutic agents is due to mutations in the RT gene. Some of the most commonly observed mutant clinically are: the Y181C mutant, in which a tyrosine Y, at codon 181, has been mutated to a cysteine C residue, and K103N where the lysine K at position 103 has been replaced by asparagine N. Other mutants which emerge with increasing frequency during treatment with known antivirals include the single mutants V106A, G190A, Y188C, and P236L; and the double mutants K103N/Y181C, K103N/P225H, K103N/V108I and K103N/L100I.

15

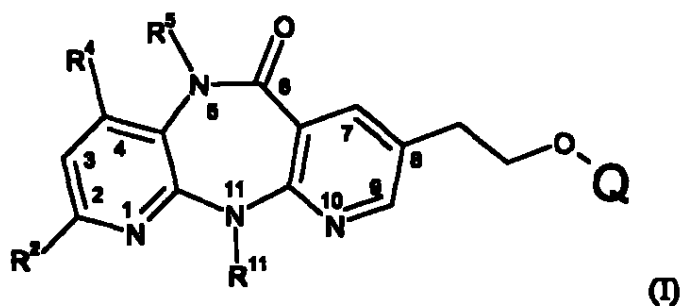
As therapy of HIV infection using antivirals continues, the emergence of new resistant strains is expected to increase. There is therefore an ongoing need for new inhibitors of RT, with different patterns of effectiveness against the various mutants.

Of particular relevance to the present invention are the HIV-RT inhibitors disclosed by U.S. Pat. 6,420,359. These compounds, which are all dipyrdo[3,2-b:2',3'-e][1,4]diazepin-6-ones bearing a 2-(quinolinyl)oxyethyl or a 2-(1-oxido-quinolinyl)oxyethyl group in the 8-position, have enhanced activity against certain clinically significant mutant strains of HIV-1. It is the object of the present invention to provide an alternative method for making the compounds disclosed by U.S. Pat. 6,420,359.

25

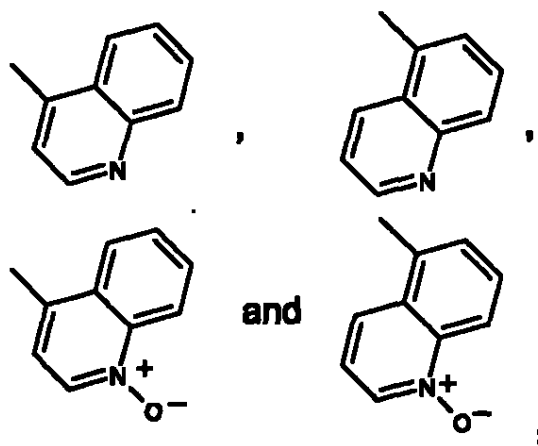
SUMMARY OF THE INVENTION

The invention provides an improved process for making compounds of the general formula I:



wherein:

- R^2 is selected from the group consisting of H, F, Cl, C_{1-4} alkyl, C_{3-4} cycloalkyl and CF_3 ;
- 5 R^4 is H or Me;
- R^5 is H, Me or Et, with the proviso that R^4 and R^5 are not both Me, and if R^4 is Me then R^5 cannot be Et;
- R^{11} is Me, Et, cyclopropyl, propyl, isopropyl, or cyclobutyl; and
- Q is selected from the group consisting of:



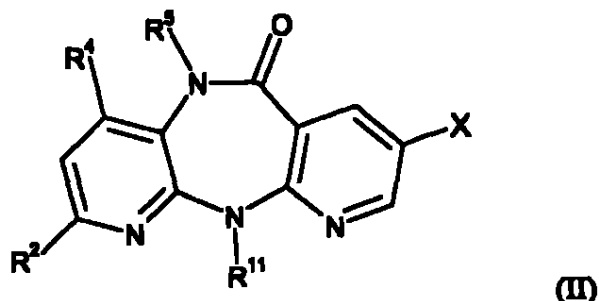
10

as well as pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

The synthetic method of the invention commences from a starting compound of the formula II

5



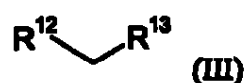
wherein R^2 , R^4 , R^5 and R^{11} are as defined above with respect to compounds of the formula I and wherein X is a chlorine, iodine, or bromine, or a fluorosulfonate moiety selected from the group consisting of $-\text{OSO}_2\text{F}$ and $-\text{OSO}_2(\text{CF}_2)_n\text{CF}_3$, wherein n is an integer between 0 and 10. Processes for making starting compounds of the formula II wherein X is bromine are described in U.S. Pat. 6,420,359. Compounds wherein X is other than bromine can be made by analogous methods which will be readily apparent to those of ordinary skill in the art.

15

It is preferred to use a compound of the formula II wherein X is bromine.

The starting compound of the formula II initially undergoes a palladium-catalyzed coupling reaction wherein it is caused to arylate a malonate or malonate surrogate of the formula III

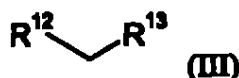
20



wherein,

- R^{12} is a cyano group or a group of the formula $-\text{COOR}^{14}$, wherein R^{14} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group group phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl, and
- R^{13} is a cyano group, a group of the formula $-\text{COOR}^{15}$ (wherein R^{15} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group group phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl), a group of the formula $-\text{SO}_2\text{R}^{16}$ (wherein R^{16} is a C₁₋₄-alkyl group, phenyl, furyl, pyridyl or benzyl), a group of the formula $-\text{P}(\text{O})(\text{OR}^{17})_2$ (wherein R^{17} is phenyl, furyl or pyridyl) or a group of the formula $-\text{SOR}^{18}$ (wherein R^{18} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group group phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl).

It is preferred to employ a malonate surrogate of the formula III

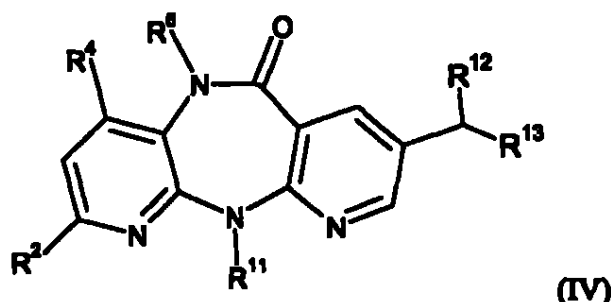


- wherein,
- R^{12} is a cyano group or a group of the formula $-\text{COOR}^{14}$, wherein R^{14} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group group phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl; and
- R^{13} is a cyano group, a group of the formula $-\text{SO}_2\text{R}^{16}$ (wherein R^{16} is a C₁₋₄-alkyl group, phenyl, furyl, pyridyl or benzyl), a group of the formula $-\text{P}(\text{O})(\text{OR}^{17})_2$ (wherein R^{17} is phenyl, furyl or pyridyl) or a group of the formula $-\text{SOR}^{18}$ (wherein R^{18} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group group phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl).
- The reaction of the compounds of the formulas II and III takes place in an organic solvent, in the presence of a palladium catalyst, a suitable ligand and strong base. Suitable solvents are, by way of non-limiting example, toluene, ethylbenzene, xylene, DMF, DMA, NMP, dioxane and THF, with toluene being preferred. Virtually any palladium catalyst may be used, such as, for example, $\text{Pd}(\text{OAc})_2$, PdCl_2 , Pd_2dba_3 and Pd on carbon, with $\text{Pd}(\text{OAc})_2$ being preferred. Suitable bases are, for example, the metal hydrides such as, for example,

NaH, the metal alkoxides such as, for example, t-BuOK, t-BuONa and Na-tert-amylate, the metal carbonates such as, for example, Na₂CO₃, K₂CO₃ and Cs₂CO₃, with NaH being preferred, and the metal phosphates such as, for example, K₃PO₄. When the reactant of the formula III is a malonate (compounds wherein R¹² and R¹³ are both carboxylic acid ester groups) then suitable ligands will be t-Bu₃P, one of the ligands described and claimed in U.S. Patent 6,307,087, or a ferrocenyl phosphine such as described in U.S. Patents 6,057,456 and USP 6,072,073. When the reactant of the formula III is not a malonate, but rather a malonate surrogate (a compound wherein R¹² and R¹³ are not both carboxylic acid ester groups) the above-mentioned ligands may be employed and, in addition, a triarylphosphine such as, by way of non-limiting example, PPh₃, o-Tol₃P, p-Tol₃P and o-Fur₃P may also be employed. In such case the preferred ligand is PPh₃.

The reaction is preferably carried out at elevated temperature, more preferably in the range between about 50 and 150°C.

The above described reaction, which couples the compounds of the formulas II and III, yields an intermediate of the formula IV

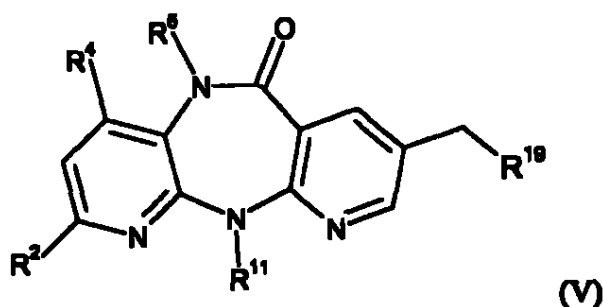


wherein R², R⁴, R⁵, R¹¹, R¹² and R¹³ are as defined above.

Isolation of the intermediate of the formula IV before going on to the next process step is optional. It has been found that a one pot synthesis wherein the intermediate IV is not isolated is quite convenient. If the intermediate IV is not isolated and the residual base is a metal hydride, such as NaH, then it is advisable to quench the base with an agent such as isopropyl alcohol before going on to the next step.

If the intermediate of the formula IV contains sulfur or phosphorus (because R^{13} in the reactant of the formula III was a group of the formula $-SO_2R^{15}$ or $-P(O)(OR^{16})_2$) then the next process step is a reductive cleavage of the sulfur or phosphorus-containing group. Methods for performing such reductive cleavage will be well known to those of ordinary skill in the art. For example, this might be accomplished by the use of Raney nickel or a dissolving metal reaction.

Subsequent to the reductive cleavage or, if the intermediate of formula IV does not contain sulfur or phosphorus, the intermediate of the formula IV is next hydrolyzed to yield a further intermediate of the formula V

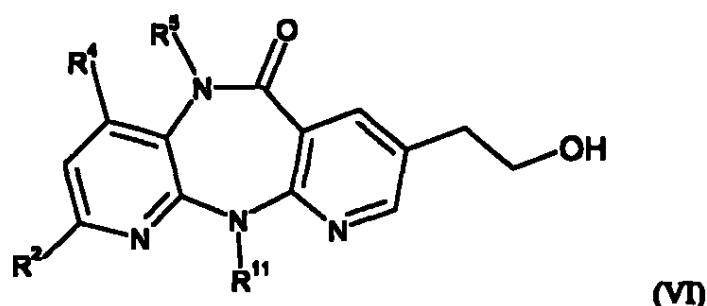


wherein R^2 , R^4 , R^5 and R^{11} are as defined above and R^{19} is $-COOH$ or, if the reactant of formula III was a malonate and mild hydrolysis conditions are employed, R^{19} may additionally be a group of the formula $-COOR^{14}$ wherein R^{14} is as described above. The hydrolysis may be performed in a manner that will be conventional and readily apparent to those of ordinary skill in the art. For example, it may be accomplished using an aqueous base, such as NaOH, preferably at ambient temperature or above.

The intermediates of the formulas IV and V are believed to be novel and constitute a part of the invention.

Isolation of the intermediate V before going on to the next step is preferred.

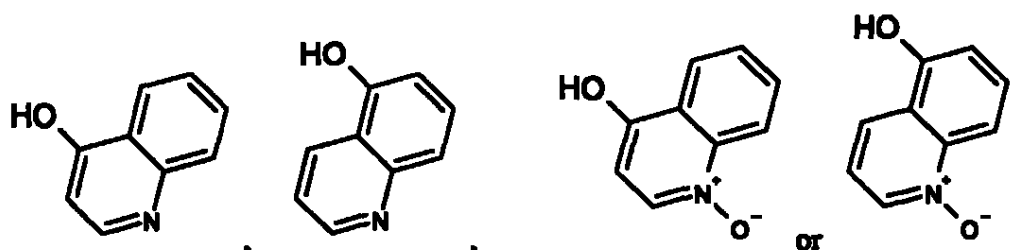
Next, the carboxylic acid or ester intermediate of the formula V is reduced to yield an alcohol of the formula VI



wherein R^2 , R^4 , R^5 and R^{11} are as defined above. Reduction is carried out in a conventional manner that will be readily apparent to those of ordinary skill in the art. Regardless of whether the intermediate of the formula V is an acid or an ester, reduction may be accomplished using boranes, borohydrides or other metal hydrides or dissolving metal reductants, with boranes being preferred for the acids and borohydrides being preferred for the esters. If a borane is to be employed it is preferred to make it *in situ* from a borohydride, such as sodium borohydride, and an electrophilic reagent such as, for example HCl.

10

Finally, the alcohol of formula VI is converted to the final product of the formula I by a condensation reaction with a reactant of the formula



This condensation may be accomplished in the manner described in U.S. Patent 6,420,359.

15

The nature and scope of the invention will be better appreciated from the following examples.

Example 1: Arylation of Malononitrile: Formation of Compound of Formula IV where
 $R^2=R^4=H$, $R^5=Me$, $R^{11}=ethyl$, and $R^{12}=R^{13}=CN$.

A flask was charged with 10.0g tricyclic bromide (compound of formula II where $R^2=R^4=H$, $R^5=Me$, $R^{11}=ethyl$, and $X=Br$; 30 mmol, 1 eq.), 0.95g triphenylphosphine (3.6

mmol, 0.12 eq.), 0.55 g Pd_2dba_3 (0.6 mmol, 0.04 eq.), and 40 mL 1,4-dioxane. To this mixture was then added 2.16g sodium hydride (90 mmol, 3 eq.) in portions over 15 minutes, using 40 mL 1,4-dioxane to complete the addition. A solution of 2.57g malononitrile (39 mmol, 1.3 eq.) in 5 mL 1,4-dioxane was then added, and the mixture
5 heated to 90°C. After 18h the mixture was cooled to ambient temperature and cautiously quenched with 100 mL of sat'd ammonium chloride solution. The pH was then adjusted to 6 with 1N HCl, and the mixture extracted with dichloromethane. The organic solution was dried (magnesium sulfate), and the solvents removed in vacuo to give 7.03g (73%) of the product as a brown oil. NMR and MS showed the desired product (Compound of Formula
10 IV where $\text{R}^2=\text{R}^4=\text{H}$, $\text{R}^5=\text{Me}$, $\text{R}^{11}=\text{ethyl}$, and $\text{R}^{12}=\text{R}^{13}=\text{CN}$).

Example 2: Arylation of Diethylmalonate: Formation of Compound of Formula IV where $\text{R}^2=\text{R}^4=\text{H}$, $\text{R}^5=\text{Me}$, $\text{R}^{11}=\text{ethyl}$, and $\text{R}^{12}=\text{R}^{13}=\text{CO}_2\text{Et}$.

15 A 500 ml two neck round bottom flask fitted with mechanical stirrer, reflux condenser and thermocouple was purged with argon for 20 minutes, then 404 mg $\text{Pd}(\text{OAc})_2$ (1.80 mmol, 0.03 eq.), 1.08g 2-(di-*t*-butylphosphino)biphenyl (3.60 mmol, 0.06 eq.), and 20.0g tricyclic bromide (compound of formula II where $\text{R}^2=\text{R}^4=\text{H}$, $\text{R}^5=\text{Me}$, $\text{R}^{11}=\text{ethyl}$, and $\text{X}=\text{Br}$; (60.0 mmol, 1 eq.) were charged. To this mixture in an inerted flask was then added 25.5g
20 K_3PO_4 (120 mmol, 2 eq.), 100 mL PhMe, and 13.8 mL diethylmalonate (90.0 mmol, 1.5 eq.) were then added. The stirred suspension was placed in an oil bath and heated at reflux under nitrogen for 24h until the bromide was consumed by HPLC. The reaction mixture was cooled to room temperature and diluted with water (150 ml) and toluene (50 ml) was added. The mixture was stirred for 1h at room temperature until all solids had dissolved.
25 The two-phase solution was then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with toluene (50 ml). The combined organic layers were filtered through a pad of Celite and concentrated under vacuum to give a viscous oil, which was evaporated to dryness to furnish an orange solid. Silica gel chromatography (1:1 EtOAc:Hex) provided 20.5g pure malonate adduct (compound of
30 formula IV where $\text{R}^2=\text{R}^4=\text{H}$, $\text{R}^5=\text{Me}$, $\text{R}^{11}=\text{ethyl}$, and $\text{R}^{12}=\text{R}^{13}=\text{CO}_2\text{Et}$), (83%), as a colorless solid, m.p. 122-123°C; ^1H NMR (400 MHz, CDCl_3) δ : 8.38 (d, $J=2.5$ Hz, 1H),

8.19 (dd, $J = 1.5, 4.6$ Hz, 1H), 8.16 (d, $J = 2.4$ Hz, 1H), 7.47 (dd, $J = 1.5, 8.0$ Hz, 1H), 7.09 (dd, $J = 4.7, 8.0$ Hz, 1H), 4.56 (s, 1H), 4.20 (m, 6H), 3.49 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ : 167.30 (s), 167.23 (s), 159.31 (s), 154.50 (s), 151.18 (d), 144.34 (d), 141.93 (d), 131.63 (s), 130.74 (d), 123.52 (s), 120.57 (s), 119.78 (d), 62.17 (t), 54.80 (d), 41.24 (t), 37.30 (q), 13.96 (q), 13.58 (q). Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_5$: C, 61.15; H, 5.87; N, 13.58. Found: C, 61.14; H, 5.66; N, 13.51.

Example 3: Arylation of Isopropylcyanoacetate and Formation of Compound of Formula V where $\text{R}^2=\text{R}^4=\text{H}$, $\text{R}^5=\text{Me}$, $\text{R}^{11}=\text{ethyl}$, and $\text{R}^{13}=\text{CO}_2\text{H}$.

- 10 An inerted 800 L reactor was charged with 12.0 Kg 60% NaH/oil (300 mol, 2.5 eq.), 0.27 Kg $\text{Pd}(\text{OAc})_2$ (1.2 mol, 0.01 eq.), 1.26 Kg PPh_3 (4.8 mol, 0.04 eq.), and 40 Kg tricyclic bromide (compound of formula II where $\text{R}^2=\text{R}^4=\text{H}$, $\text{R}^5=\text{Me}$, $\text{R}^{11}=\text{ethyl}$, and $\text{X}=\text{Br}$, 120 mol, 1 eq.). The reactor was again inerted, then 70 Kg of PhMe was charged, and the mixture heated to 60°C . To this mixture was then added a solution of 17.4L
- 15 cyanoisopropylacetate (138 mol, 1.15 eq.) in 20L PhMe via metering pump at a fixed rate over 2 hours (Caution: H_2 gas evolution). The reactor contents were then heated to 100°C and maintained there for 1.5 hours. HPLC of an aliquot showed the arylation was complete to compound of formula IV where $\text{R}^2=\text{R}^4=\text{H}$, $\text{R}^5=\text{Me}$, $\text{R}^{11}=\text{ethyl}$, $\text{R}^{12}=\text{CN}$ and $\text{R}^{13}=\text{CO}_2\text{iPr}$. The mixture was then cooled to 35°C and quenched by the addition of 19 Kg
- 20 isopropanol (308 mol, 2.6 eq.) over 20 minutes (Caution: H_2 gas evolution). 438 Kg 1M NaOH solution (417 mol, 3.5 eq.) was then added, and the mixture heated to 80°C and maintained there for 8 hours. HPLC of an aliquot showed the hydrolysis was complete to the desired carboxylic acid. The mixture was cooled to 25°C and the phases separated. The upper phase was discarded to waste, while the lower aqueous phase was returned to
- 25 the reactor. 218 Kg EtOAc was then charged and the mixture agitated for 15 minutes, then the phases were allowed to separate. The lower aqueous phase was returned to the reactor and cooled to 10°C . To this mixture was then slowly added 6N H_2SO_4 with continuous monitoring of pH until a final pH of 3.3 was achieved: this required 133 Kg of H_2SO_4 solution. The resulting slurry was then warmed to 25°C and maintained there for 1 hour.
- 30 The batch was then centrifuged and washed twice with 40 Kg H_2O . The solid was then dried at full vacuum at 40°C until LOD $<1\%$ to give 36.0 Kg of the carboxylic acid

(compound of formula V where $R^2=R^4=H$, $R^5=Me$, $R^{11}=ethyl$, and $R^{19}=CO_2H$; 96%), as an off white solid. Mp 226-228°C; 1H NMR (500MHz, DMSO) δ : 12.47 (s, 1H), 8.32 (d, $J=2.0$ Hz, 1H), 8.20 (dd, $J=4.6, 1.5$ Hz, 1H), 7.96 (d, $J=2.3$ Hz, 1H), 7.81 (dd, $J=8.0, 1.6$ Hz, 1H), 7.24 (m, $J=4.6, 8.0$ Hz, 1H), 4.08 (q, $J=7.0$ Hz, 2H), 3.63 (s, 3H), 3.43 (s, 3H), 1.17 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (125 MHz, DMSO) δ : 172.22 (s), 166.26 (s), 157.47 (s), 153.96 (s), 151.32 (d), 144.06 (d), 141.59 (d), 131.72 (d), 131.14 (s), 126.01 (s), 120.28 (d), 120.12 (s), 40.45 (t), 36.74 (q), 36.34 (t), 13.42 (q). Anal. Calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.28; H, 4.94; N, 17.56.

- 10 **Example 4: Arylation of Methylphenylsulfonyl acetate: Formation of Compound of Formula IV where $R^2=R^4=H$, $R^5=Me$, $R^{11}=ethyl$, $R^{12}=CO_2Me$ and $R^{13}=SO_2Ph$.**
A flask was charged with 165 mg Pd_2dba_3 (0.18 mmol, 0.02 eq.), 577 mg triphenylphosphine (2.2 mmol, 0.12 eq.), and 45 mL 1,4-dioxane. After stirring in an inert atmosphere for 15 minutes, 647 mg NaH (27 mmol, 3 eq.) was added in portions. To this mixture was then added 3.00g tricyclic bromide (compound of formula II where $R^2=R^4=H$, $R^5=Me$, $R^{11}=ethyl$, and $X=Br$; 9.00 mmol, 1 eq.), followed by 2.50 g (11.7 mmol, 1.3 eq.) of methylphenylsulfonyl acetate. The mixture was then heated at 60°C for 18h, cooled to ambient temperature and quenched by the addition of 0.5 mL H_2O . The dioxane was removed in vacuo to give the crude product as a grey solid, 3.5g (~90%). NMR and MS indicated the desired arylation product (Compound of Formula IV where $R^2=R^4=H$, $R^5=Me$, $R^{11}=ethyl$, $R^{12}=CO_2Me$ and $R^{13}=SO_2Ph$).

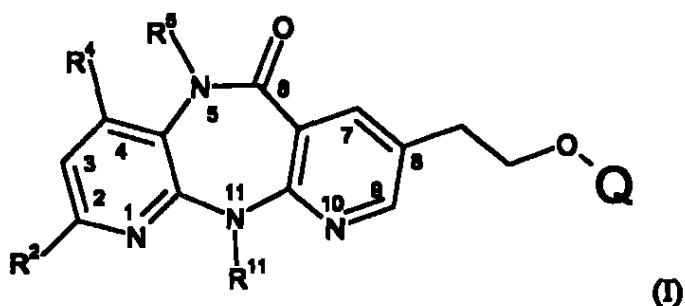
- Example 5: Arylation of Diethylphosphonyl acetonitrile: Formation of Compound of Formula IV where $R^2=R^4=H$, $R^5=Me$, $R^{11}=ethyl$, $R^{12}=CN$ and $R^{13}=P(O)(OEt)_2$.**
25 A flask was charged with 1.00g tricyclic bromide (compound of formula II where $R^2=R^4=H$, $R^5=Me$, $R^{11}=ethyl$, and $X=Br$; 3.00 mmol, 1 eq.), 55 mg Pd_2dba_3 (0.06 mmol, 0.02 eq.), 95 mg triphenylphosphine (0.36 mmol, 0.12 eq.), and 0.69g diethylphosphonyl acetonitrile (3.90 mmol, 1.3 eq.). To this mixture was then added 15 mL 1,4-dioxane, followed by 216 mg NaH (9.00 mmol, 3 eq.). The resulting mixture was then heated at 30 70°C for three hours. The mixture was cooled to ambient temperature and quenched by the cautious addition of 25 mL H_2O , and 20 mL dichloromethane was added. The pH was

then adjusted to 2.5 with 1N aq. HCl and diluted with additional H₂O (25 mL) and dichloromethane (25 mL). The phases were then separated and the organic phase concentrated to a brown oil. The oil was then triturated with 10 mL t-butylmethyl ether to give a precipitate of the product, which was filtered to give 0.95g product as an off white
s solid. NMR and MS indicated the desired arylation product (Compound of Formula IV where R²-R⁴=H, R⁵=Me, R¹¹= ethyl, R¹²=CN and R¹³=P(O)(OEt)₂).

35

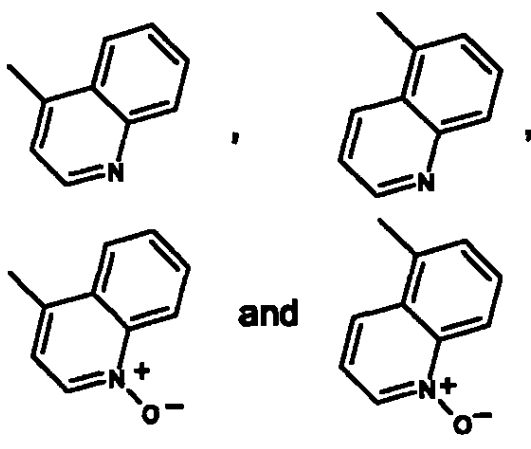
What is claimed is:

1. A process for making a compound of the formula I:



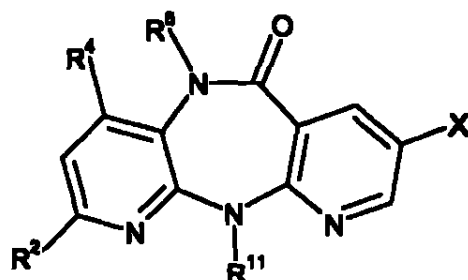
wherein:

- R^2 is selected from the group consisting of H, F, Cl, C_{1-4} alkyl, C_{3-4} cycloalkyl and CF_3 ;
 R^4 is H or Me;
 10 R^5 is H, Me or Et, with the proviso that R^4 and R^5 are not both Me, and if R^4 is Me then R^5 cannot be Et;
 R^{11} is Me, Et, cyclopropyl, propyl, isopropyl, or cyclobutyl; and
 Q is selected from the group consisting of:



- 15 which process comprises the following steps:

- (a) reacting a starting compound of the formula II

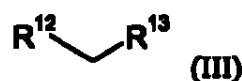


(II)

wherein R^2 , R^4 , R^8 and R^{11} are as hereinbefore defined with respect to the compound of the
 5 formula I and wherein X is a chlorine, iodine, or bromine, or a fluorosulfonate moiety
 selected from the group consisting of $-\text{OSO}_2\text{F}$ and $-\text{OSO}_2(\text{CF}_2)_n\text{CF}_3$ wherein n is an integer
 between 0 and 10,

with a malonate or malonate surrogate of the formula III

10



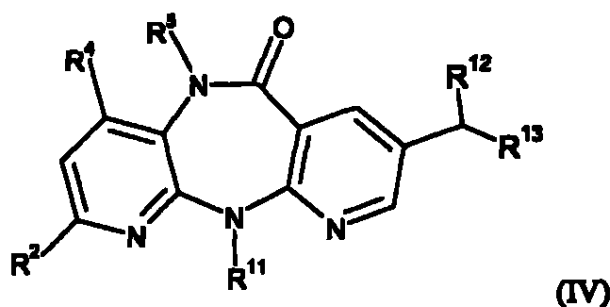
(III)

wherein,

R^{12} is a cyano group or a group of the formula $-\text{COOR}^{14}$, wherein R^{14} is a C-1-4-alkyl
 group, a C-1-4-alkyloxy-C-1-4-alkyl group group phenyl, naphthyl, thiophenyl, furyl,
 15 pyridyl, imidazole or benzyl, and
 R^{13} is a cyano group, a group of the formula $-\text{COOR}^{15}$ (wherein R^{15} is a C-1-4-alkyl
 group, a C-1-4-alkyloxy-C-1-4-alkyl group group phenyl, naphthyl, thiophenyl, furyl,
 pyridyl, imidazole or benzyl), a group of the formula $-\text{SO}_2\text{R}^{16}$ (wherein R^{16} is a C-1-4-alkyl
 group, phenyl, furyl, pyridyl or benzyl), a group of the formula $-\text{P}(\text{O})(\text{OR}^{17})_2$ (wherein R^{17}
 20 is phenyl, furyl or pyridyl) or a group of the formula $-\text{SOR}^{18}$ (wherein R^{18} is a C-1-4-alkyl
 group, a C-1-4-alkyloxy-C-1-4-alkyl group group phenyl, naphthyl, thiophenyl, furyl,
 pyridyl, imidazole or benzyl),

in an organic solvent, in the presence of a palladium catalyst, a suitable ligand and strong base,

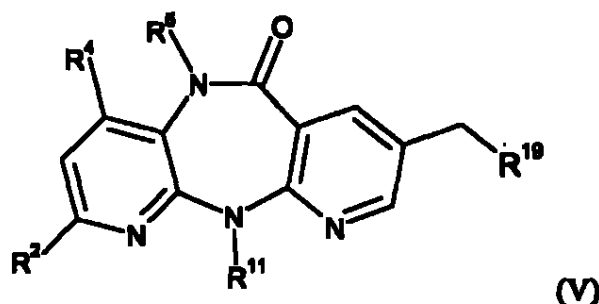
to yield an intermediate of the formula IV



wherein R^2 , R^4 , R^5 , R^{11} , R^{12} and R^{13} are as hereinbefore defined in this claim;

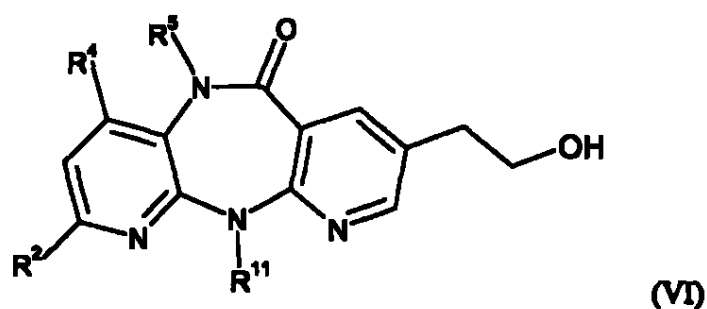
(b) reductively cleaving the sulfur or phosphorus-containing group, if the intermediate of the formula IV contains a sulfur or phosphorus-containing group;

(c) hydrolyzing the intermediate of the formula IV to yield a further intermediate of the formula V



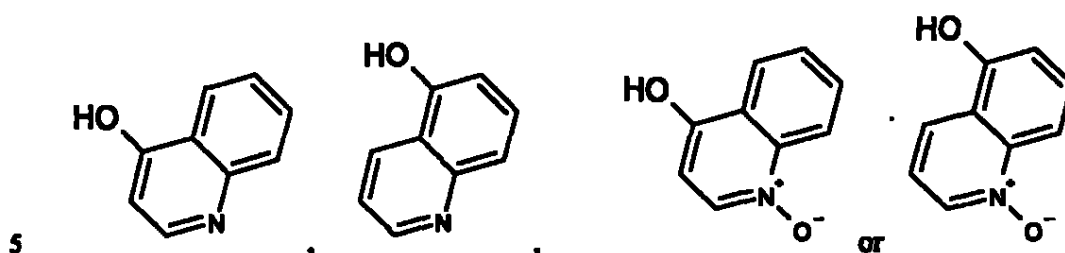
wherein R^2 , R^4 , R^5 and R^{11} are as hereinbefore defined in this claim and R^{19} is $-\text{COOH}$ or, if the reactant of formula III was a malonate and mild hydrolysis conditions are employed, wherein R^{19} may additionally be a group of the formula $-\text{COOR}^{14}$ wherein R^{14} is as hereinbefore defined in this claim;

(d) reducing the carboxylic acid or ester intermediate of the formula V to yield an alcohol of the formula VI



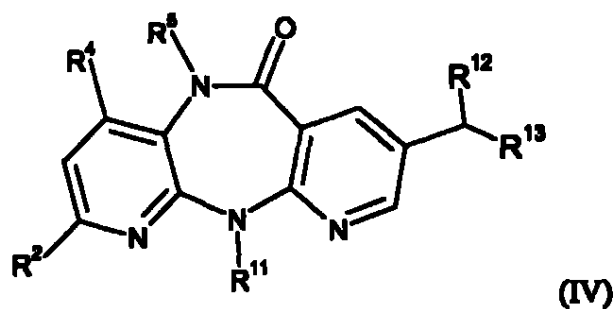
wherein R^2 , R^4 , R^5 and R^{11} are as hereinbefore defined in this claim; and

(e) condensing the alcohol of formula VI with a reactant of the formula



to yield the final product of the formula I.

10 2. A process for making a compound of the formula IV



wherein:

R^2 is selected from the group consisting of H, F, Cl, C_{1-4} alkyl, C_{3-4} cycloalkyl and CF_3 ,

15 R^4 is H or Me,

R^5 is H, Me or Et, with the proviso that R^4 and R^5 are not both Me, and if R^4 is Me then R^5 cannot be Et,

R^{11} is Me, Et, cyclopropyl, propyl, isopropyl, or cyclobutyl,

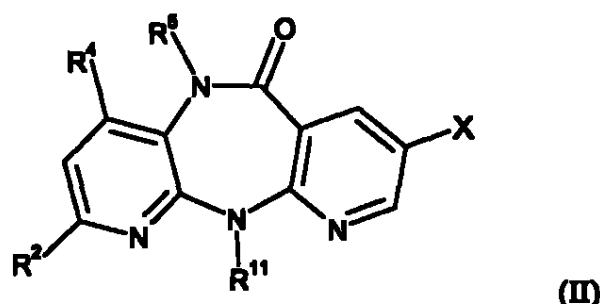
R^{12} is a cyano group or a group of the formula $-\text{COOR}^{14}$, wherein R^{14} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group group phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl, and

- 5 R^{13} is a cyano group, a group of the formula $-\text{COOR}^{15}$ (wherein R^{14} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group group phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl), a group of the formula $-\text{SO}_2\text{R}^{16}$ (wherein R^{16} is a C₁₋₄-alkyl group, phenyl, furyl, pyridyl or benzyl), a group of the formula $-\text{P}(\text{O})(\text{OR}^{17})_2$ (wherein R^{17} is phenyl, furyl or pyridyl) or a group of the formula $-\text{SOR}^{18}$ (wherein R^{18} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group group phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl),
- 10

which process comprises the following steps:

- (a) reacting a starting compound of the formula II

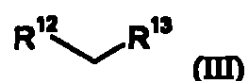
15



wherein R^2 , R^4 , R^5 and R^{11} are as hereinbefore defined in this claim and wherein X is a chlorine, iodine, or bromine, or a fluorosulfonate moiety selected from the group

20 consisting of $-\text{OSO}_2\text{F}$ and $-\text{OSO}_2(\text{CF}_2)_n\text{CF}_3$ wherein n is an integer between 0 and 10,

with a malonate or malonate surrogate of the formula III



- 25 wherein,

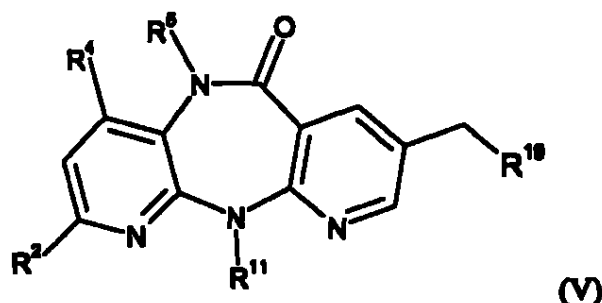
R^{12} is a cyano group or a group of the formula $-\text{COOR}^{14}$, wherein R^{14} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl, and

R^{13} is a cyano group, a group of the formula $-\text{COOR}^{15}$ (wherein R^{14} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl), a group of the formula $-\text{SO}_2\text{R}^{16}$ (wherein R^{16} is a C₁₋₄-alkyl group, phenyl, furyl, pyridyl or benzyl), a group of the formula $-\text{P}(\text{O})(\text{OR}^{17})_2$ (wherein R^{17} is phenyl, furyl or pyridyl) or a group of the formula $-\text{SOR}^{18}$ (wherein R^{18} is a C₁₋₄-alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl),

in an organic solvent, in the presence of a palladium catalyst, a suitable ligand and strong base,

to yield the compound of the formula IV.

3. A process for making a compound of the formula V



wherein:

R^2 is selected from the group consisting of H, F, Cl, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and CF₃;

R^4 is H or Me;

R^5 is H, Me or Et, with the proviso that R^4 and R^5 are not both Me, and if R^4 is Me then R^5 cannot be Et;

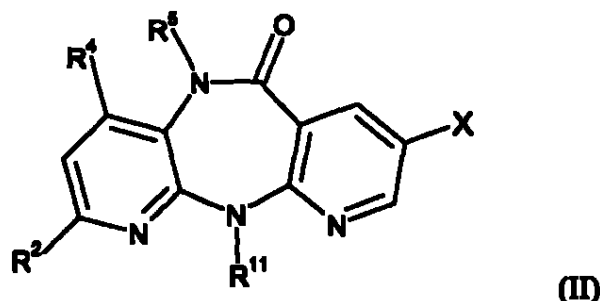
R^{11} is Me, Et, cyclopropyl, propyl, isopropyl, or cyclobutyl; and

R^{19} is $-\text{COOH}$ or a group of the formula $-\text{COOR}^{14}$ wherein R^{14} is a C_{1-4} -alkyl group, a C_{1-4} -alkyloxy- C_{1-4} -alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl;

which process comprises the following steps:

5

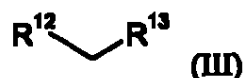
(a) reacting a starting compound of the formula II



10 wherein R^2 , R^4 , R^5 and R^{11} are as hereinbefore defined in this claim and wherein X is a chlorine, iodine, or bromine, or a fluorosulfonate moiety selected from the group consisting of $-\text{OSO}_2\text{F}$ and $-\text{OSO}_2(\text{CF}_2)_n\text{CF}_3$, wherein n is an integer between 0 and 10,

with a malonate or malonate surrogate of the formula III

15



wherein,

R^{12} is a cyano group or a group of the formula $-\text{COOR}^{14}$, wherein R^{14} is a C_{1-4} -alkyl group, a C_{1-4} -alkyloxy- C_{1-4} -alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl, and

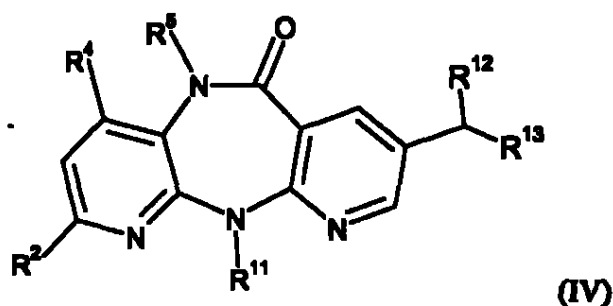
20 R^{13} is a cyano group, a group of the formula $-\text{COOR}^{15}$ (wherein R^{14} is a C_{1-4} -alkyl group, a C_{1-4} -alkyloxy- C_{1-4} -alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl), a group of the formula $-\text{SO}_2\text{R}^{16}$ (wherein R^{16} is a C_{1-4} -alkyl group, phenyl, furyl, pyridyl or benzyl), a group of the formula $-\text{P}(\text{O})(\text{OR}^{17})_2$ (wherein R^{17}

25 is phenyl, furyl or pyridyl) or a group of the formula $-\text{SOR}^{18}$ (wherein R^{18} is a C_{1-4} -alkyl

group, a C-1,4-alkyloxy-C-1,4-alkyl group phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl),

- 5 in an organic solvent, in the presence of a palladium catalyst, a suitable ligand and strong base,

to yield an intermediate of the formula IV



- 10 wherein R^2 , R^4 , R^5 , R^{11} , R^{12} and R^{13} are as hereinbefore defined in this claim;

(b) reductively cleaving the sulfur or phosphorus-containing group, if the intermediate of the formula IV contains a sulfur or phosphorus-containing group (because R^{13} in the reactant of the formula III was a group of the formula $-SO_2R^{15}$ or $-P(O)(OR^{16})_2$); and,

15

(c) hydrolyzing the intermediate of the formula IV to yield the compound of the formula V.

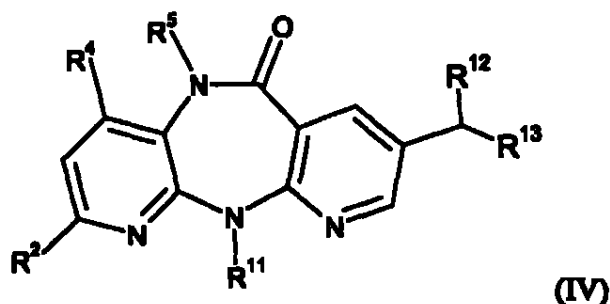
- 20 4. The process according to claim 3, wherein the reactant of the formula III is a malonate and the ligand employed is $t\text{-Bu}_3\text{P}$ or a ferrocenyl phosphine or one of the ligands described and claimed in U.S Patent 6,307,087.

5. The process according to claim 3, wherein the reactant of the formula III is a
25 malonate surrogate and the ligand employed is $t\text{-Bu}_3\text{P}$ a ferrocenyl phosphine or a triarylphosphine.

6. The process of claim 5 wherein the ligand is PPh_3 , o-Tol₃P, p-Tol₃P or o-Fur₃P.

5

7. A compound of the formula IV



wherein:

R^2 is selected from the group consisting of H, F, Cl, C₁₋₄ alkyl, C₃₋₄ cycloalkyl and CF₃;

10 R^4 is H or Me;

R^5 is H, Me or Et, with the proviso that R^4 and R^5 are not both Me, and if R^4 is Me then R^5 cannot be Et;

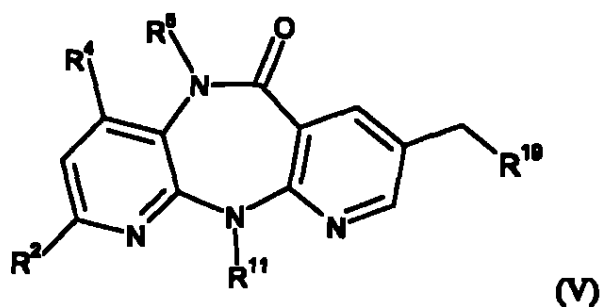
R^{11} is Me, Et, cyclopropyl, propyl, isopropyl, or cyclobutyl;

15 R^{12} is a cyano group or a group of the formula $-\text{COOR}^{14}$, wherein R^{14} is a C₁₋₄ alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl, and

20 R^{13} is a cyano group, a group of the formula $-\text{COOR}^{15}$ (wherein R^{15} is a C₁₋₄ alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl), a group of the formula $-\text{SO}_2\text{R}^{16}$ (wherein R^{16} is a C₁₋₄ alkyl group, phenyl, furyl, pyridyl or benzyl), a group of the formula $-\text{P}(\text{O})(\text{OR}^{17})_2$ (wherein R^{17} is phenyl, furyl or pyridyl) or a group of the formula $-\text{SOR}^{18}$ (wherein R^{18} is a C₁₋₄ alkyl group, a C₁₋₄-alkyloxy-C₁₋₄-alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl, imidazole or benzyl).

25

8. A compound of the formula V



wherein:

R^2 is selected from the group consisting of H, F, Cl, C_{1-4} alkyl, C_{3-4} cycloalkyl and CF_3 ;

R^4 is H or Me;

- 5 R^5 is H, Me or Et, with the proviso that R^4 and R^5 are not both Me, and if R^4 is Me then R^5 cannot be Et;

R^{11} is Me, Et, cyclopropyl, propyl, isopropyl, or cyclobutyl; and

R^{19} is $-COOH$ or a group of the formula $-COOR^{14}$ wherein R^{14} is a C_{1-4} -alkyl group, a C_{1-4} -alkyloxy- C_{1-4} -alkyl group, phenyl, naphthyl, thiophenyl, furyl, pyridyl,

- 10 imidazole or benzyl.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/19415

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/14 //(C07D471/14,243:00,221:00,221:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 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)

CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/028807 A1 (SIMONEAU) 7 March 2002 (2002-03-07) cited in the application scheme 5	1
Y	KOWALCZYK BA: "synthesis of dihalophenylacetic acids using aromatic nucleophilic substitution strategy" SYNTHESIS, vol. 12, 1997, pages 1411-1414, XP002253832 scheme 2 and 3	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"A" document member of the same patent family

Date of the actual completion of the international search

9 September 2003

Date of mailing of the international search report

26/09/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 661 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bakboord, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/19415

46

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002028807 A1	07-03-2002	AU 7037001 A	24-12-2001
		BR 0102377 A	19-02-2002
		WO 0196338 A1	20-12-2001
		CA 2411766 A1	20-12-2001
		CN 1436189 T	13-08-2003
		CZ 20024114 A3	16-04-2003
		EP 1294720 A1	26-03-2003
		NO 20025844 A	05-12-2002

PCT

47

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 9/249PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 03/19415	International filing date (day/month/year) 20/06/2003	(Earliest) Priority Date (day/month/year) 28/06/2002
Applicant BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.		

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

This International Search Report consists of a total of 4 sheets.

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

1. Basis of the report

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

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

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

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

2. ☐ Certain claims were found unsearchable (See Box I).

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

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 36.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

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

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

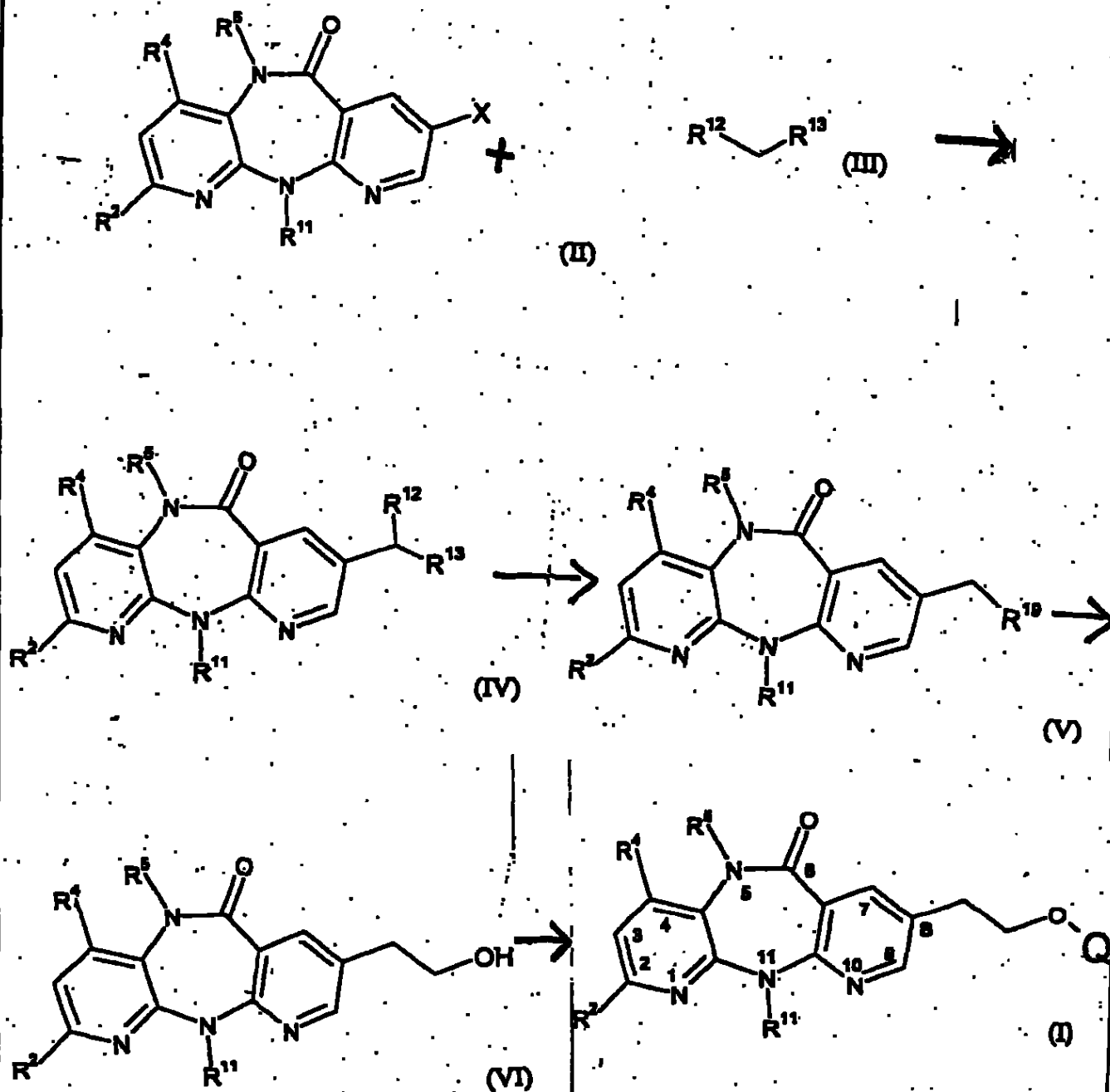
INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 03/19415

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

A process and novel intermediates for making HIV reverse transcriptase inhibitors.



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/19415

49

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/14 //(C07D471/14,243:00,221:00,221:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 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)

CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/028807 A1 (SIMONEAU) 7 March 2002 (2002-03-07) cited in the application scheme 5	1
Y	KOWALCZYK BA: "synthesis of dihalophenylacetic acids using aromatic nucleophilic substitution strategy" SYNTHESIS, vol. 12, 1997, pages 1411-1414, XP002253832 scheme 2 and 3	1

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

Z document member of the same patent family

Date of the actual completion of the international search

9 September 2003

Date of mailing of the international search report

26/09/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5018 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 051 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Bakboord, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/19415

50

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002028807	A1	07-03-2002	
		AU 7037001 A	24-12-2001
		BR 0102377 A	19-02-2002
		WO 0196338 A1	20-12-2001
		CA 2411766 A1	20-12-2001
		CN 1436189 T	13-08-2003
		CZ 20024114 A3	16-04-2003
		EP 1294720 A1	26-03-2003
		NO 20025844 A	05-12-2002

INTERNATIONAL SEARCH REP RT

Information on patent family members

International Application No

PCT/US 03/19415

51

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 2002028807	A1	07-03-2002	AU	7037001 A	24-12-2001
			BR	0102377 A	19-02-2002
			WO	0196338 A1	20-12-2001
			CA	2411766 A1	20-12-2001
			CN	1436189 T	13-08-2003
			CZ	20024114 A3	16-04-2003
			EP	1294720 A1	26-03-2003
			NO	20025844 A	05-12-2002

2. Nucleophilic Substitution of Various Fluorobenzenes with Anion of Ethyl Cyanoacetate

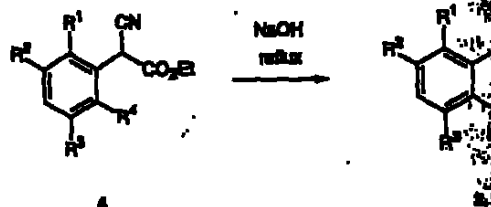
y	Starting Material	Product [Yield (%)]	Product [Yield (%)]
3b		4b (62)	
3c		4c (59.4)	4b (2.7)
3d		4d (63)	
3e		4e (63.5)	4d (1.7)
3f		4f (46)	
3g		4g (32.6)	4h (9.9)
3i		none	

3,5-dihalo fluorobenzenes (entries 1-4) were studied. A total yield of substituted products in these examples are all similar. The nucleophilic substitution of only one fluorine was observed for 3b and 3d both of which had two fluorines available for displacement. The competitive nucleophilic substitution of a small amount of bromine, instead of only fluorine, from 3c and 3e led to a mixture of products for these examples. For 3a, it is of note that nucleophilic substitution of bromine occurred in the presence of a chlorine which was also available.

In addition to 1,3,5-trifluorobenzene (3a) there are two other trifluorobenzene isomers (3f and 3g) both of which were examined (entries 5 and 6, Table 2). These two examples brought up the question of regioselectivity between the three different fluorines of 3f and the two different fluorines of 3g. Only 4f of the three potential products was produced from 3f. The fluorine displaced from 3f is the only fluorine activated by both of the other fluorines (*ortho* and *meta*). For 3g a mixture of 4g and 4h resulted. The two flanking fluorines are activated by both *ortho* and *meta* fluorines but the central fluorine is also activated by two *ortho* fluorines leading to the mixture of products. Nucleophilic substitution of 3i was attempted (entry 7) but no product was observed. It was concluded that under these standard nucleophilic substitution conditions the fluorobenzene must be activated by at least two other halogens.

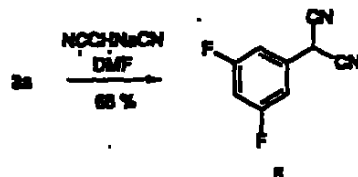
The conversion of ethyl aryloxyacetates 4 into phenylacetic acids 2 is presented in Table 3. The acidic treatment of 4a yielded 2a but in only 72% yield (entry 1). The treatment of 4a with NaOH in water gave 2a in high yield (entry 2). This procedure was adopted for all the

other examples (entries 3-8). The yields were high for making all of the phenylacetic acids.



Scheme 3

Diethyl malonate and malononitrile were substituted with ethyl cyanoacetate in typical nucleophilic substitution experiments with 3a. Diethyl malonate did not give any product, but malononitrile worked as well as ethyl cyanoacetate producing 5 in 66% yield (Scheme 4). Malononitrile 5 was treated with NaOH to yield 2a (entry 9).



Scheme 4

In summary, a process for the nucleophilic aromatic substitution of dihalo fluorobenzenes with the anion of cyanoacetate was developed. The basic decarboxylation of intermediate ethyl dihalophenylacetates yielded dihalophenylacetic acids including 3,5-difluorophenylacetic acid (2a) a key intermediate in the synthesis of the chemically important RS-25560 (1).

All materials were purchased from commercial suppliers without further purification. For the ¹H and ¹³C NMR data *J* values are in Hertz. For the ¹³C NMR spectra resonances were assigned as CH₂, CH, or C based on spectra.

Ethyl Cyano(dihalo phenyl)acetates 4a-k; General Procedure: To a slurry of NaH (0.52 g, 0.013 mol, 60% oil dispersed) (3.0 mL) under a nitrogen atmosphere was slowly added ethyl cyanoacetate (1.46 g, 0.013 mol). The solution was stirred until hydrogen evolution had ceased. In a conical reaction vial was added the NMP anion solution from above with dihalo fluorobenzene 3a-g (0.00439 mol) and then the vial was sealed. The vial was placed in an oil bath maintained at 110-115°C and with a magnetic stir bar for 30 h. The reaction vial was cooled, mixed with water (20 mL) and enough 1 N HCl (7.5 mL) to bring the pH to 3-4. The mixture was extracted 3 times with Et₂O (20 mL). The extracts were combined, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluent: 70% hexanes, 20% CH₂Cl₂, 1% HOAc; v/v/v) to give 4a-k. The yields are listed in Tables 1 and 2.

Ethyl Cyano(3,5-difluorophenyl)acetate (4a): colorless oil. IR (KBr): ν = 1750, 1626, 1601 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 1.31 (t, *J* = 7.1 Hz, 3H), 4.2 (q, *J* = 7.1 Hz, 2H), 4.71 (s, 1H), 6.84-6.91 (m, 1H), 7.00-7.08 (m, 2H).

Table 3. Phenylacetic Acid Formation

Entry	Starting Material	Product	Yield (%)
1 ^a	4a	2a	72
2	4a	2a	99
3	4b	2b	99
4	4c	2c	98
5	4d	2d	97
6	4e	2e	94
7	4f	2f	93
8	4g, 4h	2g, 2h	95
9	5	2a	93

^a Acidic conditions

53

MR (75 MHz, CDCl_3): δ = 13.87 (CH_2), 43.20 (CH), 63.87, 105.07 (t, J_{CF} = 25 Hz, CH), 111.46 (dd, J_{CF} = 18, 9 Hz, 14.61 (C), 133.0 (C), 163.25 (dd, J_{CF} = 251, 12 Hz, C), 163.89

(t): m/z = 225 (M^+).

Calcd for $\text{C}_{11}\text{H}_9\text{F}_2\text{NO}_2$: C, 58.67; H, 4.03; N, 6.22. Found: C, 58.73; H, 4.06; N, 6.58.

(3-Bromo-5-fluorophenyl)cyanoacetate (4b): colorless oil.

IR (KBr): ν = 1750, 1605, 1586 cm^{-1} .

MR (300 MHz, CDCl_3): δ = 1.31 (t, J = 7.1 Hz, 3H), 4.28 (q, 1 Hz, 2H), 4.69 (s, 1H), 7.17 (dm, J = 8.7 Hz, 1H), 7.31 (dm, 9 Hz, 1H), 7.43 (brs, 1H).

1H NMR (75 MHz, CDCl_3): δ = 13.89 (CH_2), 42.92 (CH), 63.92, 114.43 (d, J_{CF} = 23 Hz, CH), 120.30 (d, J_{CF} = 24 Hz, CH), 4 (d, J_{CF} = 10 Hz, C), 127.08 (d, J_{CF} = 3 Hz, CH), 133.29 (d, 9 Hz, C), 162.68 (d, J_{CF} = 253 Hz, C), 163.88 (C).

IR (KBr): ν = 285, 287 (M^+).

Calcd for $\text{C}_{11}\text{H}_9\text{BrFNO}_2$: C, 46.18; H, 3.17; N, 4.90. Found: C, 46.44; H, 3.10; N, 4.98.

(3-Cyano-5-fluorophenyl)acetate (4c): white crystalline solid; mp 70.7–71.2°C (hexanes).

IR (KBr): ν = 1730, 1588, 1564 cm^{-1} .

1H NMR (300 MHz, CDCl_3): δ = 1.32 (t, J = 7.1 Hz, 3H), 4.29 (q, 7.1 Hz, 2H), 4.65 (s, 1H), 7.57 (brs, 2H), 7.72 (dd, J = 1.7, 8.1 Hz).

1H NMR (75 MHz, CDCl_3): δ = 13.91 (CH_2), 42.74 (CH), 63.96, 114.51 (C), 123.76 (C), 129.86 (CH), 133.21 (C), 135.21, 163.87 (C).

IR (KBr): ν = 345, 347, 349 (M^+).

Calcd for $\text{C}_{11}\text{H}_9\text{BrFNO}_2$: C, 38.07; H, 2.61; N, 4.04. Found: C, 38.42; H, 2.59; N, 4.16.

(3-Chloro-5-fluorophenyl)cyanoacetate (4d): colorless oil.

IR (KBr): ν = 1730, 1609, 1595 cm^{-1} .

1H NMR (300 MHz, CDCl_3): δ = 1.31 (t, J = 7.1 Hz, 3H), 4.29 (q, 7.1 Hz, 2H), 4.69 (s, 1H), 7.11–7.17 (m, 2H), 7.28–7.29 (m, 2).

1H NMR (75 MHz, CDCl_3): δ = 13.89 (CH_2), 43.04 (CH), 63.91, 113.95 (d, J_{CF} = 23 Hz, CH), 114.58 (C), 117.40 (d, J_{CF} = 24 Hz, CH), 124.25 (d, J_{CF} = 3 Hz, CH), 133.02 (d, J_{CF} = 9 Hz, C), 136.22 (d, J_{CF} = 11 Hz, C), 162.77 (d, J_{CF} = 252 Hz, C), 163.88 (C).

IR (KBr): ν = 241, 243 (M^+).

Calcd for $\text{C}_{11}\text{H}_9\text{ClFNO}_2$: C, 54.67; H, 3.75; N, 5.80. Found: C, 54.81; H, 3.68; N, 5.88.

(3-Bromo-5-chlorophenyl)cyanoacetate (4e): white crystalline solid; mp 63.1–63.8°C (hexanes).

IR (KBr): ν = 1732, 1590, 1568 cm^{-1} .

1H NMR (300 MHz, CDCl_3): δ = 1.32 (t, J = 7.1 Hz, 3H), 4.29 (q, 7.1 Hz, 2H), 5.16 (s, 1H), 7.41–7.42 (m, 1H), 7.52–7.53 (m, 1H), 7.56–7.57 (m, 1H).

1H NMR (75 MHz, CDCl_3): δ = 13.89 (CH_2), 42.81 (CH), 63.94, 114.52 (C), 123.56 (C), 127.05 (CH), 129.40 (CH), 132.48 (CH), 132.95 (C), 136.10 (C), 163.85 (C).

IR (KBr): ν = 301, 303, 305 (M^+).

Calcd for $\text{C}_{11}\text{H}_9\text{BrClNO}_2$: C, 43.67; H, 3.00; N, 4.63. Found: C, 43.88; H, 2.97; N, 4.67.

Ethyl Cyano(2,3-difluorophenyl)acetate (4f): colorless oil.

IR (KBr): ν = 1752, 1503 cm^{-1} .

1H NMR (300 MHz, CDCl_3): δ = 1.21 (t, J = 7.1 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 5.49 (s, 1H), 7.23–7.34 (m, 3H).

1H NMR (125 MHz, acetone-d_6): δ = 14.10, 38.35, 64.01, 115.58, 117.90 (dd, J_{CF} = 3, 26 Hz), 118.36 (dd, J_{CF} = 9, 24 Hz), 118.69 (dd, J_{CF} = 9, 24 Hz), 121.50 (dd, J_{CF} = 8, 17 Hz), 157.48 (d, J_{CF} = 260 Hz), 159.43 (d, J_{CF} = 253 Hz), 164.78.

IR (KBr): ν = 225 (M^+).

Calcd for $\text{C}_{11}\text{H}_9\text{F}_2\text{NO}_2$: C, 58.67; H, 4.03; N, 6.22. Found: C, 58.73; H, 4.06; N, 6.58.

Ethyl Cyano(2,3-difluorophenyl)acetate (4g) and Ethyl Cyano(2,6-difluorophenyl)acetate (4h): colorless oil. A mixture of 77% 4g and 23% 4h based on ^1H NMR analysis.

IR (KBr): ν = 1752, 1628, 1599 cm^{-1} .

1H NMR (500 MHz, CDCl_3): δ = 1.26 (t, J = 7.1 Hz, 3H, major isomer), 1.26 (t, J = 7.1 Hz, 3H, minor isomer), 4.27–4.32 (m, 2H), 5.63 (s, 1H, major isomer), 5.73 (s, 1H, minor isomer), 7.20 (dd, J = 8.2, 8.2 Hz, 1H, major isomer), 7.32–7.64 (m, 3H (minor isomer), 2H (major isomer)).

1H NMR (125 MHz, acetone-d_6): δ = 14.11 (CH_2), 38.21 (CH), 64.06 (CH_2), 112.92 (d, J_{CF} = 25 Hz, CH), 115.05 (C), 115.65 (C), 119.38 (d, J_{CF} = 17 Hz, CH), 122.25 (C), 126.33 (brs, CH), 133.06 (dd, J_{CF} = 10, 10 Hz, CH), 148.28 (m, C), 151.26 (d, J_{CF} = 250 Hz, C), 151.37 (d, J_{CF} = 248 Hz, C), 164.85 (C).

IR (KBr): ν = 225 (M^+).

Calcd for $\text{C}_{11}\text{H}_9\text{F}_2\text{NO}_2$: C, 58.67; H, 4.03; N, 6.22. Found: C, 58.56; H, 4.09; N, 6.39.

3,5-Difluorophenylmalononitrile (5):

Same as general procedure for 4a–h except malononitrile instead of ethyl cyanoacetate and the chromatography eluent was 50% hexanes, 40% CH_2Cl_2 , 1% HOAc ; v/v/v. White crystalline solid; mp 129.0–129.6°C (CH_2Cl_2 /hexanes).

IR (KBr): ν = 1626, 1603 cm^{-1} .

1H NMR (300 MHz, CDCl_3): δ = 5.09 (s, 1H), 6.98 (t, J = 2.9 Hz, 1H), 7.06–7.14 (m, 2H).

1H NMR (75 MHz, CDCl_3): δ = 27.63 (t, J_{CF} = 2 Hz, CH), 106.42 (t, J_{CF} = 25 Hz, CH), 110.72 (C), 110.98 (dd, J_{CF} = 10, 18 Hz, CH), 129.37 (t, J_{CF} = 10 Hz, C), 163.65 (dd, J_{CF} = 13, 254 Hz, C).

IR (KBr): ν = 178 (M^+).

Calcd for $\text{C}_9\text{H}_5\text{F}_2\text{N}_2$: C, 60.68; H, 2.26; N, 15.73. Found: C, 60.80; H, 2.17; N, 15.77.

Dihalophenylacetic Acids 2a–f: General Procedure:

A mixture of 4a–f (1.1 mmol), NaOH (50%, 0.54 g, 6.8 mmol) and water (4.0 mL) was warmed to 95–100°C for 18 h. The reaction mixture was cooled and enough 1 N HCl (7.2 mL) was added to bring the pH to 2–4. The mixture was extracted twice with EtOAc (15 mL). The extracts were combined, dried (MgSO_4), filtered and concentrated in vacuo to give 2a–f. The yields are listed in Table 3.

3,5-Difluorophenylacetic Acid (2a): white crystalline solid; mp 67.1–68.0°C (hexanes) (lit.⁵ mp 67.6–68.9°C).

IR (KBr): ν = 1698, 1624, 1597 cm^{-1} .

1H NMR (300 MHz, CDCl_3): δ = 3.63 (s, 2H), 6.71–6.79 (m, 1H), 6.80–6.87 (m, 2H).

1H NMR (75 MHz, CDCl_3): δ = 40.16 (CH_2), 102.69 (t, J_{CF} = 25 Hz, CH), 112.14 (dd, J_{CF} = 8, 17 Hz, CH), 136.13 (t, J_{CF} = 10 Hz, C), 162.65 (dd, J_{CF} = 13, 249 Hz, C), 176.37 (C).

Calcd for $\text{C}_9\text{H}_5\text{F}_2\text{O}_2$: C, 55.82; H, 3.51. Found: C, 55.91; H, 3.50.

3-Bromo-5-fluorophenylacetic Acid (2b): white crystalline solid; mp 104.4–105.8°C (hexanes).

IR (KBr): ν = 1694, 1607, 1584 cm^{-1} .

1H NMR (300 MHz, CDCl_3): δ = 3.62 (s, 2H), 6.97 (dm, J = 9 Hz, 1H), 7.18 (ddd, J = 2, 2, 8 Hz, 1H), 7.23–7.24 (m, 1H).

1H NMR (75 MHz, CDCl_3): δ = 40.11 (CH_2), 115.46 (d, J_{CF} = 22 Hz, CH), 118.16 (d, J_{CF} = 24 Hz, CH), 122.53 (d, J_{CF} = 9 Hz, C), 128.33 (d, J_{CF} = 3 Hz, CH), 136.2 (C), 162.44 (d, J_{CF} = 252 Hz, C), 176.39 (C).

IR (KBr): ν = 232, 234 (M^+).

Calcd for $\text{C}_9\text{H}_5\text{BrFO}_2$: C, 41.23; H, 2.60. Found: C, 41.33; H, 2.61.

3,5-Dibromophenylacetic Acid (2c): white crystalline solid; mp 148.0–148.6°C (EtOAc /hexanes).

IR (KBr): ν = 1701, 1588, 1561 cm^{-1} .

5h

¹H NMR (300 MHz, CDCl₃): δ = 3.60 (s, 2H), 7.38 (d, *J* = 1.7 Hz, 3), 7.60 (t, *J* = 1.7 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃): δ = 40.09 (CH₂), 123.07 (C), 131.33 (C), 133.24 (CH), 136.70 (C), 176.37 (C).

MS (EI): *m/z* = 292, 294, 296 (*M*⁺).

cal. Calcd for C₉H₆Br₂O₂: C, 32.69; H, 2.06. Found: C, 32.61; H, 2.03.

Chloro-5-fluorophenylacetic Acid (2d): white crystalline solid; mp 10–79.6°C (hexanes).

¹(KBr): ν = 1701, 1615, 1586 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 3.63 (s, 2H), 6.93 (dm, *J* = 9 Hz, 1H), 7.03 (ddd, *J* = 8, 2, 2 Hz, 1H), 7.08–7.09 (m, 1H).

¹³C NMR (75 MHz, CDCl₃): δ = 40.35 (CH₂), 115.11 (d, *J* = 22 Hz, CH), 115.42 (d, *J*_{CF} = 25 Hz, CH), 125.59 (d, *J* = 3 Hz, CH), 135.18 (d, *J*_{CF} = 10 Hz, C), 136.42 (d, *J*_{CF} = 8 Hz, C), 162.63 (d, *J*_{CF} = 251 Hz, C), 176.51 (C).

MS (EI): *m/z* = 188, 190 (*M*⁺).

cal. Calcd for C₈H₄ClFO₂: C, 50.95; H, 3.21. Found: C, 50.56; H, 3.19.

Bromo-5-chlorophenylacetic Acid (2e): white crystalline solid; mp 10.8–121.5°C (EtOAc/hexanes).

¹(KBr): ν = 1703, 1591, 1566 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 3.60 (s, 2H), 7.23 (dd, *J* = 2, 1 Hz, 1H), 7.34 (dd, *J* = 2, 2 Hz, 1H), 7.45 (dd, *J* = 2, 2 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃): δ = 40.13 (CH₂), 122.83 (C), 128.49 (CH), 130.54 (CH), 130.87 (CH), 135.26 (C), 136.41 (C), 176.29 (C).

MS (EI): *m/z* = 248, 250, 252 (*M*⁺).

cal. Calcd for C₈H₄BrClO₂: C, 38.51; H, 2.42. Found: C, 38.94; H, 2.42.

2,6-Difluorophenylacetic Acid (2f): white crystalline solid; mp 24.1–124.8°C (EtOAc/hexanes) (lit.⁵ mp 125.0–126.0°C).

¹(KBr): ν = 1696, 1501 cm⁻¹.

¹H NMR (300 MHz, CDCl₃/with a small amount of DMSO-*d*₆): δ = 3.57 (d, *J* = 1.4 Hz, 2H), 6.84–7.00 (m, 3H).

¹³C NMR (75 MHz, CDCl₃/with a small amount of DMSO-*d*₆): δ = 34.30 (CH₂), 115.14 (dd, *J*_{CF} = 9, 24 Hz, CH), 116.20 (dd, *J*_{CF} = 9, 25 Hz, CH), 117.96 (dd, *J*_{CF} = 4, 24 Hz, CH), 123.43 (dd, *J*_{CF} = 8, 19 Hz, C), 157.08 (dd, *J*_{CF} = 3, 242 Hz, C), 158.41 (dd, *J*_{CF} = 2, 242 Hz, C), 172.42 (C).

MS (EI): *m/z* = 172 (*M*⁺).

cal. Calcd for C₈H₄F₂O₂: C, 55.82; H, 3.51. Found: C, 55.43; H, 3.48.

Synthesis of 2g and 2h:

same procedure as the synthesis of 2a–f except the starting material was a 77:23 mixture of 4g:4h. The product was a mixture of 77% 2g and 23% 2h determined by ¹H NMR analysis. Three recrystallizations from EtOAc/hexanes yielded a pure sample of 2g.

2,3-Difluorophenylacetic Acid (2g): white crystalline solid; mp 115.8–116.5°C (EtOAc/hexanes) (lit.⁶ mp 115.5–116.9°C).

¹(KBr): ν = 1694, 1495 cm⁻¹.

¹H NMR (300 MHz, CDCl₃/with a small amount of DMSO-*d*₆): δ = 3.68 (d, *J* = 1.5 Hz, 2H), 7.00–7.12 (m, 3H).

¹³C NMR (75 MHz, CDCl₃/with a small amount of DMSO-*d*₆): δ = 34.20 (dd, *J*_{CF} = 2.3, 2.5 Hz, CH₂), 116.09 (d, *J*_{CF} = 3 Hz, CH), 123.93 (dd, *J*_{CF} = 5, 7 Hz, CH), 124.30 (d, *J*_{CF} = 13 Hz, CH), 126.29 (dd, *J*_{CF} = 3, 3 Hz, CH), 149.12 (dd, *J*_{CF} = 13, 248 Hz, C), 150.50 (dd, *J*_{CF} = 13, 247 Hz, C), 172.48 (C).

MS (EI): *m/z* = 172 (*M*⁺).

Anal. Calcd for C₈H₄F₂O₂: C, 55.82; H, 3.51. Found: C, 55.82; H, 3.52.

2,6-Difluorophenylacetic Acid (2h):

¹H NMR (300 MHz, CDCl₃/with a small amount of DMSO-*d*₆): δ = 3.70 (brs, 2H), 6.84–6.93 (m, 2H), 7.17–7.27 (m, 1H) (brs, 1H).

¹³C NMR (75 MHz, CDCl₃/with a small amount of DMSO-*d*₆): δ = 27.83 (t, *J*_{CF} = 3 Hz, CH₂), 110.84–111.22 (m, C, CH), (t, *J*_{CF} = 10 Hz, CH), 161.53 (dd, *J*_{CF} = 8, 248 Hz, C), 172.48 (C).

Synthesis of 2a from 4a under Acidic Conditions:

A mixture of 4a (0.90 mmol) and 6 M HCl (5.0 mL, 30 mmol) warmed to 95–100°C for 18 h. The reaction mixture was cooled to r.t. and extracted twice with EtOAc (10 mL). The extracts combined, dried (MgSO₄), filtered and concentrated in vacuo to give 2a.

Synthesis of 2a from 5:

Same procedure as general procedure for 2a–f except more (30%, 1.52 g, 19 mmol) was used.

- (1) Martinez, G.R.; Gooding, O.W.; Repke, D.B.; Teitelbaum, P.J.; Walker, K.A.M.; Whiting, R.L. U.S. Patent 5,199,617, 1996; *Chem. Abstr.* 1996, 125, 195657.
Martinez, G.R.; Repke, D.B.; Teitelbaum, P.J.; Walker, K.A.M.; Gooding, O.W.; Whiting, R.L.; Bansal, R.P.; Dorf, A.V.; O'Yang, C. Wo. Patent 9529165, 1995; *Chem. Abstr.* 1996, 124, 176166.
Bansal, R.P.; Gooding, O.W.; Muehlendorf, A.V.; Dorf, A.V. U.S. Patent 5438150, 1995; *Chem. Abstr.* 1995, 123, 195657.
- (2) Similar use of a halophenylacetic acid: Tschuen, D.; Ramson, L.; Cai, D.; Desmond, R.; Doffing, U.H.; Kennedy, S.; Shi, Y.; Verhoeven, T.R. *J. Org. Chem.* 1994, 59, 4324.
- (3) Okuro, K.; Furumae, M.; Mihara, M.; Nomura, M.; Sakamoto, T.; Katoh, R.; Kondo, Y.; Yamanaka, H. *Pharm. Bull.* 1988, 36, 1664.
Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* 1984, 937.
Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takai, T. *Synthesis* 1985, 506.
Owaka, A.; Kobayashi, T.; Suzuki, H. *Synthesis* 1983, 1433.
Lindley, J. *Tetrahedron* 1984, 40, 1433.
Filler, R.; Woods, S.M. *Org. Synth.* 1977, 57, 80.
Yakobson, G.O.; Vlasov, V.M. *Synthesis* 1976, 657.
- (4) Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* 1951, 49, 27.
- (5) Sample from Aldrich Chemical Company.
- (6) Sample from Lancaster Synthesis, Inc.

From the INTERNATIONAL BUREAU

PCT**NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES**

(PCT Rule 47.1(c), first sentence)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

08 January 2004 (08.01.2004)

Applicant's or agent's file reference

9/249PCT

IMPORTANT NOTICE

International application No.

PCT/US2003/019415

International filing date (day/month/year)

20 June 2003 (20.06.2003)

Priority date (day/month/year)

28 June 2002 (28.06.2002)

Applicant

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DE, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM

In accordance with Rule 47.1(c), third sentence, 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).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 08 January 2004 (08.01.2004) under No. WO 2004/002989

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

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, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 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>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume IA, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

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

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

Authorized officer

Gijsbertus Beijer - Carlos Roy

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

56

PCT REQUEST

9/249PCT

Original (for SUBMISSION) - printed on 20.06.2003 09:06:09 AM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.04.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	9/249PCT
I	Title of invention	PROCESS AND INTERMEDIATES FOR MAKING NON-NUCLEOSIDE HIV-1 REVERSE TRANSCRIPTASE INHIBITORS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States
II-4	Name	BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
II-5	Address:	900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	203-798-4868
II-9	Facsimile No.	203-798-4408
III-1	Applicant and/or inventor	
III-1-1	This person is:	inventor only
III-1-4	Name (LAST, First)	BUSACCA, Carl, A.
III-1-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America

57

PCT REQUEST

9/249PCT

Original (for SUBMISSION) - printed on 20.08.2003 09:08:09 AM

III-2	Applicant and/or inventor	
III-2-1	This person is:	inventor only
III-2-4	Name (LAST, First)	ERIKSSON, Magnus, C.
III-2-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-3	Applicant and/or inventor	
III-3-1	This person is:	inventor only
III-3-4	Name (LAST, First)	KIM, Ji-Young
III-3-5	Address:	523 Waymarket Drive Ann Arbor, MI 48103 United States of America
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent international Authorities as:	agent
IV-1-1	Name (LAST, First)	RAYMOND, Robert, P.
IV-1-2	Address:	Boehringer Ingelheim Corporation 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
IV-1-3	Telephone No.	203-798-9988
IV-1-4	Facsimile No.	203-798-4408
IV-1-5	Agent's registration No.	25,089
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	DEVLIN, Mary-Ellen, M.(27,928); STEMPEL, Alan, R.(28,991); BOTTINO, Anthony, P.(41,629); FOCCHIARI, Susan, K.(45,016); DATLOW, Philip, I.(41,482); WITKOWSKI, Timothy, X.(40,232); DOW, David, A.(46,124)

58

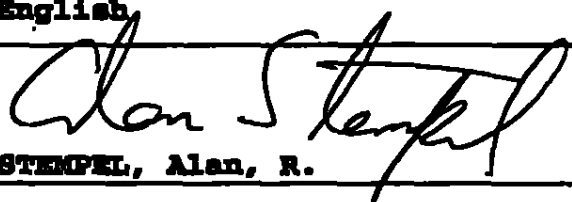
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BE CA CH LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
V-3	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.8(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-4 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 18 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-4	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	28 June 2002 (28.06.2002)
VI-1-2	Number	60/391,979
VI-1-3	Country	US

59

PCT REQUEST

9/249PCT

Original (for SUBMISSION) - printed on 20.06.2003 09:06:09 AM

VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	17 December 2002 (17.12.2002)	
VI-2-2	Number	60/434,052	
VI-2-3	Country	US	
VI-3	Priority document request		
	The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	12	-
IX-3	Claims	10	-
IX-4	Abstract	1	EXABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	28	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	STEMPEL, Alan, R.	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
------	---	--

60

5/5

PCT REQUEST

9/249PCT

Original (for SUBMISSION) - printed on 20.06.2003 09:08:09 AM

10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

PATENT COOPERATION TREATY

61

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

AUG 21 2003

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of AmericaFILE DEMAND LD = 1/28/2004
EJTBMS MAIL PM - 12/28/2004

Date of mailing (day/month/year) 07 August 2003 (07.08.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 9/249PCT	
International application No. PCT/US03/19415	International filing date (day/month/year) 20 June 2003 (20.06.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 28 June 2002 (28.06.02)
Applicant BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(a) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(a) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
28 June 2002 (28.06.02)	60/391,979	US	25 July 2003 (25.07.03)
17 Deca 2002 (17.12.02)	60/434,052	US	28 July 2003 (28.07.03)

received
4/8/03

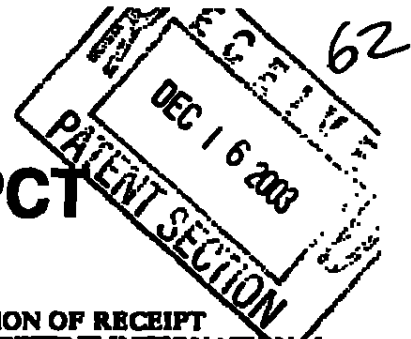
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.95	Authorized officer Alexandre BOUVIER (Fax 338-8995) Telephone No. (41-22) 338 8766
--	--

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMININ AUTHORITY

AKS

PCT



To:

Raymond, Robert P.
BOEHRINGER INGELHEIM CORPORATION
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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

Europe Patent - 12/20/2004

Date of mailing
(day/month/year)

08-12-2003

Applicant's or agent's file reference
9/249PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US 03/ 19415

International filing date (day/month/year)

20/06/2003

Priority date (day/month/year)

28/06/2002

Applicant

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

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

24/11/2003

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the PCT Applicant's Guide, Volume II.

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

received
12/10/03 K

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

Name and mailing address of the IPEA/

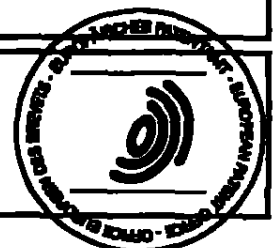


European Patent Office
D-80298 Munich
Tel (+49-89) 2399-0, Tlx 523656 epmu d
Fax (+49-89) 2399-4465

Authorized officer

OBERHAUSER A S

Tel (+49-89) 2399-8139



The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference 9/249PCT	
International application No. PCT/US03/19415	International filing date (day/month/year) 20 Jun 2003
(Earliest) Priority date (day/month/year) 28 Jun 2002	
Title of invention Process and Intermediates for Making Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. 900 Ridgebury Road, P.O. Box 388 Ridgefield, Connecticut USA 08877-0388	
Telephone No. 203-798-9988	
Facsimile No. 203-798-4408	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: US	State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (that is, country) of nationality:	
State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (that is, country) of nationality:	
State (that is, country) of residence:	
☐ Further applicants are indicated on a continuation sheet.	

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

The following person is ☒ agent ☐ common representative
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

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

RAYMOND, Robert P.; STEMPEL, Alan R.; DEVLIN, Mary-Ellen M.;
 BOTTINO, Anthony P.; POCCHIARI, Susan K.; DATLOW, Philip I.;
 WITKOWSKI, Timothy X.; DOW, David A.; MORRIS, Michael P.
 c/o BOEHRINGER INGELHEIM CORPORATION
 900 Ridgebury Road, P.O. Box 388
 Ridgefield, Connecticut 06877-0388 USA

Telephone No.
203-798-9888

Facsimile No.
203/798-4408

Teleprinter No.

Agent's registration No. with the Office

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

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|----------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) Request For Detailed Exam | : | 1 sheets |

For International Preliminary
Examining Authority use only

received not received

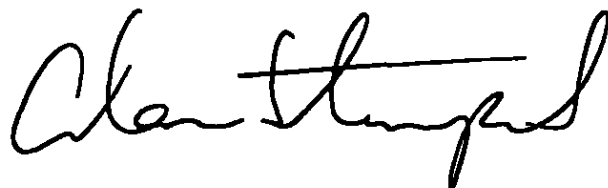
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|---|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☐ copy of general power of attorney;
reference number, if any: | |

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

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



Alan R. Stempel, Agent

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due
to CORRECTIONS under Rule 60.1(b):

- | | |
|--|---|
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | ☐ The applicant has been informed accordingly. |
| 4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5. | |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | |

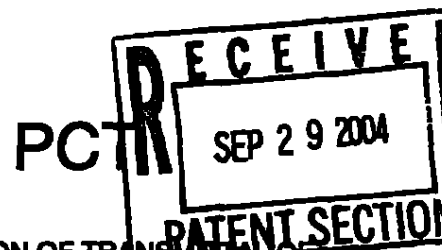
For International Bureau use only

Demand received from IPEA on:

PATENT COÖPERATION TREATY

ARS 66

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



To:

Raymond, Robert P.
BOEHRINGER INGELHEIM CORPORATION
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMISSION OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

ENTRE U.P. - 12.28.04

Date of mailing
(day/month/year)

24.09.2004

Applicant's or agent's file reference
9249PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US 03/19415

International filing date (day/month/year)
20.06.2003

Priority date (day/month/year)
28.08.2002

Applicant

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

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

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

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

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

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

received
9/30/04

Name and mailing address of the international
preliminary examining authority:



European Patent Office
D-80296 Munich
Tel. +49 89 2399 - 0 Tx: 523856 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Hebert, W

Tel. +49 89 2399-2152



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 9/249PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/16)	
International application No. PCT/US 03/19415	International filing date (day/month/year) 20.08.2003	Priority date (day/month/year) 28.06.2002
International Patent Classification (IPC) or both national classification and IPC C07D471/14		
Applicant BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

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

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 68.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 24.11.2003	Date of completion of this report 24.09.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80289 Munich Tel. +49 89 2369 - 0 Tlx 523858 epmu d Fax: +49 89 2369 - 4485	Authorized Officer Bakboord, J Telephone No. +49 89 2369-2168 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/US 03/19415**

I. Basis of the report

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

Description, Pages

1-12 as originally filed

Claims, Numbers

1-8 as originally filed

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

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

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

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

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/US 03/19415**

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

1. Statement

Novelty (N)	Yes: Claims	1-8
	No: Claims	
Inventive step (IS)	Yes: Claims	1-8
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-8
	No: Claims	

2. Citations and explanations

see separate sheet

20

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

V.1 The present application relates to a process and intermediates for the synthesis of dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-ones bearing a 2-(quinolinyl)oxyethyl or a 2-(1-oxido-quinolinyl)oxyethyl group in the 8-position.

V.2 Reference is made to the following documents:

D1: US 20020028807-A, cited in the document

D2: KOWALCZYK BA ET AL: 'SYNTHESIS OF DIHALOPHENYLACETIC ACIDS USING AROMATIC NUCLEOPHILIC SUBSTITUTION STRATEGY', synthesis, vol. 12, 1997, pages 1411-1414.

V.3 Novelty

Document D1 discloses the nucleophilic substitution on a compound of formula II, which leads to the 8-(2-propenyl) derivative. Ozonolysis of the double bond and reduction then leads to a compound of formula IV (Scheme 5).

Document D2 discloses the reaction of a halogenated benzyl ring with a 'malonate type' nucleophile followed by hydrolysis and decarboxylation to give phenyl acetic acids (Scheme 2 and 3).

A process for making a compound of formula I is disclosed in none of the documents. Claim 1 therefore fulfills the requirements of Art 33(2) PCT.

A process for making a compound of formula IV is disclosed in none of the documents. Claim 2 therefore fulfills the requirements of Art 33(2) PCT.

A process for making a compound of formula V is disclosed in none of the documents. Claims 3-6 therefore fulfill the requirements of Art 33(2) PCT.

A compound of formula IV is disclosed in none of the documents. Claim 7 therefore fulfills the requirements of Art 33(2) PCT.

A compound of formula V is disclosed in none of the documents. Claim 8

71

therefore fulfills the requirements of Art 33(2) PCT.

V.4 Inventive step

Starting from document D1 the problem to be solved may be regarded as to how to provide a novel possibly improved process for the synthesis of compounds of formula I. The solution of the applicant resides in replacing the process for the synthesis of a compound of formula VI, (which in document D1 is performed by alkylation of the 8-halide derivative to yield a 8-(2-propenyl) derivative, which after ozonolysis and reduction gives a compound of formula VI), for a nucleophilic replacement with a malonate derivative to yield the 8-('malonate') derivative (formula IV), hydrolysis then gives a compound of formula V, which after reduction gives the compound of formula VI. A nucleophilic replacement of an aromatic halide with a malonate derivative followed by hydrolysis to give an aromatic carboxylic acid is already known from document D2. For a person skilled in the art it would therefore not seem surprising this route can be used to come to compounds of formula VI. Inventive step can therefore not be acknowledged for the present application (Art 33(3) PCT).

Traducción

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)

72

Referencia del expediente del agente o solicitante 9/248PCT	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)
Solicitud Internacional No. PCT/US03/19415	Fecha de presentación internacional (día/mes/año) 20.06.2003	Fecha de prioridad (día/mes/año) 28.06.2002
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07D 471/14		
Solicitante BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.		

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.

2. Este INFORME consta de una total de 5 hojas, incluyendo la portada

☐ Este informe también se acompaña de ANEXOS, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

Estos anexos constan de un total de _____ hojas.

3. Este informe contiene indicaciones relativas a los siguientes aspectos:

I ☒ Fundamentos del Informe

II ☐ Prioridad

III ☐ No se establece concepto relativo a la novedad, nivel inventivo y aplicación industrial

IV ☐ Carencia de unidad de la invención

V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración

VI ☐ Ciertos documentos citados

VII ☐ Ciertos defectos de la solicitud internacional

VIII ☐ Ciertas observaciones respecto a la solicitud internacional

Fecha de presentación de la demanda 24.11.2003	Fecha de terminación de este reporte 24.09.2004
Nombre y dirección de correo de la autoridad encargada del examen preliminar  Oficina Europea de Patentes D-80289 Munich Tel. +49 89 2369 - 0 Tx: 523856 epmu d Fax: +49 89 2369 - 4465	Funcionario Autorizado Bakboord, J Teléfono No. +49 89 2369 2168

Formato PCT/IPEA409 (portada) (julio 1998)

I. Base del Informe

1. Respecto a los elementos de la solicitud internacional: *(Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se refieren en este Informe como "originalmente presentadas" y no se anexan a este Informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17).)*

La descripción, páginas

1-12 como se presentaron originalmente

Las reivindicaciones, números

1-8 como se presentaron originalmente

2. Respecto al lenguaje, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje _____ el cual es:

- ☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).
☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).
☐ el lenguaje de la traducción entregada con propósitos del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier secuencia de nucleótido y/o amino ácidos divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

- ☐ contenido en la solicitud internacional en forma escrita
☐ presentado junto con la solicitud internacional en forma legible por computador
☐ entregado posteriormente a esta Administración en forma legible por computador
☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.
☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. ☐ Las modificaciones han dado como resultado la cancelación de:

- ☐ la descripción, páginas _____.
☐ las reivindicaciones, Nos. _____.
☐ los dibujos, página _____.

5. ☐ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)).

(Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este informe.)

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

Novedad (N)	Reivindicaciones	1-8	SI
	Reivindicaciones		NO
Nivel inventivo (NI)	Reivindicaciones		SI
	Reivindicaciones	1-8	NO
Aplicación industrial (AI)	Reivindicaciones	1-8	SI
	Reivindicaciones		NO

2. Citas y explicaciones (Regla 70.7)

Ver Hoja Separada

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

V.1 La presente solicitud se relaciona con un proceso e intermediarios para la síntesis de dipirido[3,2-b:2',3'-e][1,4]diazepin-6-onas que poseen un grupo 2-(quinolinil)oxietil o un 2-(1-oxido-quinolinil)oxoetil en la posición 8.

V.2 Se hace referencia a los siguientes documentos:

D1: US 20020028807-A, citado en el documento

D2: KOWALCZYK BA ET AL: 'SÍNTESIS DE ÁCIDOS DIHALOFENILACÉTICOS UTILIZANDO UNA ESTRATEGIA DE SUSTITUCIÓN NUCLEOFÍLICA AROMÁTICA', síntesis, vol. 12, 1997, páginas 1411-1414.

V.3 Novedad

El documento D1 revela la sustitución nucleofílica sobre un compuesto de fórmula II, que conlleva a la formación del derivado 8-(2-propenilo). La ozonización del doble enlace y la reducción produce luego un compuesto de fórmula IV (Esquema 5).

El documento D2 revela la reacción de un anillo bencilo halogenado con un nucleófilo del 'tipo malonato' seguido por la hidrólisis y decarboxilación para producir los ácidos fenil acéticos (Esquema 2 y 3).

En ninguno de los documentos ha revelado un proceso para hacer un compuesto de fórmula I. Así, la reivindicación 1 cumple con los requerimientos del Artículo 33(2) del PCT.

En ninguno de los documentos ha revelado un proceso para hacer un compuesto de fórmula IV. Así, la reivindicación 2 cumple con los requerimientos del Artículo 33(2) del PCT.

En ninguno de los documentos ha revelado un proceso para hacer un compuesto de fórmula V. Así, las reivindicaciones 3-6 cumplen con los requerimientos del Artículo 33(2) del PCT.

En ninguno de los documentos se revela el compuesto de fórmula IV. La reivindicación 7 entonces cumple los requerimientos del Artículo 33(2) PCT.

76

En ninguno de los documentos se revela el compuesto de fórmula V. La reivindicación 8 entonces cumple los requerimientos del Artículo 33(2) PCT.

V.4 Nivel Inventivo

Comenzando por el documento D1 el problema a resolver puede considerarse como el de proporcionar un novedoso y posiblemente mejorado proceso para la síntesis de los compuestos de fórmula I. La solución del solicitante se basa en reemplazar el proceso por la síntesis de un compuesto de fórmula VI, (el cual en el documento D1 se realiza por la alquilación de un derivado de 8-haluro para obtener el derivado 8-(2-propenilo), que luego de la ozonólisis y reducción proporciona un compuesto de fórmula VI), para el reemplazo nucleofílico con el derivado de malonato y obtener el derivado de 8-('malonato') (fórmula IV), la hidrólisis luego proporciona un compuesto de fórmula V, el cual luego de la reducción produce un compuesto de fórmula VI. Un reemplazo nucleofílico de un haluro aromático con un derivado de malonato seguido de la hidrólisis para proporcionar un ácido carboxílico que es ya conocido a partir del documento D2. Para una persona versada en la materia no parecería entonces sorprendente que esta ruta pueda ser utilizada para llegar a los compuestos de fórmula VI. De esta forma, no puede reconocerse el nivel inventivo para la presente solicitud (Art 33(3) PCT).

**PROCEDIMIENTOS E INTERMEDIOS PARA PREPARAR INHIBIDORES DE
TRANSCRIPTASA INVERSA DE HIV-1 NO NUCLEÓSIDOS**

5 CAMPO TÉCNICO DE LA INVENCION

La invención se refiere a un procedimiento nuevo y a intermedios nuevos para la síntesis de ciertos inhibidores de transcriptasa inversa no nucleósidos.

ANTECEDENTES DE LA INVENCION

10 La enfermedad conocida como el síndrome de inmunodeficiencia adquirida (SIDA) está causada por el virus de la inmunodeficiencia humana (HIV), particularmente la cepa conocida como HIV-1. Para que el HIV se replique por una célula huésped, la información del genoma viral debe integrarse en el DNA de la célula huésped. Sin embargo, el HIV es un retrovirus, lo que significa que su información
15 genética está en forma de RNA. El ciclo de replicación del HIV, por lo tanto, requiere una etapa de transcripción del genoma viral (RNA) en el DNA. La transcripción del RNA viral en el DNA se logra por una enzima que se ha denominado acertadamente transcriptasa inversa (RT). El virión del HIV incluye una copia de la RT con el RNA viral.

20 La transcriptasa inversa tiene tres funciones enzimáticas conocidas. Actúa como una DNA polimerasa RNA-dependiente, como una ribonucleasa y como una DNA polimerasa DNA-dependiente. Actuando como una DNA polimerasa RNA-dependiente, la RT transcribe una copia de DNA monocatenario del RNA viral. Actuando como una ribonucleasa, la RT destruye el RNA viral original y libera el DNA recientemente producido del RNA original. Finalmente, actuando como una DNA
25 polimerasa DNA-dependiente, la RT hace una segunda cadena de DNA, complementaria, usando la primera cadena de DNA como un modelo. Las dos cadenas forman DNA de cadena doble, que se integra en el genoma de la célula huésped por otra enzima llamada integrasa.

30 Los compuestos que inhiben las funciones enzimáticas de la transcriptasa inversa del HIV-1 inhibirán la replicación del HIV-1 en células infectadas. Tales compuestos son útiles en la prevención o el tratamiento de infección por HIV-1 en sujetos humanos, como se demuestra por inhibidores de RT conocidos tales como 3'-azlodo-3'-desoxitimidina (AZT), 2',3'-didesoxinosina (ddI), 2',3'-didesoxicitidina (ddC),

d4T, 3TC, nevirapina, delavirdina, efavirenz y abacavir, los Inhibidores de RT hasta ahora aprobados como fármacos para uso en el tratamiento de infección por HIV.

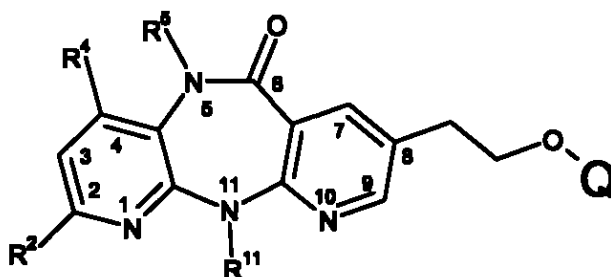
Como con cualquier terapia antiviral, el uso de Inhibidores de RT en el tratamiento de Infección por HIV finalmente conduce a un virus que es menos sensible al fármaco dado. La resistencia (la sensibilidad reducida) a estos fármacos es el resultado de mutaciones que ocurren en el segmento del gen *pol* de la transcriptasa inversa. Se han caracterizado varias cepas mutantes del HIV y la resistencia a agentes terapéuticos conocidos se debe a mutaciones en el gen de la RT. Algunos de los mutantes más comúnmente observados clínicamente son: el mutante Y181C, en el que una tirosina Y, en el codon 181, ha mutado a un residuo cisteína C y K103N, en el que la lisina K en la posición 103 se ha sustituido por asparagina N. Otros mutantes que surgen con creciente frecuencia durante el tratamiento con antivirales conocidos incluyen a los mutantes simples V106A, G190A, Y188C y P238L: y a los mutantes dobles K103N/Y181C, K013N/P225H, K103N/V108I y K103N/L100I.

Como la terapia de infección por HIV que usa antivirales continúa, se espera que aumente la aparición de nuevas cepas resistentes. Hay por lo tanto una necesidad en curso de nuevos inhibidores de RT, con diferentes modelos de eficacia contra los diversos mutantes.

De particular importancia para la presente invención son los Inhibidores de HIV-RT descritos por la patente de EE.UU. N°. 6.420.359. Estos compuestos, que son todos dihidrido[3,2-b:2',3'-e][1,4]diazepin-6-onas que llevan un grupo 2-(quinolinil)oxietilo o un grupo 2-(1-oxido-quinolinil)oxietilo en la posición 8, tienen una actividad realzada contra ciertas cepas mutantes de HIV-1 clínicamente significativas. Es el objeto de la presente invención proporcionar un método alternativo para preparar los compuestos descritos por la patente de EE.UU. N°. 6.420.359.

SUMARIO DE LA INVENCION

La invención proporciona un procedimiento mejorado para hacer los compuestos de la fórmula general I:



(I)

en la que:

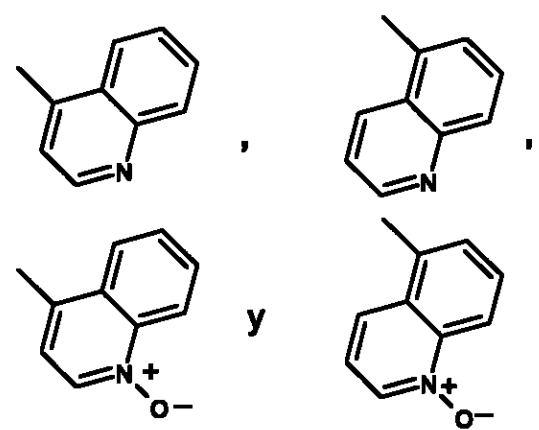
R^2 se selecciona del grupo que consiste en H, F, Cl, alquilo C_{1-4} , cicloalquilo C_3-4 y CF_3 ;

5 R^4 es H o Me;

R^5 es H, Me o Et, con la condición de que R^4 y R^5 no sean ninguno Me y si R^4 es Me entonces R^5 no pueda ser Et;

R^{11} es Me Et, ciclopropilo, propilo, Isopropilo o ciclobutilo; y

Q se selecciona del grupo que consiste en:



10

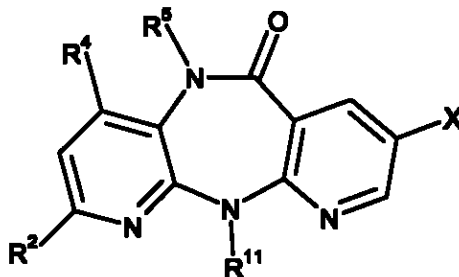
;

así como sus sales farmacéuticamente aceptables.

DESCRIPCIÓN DETALLADA DE LA INVENCION

El método sintético de la invención comienza a partir de un compuesto de partida de la fórmula II

5



(II)

en la que R^2 , R^4 , R^5 y R^{11} son como se define anteriormente en lo que concierne a los compuestos de la fórmula I y en la que X es un cloro, yodo o bromo, o un resto fluorosulfonato seleccionado del grupo que consiste en $-\text{OSO}_2\text{F}$ y $-\text{OSO}_2(\text{CF}_2)_n\text{CF}_3$ en el que n es un número entero entre 0 y 10. Se describen procesos para preparar compuestos de partida de la fórmula II en la que X es bromo en la patente de EE.UU. N°. 6.420.359. Pueden hacerse compuestos en los que X es diferente a bromo por métodos análogos que serán fácilmente evidentes para los expertos en la técnica ordinaria.

15

Se prefiere usar un compuesto de la fórmula II en la que X es bromo.

El compuesto de partida de la fórmula II inicialmente sufre una reacción de acoplamiento catalizada por paladio en la que se lleva a cabo la arilación de un malonato o sustituyente de malonato de la fórmula III

20



(III)

en la que,

R^{12} es un grupo ciano o un grupo de la fórmula $-\text{COOR}^{14}$, en la que R^{14} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo, y

25

R^{13} es un grupo ciano, un grupo de la fórmula $-\text{COOR}^{15}$ (en la que R^{15} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo), un grupo de la fórmula $-\text{SO}_2\text{R}^{16}$ (en la que R^{16} es un grupo alquilo C_{1-4} , fenilo, furilo, piridilo o bencilo), un grupo de la fórmula -

$P(O)(OR^{17})_2$ (en la que R^{17} es fenilo, furilo o piridilo) o un grupo de la fórmula $-SOR^{18}$ (en la que R^{18} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo).

Se prefiere emplear un sustituyente de malonato de la fórmula III

5



en la que,

R^{12} es un grupo ciano o un grupo de la fórmula $-COOR^{14}$, en la que R^{14} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo; y

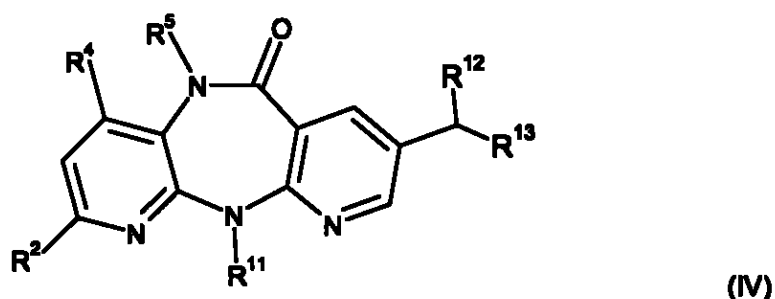
R^{13} es un grupo ciano, un grupo de la fórmula $-SO_2R^{16}$ (en la que R^{16} es un grupo alquilo C_{1-4} , fenilo, furilo, piridilo o bencilo), un grupo de la fórmula $-P(O)(OR^{17})_2$ (en la que R^{17} es fenilo, furilo o piridilo) o un grupo de la fórmula $-SOR^{18}$ (en la que R^{18} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo).

La reacción de los compuestos de las fórmulas II y III tiene lugar en un disolvente orgánico, en presencia de un catalizador de paladio, un ligando adecuado y base fuerte. Disolventes adecuados son, como ejemplo no restrictivo, tolueno, etilbenceno, xileno, DMF, DMA, NMP, dioxano y THF, prefiriéndose tolueno. Puede usarse prácticamente cualquier catalizador de paladio, tales como, por ejemplo, $Pd(OAc)_2$, $PdCl_2$, Pd_2dba_3 y Pd sobre carbono, prefiriéndose $Pd(OAc)_2$. Bases adecuadas son, por ejemplo, los hidruros metálicos tales como, por ejemplo, NaH , los alcóxidos metálicos tales como, por ejemplo, $t-BuOK$, $t-BuONa$ y Na -terc-amilato, los carbonatos metálicos tales como, por ejemplo, Na_2CO_3 , K_2CO_3 y Ca_2CO_3 , prefiriéndose NaH y los fosfatos metálicos tales como, por ejemplo, K_3PO_4 . Cuando el reactivo de la fórmula III es un malonato (compuestos en los que R^{12} y R^{13} son ambos grupos éster de ácido carboxílico) entonces ligandos adecuados serán $T-Bu_3P$, uno de los ligandos descritos y reivindicados en la patente de EE.UU. N°. 6.307.087, o una fosfina de ferrocenilo tal como se describe en la patente de EE.UU. N°. 6.057.456 y patente de EE.UU. N°. 6.072.073. Cuando el reactivo de la fórmula III no es un malonato, sino más bien un sustituyente de malonato (un compuesto en el que R^{12} y R^{13} no son ninguno grupos éster de ácido carboxílico) pueden emplearse los ligandos mencionados anteriormente y, además, también puede emplearse una triarilfosfina tal

como, como ejemplo no restrictivo, PPh_3 , $\text{o-Tol}_3\text{P}$, $\text{p-Tol}_3\text{P}$ y $\text{o-Fur}_3\text{P}$. En tal caso el ligando preferido es PPh_3 .

La reacción preferiblemente se lleva a cabo a temperatura elevada, más preferiblemente en el intervalo entre aproximadamente 50 y 150°C.

- 5 La reacción descrita anteriormente, que acopla los compuestos de las fórmulas II y III, proporciona un intermedio de la fórmula IV

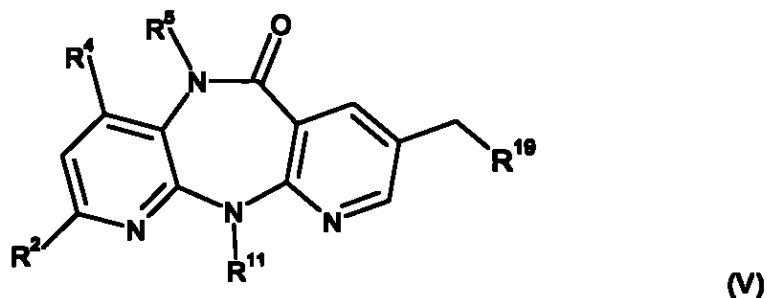


en la que R^2 , R^4 , R^5 , R^{11} , R^{12} y R^{13} son como se definen anteriormente.

- 10 El aislamiento del intermedio de la fórmula IV antes de continuar a la siguiente etapa del procedimiento es opcional. Se ha encontrado que es bastante conveniente una síntesis *in situ* en la que el intermedio IV no se aisle. Si el intermedio IV no se aísla y la base residual es un hidruro metálico, tal como NaH, entonces es aconsejable inactivar la base con un agente tal como alcohol isopropilo antes de continuar a la siguiente etapa.

- 15 Si el intermedio de la fórmula IV contiene azufre o fósforo (porque R^{13} en el reactivo de la fórmula III era un grupo de la fórmula $-\text{SO}_2\text{R}^{16}$ o $-\text{P}(\text{O})(\text{OR}^{16})_2$ entonces la siguiente etapa del procedimiento es una eliminación reductora del grupo que contiene azufre o fósforo. Los métodos para realizar tal eliminación reductora serán bien conocidos para los expertos en la técnica ordinaria. Por ejemplo, esto podría
- 20 lograrse mediante el uso de níquel Raney o de una reacción de metal en disolución.

Subsecuente a la eliminación reductora o, si el intermedio de la fórmula IV no contiene azufre o fósforo, se hidroliza después el intermedio de la fórmula IV para proporcionar un intermedio más de la fórmula V

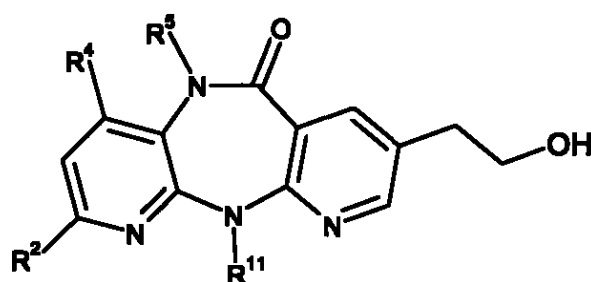


en la que R^2 , R^4 , R^6 y R^{11} son como se define anteriormente y R^{10} es $-\text{COOH}$ o, si el reactivo de fórmula III fuera un malonato y se emplean condiciones de hidrólisis suaves, R^{10} puede además ser un grupo de la fórmula $-\text{COOR}^{14}$ en la que R^{14} es como se describe anteriormente. La hidrólisis puede realizarse de una manera que será convencional y fácilmente evidente para los expertos en la técnica ordinaria. Por ejemplo, puede lograrse usando una base acuosa, tal como NaOH , preferiblemente a temperatura ambiente o mayor.

Los intermedios de las fórmulas IV y la V se cree que son nuevos y constituyen una parte de la invención.

Se prefiere el aislamiento del Intermedio V antes de continuar a la siguiente etapa.

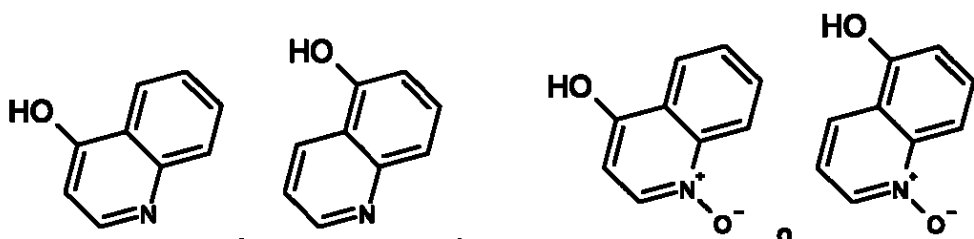
Después, el Intermedio de ácido carboxílico o de éster de la fórmula V se reduce para proporcionar un alcohol de la fórmula VI



(VI)

en la que R^2 , R^4 , R^6 y R^{11} son como se define anteriormente. La reducción se lleva a cabo de una manera convencional que será fácilmente evidente para los expertos en la técnica ordinaria. Independientemente de si el intermedio de la fórmula V es un ácido o un éster, la reducción puede lograrse usando boranos, borohidruros u otros hidruros metálicos o disolviendo reductores de metal, prefiriéndose boranos para los ácidos y prefiriéndose borohidruros para los ésteres. Si se va a emplear un borano se prefiere hacerlo *in situ* a partir de un borohidruro, tal como borohidruro de sodio y un reactivo electrofílico tal como, por ejemplo, HCl .

Finalmente, el alcohol de la fórmula VI se convierte al producto final de la fórmula I por una reacción de condensación con un reactivo de la fórmula



25

Esta condensación puede lograrse de la manera descrita en la patente de EE.UU. N°. 6.420.359.

La naturaleza y el alcance de la invención se apreciarán mejor a partir de los ejemplos siguientes.

5

Ejemplo 1: Atilación de malononitrilo: Formación del compuesto de fórmula IV en el que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} =$ etilo y $R^{12} = R^{13} = CN$.

Se cargó un matraz con 10,0 g de bromuro tricíclico (el compuesto de fórmula II en el que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} =$ etilo y $X = Br$; 30 mmol, 1 eq.), 0,95 g de trifenilfosfina (3,6 mmol, 0,12 eq.), 0,55 g de Pd_2dba_3 (0,6 mmol, 0,04 eq.) y 40 ml de 1,4-dioxano. A esta mezcla después se añadió 2,16 g de hidruro de sodio (90 mmol, 3 eq.) en porciones durante 15 minutos, usando 40 ml de 1,4-dioxano para completar la adición. Después se añadió una solución de 2,57 g de malononitrilo (39 mmol, 1,3 eq.) en 5 ml de 1,4-dioxano y se calentó la mezcla a 90°C. Después de 18 horas la mezcla se enfrió a temperatura ambiente y se inactivó con precaución con 100 ml de solución de cloruro de amonio saturado. Después se ajustó el pH a 6 con HCl 1N y se extrajo la mezcla con diclorometano. Se secó la solución orgánica (sulfato de magnesio) y se eliminaron los disolventes al vacío para dar 7,03 g (73%) del producto como un aceite marrón. RMN y MS mostraron el producto deseado (compuesto de fórmula IV en el que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} =$ etilo y $R^{12} = R^{13} = CN$).

20

Ejemplo 2: Atilación de dietilmalonato: Formación del compuesto de fórmula IV en el que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} =$ etilo y $R^{12} = R^{13} = CO_2Et$.

Un matraz de 500 ml de fondo redondo de dos bocas equipado con agitador mecánico, condensador de reflujo y termopar se purgó con argón durante 20 minutos, después se cargaron 404 mg de $Pd(OAc)_2$ (1,80 mmol, 0,03 eq.), 1,08 g de 2-(di-*t*-butilfosfino) bifenilo (3,60 mmol, 0,06 eq.) y 20,0 g de bromuro tricíclico (compuesto de la fórmula II en la que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} =$ etilo y $X = Br$); (60,0 mmol, 1 eq.). A esta mezcla en un matraz en atmósfera inerte después se añadió 25,5 g de K_3PO_4 (120 mmol, 2 eq.), 100 ml de PhMe y se añadieron después 13,8 ml de dietilmalonato (90,0 mmol, 1,5 eq.). La suspensión agitada se colocó en un baño de aceite y se calentó a reflujo en nitrógeno durante 24 horas hasta que el bromuro se consumió por HPLC. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con agua (150 ml) y se añadió tolueno (50 ml). La mezcla se agitó durante 1 hora a temperatura ambiente hasta que todos los sólidos se habían disuelto. La solución de dos fases

25

30

35

después se transfirió a un embudo separador y se separaron las capas. La capa acuosa se extrajo con tolueno (50 ml). Las capas orgánicas combinadas se filtraron a través de una almohadilla de Celite y se concentraron al vacío para dar un aceite viscoso, que se evaporó hasta secado para formar un sólido naranja. La cromatografía de gel de sílice (1:1 EtOAc:Hex) proporcionó 20,5 g de aducto de malonato puro (compuesto de fórmula IV en la que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} = \text{etilo}$ y $R^{12} = R^{13} = CO_2Et$), (83%), como un sólido incoloro, p.f. 122-123°C; RMN 1H (400 MHz, $CDCl_3$) δ : 8,38 (d, $J = 2,5$ Hz, 1H), 8,19 (dd, $J = 1,5, 4,6$ Hz, 1H), 8,16 (d, $J = 2,4$ Hz, 1H), 7,47 (dd, $J = 1,5, 8,0$ Hz, 1H), 7,09 (dd, $J = 4,7, 8,0$ Hz, 1H), 4,56 (s, 1H), 4,20 (m, 6H), 3,49 (s, 3H), 1,25 (t, $J = 7,1$ Hz, 9H). RMN ^{13}C (100 MHz, $CDCl_3$) δ : 167,30 (s), 167,23 (s), 159,31 (s), 154,50 (s), 151,18 (d), 144,34 (d), 141,93 (d), 131,63 (s), 130,74 (d), 123,52 (s), 120,57 (s), 119,78 (d), 62,17 (t), 54,80 (d), 41,24 (t), 37,30 (q), 13,96 (q), 13,58 (q). Análisis calculado para $C_{21}H_{24}N_4O_8$: C, 61,15; H, 5,87; N, 13,58. Encontrado: C, 61,14; H, 5,66; N, 13,51.

15

Ejemplo 3: Arilación de Isopropilcianoacetato y formación del compuesto de fórmula V en el que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} = \text{etilo}$ y $R^{10} = CO_2H$.

Se cargó un reactor esterilizado de 800 l con 12,0 kg de 60% de NaH/aceite (300 mol, 2,5 eq.), 0,27 kg de $Pd(OAc)_2$ (1,2 mol, 0,01 eq.), 1,26 kg de PPh_3 (4,8 mol, 0,04 eq.) y 40 kg de bromuro tricíclico (el compuesto de fórmula II en el que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} = \text{etilo}$ y $X = Br$; 120 mol, 1 eq.). El reactor se esterilizó de nuevo, después se cargaron 70 kg de PhMe y se calentó la mezcla a 60°C. A esta mezcla después se añadió una solución de 17,4 l de clanoisopropilacetato (138 mol, 1,15 eq.) en 20 l de PhMe vía bomba dosificadora a una velocidad fija durante 2 horas (Precaución: desprendimiento de gas H_2). El contenido del reactor después se calentó a 100°C y se mantuvo así durante 1,5 horas. El HPLC de una alícuota mostró que la arilación era completa para el compuesto de fórmula IV en la que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} = \text{etilo}$, $R^{12} = CN$ y $R^{13} = CO_2IPr$. La mezcla después se enfrió a 35°C y se inactivó por la adición de 19 kg de Isopropanol (308 mol, 2,6 eq.) durante 20 minutos (Precaución: desprendimiento de gas H_2). Después se añadió 438 kg de solución de NaOH 1M (417 mol, 3,5 eq.) y se calentó la mezcla a 80°C y se mantuvo así durante 8 horas. El HPLC de una alícuota mostró que la hidrólisis era completa para el ácido carboxílico deseado. La mezcla se enfrió a 25°C y se separaron las fases. La fase superior se desechó, mientras que la fase acuosa inferior se devolvió al reactor. Después se cargaron 218 kg de EtOAc y se agitó la mezcla durante 15 minutos,

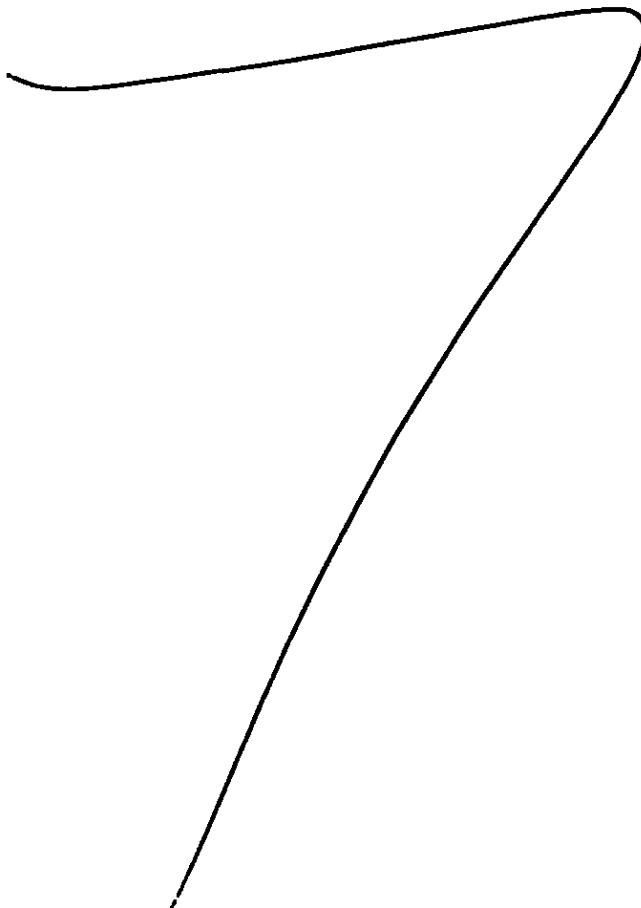
después se dejó que se separaran las fases. La fase acuosa inferior se devolvió al reactor y se enfrió a 10°C. A esta mezcla después se añadió lentamente H₂SO₄ 6 N con monitorización continua del pH hasta que se alcanzó un pH final de 3,3: esto requirió 133 kg de solución de H₂SO₄. La mezcla resultante después se calentó a 25°C y se mantuvo así durante 1 hora. El lote después se centrifugó y se lavó dos veces con 40 kg de H₂O. El sólido después se secó completamente al vacío a 40°C hasta LOD < 1% para dar 36,0 kg del ácido carboxílico (compuesto de fórmula V en el que R²= R⁴= H, R⁵= Me, R¹¹= etilo y R¹⁸= CO₂H; 96%), como un sólido blanco. P.f. 226-228°C; RMN ¹H (500 MHz, DMSO) δ: 12,47 (s, 1H), 8,32 (d, J= 2,0 Hz, 1H), 8,20 (dd, J= 4,6, 1,5 Hz, 1H), 7,96 (d, J= 2,3 Hz, 1H), 7,81 (dd, J= 8,0, 1,6 Hz, 1H), 7,24 (m, J= 4,6, 8,0 Hz, 1H), 4,08 (q, J= 7,0 Hz, 2H), 3,63 (s, 3H), 3,43 (s, 3H), 1,17 (t, J= 7,0 Hz, 3H). RMN ¹³C (125 MHz, DMSO) δ: 172,22 (s), 168,26 (s), 157,47 (s), 153,96 (s), 151,32 (d), 144,06 (d), 141,59 (d), 131,72 (d), 131,14 (s), 126,01 (s), 120,28 (d), 120,12 (s), 40,45 (t), 36,74 (q), 36,34 (t), 13,42 (q). Análisis calculado para C₁₆H₁₆N₄O₃: C, 61,53; H, 5,16; N, 17,94. Encontrado: C, 61,28; H, 4,94; N, 17,56.

Ejemplo 4: Arilación de acetato de metilfenilsulfonilo: Formación del compuesto de fórmula IV en el que R²= R⁴= H, R⁵= Me, R¹¹= etilo, R¹²= CO₂Me y R¹³= SO₂Ph.

Se cargó un matraz con 165 mg de Pd₂dba₃ (0,18 mmol, 0,02 eq.), 577 mg de trifenilfosfina (2,2 mmol, 0,12 eq.) y 45 ml de 1,4-dioxano. Después de agitar en una atmósfera inerte durante 15 minutos, se añadió 647 mg de NaH (27 mmol, 3 eq.) en porciones. A esta mezcla después se añadió 3,00 g de bromuro tricíclico (el compuesto de fórmula II en el que R²= R⁴= H, R⁵= Me, R¹¹= etilo y X= Br; 9,00 mmol, 1 eq.), seguido de 2,50 g (11,7 mmol, 1,3 eq.) de acetato metilfenilsulfonil. La mezcla después se calentó a 60°C durante 18 horas, se enfrió a temperatura ambiente y se inactivó por la adición de 0,5 ml de H₂O. Se eliminó el dioxano al vacío para dar el producto bruto como un sólido gris, 3,5 g (~90%). RMN y MS indicaron el producto de arilación deseado (compuesto de fórmula IV en el que R²= R⁴= H, R⁵= Me, R¹¹= etilo, R¹²= CO₂Me y R¹³= SO₂Ph).

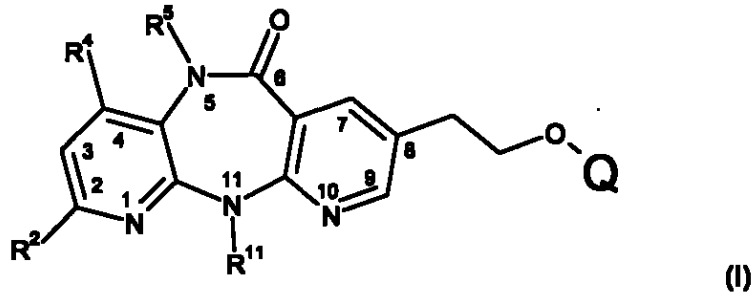
Ejemplo 5: Arilación de dietilfosfonil acetonitrilo: Formación del compuesto de fórmula IV en el que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} = \text{etilo}$, $R^{12} = CN$ y $R^{13} = P(O)(OEt)_2$.

- Se cargó un matraz con 1,00 g de bromuro tricíclico (el compuesto de fórmula II en el que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} = \text{etilo}$ y $X = Br$; 3,00 mmol, 1 eq.), 55 mg de Pd_2dba_3 (0,06 mmol, 0,02 eq.), 95 mg de trifenilfosfina (0,36 mmol, 0,12 eq.) y 0,69 g de dietilfosfonil acetonitrilo (3,90 mmol, 1,3 eq.). A esta mezcla después se añadió 15 ml de 1,4-dioxano, seguido por 216 mg de NaH (9,00 mmol, 3 eq.). La mezcla resultante después se calentó a 70°C durante tres horas. La mezcla se enfrió a temperatura ambiente y se inactivó por la adición cautelosa de 25 ml de H_2O y se añadió 20 ml de diclorometano. Después se ajustó el pH a 2,5 con HCl 1N ac. y se diluyó con H_2O adicional (25 ml) y diclorometano (25 ml). Las fases después se separaron y la fase orgánica se concentró en un aceite marrón. El aceite después se trituró con 10 ml de t-butil-metil-éter para dar un precipitado del producto, que se filtró para dar 0,95 g de producto como un sólido blanco. RMN y MS indicaron el producto de arilación deseado (compuesto de fórmula IV en el que $R^2 = R^4 = H$, $R^5 = Me$, $R^{11} = \text{etilo}$, $R^{12} = CN$ y $R^{13} = P(O)(OEt)_2$).



REIVINDICACIONES

1. Un procedimiento para preparar un compuesto de la fórmula I:



5 en la que:

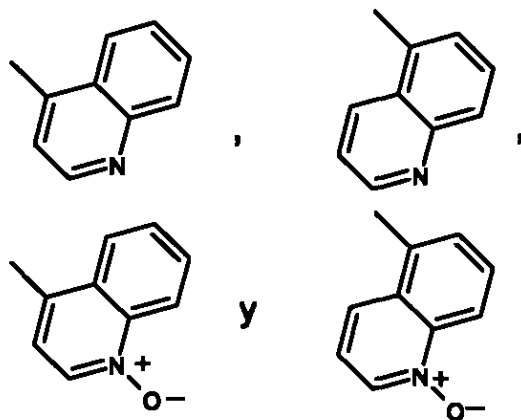
R^2 se selecciona del grupo que consiste en H, F, Cl, alquilo C_{1-4} , cicloalquilo C_3-4 y CF_3 ;

R^4 es H o Me;

10 R^5 es H, Me o Et, con la condición de que R^4 y R^5 no sean ninguno Me y si R^4 es Me entonces R^5 no pueda ser Et;

R^{11} es Me, Et, ciclopropilo, propilo, isopropilo o ciclobutilo; y

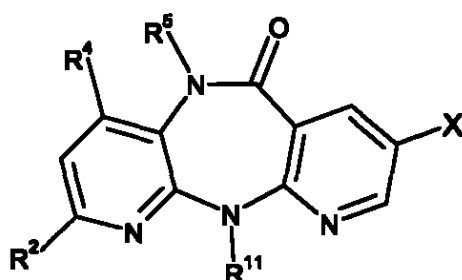
Q se selecciona del grupo que consiste en



15

procedimiento que comprende las etapas siguientes:

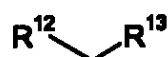
(a) hacer reaccionar un compuesto de partida de la fórmula II



(II)

en la que R², R⁴, R⁵ y R¹¹ son como se define anteriormente en lo que concierne al compuesto de la fórmula I y en la que X es un cloro, yodo o bromo, o un resto fluorosulfonato seleccionado del grupo que consiste en -OSO₂F y -OSO₂(CF₂)_nCF₃ en el que n es un número entero entre 0 y 10,

con un malonato o sustituyente de malonato de la fórmula III



(III)

10 en la que,

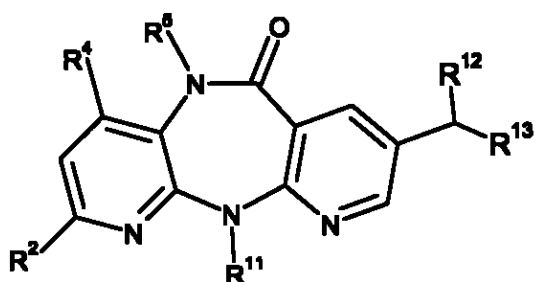
R¹² es un grupo ciano o un grupo de la fórmula -COOR¹⁴, en la que R¹⁴ es un grupo alquilo C₁₋₄, un grupo alquilo C₁₋₄, un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo, y

R¹³ es un grupo ciano, un grupo de la fórmula -COOR¹⁵ (en la que R¹⁵ es un grupo alquilo C₁₋₄, un grupo alquilo C₁₋₄, un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo), un grupo de la fórmula -SO₂R¹⁶ (en la que R¹⁶ es un grupo alquilo C₁₋₄, fenilo, furilo, piridilo o bencilo), un grupo de la fórmula -P(O)(OR¹⁷)₂ (en la que R¹⁷ es fenilo, furilo o piridilo) o un grupo de la fórmula -SOR¹⁸ (en la que R¹⁸ es un grupo alquilo C₁₋₄, un grupo alquilo C₁₋₄, un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo),

20 en un disolvente orgánico, en presencia de un catalizador de paladio, un ligando adecuado y base fuerte,

para proporcionar un intermedio de la fórmula IV

14

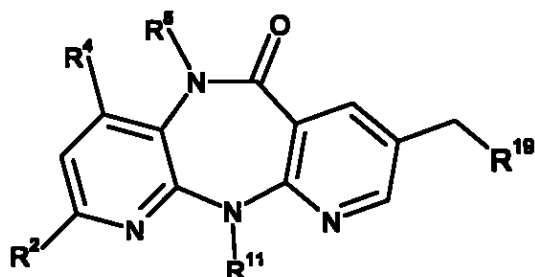


(IV)

en la que R², R⁴, R⁵, R¹¹, R¹² y R¹³ son como se define anteriormente en esta reivindicación;

(b) eliminar por reducción el grupo que contiene azufre o fósforo, si el intermedio de la fórmula IV contiene un grupo que contiene azufre o fósforo;

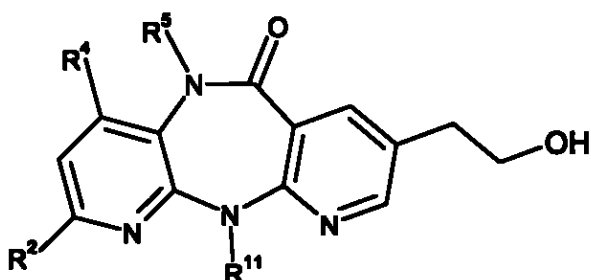
(c) hidrolizar el intermedio de la fórmula IV para proporcionar un intermedio más de la fórmula V



(V)

en la que R², R⁴, R⁵ y R¹¹ son como se define anteriormente en esta reivindicación y R¹⁹ es -COOH o, si el reactivo de la fórmula III fuera un malonato y se emplean condiciones de hidrólisis suaves, en la que R¹⁹ además puede ser un grupo de la fórmula -COOR¹⁴ en la que R¹⁴ es como define anteriormente en esta reivindicación;

(d) reducir el intermedio de ácido carboxílico o de éster de la fórmula V para proporcionar un alcohol de la fórmula VI

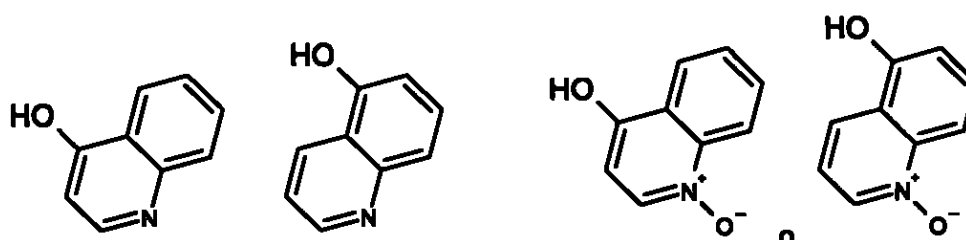


(VI)

en la que R², R⁴, R⁵ y R¹¹ son como se define anteriormente en esta reivindicación; y

(e) condensar el alcohol de fórmula VI con un reactivo de la fórmula

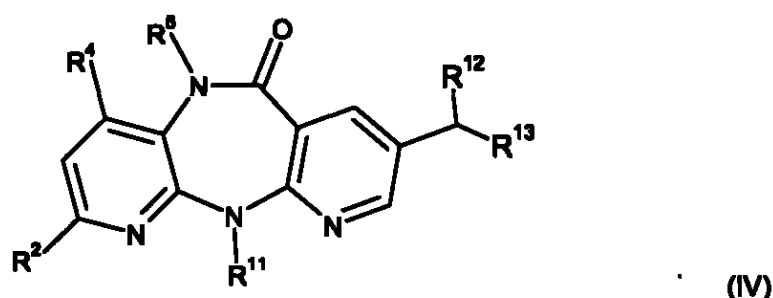
15



para proporcionar el producto final de la fórmula I.

5

2. Un procedimiento para preparar un compuesto de la fórmula IV



en la que:

10 R^2 se selecciona del grupo que consiste en H, F, Cl, alquilo C_{1-4} , cicloalquilo C_3-4 y CF_3 .

R^4 es H o Me,

R^5 es H, Me o Et, con la condición de que R^4 y R^5 no sean ninguno Me y si R^4 es Me entonces R^5 no pueda ser Et,

15 R^{11} es Me, Et, ciclopropilo, propilo, isopropilo o ciclobutilo,

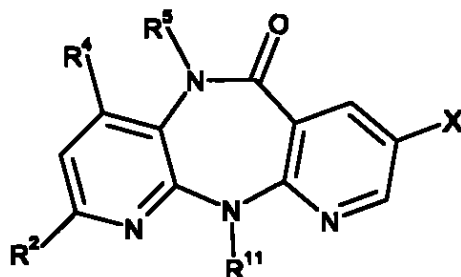
R^{12} es un grupo ciano o un grupo de la fórmula $-COOR^{14}$, en la que R^{14} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo, y

20 R^{13} es un grupo ciano, un grupo de la fórmula $-COOR^{16}$ (en la que R^{16} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo), un grupo de la fórmula $-SO_2R^{18}$ (en la que R^{18} es un grupo alquilo C_{1-4} , fenilo, furilo, piridilo o bencilo), un grupo de la fórmula $-P(O)(OR^{17})_2$ (en la que R^{17} es fenilo, furilo o piridilo) o un grupo de la fórmula $-SOR^{18}$ (en la que R^{18} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo),

25

procedimiento que comprende las etapas siguientes:

- (a) hacer reaccionar un compuesto de partida de la fórmula II



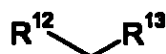
(II)

5

en la que R^2 , R^4 , R^5 y R^{11} son como se define anteriormente en esta reivindicación y en la que X es un cloro, yodo o bromo, o un resto fluorosulfonato seleccionado del grupo que consiste en $-\text{OSO}_2\text{F}$ y $-\text{OSO}_2(\text{CF}_2)_n\text{CF}_3$, en el que n es un número entero entre 0 y 10,

10

con un malonato o sustituyente de malonato de la fórmula III



(III)

en la que,

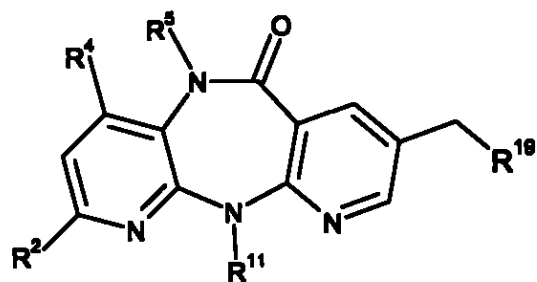
- 15 R^{12} es un grupo ciano o un grupo de la fórmula $-\text{COOR}^{14}$, en la que R^{14} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo, y

- 20 R^{13} es un grupo ciano, un grupo de la fórmula $-\text{COOR}^{15}$ (en la que R^{15} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo), un grupo de la fórmula $-\text{SO}_2\text{R}^{16}$ (en la que R^{16} es un grupo alquilo C_{1-4} , fenilo, furilo, piridilo o bencilo), un grupo de la fórmula $-\text{P}(\text{O})(\text{OR}^{17})_2$ (en la que R^{17} es fenilo, furilo o piridilo) o un grupo de la fórmula $-\text{SOR}^{18}$ (en la que R^{18} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo),

- 25 en un disolvente orgánico, en presencia de un catalizador de paladio, un ligando adecuado y base fuerte,

para proporcionar el compuesto de fórmula IV.

3. Un procedimiento para preparar un compuesto de la fórmula V



(V)

en la que:

R^2 se selecciona del grupo que consiste en H, F, Cl, alquilo C_{1-4} , cicloalquilo C_3-

5 4 y CF_3 ;

R^4 es H o Me;

R^5 es H, Me o Et, con la condición de que R^4 y R^5 no sean ninguno Me y si R^4 es Me entonces R^5 no pueda ser Et;

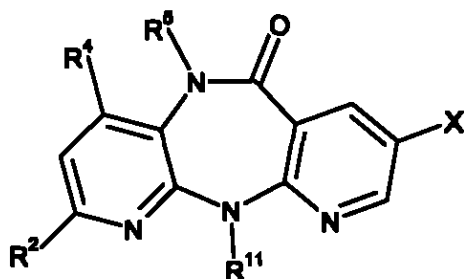
R^{11} es Me, Et, ciclopropilo, propilo, isopropilo o ciclobutilo; y

10 R^{19} es $-COOH$ o un grupo de la fórmula $-COOR^{14}$ en la que R^{14} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo;

procedimiento que comprende las etapas siguientes:

(a) hacer reaccionar un compuesto de partida de la fórmula II

15



(II)

en la que R^2 , R^4 , R^5 y R^{11} son como se define anteriormente en esta reivindicación y en la que X es un cloro, yodo o bromo, o un resto fluorosulfonato seleccionado del grupo que consiste en $-OSO_2F$ y $-OSO_2(CF_2)_nCF_3$ en el que n es un número entero entre 0 y 10,

20

con un malonato o sustituyente de malonato de la fórmula III



en la que,

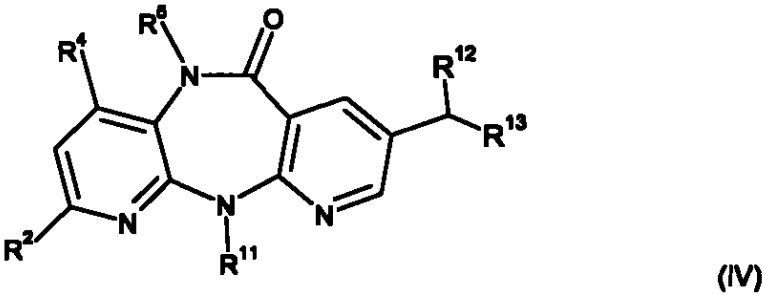
- 5
- R^{12} es un grupo clavo o un grupo de la fórmula $-\text{COOR}^{14}$, en la que R^{14} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo, y

R^{13} es un grupo clavo, un grupo de la fórmula $-\text{COOR}^{15}$ (en la que R^{15} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo), un grupo de la fórmula $-\text{SO}_2\text{R}^{16}$ (en la que R^{16} es un grupo alquilo C_{1-4} , fenilo, furilo, piridilo o bencilo), un grupo de la fórmula $-\text{P}(\text{O})(\text{OR}^{17})_2$ (en la que R^{17} es fenilo, furilo o piridilo) o un grupo de la fórmula $-\text{SOR}^{18}$ (en la que R^{18} es un grupo alquilo C_{1-4} , un grupo alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo),

10

en un disolvente orgánico, en presencia de un catalizador de paladio, un ligando adecuado y base fuerte,

para proporcionar un intermedio de la fórmula IV



- 20
- en la que R^2 , R^4 , R^8 , R^{11} , R^{12} y R^{13} son como se define anteriormente en esta reivindicación;

(b) eliminar por reducción el grupo que contiene azufre o fósforo, si el intermedio de la fórmula IV contiene un grupo que contiene azufre o fósforo (porque R^{13} en el reactivo de la fórmula III era un grupo de la fórmula $-\text{SO}_2\text{R}^{16}$ o $-\text{P}(\text{O})(\text{OR}^{16})_2$); y,

25

(c) hidrolizar el intermedio de la fórmula IV para proporcionar el compuesto de fórmula V.

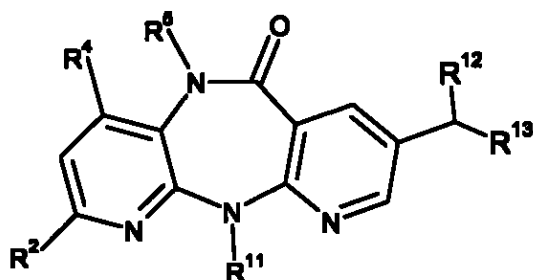
95

4. El procedimiento de acuerdo con la reivindicación 3, en el que el reactivo de la fórmula III es un malonato y el ligando empleado es T-Bu₃P o una ferrocenil fosfina o uno de los ligandos descritos y reivindicados en la patente de EE.UU. N°. 6.307.087.

5 El procedimiento de acuerdo con la reivindicación 3, en el que el reactivo de la fórmula III es un sustituyente de malonato y el ligando empleado es T-Bu₃P, una ferrocenil fosfina o una triarilfosfina.

6. El procedimiento de la reivindicación 5 en el que el ligando es PPh₃, o-Tol₃P, p-Tol₃P u o-Fur₃P.

7. Un compuesto de la fórmula IV



(IV)

en la que:

15 R² se selecciona del grupo que consiste en H, F, Cl, alquilo C₁₋₄, cicloalquilo C₃₋₄ y CF₃;

R⁴ es H o Me;

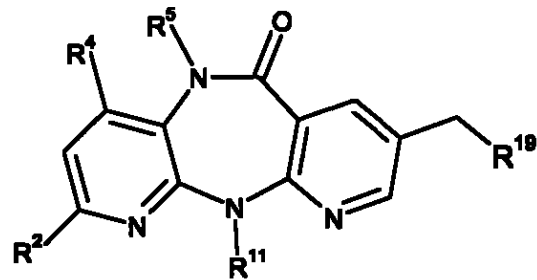
R⁶ es H, Me o Et, con la condición de que R⁴ y R⁶ no sean ninguno Me y si R⁴ es Me entonces R⁶ no pueda ser Et;

20 R¹¹ es Me, Et, ciclopropilo, propilo, isopropilo o ciclobutilo;

R¹² es un grupo clavo o un grupo de la fórmula -COOR¹⁴, en la que R¹⁴ es un grupo alquilo C₁₋₄, un grupo alquilo C₁₋₄-alquilo C₁₋₄, un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo, y

25 R¹³ es un grupo clavo, un grupo de la fórmula -COOR¹⁶ (en la que R¹⁴ es un grupo alquilo C₁₋₄, un grupo alquilo C₁₋₄-alquilo C₁₋₄, un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo), un grupo de la fórmula -SO₂R¹⁶ (en la que R¹⁶ es un grupo alquilo C₁₋₄, fenilo, furilo, piridilo o bencilo), un grupo de la fórmula -P(O)(OR¹⁷)₂ (en la que R¹⁷ es fenilo, furilo o piridilo) o un grupo de la fórmula -SOR¹⁸ (en la que R¹⁸ es un grupo alquilo C₁₋₄, un grupo alquilo C₁₋₄-alquilo C₁₋₄, un grupo fenilo, naftilo, tiofenilo, furilo, piridilo, imidazol o bencilo).

8. Un compuesto de la fórmula V



(V)

en la que:

5 R^2 se selecciona del grupo que consiste en H, F, Cl, alquilo C_{1-4} , cicloalquilo C_3 ,
4 y CF_3 ;

R^4 es H o Me;

R^5 es H, Me o Et, con la condición de que R^4 y R^5 no sean ninguno Me y si R^4
es Me entonces R^5 no pueda ser Et;

10 R^{11} es Me, Et, ciclopropilo, propilo, isopropilo o ciclobutilo; y

R^{18} es $-COOH$ o un grupo de la fórmula $-COOR^{14}$ en la que R^{14} es un grupo
alquilo C_{1-4} , un grupo alquilo C_{1-4} -alquilo C_{1-4} , un grupo fenilo, naftilo, tiofenilo,
furilo, piridilo, imidazol o bencilo.

15

20

25

PRP/WPCL7612/ID-000228

30

Resumen de la Invención

Un procedimiento e intermedios nuevos para preparar Inhibidores de
transcriptasa inversa del HIV tal como se describe en la patente de EE.UU. N°. 5
6.420.359.

10

15

20

25

30

35 PRP/WPCL7612/ID-000228

Expediente No		05007452	No de Folia
Item		No de unidades	
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS: X	1	

Observaciones:

SOBRE BLANCO ARTE FINAL

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO

Folios: 99

RECIBO OFICIAL DE CAJA : 05 - 3,506
FECHA : ENERO 17 DE 2005

Radicación : 05007452 00000000
Fecha (AMD): 2005-01-28 17:09:30
Trámite : 011 PET-PATENT 379 FASE INICI 411 PRESENTA
Dependencia: 2820 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	32758705	17/01/2005	25,385,000.00

***** CONCEPTO *****

CANT. REENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
	TOTAL :	\$ 443,000.

SDM: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Cdo 07612-841-008-1

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03087452 00000000 Folios: 99
Fecha (HH): 2005-01-28 17:09:30
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTM
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
TRAMITE

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

Firma Responsable: Claudia M. Nava

Fecha:

Folio 104

2020
Bogotá DC

Doctor
EMILIO FERRERO
Apoderado
BOEHRINGER INGELHEIM CHEMICALS, INC

REFERENCIA:	Radicación No.	05-7452
	Solicitud Internacional	PCT/US2003/019415
	Fecha inicio fase nacional	28-01-2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	012
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en 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

05 ABR. 2005


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202027

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
E-mail: info sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia