Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21. **EXPEDIENTE No.** 05-7450

54. **TITULO** METODO MEJORADO PARA PREPARAR NEVIRAPINA

51. **CLASIFICACION INTERNACIONAL**

71. **SOLICITANTE** BOEHRINGER INGELHEIM CHEMICALS, INC.

DOMICILIO Petersburg, Estado de Virginia, Estados Unidos de América.

74. **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén.

92. **BOGOTA, D.C.,**

FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05007430 00000000 Folios: 86
Fecha (AMD): 2005-01-28 17:08:23 ción
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT
ENTRADA EN FASE NACIONAL 28-01-2005

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)

Nombre: **BOEHRINGER INGELHEIM CHEMICALS, INC**
sociedad constituida y existente bajo las leyes de Delaware, Estados Unidos de América
Dirección: 2820 North Normandy Drive, P.O. Box 1658, Petersburg, Virginia 23805, Estados Unidos de América
Domicilio: Petersburg, Virginia, 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. **Robert F. Jr. BOSWELL**
Boehringer Ingelheim Chemicals, Inc
2820 North Normandy Drive,
P.O. Box 1658, Petersburg,
Virginia 23805,
Estados Unidos de América

2. **Bernard Franklin GUPTON**
Boehringer Ingelheim Chemicals, Inc
2820 North Normandy Drive,
P.O. Box 1658, Petersburg,
Virginia 23805,
Estados Unidos de América

3. **Young S. LO**
Boehringer Ingelheim Chemicals, Inc
2820 North Normandy Drive,
P.O. Box 1658, Petersburg,
Virginia 23805,
Estados Unidos de América

5 PCT (86)

Solicitud Internacional No. PCT/US2003/017376 Fecha: 2 de Junio de 2003
Publicación Internacional No. WO 2004/002988 A1 Fecha: 8 de Enero de 2004

6 Título (54)

MÉTODO MEJORADO PARA PREPARAR NEVIRAPINA

7 Clasificación Internacional (51) C07D 471/14

8 Prioridad SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	28 de Junio de 2002	60/392.690

9 Comprobante de pago N .: 05 – 4.988 **Fecha:** 24 de enero de 1005

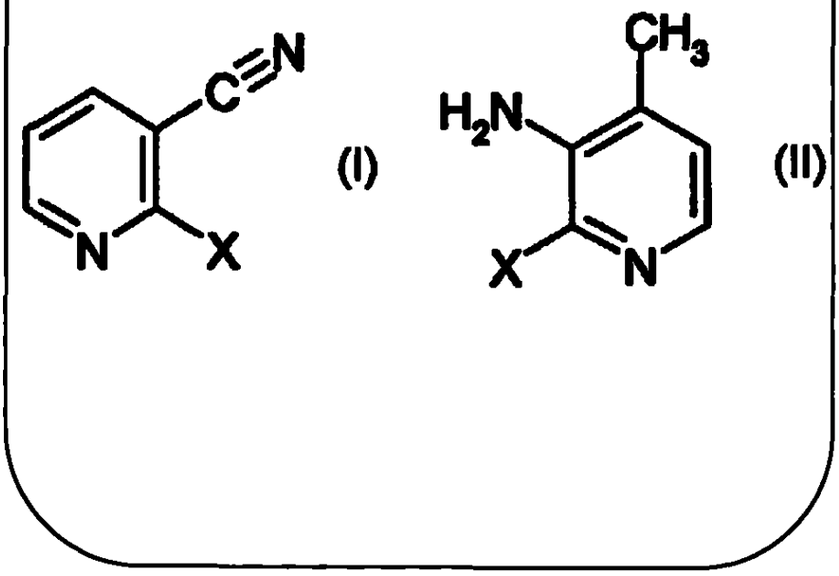
10

Anexos:

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 443.000.oo.
- [ ] Comprobante de pago por reivindicación de prioridad.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] 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.
- [x] 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



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTA, 8 – COLOMBIA

181

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of-Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER-OF-ATTORNEY

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

BOEHRINGER INGELHEIM CHEMICALS, INC.

domiciliado (s) en/of 2820 North Normandy Drive, P.O. Box 1658,

Petersburg, Virginia 23805, Estados Unidos de América

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera Nº 72-35, Bogotá, Colombia, en obedecimiento 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 mis (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 de aquél. 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 suplentes, en su caso, podrán ejercer la representación, en su orden, uno o 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, nombres de dominio, 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

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4a Nº 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 Consul 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 or 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 Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its 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 or Court cancellation,

28 ENE 2005

JUAN MANUEL BOTERO LEDINA

4

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 19, 2004**

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

8. Number : **2004-13224**

9. Seal :

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA

28 ENE 2005

JUAN MANUEL NOTARIO MOLDINA
NOTARIO

10. Signature

Secretary of the State

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, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

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.

Dado y firmado hoy/Given and signed this 25th day of October, 2004

en/in Ridgefield, Connecticut USA

por/by Mary-Ellen M. Devlin, Assistant Secretary

Firma/Signature

Personally appeared, Mary-Ellen M. DEVLIN, signer and sealer of the foregoing instrument and acknowledged the same to be her free act and deed before me this 25th day of October, 2004.

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
25 OCT. 2005
JUAN MANUEL BOTERO MEDINA
NOTARIO

Jeanne E. ROGERS
Notary Public
My Commission Expires: Nov. 30, 2006

6

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 **January 11, 2005**

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

8. Number : **2005-0315**

9. Seal :

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA HAGO CONSTAR QUE LA FOTOCOPIA CONCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

18 ENE 2005

JUAN MANUEL BUTERO MEDINA
NOTARIO

10. Signature

Susan Bysiewicz

Secretary of the State

7

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____

de 200 ___ ante mí, Notario Público o Funcionario Autorizado 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 _____ day of _____

200 ___ before me, a Notary Public or Attesting Official of

_____

personally appeared _____

_____

_____

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 O FUNCIONARIO AUTORIZADO — NOTARY PUBLIC OR ATTESTING OFICIAL —

CERTIFICACIÓN NOTARIAL (SOCIEDAD)

A los 25 días del mes de octubre

de 200 4 compareció(eron) ante mí,

MARY-ELLEN M. DEVLIN

_____

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

Boehringer Ingelheim Chemicals, Inc.

_____

Certifico:

1. Que he visto los siguientes documentos:*

nombramiento/Resolución de la Junta Directiva en Ridgefield, Connecticut fechado 16 Julio 2004

2. Que dichos documentos prueban lo siguiente:

2.1. Que MARY-ELLEN M. DEVLIN es Secretaria-Asistente de Boehringer Ingelheim Chemicals Inc. es una Sociedad/Compañía legalmente constituída y existente de acuerdo con las leyes de l estado de Delaware

2.2. Que el domicilio de dicha Sociedad/Compañía es

2820 North Normandy Drive

Petersburg, Virginia 23805 EUA

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

2.4. Que el(los) Sr.(Sres.)

MARY-ELLEN M. DEVLIN

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

Ciudad Ridgefield

Estado Connecticut 06877 EUA

Hoy 25 octubre de 2004

NOTARIAL CERTIFICATION (CORPORATION)

On this 25th day of October

2004 ___ appeared before me

Mary-Ellen M. Devlin

_____

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

BOEHRINGER INGELHEIM CHEMICALS, INC.

_____

I certify:

1. That I have seen the following documents:*

Appointment/Resolution by the Board of Directors in Ridgefield, Connecticut dated July 16, 2004.

2. That the above documents duly prove the following:

2.1. That Mary-Ellen M. Devlin is Assistant Secretary to BOEHRINGER INGELHEIM CHEMICALS, INC., which is a Corporation/Company legally constituted and in existence in accordance with the laws of the State of Delaware.

2.2. That the domicile of said Corporation/Company is

2820 North Normandy Drive

Petersburg, Virginia 23805 USA

2.3. That the purpose or 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 Ms.(Messrs.) Mary-Ellen M. Devlin

_____

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

City Ridgefield

State Connecticut 06877 USA

This 25th day of October 2004

— NOTARIO PÚBLICO O FUNCIONARIO AUTORIZADO — NOTARY PUBLIC OR ATTESTING OFICIAL —

* Los documentos deben identificarse con fecha y origen

* Documents must be identified with date and origin

I, Jeanne E. Rogers, Notary Public for the State of Connecticut, do hereby attest that the above Corporate information is true and accurate.

Jeanne E. Rogers

CAVELIER ABOGADOS

WPPODE01-181 (MINUTA N°12.1.1.2.6 USA)

8

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: .....

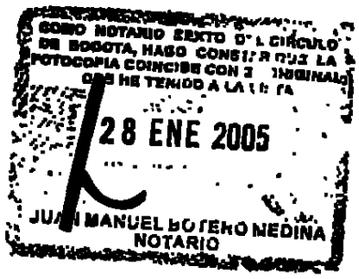
This public document

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

....

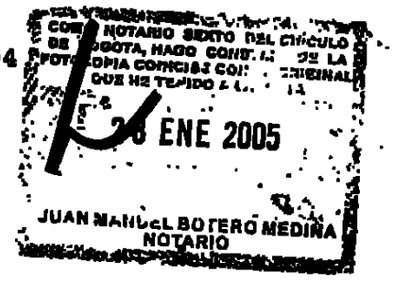


TRADUCCIÓN OFICIAL 009/2004 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL **BOEHRINGER INGELHEIM CHEMICALS, INC** EMPRESA DOMICILIADA EN 2820 NORTH NORMANDY DRIVE, P.O. BOX 1658, PETERSBURG, VIRGINIA 23805, ESTADOS UNIDOS DE AMÉRICA OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA 831; LUZ CLEMENCIA DE PAEZ TPA 23555 Y A GERMÁN CAVELIER, TPA 832. FIRMADO HOY 25 DE OCTUBRE DE 2004 EN RIDGEFIELD, CONNECTICUT, ESTADOS UNIDOS DE AMÉRICA POR MARY ELLEN M. DEVIN, SECRETARIA ASISTENTE.

MARY-ELLEN M. DEVLIN, FIRMANTE Y SELLANTE DEL DOCUMENTO PRECEDENTE COMPARECIÓ Y RECONOCIÓ QUE LO FIRMÓ COMO UN ACTO DE SU LIBRE VOLUNTAD ANTE MI EL 25 DE OCTUBRE DE 2004

FIRMADO: JEANNE E. ROGERS, NOTARIO PÚBLICO.

MI CARGO VENCE EL 30 DE NOVIEMBRE DE 2006.



APOSTILLA:

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

1. Estados Unidos de América

Este documento público

2. ha sido firmado por JEANNE E. ROGERS
3. quien actúa en su calidad de NOTARIO PÚBLICO
4. para el estado de Connecticut por el período comprendido entre el 26 de noviembre de 2001 y el 30 de noviembre de 2006

CERTIFICADO

5. Hartford, Connecticut

6. el 19 de n viembre de 2004

7. por SUSAN BYSIEWICZ, secretario de estado de Connecticut

8. Número 2004-13224

9. Sello:

SELLO REALZADO ESTADO DE CONNECTICUT

10. Firma: Susan Bysiewicz, secretario de estado

CERTIFICACIÓN NOTARIAL en inglés y en español de fecha 25 de octubre de 2004 para certificar la comparecencia de MARY-ELLEN M. DEVLIN en su calidad de representante de BOEHRINGER INGELHEIM CHEMICALS INC., la existencia legal de dicha firma y su domicilio y además la capacidad de la antedicha representante para otorgar este poder. Ridgefield, Connecticut 06877, Estados Unidos de América. 25 de octubre de 2004.

Yo, Jeanne E. Rogers, notario público para el estado de Connecticut, por el presente certifico que la precedente información corporativa es verídica y exacta.

Firmado: Jeanne E. Rogers, notario público. Vence el 30 de noviembre de 2006.

2 ENE 2005

JUAN MAL... EL GUTIERO MEDINA NOTARIO

APOSTILLA:

(Convención de La Haya del 5 de octubre de 1961

1. Estados Unidos de América

Este documento público

2. ha sido firmado por JEANNE E. ROGERS

3. quien actúa en su calidad de NOTARIO PÚBLICO

4. para el estado de Connecticut por el período comprendido entre el 26 de noviembre de 2001 y el 30 de noviembre de 2006

CERTIFICADO

MINISTERIO DE RELACIONES EXTERIORES

082970

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA

2005 JAN 27 P 12:43

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

NO SE ASUME RESPONSABILIDAD DEL TEXTO

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) QUE APARECE(N) EN EL PRESENTE DOCUMENTO

COINCIDE(N) CON LA FIRMA REGISTRADA POR EL (ELLOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA, 27 ENE 2005

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA PRESENTE FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

28 ENE 2005

JUAN MANUEL ESTUPIÑAN CARDENAS
NOTARIO SEXTO

5.Hartford, Connecticut

6.el 11 de enero de 2005

7.por SUSAN BYSIEWICZ, secretario de estado de Connecticut

8.Número 2005-0315

9.Sello:

SELLO REALZADO ESTADO DE CONNECTICUT

10.Firma: Susan Bysiewicz, secretario de estado

COLO-14468-841-001-4

WPCL002G ID 6431

Bogotá, 27 de enero de 2005

Eduardo Calado N.

[illegible]

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

28 ENE 2005

JUAN MANUEL BOTERO MEDINA
NOTARIO

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

Leopoldo Leire Cañedo Vaquero

COINCIDE(N) CON LA FIRMA REGISTRADA POR EL (ELLOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA, 27 ENE 2005

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 JAN 27 P 12:43

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

082969

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR LA COINCIDENCIA CON EL QUE HE TENIDO A LA VISTA

28 ENE 2005

JUAN MANUEL COYERO MEDINA
NOTARIO

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. Country: United States of America

This public document

2. has been signed by Angela B. Burke

3. acting in the capacity of A Notary Public for the Commonwealth of Virginia

4. bears the seal/stamp of Angela B. Burke, Notary Public
Commonwealth of Virginia

Certified

5. at Richmond, Virginia

6. This 17th day of November, 2004

7. by the Secretary of the Commonwealth of Virginia

8. No. 79756

9. Seal/Stamp:

10. Signature:

Anita A. Rimler
Secretary of the Commonwealth

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTA, 8 – COLOMBIA

13

CESION

Yo, (nosotros) abajo firmado (s)
1. Robert F. BOSWELL, Jr.
2. Bernard Franklin GUPTON
3. Young S. LO

domiciliado(s) en
1. Boehringer Ingelheim Chemicals, Inc.,
2820 North Normandy Drive, P.O. Box 1658,
Petersburg, Virginia 23805,
Estados Unidos de América
2. Boehringer Ingelheim Chemicals, Inc.,
2820 North Normandy Drive, P.O. Box 1658,
Petersburg, Virginia 23805,
Estados Unidos de América
3. Boehringer Ingelheim Chemicals, Inc.,
2820 North Normandy Drive, P.O. Box 1658,
Petersburg, Virginia 23805,
Estados Unidos de América

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención: **MÉTODO MEJORADO PARA PREPARAR NEVIRAPINA**

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad **BOEHRINGER INGELHEIM CHEMICALS, INC.**

constituida y existente de conformidad con las leyes de

domiciliada en 2820 North Normandy Drive,
P.O. Box 1658, Petersburg,
Virginia 23805, Estados Unidos de América

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.

ASSIGNMENT

I (we), the undersigned
1. Robert F. BOSWELL, Jr.
2. Bernard Franklin GUPTON
3. Young S. LO

of
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2820 North Normandy Drive, P.O. Box 1658,
Petersburg, Virginia 23805,
United States of America
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Petersburg, Virginia 23805,
United States of America

state(s) under oath to be sole and true inventor(s) of the invention: **IMPROVED METHOD OF MAKING NEVIRAPINE**

state as well, that assign, without reservations or limitations in favour of **BOEHRINGER INGELHEIM CHEMICALS, INC.**

a corporation constituted and existing in conformity with the laws of

domiciled in 2820 North Normandy Drive,
P.O. Box 1658, Petersburg,
Virginia 23805, United States of America

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

Dado y firmado hoy/Given and signed this 16th day of November 2004
en/in Petersburg, VA USA

Firma/Signature

Robert F. Boswell Jr.
1. Robert F. BOSWELL, Jr.

Bernard Franklin Gupton
3. Bernard Franklin GUPTON

Young S. Lo
2. Young S. LO

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los 10 días del mes de Noviembre de 200 4 Ante mí, Notario Público de Estado de Virginia

compareció(eron) personalmente Robert F. BOSWELL, Jr.

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

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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.

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Sworn to and subscribed before me this 10th day of November 2004

TRADUCCIÓN OFICIAL No. 05.12/04 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. Robert F. BOSWELL, Jr.
2. Bernard Franklin GUPTON
3. Young S. LO

de

1. Boehringer Ingelheim Chemicals, Inc., .
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   Petersburg, Virginia 23805
   Estados Unidos de América

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3. Boehringer Ingelheim Chemicals, Inc.,
   2820 North Normandy Drive, P.O. Box 1658
   Petersburg, Virginia 23805
   Estados Unidos de América

inventores de la invención **"MÉTODO MEJORADO PARA PREPARAR NEVIRAPINA"**, ceden los derechos inherentes a dicha invención a **BOEHRINGER INGELHEIM CHEMICALS, INC.**, sociedad domiciliada en 2820 North Normandy Drive, P.O. Box 1658, Petersburg, Virginia 23805, Estados Unidos de América,.

Dado y firmado hoy 10 de noviembre de 2004
En Petersburg, VA, E.U.A.

(Firma)	(Firma)	(Firma)
Robert F. BOSWELL, Jr.	Bernard Franklin GUPTON	Young S. LO

CERTIFICADO NOTARIAL (INDIVIDUO) en inglés y español referente a la capacidad legal de **Robert F. Boswell, Jr.** para otorgar el documento anterior. Dado en el Estado de Virginia, el 10 de noviembre de 2004.

CERTIFICADO NOTARIAL (INDIVIDUO) en inglés y español referente a la capacidad legal de **Robert F. BOSWELL, Jr.** para otorgar el documento anterior. Dado en el Estado de Virginia, el 10 de noviembre de 2004.

CERTIFICADO NOTARIAL (INDIVIDUO) en inglés y español referente a la capacidad legal de **Bernard Franklin GUPTON** para otorgar el documento anterior. Dado en el Estado de Virginia, el 10 de noviembre de 2004.

CERTIFICADO NOTARIAL (INDIVIDUO) en inglés y español referente a la capacidad legal de **Young S. LO** para otorgar el documento anterior. Dado en el Estado de Virginia, el 10 de noviembre de 2004.

(Sello notarial)

Ciudad/Condado de Petersburg, Estado de Virginia

Juramentado y suscrito ante mí hoy 10 de noviembre de 2004. Certifican mi firma y sello oficial.

(Firmado) Angela B. Burke, Notario Público

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 Angela B Burke

3. Actuando en su capacidad de Notario Público del Estado de Virginia

4. Lleva el sello/timbre de Angela B Burke, Notario Público, Estado de Virginia.

CERTIFICADO

5. En Richmond, Virginia 6. el 17 de noviembre de 2004

7. Por el Secretario del Estado de Virginia.

8. No. 79756

9. Sello: (sello seco) SELLO DEL ESTADO DE VIRGINIA.

10. Firma: (Firma ilegible) Secretario de Estado.

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

COLO 14468-841-001-4

WPC 14468 - ID 4

DIC 10/04

María E. Martelo.

TRADUCCION No: 05.12.04

MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
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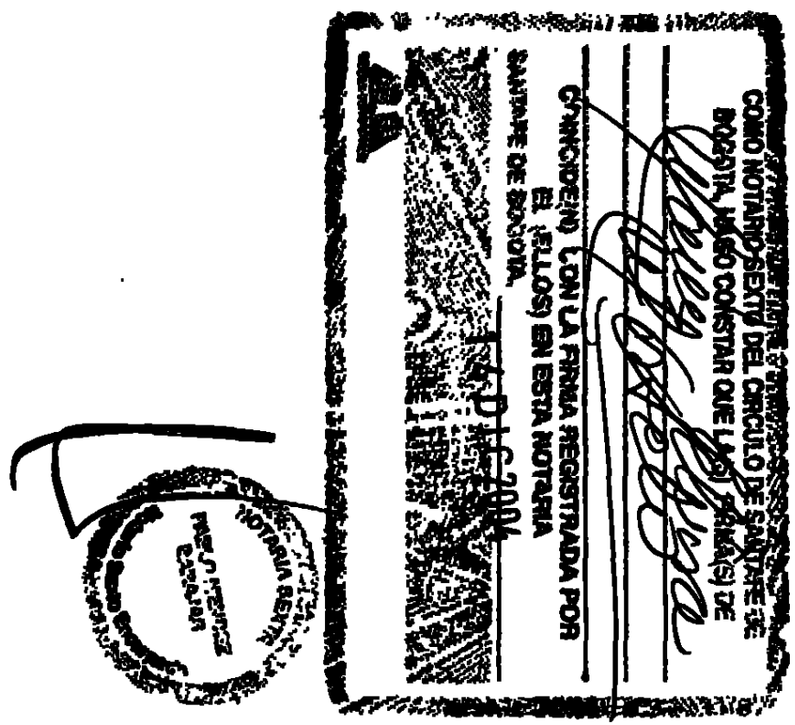

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, 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.

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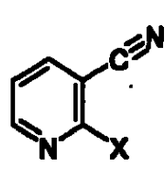
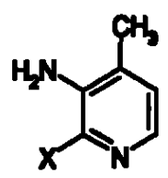
(54) Title: IMPROVED METHOD OF MAKING NEVIRAPINE



(I)



(II)

(57) Abstract: A process for making nevirapine, comprising the following steps: (a) reacting a 2-halo-3-pyridinecarbonitrile of the formula (I), wherein X is a fluorine, chlorine, bromine or iodine atom, preferably chlorine or bromine, with cyclopropylamine, to yield 2-(cyclopropylamino)-3-pyridinecarbonitrile; (b) hydrolyzing the 2-(cyclopropylamino)-3-pyridinecarbonitrile to yield 2-(cyclopropylamino)-3-pyridine carboxylic acid; (c) isolating the 2-(cyclopropylamino)-3-pyridine carboxylic acid from the reaction medium; (e) treating the 2-(cyclopropylamino)-3-pyridine carboxylic acid with a chlorinating agent, to yield 2-(cyclopropylamino)-3-pyridinecarbonyl chloride; (f) reacting the 2-(cyclopropylamino)-3-pyridine carbonyl chloride with a 2-halo-4-methyl-3-pyridinamine of the formula (I), wherein X is a fluorine, chlorine, bromine or iodine atom, preferably chlorine or bromine, to produe an N-(2-halo-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide; and (g) cyclizing the N-(2-halo-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide by treatment with a strong base, to yield nevirapine.

IMPROVED METHOD FOR MAKING NEVIRAPINE

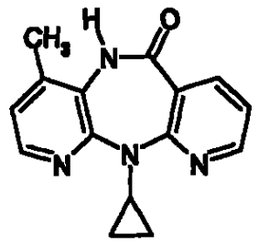
BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

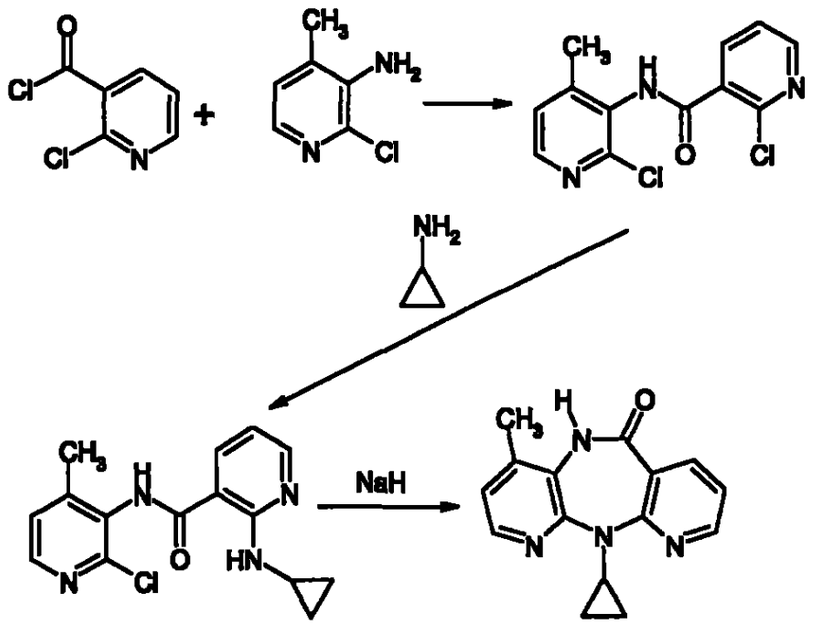
The invention relates to an improved method for making nevirapine, and to several novel intermediates which are produced during the course of carrying out the improved method.

2. BACKGROUND INFORMATION

Nevirapine is a non-nucleoside inhibitor of HIV reverse transcriptase, which is useful in the treatment of HIV infection in humans. The chemical name for nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one. Its structural formula is:



The earliest known synthesis of nevirapine, by Hargrave et al., is described in US Patent 5,366,972. The synthetic method employed is depicted in the following reaction Scheme 1.



Scheme 1

In the method of Hargrave et al., 2-chloronicotinoyl chloride is formed by reacting 2-chloronicotinic acid with thionyl chloride. Next, as shown in Scheme 1, the reaction of 2-chloronicotinoyl chloride with 2-chloro-4-methyl-3-pyridinamine produces 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridinecarboxamide. This is reacted with cyclopropylamine to give N-(2-chloro-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide. The final step is the cyclization to produce nevirapine, which occurs on treatment of the final intermediate with sodium hydride.

A refinement of the above process, described by Schneider et al. in U.S. Patent 5,569,760, is presently used for the commercial manufacture of nevirapine. In this improvement of the synthesis, the reaction of 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridinecarboxamide with cyclopropylamine is carried out in the presence of a neutralizing agent, which is an oxide or hydroxide of an an element of the second main or

second subgroup of the periodic table. It is preferred to use as the neutralizing agent an oxide or hydroxide of an alkaline earth metal or of zinc, with calcium oxide being particularly preferred.

While the synthesis provided by U.S. Patent 5,366,972 is the best known to date, it nevertheless suffers from several significant drawbacks. First, because the reaction of cyclopropylamine with 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridinecarboxamide is carried out at elevated temperature (between 130° to 150°C) and because cyclopropyl amine is so highly volatile, this reaction must be carried out in a high pressure reaction vessel. Second, 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridinecarboxamide becomes thermally unstable above about 145°C, and allowing the temperature of the reaction mixture to go above this temperature poses the risk of an explosion. Therefore, it is prudent to carefully control the temperature of the reaction mixture so that it remains below 145°C until substantially all of this material has been consumed by the reaction. Maintaining such tight control of the temperature of the reaction mixture is difficult at best, and it is made all the more difficult by the fact that the reaction is itself exothermic. Third, it is necessary to remove the neutralizing agent by filtration. Finally, due to the production of side products, the overall yield of the synthesis is only about 25%.

There is thus a need for a better synthesis for nevirapine.

BRIEF SUMMARY OF THE INVENTION

The present invention satisfies this need by providing a synthesis for nevirapine that is safer, higher yielding and more economical than any method yet known.

DETAILED DESCRIPTION OF THE INVENTION

The improved synthesis of nevirapine provided by the present invention is depicted below in reaction Scheme 2.

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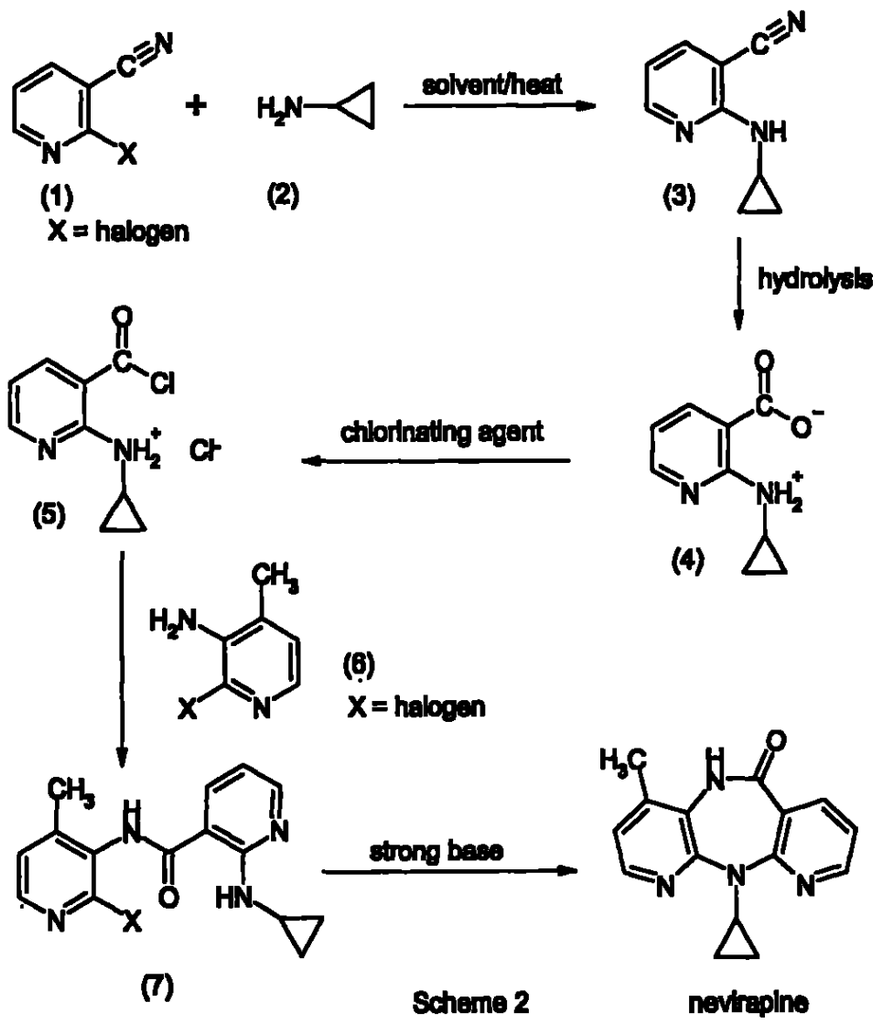
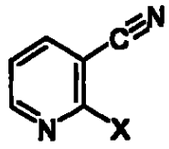


In the first reaction step, a 2-halo-3-pyridinecarbonitrile (1) of the formula



wherein X is a fluorine, chlorine, bromine or iodine atom, preferrably chlorine or bromine, is reacted with cyclopropylamine (2), to yield 2-(cyclopropylamino)-3-pyridinecarbonitrile

(3). This reaction is carried out in an inert, organic solvent, with or without water, at elevated temperature. Appropriate organic solvents are C_1 to C_6 straight or branched chain alcohols, tetrahydrofuran, dimethylformamide, diglyme, toluene, and the like. The preferred solvents are ethanol and 1-propanol, with or without water. Optionally, a base, either organic or inorganic, such as triethylamine, diisopropylethylamine, potassium phosphate, sodium carbonate, potassium carbonate and the like, can be added as an acid scavenger. The reaction can be carried out at a temperature between ambient temperature and reflux temperature, but it is preferred that the temperature be between 77° and 100°C.

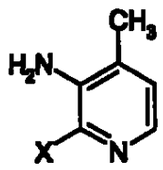
The 2-(cyclopropylamino)-3-pyridinecarbonitrile is next hydrolyzed to yield 2-(cyclopropylamino)-3-pyridine carboxylic acid (4), which predominantly exists as the zwitterion when isolated according to the disclosed procedures and is, therefore, represented as such in Scheme 2. Isolation of the nitrile prior to hydrolysis is optional. The hydrolysis of the nitrile to the carboxylic acid can be carried out in a conventional manner, using a strongly acidic or basic solution. The hydrolysis is preferrably carried out using an aqueous mixture of hydrogen peroxide and a strong base, such as sodium or potassium hydroxide, or an aqueous mixture of a strong base, such as sodium or potassium hydroxide, and an alcohol of 1 to 6 carbon atoms. Most preferrably, the hydrolysis is carried out using aqueous 1-propanol and potassium hydroxide. Heating to reflux will accelerate the rate of hydrolysis.

The 2-(cyclopropylamino)-3-pyridine carboxylic acid is next isolated from the reaction medium. This is conveniently accomplished by adjusting the pH to the isoelectric point, which is reached at about pH 6. This produces the zwitterion, which precipitates out and is then separated by filtration and dried. If an aqueous alcohol and a base are used to conduct the hydrolysis, the alcohol is first removed by distillation.

Subsequently, the 2-(cyclopropylamino)-3-pyridine carboxylic acid is treated with a chlorinating agent, to yield 2-(cyclopropylamino)-3-pyridinecarbonyl chloride (5). Appropriate chlorinating agents are, for example, thionyl chloride, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride, phosgene and oxalyl

chloride. The chlorination is performed in a manner known to those skilled in the art of organic synthesis. In general it is preferred to reflux the carboxylic acid (4) with the chlorinating agent, which will either be used neat or in solution with a suitable aprotic solvent such as, for example, toluene, acetonitrile, tetrahydrofuran, or the like. It is preferred to perform the chlorination by refluxing with neat thionyl chloride, any excess of which can later be conveniently removed by evaporation. As most chlorinating agents produce hydrochloric acid, the product (5) of this reaction step is depicted in Scheme 2 as the hydrochloride.

The 2-(cyclopropylamino)-3-pyridinecarbonyl chloride (5) is next reacted with a 2-halo-4-methyl-3-pyridinamine (6) of the formula



wherein X is a fluorine, chlorine, bromine or iodine atom, preferrably chlorine or bromine. The most preferred reactant is 2-chloro-4-methyl-3-pyridinamine. This produces an N-(2-halo-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide(7), wherein X is a fluorine, chlorine, bromine or iodine atom, preferrably chlorine or bromine.. It is essential to first remove any remaining chlorinating agent, as this would react with the pyridinecamine. If a highly volatile chlorinating agent, such as thionyl chloride, is used neat, then it may be removed by evaporation to leave the acid chloride (5) as a solid. If the chlorination is done in a solvent, then it is preferable to employ a solvent that is high boiling, so that chlorinating agent may be removed by evaporation, leaving the acid chloride dissolved in the solvent. In any event, the acid chloride (5) is to be maintained under anhydrous conditions. The acid chloride (5) and the pyridinecamine (6) are reacted by dissolution in a suitable anhydrous solvent such as, for example acetonitrile, tetrahydrofuran, diglyme, dimethylformamide, dioxane, methylene chloride, or toluene. Optionally a base, either organic or inorganic, such as triethylamine,

diisopropylethylamine, potassium phosphate, potassium hydrogen phosphate, sodium carbonate, sodium hydroxide, potassium hydroxide or the like, may be added to the reaction mixture as an acid scavenger. The reaction rate may be increased by heating up to the boiling point of the solvent.

Finally, the carboxamide (7) is cyclized to yield nevirapine. The cyclization is induced by treating the carboxamide (7) with a strong base, such as sodium hydride (NaH) or sodium hexamethyldisilazane (NaHMDS) in an inert anhydrous organic solvent, such as diglyme, toluene, or tetrahydrofuran, at from -30°C to 130°C.

The synthesis of the intermediate 2-(cyclopropylamino)-3-pyridinecarbonitrile by means of the reaction of 2-chloro-3-pyridinecarbonitrile with cyclopropylamine is known from G. E. Hardtmann et al, *J. Med. Chem. 1974*, 17, 636.

The intermediates, 2-(cyclopropylamino)-3-pyridine carboxylic acid (4)and 2-(cyclopropylamino)-3-pyridinecarbonyl chloride (5) are believed to be novel and, thus, are considered to be aspects of the invention.

It is preferred to use 2-chloro-3-pyridinecarbonitrile as starting material (1) since syntheses for this substance are known and it is commercially available. Other 2-halo-3-pyridinecarbonitriles can be readily synthesized in an analogous manner.

Cyclopropylamine, the starting material (2), is also commercially available.

It is preferred to use 2-chloro-4-methyl-3-pyridinamine as reactant (6) since syntheses for this substance are known from U.S. Patents 6,399,781; 5,686,618; 5,668,287; 5,654,429 and 5,200,522. Other 2-halo-4-methyl-3-pyridinamines can be readily synthesized in an analogous manner.

The following examples further illustrate the preparation of nevirapine using the improved process provided by the present invention. While each step of the reaction

sequence can be carried out by first isolating the product of the preceding step, some of the reaction steps may be carried out sequentially, in one reaction vessel, without isolation of the intermediate formed by the preceding step, thus reducing costs associated with vessel time, cleanup, and labor. The following Examples 1-6 illustrate the approach wherein the intermediate formed at the completion of each step is isolated. Examples 7 and 8 illustrate how some of the reaction steps may be carried out sequentially, in one reaction vessel, without isolation of the intermediate formed by the preceding step.

Example 1. Preparation of 2-(cyclopropylamino)-3-pyridinecarbonitrile

A reaction flask equipped with a mechanical stirrer, temperature controller, condenser and addition funnel was charged with 2-chloro-3-pyridinecarbonitrile (69.25g, 0.50mol), 300 ml of ethanol and 200 ml of water. With agitation, cyclopropylamine (114g, 2.0mol) was added dropwise over 30 minutes at a temperature <30 °C. When the addition was completed, the stirred reaction mixture was heated to reflux temperature for 20 hours. The reaction mixture was cooled to 60 °C and then 350 ml of excess cyclopropylamine and ethanol were removed by vacuum distillation using water aspirator vacuum. The remaining aqueous solution was cooled to ambient temperature and allowed to stand overnight. The solid product was collected by filtration and the filter cake rinsed with water. The yield was 81.51g (theoretical yield is 79.5g).

Example 2. Preparation of 2-(cyclopropylamino)-3-pyridine carboxylic acid (zwitterion)

A 45% aqueous KOH solution (187g, 1.5mol) was charged to a mixture of the product from Example 1 and 300 ml of 1-propanol. The mixture was heated at reflux temperature for about 5 hours whereupon TLC analysis showed complete hydrolysis of the nitrile. The reaction mixture was cooled to ambient temperature and treated with 94g of water that was needed to remove the 1-propanol by azeotropic distillation. About 330g of water/1-propanol azeotrope was distilled off at 62 °C and 21.1 in. Hg. Water (130g) was added to the reaction mixture and the mixture chilled to 5-10 °C. Concentrated hydrochloric acid (148g, 1.5mol) was added at such a rate that the temperature could be maintained below 30 °C. After about 80-90% of the acid was added the zwitterion began to precipitate out,

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making the mixture quite thick. When all the acid had been added, the solid product was collected by filtration, using 90ml of cold water to rinse out the reaction vessel onto the filter cake. The product was dried to yield 68.12g. of the zwitterion.

Example 3. Preparation of 2-(cyclopropylamino)-3-pyridinecarbonyl chloride

Thionyl chloride (25ml, 40.8g, 0.343mol) was charged in a thin stream to 9.00g, 0.048mol, of 2-(cyclopropylamino)-3-pyridine carboxylic acid from Example 2 in acetonitrile. The mixture was heated at reflux temperature for 30 minutes. The mixture was allowed to cool and the thionyl chloride was distilled off at 40 °C/23 in. Hg until the pot contents became thick. Toluene (25ml) was added and distillation of thionyl chloride and toluene at 40 °C was continued until about one-half of the liquid was distilled. The remaining solution was allowed to cool and stirred to promote crystallization. Heptane (25ml) was added to the mixture with stirring and the mixture filtered under a nitrogen atmosphere to obtain the title compound.

Example 4. Preparation of N-(2-chloro-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide

A solution of 2-chloro-4-methyl-3-pyridinamine (5.70g, 0.040mol) in 10 ml of acetonitrile was charged rapidly dropwise to a mixture of the acid chloride from Example 3, ground anhydrous potassium phosphate (8.49g, 0.04mol) and 40 ml of acetonitrile. The reaction mixture was heated at 50°C for 20 hours and the reaction progress monitored by HPLC analysis. When the reaction was complete, the reaction mixture was cooled to ambient temperature and treated with 50 ml of water, giving a solution having a pH of about 4.5-5. The mixture was acidified to pH 1 by addition of dilute HCl solution and stirred for 30 min at ambient temperature. The reaction mixture was filtered to remove any insoluble material and the filtrate was basified to pH 9-10 with dilute sodium hydroxide solution and stirred for 30 minutes at ambient temperature. The mixture was then acidified to pH 7-8 by addition of dilute HCl, forming a dark oily layer on top of the solution. Water was added, as this had been observed during past experiments of a similar nature to hasten crystallization. The oily layer crystallized slowly on stirring overnight. The solid product was collected and dried in a vacuum oven at 50 °C to obtain 9.37g of the title compound.

Example 5. Preparation of 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (nevirapine) using sodium hexamethyldisilazane

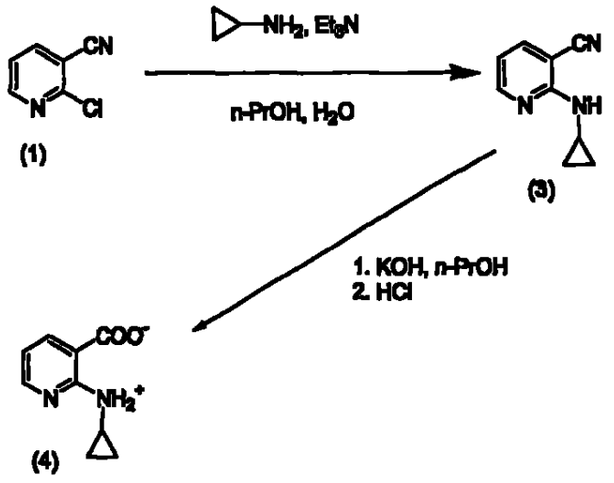
A reaction flask equipped with a magnetic stirrer, temperature controller thermocouple, addition funnel and condenser with an oil bubbler for exclusion of ambient air was inerted with nitrogen and charged with 3.02g (0.010mol) of N-(2-chloro-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide from Example 4 and 30 ml of anhydrous THF. A 40% solution of sodium hexamethyldisilazane in THF (12.7ml, 0.025mol) was added dropwise maintaining the temperature of the reaction mixture at no more than 30 °C. When the addition of the NaHMDS solution was completed, the reaction mixture was heated to reflux temperature (about 63-66 °C). When the reaction was completed (HPLC analysis), the mixture was cooled to ambient temperature. The reaction mixture was treated with 1.55g (0.050mol) of methanol and 0.45g of water (0.025mol). The mixture was concentrated on a rotary evaporator at 25-30 in. Hg with a 50-60° water bath temperature. The residual product weighing 4.44g was triturated with 50 ml of water and the pH 10-12 solution was acidified to pH 3 by adding 10% HCl solution. The solid product was collected by filtration and the filter cake rinsed three times with 10 ml portions of water. The filter cake was dried in a vacuum oven at 50-60°C to obtain nevirapine.

Example 6. Preparation of 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (nevirapine) using sodium hydride

A 500ml 4NRB flask with stirrer, temperature controller thermocouple, addition funnel and condenser with an oil bubbler to exclude air was inerted with nitrogen and charged with 15.00g of 60% sodium hydride in a mineral oil slurry and 120 ml of diglyme. The mixture was heated to 130 °C and treated dropwise with a solution of 41.7g (0.138mol) of N-(2-chloro-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide, from Example 4, in 70 ml of diglyme at 80 °C. The reaction mixture was heated at 130 °C until hydrogen evolution ceased. The mixture was cooled to ambient temperature and water (6.75g) was added dropwise cautiously. When hydrogen evolution ceased, an additional 100 ml of water was added. Acetic acid (20ml) was added to reduce the pH of the mixture

from 11-13 to about 7. An additional 100 ml of water was added and the reaction mixture stirred under ambient conditions for 30 minutes while the product crystallized. The solid product was collected by filtration and the filter cake rinsed with 100 ml of water followed by 50 ml of cyclohexane to remove any residual mineral oil from the mineral oil-sodium hydride slurry. The wet cake was dried in a vacuum oven at 50 °C for 18 hours to obtain 35.58g of nevirapine.

Example 7. A One-Pot Synthesis of 2-(cyclopropylamino)-3-pyridine carboxylic acid from 2-chloro-3-pyridinecarbonitrile



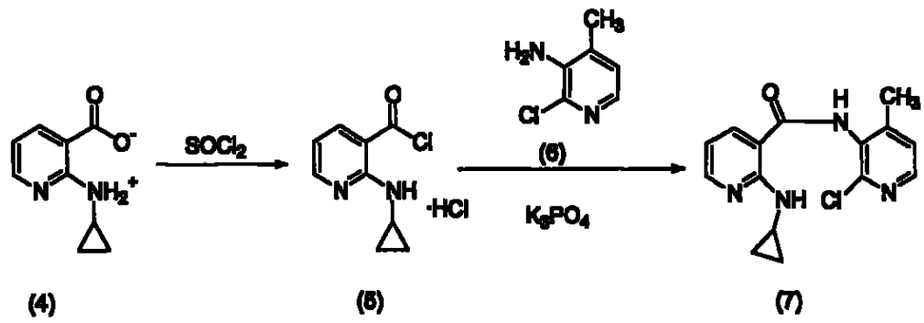
A one liter 4NRB flask with stirrer, condenser, temperature controller thermocouple and addition funnel was charged with 2-chloro-3-pyridinecarbonitrile (27.70g, 0.20mol) followed by 120ml of 1-propanol and 80 ml of water. Triethylamine (20.2g, 0.20mol) was added in one portion followed by addition of cyclopropylamine (17.10g, 0.30mol) over a period of 2 minutes. The reaction mixture was heated at reflux (86-87 °C) and after 2.5 hours, a tlc analysis (silica gel, MTBE mobile phase) showed some product formation. After stirring at reflux for 16 hours, tlc analysis showed a little starting material remaining. HPLC analysis showed 22% starting material-75% 2-(cyclopropylamino)-3-pyridinecarbonitrile. An additional 0.1mol (10.1g) of triethylamine (total of 30.3g, 0.30mol of triethylamine) and 0.03mol of cyclopropylamine (1.70g) were added and the

mixture continued to be heated at reflux for another 3 hours. HPLC analysis showed 15% starting material remaining. An additional 4.0g of cyclopropylamine (total 0.40mol) was added and the mixture heated at reflux for another 18 hours. At the end of that time HPLC analysis showed 2.9% starting material.

Potassium hydroxide (33.6g, 0.60mol) was added and the mixture heated to about 40 °C under vacuum for about 15 minutes to remove any volatile amines. The mixture was then heated at reflux for 5 hours under atmospheric pressure to hydrolyze the nitrile to the carboxylic acid. Water (80ml) was added and n-propanol was distilled off as an azeotrope with water (azeotrope boiling point is 87.7 °C, 28.3% water, 71.7% n-propanol). When the distilling head temperature increased to 92 °C the distillation was stopped and the reaction mixture allowed to cool.

The reaction mixture was chilled to about 10 °C with an ice-methanol bath and 50ml (59.2g) of 37% HCl solution was added dropwise, maintaining the reaction mixture at no more than 25 °C. All of the HCl was added and after stirring about 2 minutes longer crystallization of the 2-(cyclopropylamino)-3-pyridine carboxylic acid began and the product set up to a cake. Water (100ml) was added to break up the solid mass and make the mixture stirrable. After about 30 minutes, the solid was collected by filtration. Additional solid was obtained by concentrating the filtrate. After drying by air aspiration for about 2 hours, the wet-cake solid weighed 23.02g. HPLC showed 97% 2-(cyclopropylamino)-3-pyridine carboxylic acid and two small unknown impurity peaks of 1.8% and 1.3% concentrations. The solid was dried in a vacuum oven at 50 °C for 65 hours to yield 18.19g.

Example 8. A One-Pot Synthesis of N-(2-chloro-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide from 2-chloro-4-methyl-3-pyridinamine and 2-(cyclopropylamino)-3-pyridine carboxylic acid (zwitterion)



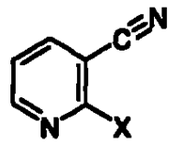
(4) (5) (7)

A 250ml 4NRB flask equipped with a mechanical stirrer, condenser, addition funnel, and temperature controller thermocouple, was charged with 2-(cyclopropylamino)-3-pyridine carboxylic acid (18.46g, 0.10mol). Thionyl chloride (22ml, 0.30 mol) was added in a thin stream to the reaction flask with stirring and the mixture heated to reflux for 32 minutes. The reaction mixture was cooled and the condenser was replaced with a vacuum distillation head. The thionyl chloride was distilled off at 40 °C at 23in Hg vacuum until the distillation pot contents became thick. Toluene (30ml) was added and distillation continued until about most of the liquid was distilled off. Another 30 ml of toluene was added and about one-half of the solvent was distilled off under vacuum. Acetonitrile (60ml) was added to the residual mixture. A solution of 2-chloro-4-methyl-3-pyridinamine (11.4g, 0.080mol) in 40 ml of acetonitrile was added dropwise and the reaction mixture heated to 50 °C and stirred overnight. Finely crushed potassium phosphate was added after the 2-chloro-4-methyl-3-pyridinamine addition. After 16 hrs at 50 °C 100 ml of water was added to the stirred reaction mixture (pH 4-5). The reaction mixture was filtered to remove a small quantity of insoluble material. The filtrate (2 layers) was basified to pH 10-11 with 50% aqueous NaOH solution and then acidified back to pH 8. Most of the product was found in the toluene layer by HPLC analysis. The toluene layer was extracted with 300 ml dilute HCl solution (pH 1). The aqueous acid layer was basified to pH 8 using 10% aqueous NaOH resulting in the separation of an oily layer that crystallized slowly with trituration. After standing over 2 days, the solid product was collected and dried in vacuo at 50 °C to yield 21.40g tan solid title compound.

CLAIMS:

1. A process for making nevirapine, comprising the following steps:

(a) reacting a 2-halo-3-pyridinecarbonitrile of the formula



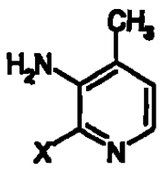
wherein X is a fluorine, chlorine, bromine or iodine atom, preferably chlorine or bromine, with cyclopropylamine, to yield 2-(cyclopropylamino)-3-pyridinecarbonitrile;

(b) hydrolyzing the 2-(cyclopropylamino)-3-pyridinecarbonitrile to yield 2-(cyclopropylamino)-3-pyridine carboxylic acid;

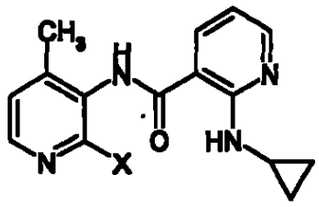
(c) isolating the 2-(cyclopropylamino)-3-pyridine carboxylic acid from the reaction medium;

(d) treating the 2-(cyclopropylamino)-3-pyridine carboxylic acid with a chlorinating agent, to yield 2-(cyclopropylamino)-3-pyridinecarbonyl chloride;

(e) reacting the 2-(cyclopropylamino)-3-pyridine carbonyl chloride with a 2-halo-4-methyl-3-pyridinamine of the formula



wherein X is a fluorine, chlorine, bromine or iodine atom, preferably chlorine or bromine, to produce an N-(2-halo-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide of the formula



wherein X is a fluorine, chlorine, bromine or iodine atom, preferably chlorine or bromine; and

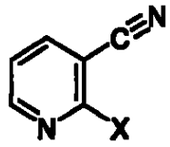
(f) cyclizing the N-(2-halo-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide by treatment with a strong base, to yield nevirapine.

2. 2-(Cyclopropylamino)-3-pyridine carboxylic acid.

3. 2-(Cyclopropylamino)-3-pyridinecarbonyl chloride .

4. A process for making 2-(cyclopropylamino)-3-pyridine carboxylic acid, which process comprises the following steps:

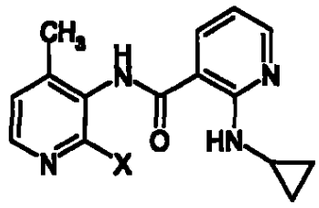
(a) reacting a 2-halo-3-pyridinecarbonitrile of the formula



wherein X is a fluorine, chlorine, bromine or iodine atom, preferably chlorine or bromine, with cyclopropylamine, to yield 2-(cyclopropylamino)-3-pyridinecarbonitrile; and

(b) hydrolyzing the 2-(cyclopropylamino)-3-pyridinecarbonitrile to yield 2-(cyclopropylamino)-3-pyridine carboxylic acid.

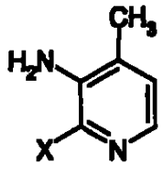
5. A process for preparing an N-(2-halo-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide of the formula



wherein X is a fluorine, chlorine, bromine or iodine atom, preferably chlorine or bromine, which comprises the following steps:

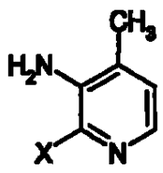
(a) treating 2-(cyclopropylamino)-3-pyridine carboxylic acid with a chlorinating agent, to yield 2-(cyclopropylamino)-3-pyridinecarbonyl chloride; and

(b) reacting the 2-(cyclopropylamino)-3-pyridine carbonyl chloride with a 2-halo-4-methyl-3-pyridinamine of the formula



wherein X is a fluorine, chlorine, bromine or iodine atom, preferably chlorine or bromine, to produce the N-(2-halo-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide.

6. A process for preparing an N-(2-halo-4-methyl-3-pyridinyl)-2-(cyclopropylamino)-3-pyridinecarboxamide which comprises reacting 2-(cyclopropylamino)-3-pyridine carbonyl chloride with a 2-halo-4-methyl-3-pyridinamine of the formula



wherein X is a fluorine, chlorine, bromine or iodine atom, preferably chlorine or bromine.

PATENT COOPERATION TREATY

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APS

PATENT SECTION SEP 23 2003

From the INTERNATIONAL SEARCHING AUTHORITY

To:
BOEHRINGER INGELHEIM CORPORATION
Attn. Raymond, Robert P.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
UNITED STATES OF AMERICA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

FILE DUMPED - LD = 1/28/04
ENTERS PAT'L PH - 12/28/04

	Date of mailing (day/month/year) 19/09/2003
Applicant's or agent's file reference 10/050PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 03/17376	International filing date (day/month/year) 02/06/2003
Applicant BOEHRINGER INGELHEIM CHEMICALS, INC.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO
   34, chemin des Colombettes
   1211 Geneva 20, Switzerland
   Facsimile No.: (41-22) 740.14.35

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

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

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

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

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

   Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

   Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	John De Bruijn received 9/24/03

Form PCT/ISA/220 (July 1998)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
10/050PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 03/17376	02/06/2003	28/06/2002
Applicant		
BOEHRINGER INGELHEIM CHEMICALS, 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.

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

1. Basis of the report

   a. With regard to the language, the international search was carried out on the basis of 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 readble 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,

   [X] the text is approved as submitted by the applicant.

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

5. With regard to the abstract,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box 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.

INTERNATI NAL SEARCH REPORT

International Application No
PCT/US 03/17376

38

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/14 C07D213/82 C07D213/78 C07D213/80 C07D213/85
//A61K31/551,(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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 366 972 A (HARGRAVE KARL D ET AL) 22 November 1994 (1994-11-22) cited in the application column 6, line 58 - column 7, line 66; column 11, line 43 - column 12, line 13 column 6, line 58 -column 7, line 66	1
A	US 5 569 760 A (SCHNEIDER HEINRICH ET AL) 29 October 1996 (1996-10-29) cited in the application columns 1 and 2, scheme	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.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 2003	19/09/2003

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

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATI NAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/17376

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATI NAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/17376

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		PT 667348 T	31-08-2000

PCT REQUEST

10/050PCT

Original (for SUBMISSION) - printed on 02.06.2003 10:50:13 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	10/050PCT
I	Title of invention	IMPROVED METHOD OF MAKING NEVIRAPINE
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States
II-4	Name	BOEHRINGER INGELHEIM CHEMICALS, INC.
II-5	Address:	2820 North Normandy Drive P.O. Box 1658 Petersburg, VA 23805 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)	BOSWELL, Robert, F., Jr.
III-1-5	Address:	Boehringer Ingelheim Chemicals, Inc. 2820 North Normandy Drive P.O. Box 1658 Petersburg, VA 23805 United States of America

III-2	Applicant and/or inventor	
III-2-1	This person is:	inventor only
III-2-4	Name (LAST, First)	GUPTON, Bernard, Franklin
III-2-5	Address:	Boehringer Ingelheim Chemicals, Inc. 2820 North Normandy Drive P.O. Box 1658 Petersburg, VA 23805 United States of America
III-3	Applicant and/or inventor	
III-3-1	This person is:	inventor only
III-3-4	Name (LAST, First)	LO, Young, S.
III-3-5	Address:	Boehringer Ingelheim Chemicals, Inc. 2820 North Normandy Drive P.O. Box 1658 Petersburg, VA 23805 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); POCCHIARI, Susan, K.(45,016); DATLOW, Philip, I.(41,482); WITKOWSKI, Timothy, X.(40,232); DOW, David, A.(46,124)

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 BZ 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 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-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	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	60/392,690
VI-1-3	Country	US

PCT REQUEST 10/050PCT

Original (for SUBMISSION) - printed on 02.06.2008 10:50:13 AM

VI-2	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	
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	13	-
IX-3	Claims	4	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	23	
	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-19	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	Alan Stempel	
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	
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

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

Date of mailing (day/month/year) 29 July 2003 (29.07.03)	
Applicant's or agent's file reference 10/050PCT	IMPORTANT NOTIFICATION
International application No. PCT/US03/17376	International filing date (day/month/year) 02 June 2003 (02.06.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 28 June 2002 (28.06.02)
Applicant BOEHRINGER INGELHEIM CHEMICALS, 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(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
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(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

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)	60/392,690	US	07 July 2003 (07.07.03)

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

Facsimile No. (41-22) 338.89.70

Authorized officer
Hélène CAMPIN (Fax 338 8970)

Telephone No. (41-22) 338 9718

PATENT COOPERATION TREATY

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 10/050PCT	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2003/017376	02 June 2003 (02.06.2003)	28 June 2002 (28.06.2002)

Applicant
BOEHRINGER INGELHEIM CHEMICALS, 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, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, 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 2004/002988

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 I/A, 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

Form PCT/IB/308 (April 2002)

PATENT COOPERATION TREATY

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	IMPORTANT NOTICE
10/050PCT	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2003/017376	02 June 2003 (02.06.2003)	28 June 2002 (28.06.2002)

Applicant

BOEHRINGER INGELHEIM CHEMICALS, 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, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, 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 2004/002988

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 I/A, 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

National Phase 12/28/04

PATENT COOPERATION TREATY

PCT/US2003/017

AR549

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

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

ENTRS NAT'L PH - 12/28/2004

Date of mailing (day/month/year)	
08 January 2004 (08.01.2004)	
Applicant's or agent's file reference	**IMPORTANT INFORMATION**
10/050PCT	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US2003/017376	02 June 2003 (02.06.2003)	28 June 2002 (28.06.2002)

Applicant

BOEHRINGER INGELHEIM CHEMICALS, INC.

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR
   National: AU, BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NI, NO, PL, RO, RU, SK

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   AP: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW
   EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
   OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
   National: AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SC, SD, SE, SG, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1) (a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3) (b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

received
1/21/04

RECEIVED
JAN 20 2004
PATENT SECTION

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

Form PCT/IB/332 (September 1997)

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: 10/050PCT
International application No.: PCT/US03/17376	International filing date *(day/month/year)*: 02 June 2003	(Earliest) Priority date *(day/month/year)*: 38 June 2002
Title of invention: Improved Method for Making Nevirapine		

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)*	Telephone No.: 203-798-9988 Facsimile No.: 203-798-4408 Teleprinter No.: Applicant's registration No. with the Office:
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. 900 Ridgebury Road, P.O. Box 368 Ridgefield, Connecticut USA 06877-0368	

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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.

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International application No.
PCT/US03/17376

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 368
Ridgefield, Connecticut 06877-0368 USA

Telephone No.
203-798-9988

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:

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Sheet No. 9

International application No.
PCT/US03/17378

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:			For International Preliminary Examining Authority use only: received	not received
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	☐	☐

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

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

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:

53

PATENT COOPERATION TREATY

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PCT NEW SECTION

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

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

ETATS UNIS PM- 12/28/2004

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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

Date of mailing *(day/month/year)*	27-11-2003
Applicant's or agent's file reference: 10/050PCT	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/17376	02/06/2003	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:

20/11/2003

2. This date of receipt is:

- [X] 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
12/5/03

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/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	KEMLE S Y G Tel. (+49-89) 2399-8588

Form PCT/IPEA/402 (July 1998) P20452 (24/11/2003)

PATENT COOPERATION TREATY

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AKS

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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 TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

ENTER PAT'L PH — 12/28/2004

Date of mailing (day/month/year)	24.05.2004
Applicant's or agent's file reference: 10/050PCT	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 03/17376	02.06.2003	28.06.2002

Applicant
BOEHRINGER INGELHEIM CHEMICALS, 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 inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel. +49 89 2399-8042

Form PCT/IPEA/416 (January 2004)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 10/050PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/17376	International filing date (day/month/year) 02.06.2003	Priority date (day/month/year) 28.06.2002

International Patent Classification (IPC) or both national classification and IPC
C07D471/14

Applicant
BOEHRINGER INGELHEIM CHEMICALS, 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 4 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 66.2(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	Date of completion of this report
20.11.2003	24.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ousset, J-B Telephone No. +49 89 2399-8271

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/US 03/17376

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

1-13 as originally filed

Claims, Numbers

1-6 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:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 2-4,5(part),6(part) .

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	2-4,5(part),6(part)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2-4,5(part),6(part)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	2-4,5(part),6(part)
	No:	Claims	

2. Citations and explanations

   see separate sheet

SECTION V

1). Relevant prior art is represented by:

D1: US-A-5 366 972 (HARGRAVE KARL D ET AL) 22 November 1994 (1994-11-22) cited in the application
D2: US-A-5 569 760 (SCHNEIDER HEINRICH ET AL) 29 October 1996 (1996-10-29) cited in the application

2). None of the cited documents discloses the claimed intermediates in which the position 2 of the pyridyl ring is substituted by the group cyclopropylamino.
Novelty is thus acknowledged.

3). D1 represents the closest prior art, since it discloses also a process to make available the same end compound.

The problem underlying the current application appears to be the provision of a further process to make available nevirapine and the corresponding intermediate derivatives.

In view of the examples given in the description, the problem has been solved.

Since in D1, the cyclopropylamino group is introduced after the condensation of the two different pyridyl entities, the skilled person cannot find in D2 the information, which would let him know that this cyclopropylamino group could be introduced before the condensation.
Therefore, the proposed process is the result of an inventive approach.
Since the process is inventive, the claimed intermediates are also inventive, because they are necessary for the making of the inventive process.

4). There is no objection with regard to industrial applicability.

Traducción

TRATADO DE COOPERACIÓN DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 del PCT)

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Referencia del expediente del agente o solicitante: 10-050PCT	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)
Solicitud Internacional No.: PCT/US03/17376	Fecha de presentación internacional (*día/mes/año*): 02.06.2003	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 CHEMICALS, 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 4 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	Fecha de terminación de este reporte
20.11.2003	24.05.2004
Nombre y dirección de correo de la autoridad encargada del examen preliminar Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Funcionario Autorizado Ousset, J-B Teléfono No. +49 89 2399-8271

Formato PCT/IPEA/409 (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 – 13 como se presentaron originalmente

Las reivindicaciones, número

1 – 6 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.)

6. Observaciones adicionales, si es necesario:

IV. Falta de Unidad de Invención

1. En respuesta a la invitación a restringir o pagar tasas adicionales, el solicitante ha:

☐ restringido las reivindicaciones.

☐ pagado tasas adicionales.

☐ pagado tasas adicionales bajo protesta.

☒ no ha restringido ni ha pagado tasas adicionales.

2. ☐ Esta autoridad encontró que el requerimiento de unidad de invención no se cumple y elige, de acuerdo a la Regla 68.1, no invitar al solicitante a restringir o pagar tasas adicionales.

3. Esta autoridad considera que el requerimiento de unidad de invención de acuerdo con las Reglas 13.1, 13.2 y 13.3 se

☐ cumple.

☐ no se cumple por las siguientes razones:

4. Consecuentemente, las siguientes partes de la solicitud internacional están sujetas al examen preliminar internacional que se establece en este reporte:

☐ todas sus partes

☒ Las partes relacionadas con las reivindicaciones Nos. 2-4, 5 (en parte), 6 (en parte)

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)	SI	Reivindicaciones	2-4, 5 (en parte), 6 (en parte)
	NO	Reivindicaciones	
Nivel inventivo (NI)	SI	Reivindicaciones	2-4, 5 (en parte), 6 (en parte)
	NO	Reivindicaciones	
Aplicación industrial (AI)	SI	Reivindicaciones	2-4, 5 (en parte), 6 (en parte)
	NO	Reivindicaciones	

2. Citas y explicaciones (Regla 70.7)

Ver hoja separada

SECCIÓN V

1.) El arte previo relevante está representado por:

D1: US-A-5 366 972 (HARGRAVE KARL D ET AL) 22 de Noviembre de 1994 (1994-11-22) citado en la solicitud.

D2: US-A-5 569 760 (SCHNEIDER HEINRICH ET AL) 29 de Octubre de 1996 (1996-10-29) citada en la solicitud.

2.) Ninguno de los documentos citados revelan los intermediarios reivindicados en los cuales la posición 2 del anillo de piridilo es sustituido por el grupo ciclopropilamino. De esta forma se reconoce la novedad.

3.) D1 representa el arte previo más cercano, debido a que revela también el proceso para hacer disponible el mismo compuesto final.

El problema que trata de resolver la presente invención parece ser el de proporcionar de un proceso adicional para hacer disponible la nevirapina y sus correspondientes derivados intermediarios.

En vista de los ejemplos dados en la descripción, el problema ha sido resuelto.

Debido a que en D1, el grupo de ciclopropilamino es introducido después de la condensación de dos diferentes entidades de piridilo, una persona versada no hubiera encontrado en D2 la información que lo llevara a saber que este grupo ciclopropilamino puede ser introducido antes de la condensación.

Entonces, el proceso propuesto es el resultado de un enfoque inventivo. Debido a que el proceso es inventivo, los intermediarios reivindicados también son inventivos, debido a que son necesarios para llevar a cabo el proceso inventivo.

4. No hay ninguna objeción con respecto a la aplicabilidad industrial.

MÉTODO MEJORADO PARA PREPARAR NEVIRAPINA

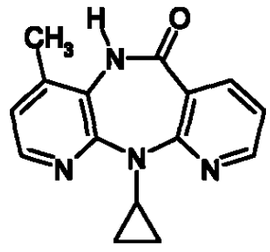
ANTECEDENTES DE LA INVENCIÓN

1. CAMPO TÉCNICO

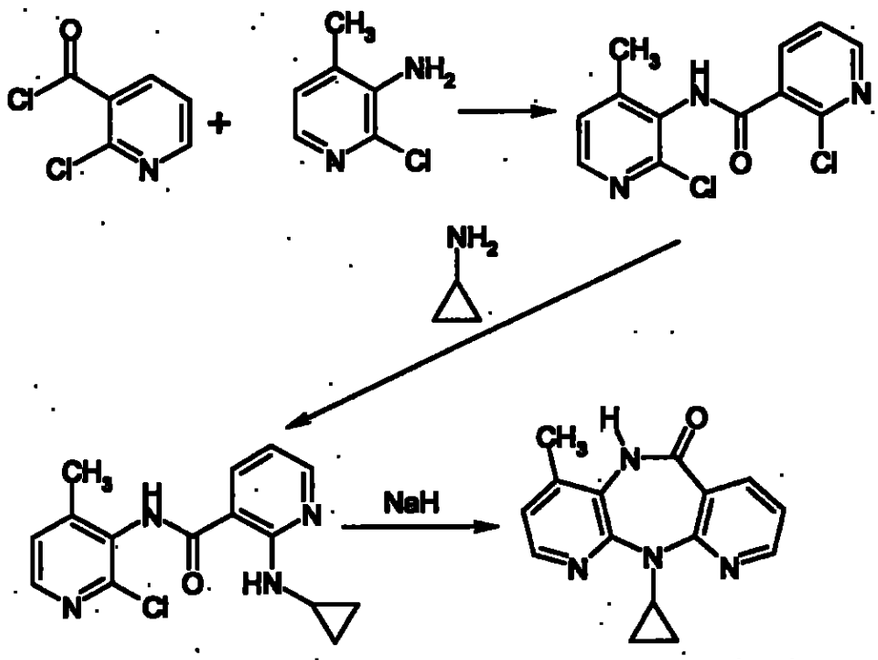
La invención se refiere a un método mejorado para preparar nevirapina y a varios nuevos compuestos intermedios que se producen durante el transcurso de llevar a cabo el método mejorado.

2. INFORMACIÓN DE ANTECEDENTES

Nevirapina es un inhibidor no nucleósido de la transcriptasa inversa de VIH, que es útil en el tratamiento de infecciones por VIH en seres humanos. El nombre químico de nevirapina es 11-ciclopropil-5,11-dihidro-4-metil-6H-dipirido[3,2-b:2',3'-e][1,4]diazepin-6-ona. Su fórmula estructural es:



La síntesis de nevirapina más temprana conocida, de Hargrave et al., se describe en la patente de EE.UU. 5.366.972. El método de síntesis empleado se describe en el siguiente Esquema de reacción 1.



Esquema 1

En el método de Hargrave et al. se forma cloruro de 2-cloronicotinoílo haciendo reaccionar ácido 2-cloronicotínico con cloruro de tionilo. Seguidamente, como se muestra en el Esquema 1, la reacción de cloruro de 2-cloronicotinoílo con 2-cloro-4-metil-3-piridinamina produce 2-cloro-N-(2-cloro-4-metil-3-piridinil)-3-piridincarboxamida. Ésta se hace reaccionar con ciclopropilamina para dar N-(2-cloro-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida. La etapa final es la ciclación para producir nevirapina, que se produce tras el tratamiento del producto intermedio final con hidruro de sodio.

Un refinamiento del procedimiento anterior, descrito por Schneider et al. en la patente de EE.UU. 5.569.760, se utiliza actualmente para la fabricación comercial de nevira-

pina. En esta mejora de la síntesis, la reacción de 2-cloro-N-(2-cloro-4-metil-3-piridinil)-3-piridincarboxamida con ciclopropilamina se lleva a cabo en presencia de un agente neutralizante, que es un óxido o hidróxido de un elemento del segundo grupo principal o del segundo subgrupo de la Tabla Periódica. Se prefiere utilizar en calidad de agente neutralizante un óxido o hidróxido de un metal alcalinotérreo o de cinc, siendo particularmente preferido óxido de calcio.

Mientras que la síntesis proporcionada por la patente de EE.UU. 5.366.972 es la mejor conocida hasta la fecha, adolece no obstante de varios inconvenientes significativos. En primer lugar, debido a que la reacción de ciclopropilamina con 2-cloro-N-(2-cloro-4-metil-3-piridinil)-3-piridincarboxamida se lleva a cabo a temperatura elevada (entre 130° y 150°C) y dado que ciclopropilamina es tan altamente volátil, esta reacción se debe llevar a cabo en un recipiente de reacción a presión elevada. En segundo lugar, 2-cloro-N-(2-cloro-4-metil-3-piridinil)-3-piridincarboxamida se vuelve térmicamente inestable por encima de aproximadamente 145°C, y al permitir que la temperatura de la mezcla de reacción supere esta temperatura, crea el riesgo de una explosión. Por lo tanto, es prudente controlar cuidadosamente la temperatura de la mezcla de reacción, de modo que permanezca por debajo de 145°C hasta que esencialmente la totalidad de este material haya sido consumido por la reacción. En el mejor de los casos, es difícil mantener un control tan estrecho de la temperatura de la mezcla de reacción, y se dificulta mucho más por el hecho de que la propia reacción sea exotérmica. En tercer lugar, es necesario separar el agente neutralizante mediante filtración. Finalmente, debido a la producción de productos secundarios, el rendimiento global de la síntesis es sólo de aproximadamente 25%.

Existe por lo tanto la necesidad de una mejor síntesis

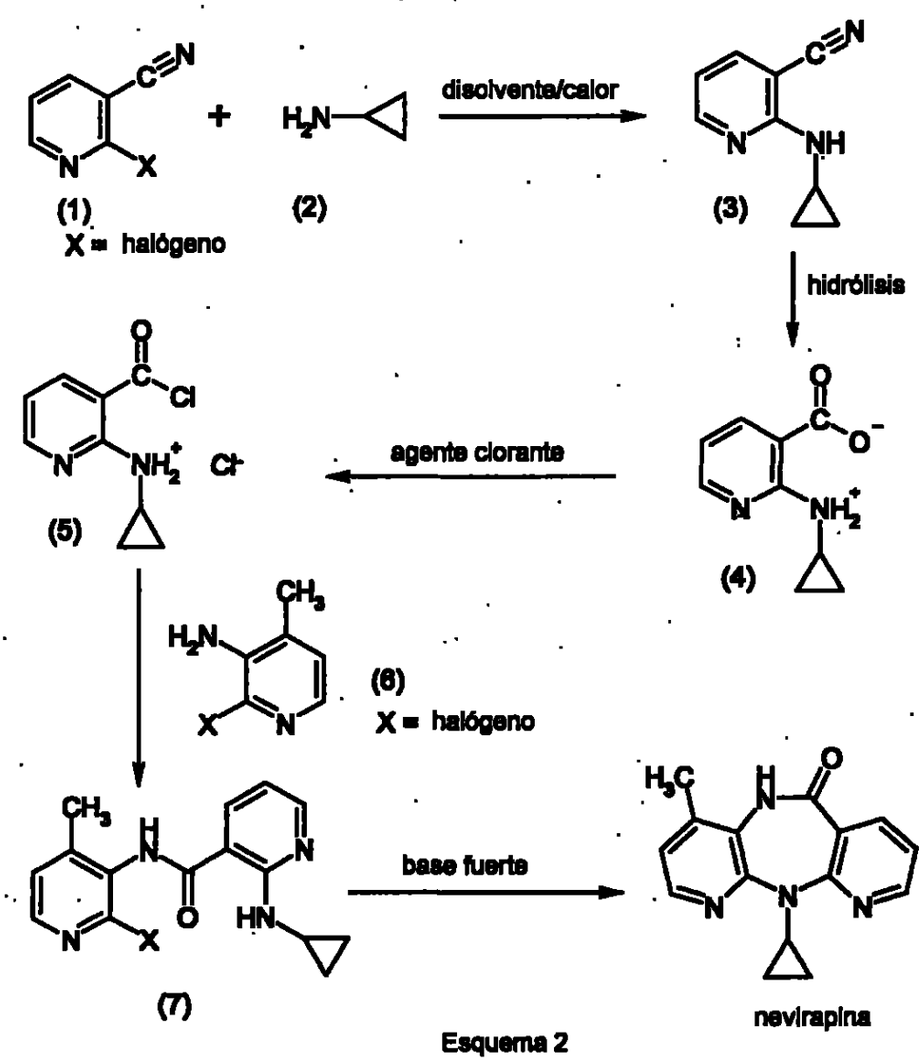
de nevirapina.

BREVE SUMARIO DE LA INVENCIÓN

La presente invención satisface esta necesidad al proporcionar una síntesis de nevirapina que es más segura, con un mayor rendimiento y más económica que cualquier método hasta ahora conocido.

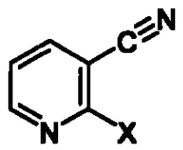
DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La síntesis mejorada de nevirapina proporcionada por la presente invención se describe a continuación en el Esquema de reacción 2.



Esquema 2

En la primera etapa de reacción, un 2-halo-3-piridincarbonitrilo (1) de la fórmula



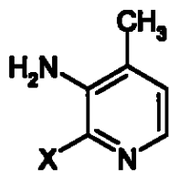
en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo, se hace reaccionar con ciclopropilamina (2), para proporcionar 2-(ciclopropilamino)-3-piridincarbonitrilo (3). Esta reacción se lleva a cabo en un disolvente orgánico inerte, con o sin agua, a temperatura elevada. Disolventes orgánicos apropiados son alcoholes C_1 a C_6 de cadena lineal o ramificada, tetrahidrofurano, dimetilformamida, diglima, tolueno y similares. Los disolventes preferidos son etanol y 1-propanol, con o sin agua. Opcionalmente, se puede añadir en calidad de un agente depurador de ácidos una base, ya sea orgánica o inorgánica, tal como trietilamina, diisopropiletilamina, fosfato de potasio, carbonato de sodio, carbonato de potasio y similares. La reacción se puede llevar a cabo a una temperatura entre la temperatura ambiente y la temperatura de reflujo, pero se prefiere que la temperatura oscile entre 77° y 100°C.

El 2-(ciclopropilamino)-3-piridincarbonitrilo se hidroliza seguidamente para proporcionar ácido 2-(ciclopropilamino)-3-piridina-carboxílico (4) que existe predominantemente en calidad del ion híbrido cuando se aísla de acuerdo con los procedimientos descritos y, por lo tanto, se representa como tal en el Esquema 2. El aislamiento del nitrilo antes de la hidrólisis es opcional. La hidrólisis del nitrilo en el ácido carboxílico se puede llevar a cabo de una manera convencional, utilizando una solución de carácter fuertemente ácido o básico. La hidrólisis se lleva a cabo preferiblemente utilizando una mezcla acuosa de peróxido de hidrógeno y una base fuerte tal como hidróxido de sodio o potasio, o una mezcla acuosa de una base fuerte tal como hidróxido de sodio o potasio, y un alcohol de 1 a 6 átomos de carbono. Lo más preferiblemente, la hidrólisis se lleva a cabo utilizando 1-propanol acuoso e hidróxido de potasio. El calentamiento a reflujo acelerará la velocidad de hidrólisis.

El ácido 2-(ciclopropilamino)-3-piridina-carboxílico se aísla seguidamente a partir del medio de reacción. Esto se consigue convenientemente ajustando el pH en el punto isoeléctrico, que se alcanza aproximadamente a pH 6. Esto produce el ion híbrido que precipita y se separa luego por filtración y se seca. Si para llevar a cabo la hidrólisis se utilizan un alcohol acuoso y una base, el alcohol se separa primeramente por destilación.

Subsiguientemente, el ácido 2-(ciclopropilamino)-3-piridina-carboxílico se trata con un agente clorante, para proporcionar cloruro de 2-(ciclopropilamino)-3-piridincarbonilo (5). Agentes clorantes apropiados son, por ejemplo, cloruro de tionilo, oxicloruro de fósforo, tricloruro de fósforo, pentacloruro de fósforo, fosgeno y cloruro de oxalilo. La cloración se efectúa de una manera conocida por los expertos en la técnica de la síntesis orgánica. En general, se prefiere someter a reflujo el ácido carboxílico (4) con el agente clorante, que se utilizará de forma pura o en solución con un disolvente aprótico adecuado tal como, por ejemplo, tolueno, acetonitrilo, tetrahidrofurano o similares. Se prefiere realizar la cloración mediante reflujo con cloruro de tionilo puro, cualquier exceso del cual puede ser posteriormente separado convenientemente por evaporación. Dado que la mayoría de los agentes clorantes producen ácido clorhídrico, el producto (5) de esta etapa de reacción se describe en el Esquema 2 en forma del hidrocloruro.

El cloruro de 2-(ciclopropilamino)-3-piridincarbonilo (5) se hace reaccionar seguidamente con una 2-halo-4-metil-3-piridinamina (6) de la fórmula



en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo. El reaccionante más preferido es 2-cloro-4-metil-3-metil-piridinamina. Ésta produce una N-(2-halo-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridin-carboxamida (7), en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo. Es esencial separar primero cualquier agente clorante remanente, ya que éste reaccionaría con la piridinamina. Si un agente clorante muy volátil, tal como cloruro de tionilo, se utiliza puro, entonces éste se puede separar por evaporación para dejar el cloruro de ácido (5) en forma de un sólido. Si la cloración se realiza en un disolvente, entonces es preferible emplear un disolvente que tenga un elevado punto de ebullición, de modo que el agente clorante pueda separarse por evaporación, dejando el cloruro de ácido disuelto en el disolvente. En cualquier caso, el cloruro de ácido (5) se ha de mantener en condiciones anhidras. El cloruro de ácido (5) y la piridinamina (6) se hacen reaccionar mediante disolución en un disolvente anhidro adecuado tal como, por ejemplo, acetonitrilo, tetrahidrofurano, diglima, dimetilformamida, dioxano, cloruro de metileno o tolueno. Opcionalmente, en calidad de un agente depurador de ácidos se puede añadir a la mezcla de reacción una base, ya sea orgánica u inorgánica, tal como trietilamina, diisopropiletilamina, fosfato de potasio, hidrógeno-fosfato de potasio, carbonato de sodio, hidróxido de sodio, hidróxido de potasio o similares. La velocidad de reacción se puede incrementar calentando hasta el punto de ebullición del disolvente.

Finalmente, la carboxamida (7) se cicla para proporcionar nevirapina. La ciclación se induce tratando la carboxamida (7) con una base fuerte tal como hidruro de sodio (NaH) o hexametildisilazano de sodio (NaHMDS) en un disolvente orgánico anhidro inerte tal como diglima, tolueno o tetrahidrofurano, a -30°C hasta 130°C.

La síntesis del producto intermedio 2-(ciclopropilami-

no)-3-piridincarbonitrilo por medio de la reacción de 2-cloro-3-piridincarbonitrilo con ciclopropilamina es conocida a partir de G.E. Hardtmann et al, J. Med. Chem. 1974, 17, 636.

Los productos intermedios ácido 2-(ciclopropilamino)-3-piridina-carboxílico (4) y cloruro de 2-(ciclopropilamino)-3-piridincarbonilo (5) se piensan que son nuevos y, así, se consideran aspectos de la invención.

Se prefiere utilizar 2-cloro-3-piridincarbonitrilo como material de partida (1), ya que las síntesis de estas sustancias son conocidas y se encuentra comercialmente disponible. De manera análoga se pueden sintetizar fácilmente otros 2-halo-3-piridincarbonitrilos.

Ciclopropilamina, el material de partida (2), está también disponible en el comercio.

Se prefiere utilizar 2-cloro-4-metil-3-piridinamina como reaccionante (6), ya que las síntesis de estas sustancias son conocidas a partir de las patentes de EE.UU. 6.399.781; 5.686.618; 5.668.287; 5.654.429 y 5.200.522. De una manera análoga se pueden sintetizar fácilmente otras 2-halo-4-metil-3-piridinaminas.

Los siguientes ejemplos ilustran adicionalmente la preparación de nevirapina utilizando el procedimiento mejorado proporcionado por la presente invención. Mientras que cada etapa de la secuencia de reacción se puede llevar a cabo aislando primeramente el producto de la etapa precedente, algunas de las etapas de reacción se pueden llevar a cabo secuencialmente, en un recipiente de reacción, sin aislamiento del producto intermedio formado por la etapa precedente, reduciendo así los costos asociados con el tiempo en el recipiente, la limpieza y el trabajo. Los siguientes Ejemplos 1-6 ilustran el enfoque en el que se aísla el producto intermedio formado al completarse cada etapa. Los Ejemplos 7 y 8 ilustran la forma en que pueden llevarse a cabo secuencialmente algunas de las etapas de

reacción, en un recipiente de reacción, sin aislamiento del producto intermedio formado por la etapa precedente.

Ejemplo 1. Preparación de 2-(ciclopropilamino)-3-piridincarbonitrilo

Un matraz de reacción equipado con un agitador mecánico, controlador de temperatura, condensador y embudo de adición se cargó con 2-cloro-3-piridincarbonitrilo (69,25 g, 0,50 mol), 300 ml de etanol y 200 ml de agua. Con agitación, se añadió ciclopropilamina (114 g, 2,0 mol) gota a gota a lo largo de 30 minutos a una temperatura < 30°C. Cuando se completó la adición, la mezcla de reacción agitada se calentó a la temperatura de reflujo durante 20 horas. La mezcla de reacción se enfrió hasta 60°C y luego se separaron por destilación en vacío, utilizando el vacío del aspirador de agua, 350 ml de cloropropilamina en exceso y etanol. La solución acuosa remanente se enfrió hasta la temperatura ambiente y se dejó reposar durante una noche. El producto sólido se recogió por filtración y la torta de filtración se aclaró con agua. El rendimiento era 81,51 g (el rendimiento teórico es 79,5 g).

Ejemplo 2. Preparación de ácido 2-(ciclopropilamino)-3-piridina-carboxílico (ion híbrido)

Una solución acuosa al 45% de KOH (187 g, 1,5 mol) se cargó a una mezcla del producto del Ejemplo 1 y 300 ml de 1-propanol. La mezcla se calentó a la temperatura de reflujo durante aproximadamente 5 horas, tras lo cual el análisis por CCD mostró una hidrólisis completa del nitrilo. La mezcla de reacción se enfrió hasta la temperatura ambiente y se trató con 94 g de agua que se necesitaron para separar el 1-propanol por destilación azeotrópica. Aproximadamente 330 g de azeótropo de agua/1-propanol se separan por destilación a 62°C y 535,9 mm de Hg. A la mezcla de reacción se añadió agua (130 g) y la mezcla se enfrió bruscamente hasta 5-10°C.

Se añadió ácido clorhídrico concentrado (148 g, 1,5 mol) a una velocidad tal que la temperatura podía mantenerse por debajo de 30°C. Después de añadir aproximadamente el 80-90% del ácido, el ion híbrido comenzó a separarse por precipitación, haciendo que la mezcla se volviera bastante espesa. Cuando se hubo añadido la totalidad del ácido, el producto sólido se recogió por filtración utilizando 90 ml de agua fría para aclarar el recipiente de reacción sobre la torta de filtración. El producto se secó para proporcionar 68,12 g del ion híbrido.

Ejemplo 3. Preparación de cloruro de 2-(ciclopropilamino)-3-piridincarbonilo

Cloruro de tionilo (25 ml, 40,8 g, 0,343 mol) se cargó en una corriente fina a 9,00 g (0,048 mol) de ácido 2-(ciclopropilamino)-3-piridina-carboxílico procedente del Ejemplo 2 en acetonitrilo. La mezcla se calentó a la temperatura de reflujo durante 30 minutos. La mezcla se dejó enfriar y el cloruro de tionilo se separó por destilación a 40°C/ 584,2 mm de Hg hasta que el contenido del recipiente se volvió espeso. Se añadió tolueno (25 ml) y se continuó la destilación de cloruro de tionilo y tolueno a 40°C hasta que se destiló aproximadamente la mitad del líquido. La solución remanente se dejó enfriar y se agitó para fomentar la cristalización. A la mezcla se añadió con agitación heptano (25 ml) y la mezcla se filtró bajo una atmósfera de nitrógeno para obtener el compuesto del título.

Ejemplo 4. Preparación de N-(2-cloro-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida

Una solución de 2-cloro-4-metil-3-piridinamina (5,70 g, 0,040 mol) en 10 ml de acetonitrilo se cargó rápidamente gota a gota a una mezcla del cloruro de ácido procedente del Ejemplo 3, fosfato de potasio anhidro molido (8,49 g, 0,04 mol) y 40 ml de acetonitrilo. La mezcla de reacción se

calentó a 50°C durante 20 horas, y el progreso de la reacción se vigiló mediante el análisis por HPLC. Cuando se completó la reacción, la mezcla de reacción se enfrió hasta la temperatura ambiente y se trató con 50 ml de agua, dando una solución con un pH de aproximadamente 4,5-5. La mezcla se acidificó hasta pH 1 mediante la adición de solución diluida de HCl y se agitó durante 30 min a la temperatura ambiente. La mezcla de reacción se filtró para separar cualquier material insoluble, y el filtrado se basificó hasta pH 9-10 con solución diluida de hidróxido de sodio y se agitó durante 30 minutos a la temperatura ambiente. A continuación, la mezcla se acidificó hasta pH 7-8 mediante la adición de HCl diluido, formando una capa oleosa oscura sobre la parte superior de la solución. Se añadió agua, ya que se había observado durante experimentos anteriores de una naturaleza similar que aceleraba la cristalización. La capa oleosa cristalizó lentamente al agitar durante una noche. El producto sólido se recogió y secó en una estufa de vacío a 50°C, para obtener 9,37 g del compuesto del título.

Ejemplo 5: Preparación de 11-ciclopropil-5,11-dihidro-4-metil-6H-dipirido[3,2-b:2',3'-e][1,4]diazepin-6-ona (nevirapina) utilizando hexametildisilazano de sodio

Un matraz de reacción equipado con un agitador magnético, controlador de temperatura termopar, embudo de adición y condensador con un burbujeador de aceite para la exclusión del aire ambiente se inertizó con nitrógeno y se cargó con 3,02 g (0,010 mol) de N-(2-cloro-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida procedente del Ejemplo 4 y 30 ml de THF anhidro. Se añadió gota a gota, manteniendo la temperatura de la mezcla de reacción a no más de 30°C, una solución al 40% de hexametildisilazano de sodio en THF (12,7 ml, 0,025 mol). Cuando se completó la adición de la solución de NaHMDS, la mezcla de reacción se calentó a la temperatura de reflujo (aproximadamente 63-

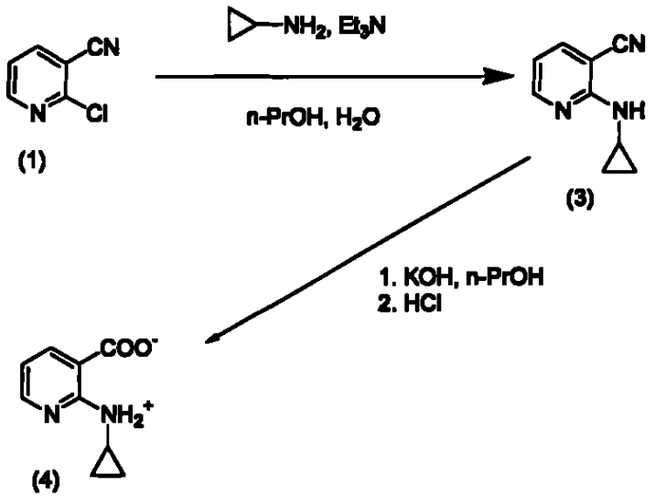
66°C). Cuando se completó la reacción (análisis por HPLC), la mezcla se enfrió hasta la temperatura ambiente. La mezcla de reacción se trató con 1,55 g (0,050 mol) de metanol y 0,45 g de agua (0,025 mol). La mezcla se concentró en un evaporador rotatorio a 635-762 mm de Hg con una temperatura del baño de agua de 50-60°. El producto residual que pesada 4,44 g se trituró con 50 ml de agua, y la solución de pH 10-12 se acidificó hasta pH 3 añadiendo solución al 10% de HCl. El producto sólido se recogió por filtración y la torta de filtración se aclaró tres veces con porciones de 10 ml de agua. La torta de filtración se secó en una estufa de vacío a 50-60°C para obtener nevirapina.

Ejemplo 6: Preparación de 11-ciclopropil-5,11-dihidro-4-metil-6H-dipirido[3,2-b:2',3'-e][1,4]diazepin-6-ona (nevirapina) utilizando hidruro de sodio

Un matraz 4NRB de 500 ml con agitador, controlador de temperatura termopar, embudo de adición y condensador con un burbujeador de aceite para excluir el aire se inertizó con nitrógeno y se cargó con 15,00 g de hidruro de sodio al 60% en una suspensión de aceite mineral y 120 ml de diglima. La mezcla se calentó hasta 130°C y se trató gota a gota con una solución de 41,7 g (0,138 mol) de N-(2-cloro-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida, procedente del Ejemplo 4, en 70 ml de diglima a 80°C. La mezcla de reacción se calentó a 130°C hasta que cesó el desprendimiento de hidrógeno. La mezcla se enfrió hasta la temperatura ambiente y se añadió gota a gota cuidadosamente agua (6,75 g). Cuando cesó el desprendimiento de hidrógeno, se añadieron 100 ml adicionales de agua. Para reducir el pH de la mezcla desde 11-13 hasta aproximadamente 7 se añadió ácido acético (20 ml). Se añadieron 100 ml adicionales de agua, y la mezcla de reacción se agitó en condiciones ambiente durante 30 minutos, al tiempo que cristalizaba el producto. El producto sólido se recogió por filtración, y la

torta de filtración se aclaró con 100 ml de agua, seguido de 50 ml de ciclohexano para separar cualquier aceite mineral residual de la suspensión de aceite mineral de hidruro de sodio. La torta húmeda se secó en una estufa de vacio a 50°C durante 18 horas para obtener 35,58 g de nevirapina.

Ejemplo 7. Síntesis en un recipiente de ácido 2-(ciclopropilamino)-3-piridina-carboxílico a partir de 2-cloro-3-piridincarbonitrilo



Un matraz 4NRB de un litro con agitador, condensador, controlador de la temperatura termopar y embudo de adición se cargó con 2-cloro-3-piridincarbonitrilo (27,70 g, 0,20 mol), seguido de 120 ml de 1-propanol y 80 ml de agua. Se añadió en una porción trietilamina (20,2 g, 0,20 mol), seguido de la adición de ciclopropilamina (17,10 g, 0,30 mol) a lo largo de un período de 2 minutos. La mezcla de reacción se calentó a reflujo (86-87°C) y, después de 2,5 horas, un análisis por CCD (gel de sílice, fase móvil MTBE) mostró una cierta formación de producto. Después de agitar a reflujo durante 16 horas, el análisis por CCD mostró un poco de material de partida remanente. El análisis por HPLC

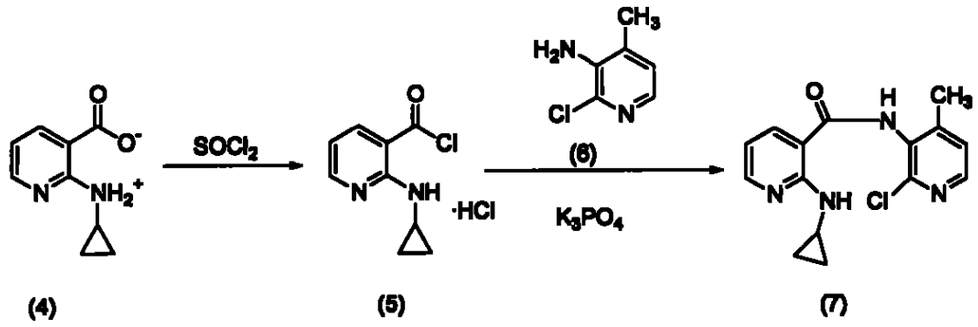
mostró 22% de material de partida-75% de 2-(ciclopropilamino)-3-piridincarbonitrilo. Se añadieron 0,1 mol (10,1 g) de trietilamina (total de 30,3 g, 0,30 mol de trietilamina) y 0,03 mol de ciclopropilamina (1,70 g) adicionales, y la mezcla se continuó calentando a reflujo durante otras 3 horas. El análisis por HPLC mostró 15% de material de partida remanente. Se añadieron 4,0 g adicionales de ciclopropilamina (total 0,40 mol) y la mezcla se calentó a reflujo durante otras 18 horas. Al término de este tiempo, el análisis por HPLC mostró 2,9% de material de partida.

Se añadió hidróxido de potasio (33,6 g, 0,60 mol) y la mezcla se calentó hasta aproximadamente 40°C bajo vacío durante aproximadamente 15 minutos para separar cualesquiera aminas volátiles. A continuación, la mezcla se calentó a reflujo durante 5 horas bajo presión atmosférica para hidrolizar el nitrilo en el ácido carboxílico. Se añadió agua (80 ml) y se separó por destilación n-propanol en forma de un azeótropo con agua (el punto de ebullición del azeótropo es de 87,7°C, 28,3% de agua, 71,7% de n-propanol). Cuando la temperatura de la cabeza de destilación aumentó hasta 92°C, se detuvo la destilación y se dejó que la mezcla de reacción se enfriara.

La mezcla de reacción se enfrió bruscamente hasta aproximadamente 10°C con un baño de hielo-metanol y 50 ml (59,2 g) de solución al 37% de HCl se añadieron gota a gota, manteniendo la mezcla de reacción en no más de 25°C. Se añadió la totalidad del HCl y, después de agitar durante aproximadamente 2 minutos, comenzó una cristalización más larga del ácido 2-(ciclopropilamino)-3-piridina-carboxílico y el producto se convirtió en una torta. Se añadió agua (100 ml) para disgregar la masa sólida y hacer agitable la mezcla. Después de aproximadamente 30 minutos, el sólido se recogió por filtración. Se obtuvo un sólido adicional concentrando el filtrado. Después de secar mediante

aspiración por aire durante aproximadamente 2 h, el sólido a modo de torta húmeda pesaba 23,02 g. La HPLC mostró 97% de ácido 2-(ciclopropilamino)-3-piridina-carboxílico y dos pequeños picos de impurezas desconocidas de concentraciones 1,8% y 1,3%. El sólido se secó en una estufa de vacío a 50°C durante 65 horas para proporcionar 18,19 g.

Ejemplo 8. Síntesis en un recipiente de N-(2-cloro-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida a partir de 2-cloro-4-metil-4-piridinamina y ácido 2-(ciclopropilamino)-3-piridina-carboxílico (ion híbrido)



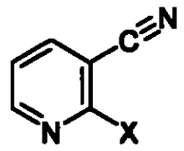
Un matraz 4NRB de 250 ml equipado con un agitador magnético, condensador, embudo de adición y controlador de la temperatura termopar, se cargó con ácido 2-(ciclopropilamino)-3-piridina-carboxílico (18,46 g, 0,10 mol). Se añadió cloruro de tionilo (22 ml, 0,30 mol) en una corriente delgada al matraz de reacción con agitación, y la mezcla se calentó a reflujo durante 32 minutos. La mezcla de reacción se enfrió, y el condensador se reemplazó por un cabezal de destilación en vacío. El cloruro de tionilo se separó por destilación a 40°C a un vacío de 584,2 mm de Hg hasta que el contenido del recipiente de destilación se volvió espeso. Se añadió tolueno (30 ml) y la destilación se continuó hasta que se separó por destilación aproximadamente la mayoría del líquido. Se añadieron otros 30 ml de tolueno,

y aproximadamente la mitad del disolvente se separó por destilación en vacío. A la mezcla residual se añadió acetonitrilo (60 ml). Se añadió gota a gota una solución de 2-cloro-4-metil-3-piridinamina (11,4 g, 0,080 mol) en 40 ml de acetonitrilo, y la mezcla de reacción se calentó hasta 50°C y se agitó durante una noche. Después de la adición de 2-cloro-4-metil-3-piridinamina se añadió fosfato de potasio finamente desmenuzado. Después de 16 h a 50°C, se añadieron 100 ml de agua a la mezcla de reacción agitada (pH 4-5). La mezcla de reacción se filtró para separar una pequeña cantidad de material insoluble. El filtrado (2 capas) se basificó hasta pH 10-11 con solución acuosa al 50% de NaOH y luego se acidificó de nuevo hasta pH 8. La mayoría del producto se encontró en la capa de tolueno mediante análisis por HPLC. La capa de tolueno se extrajo con 300 ml de solución diluida de HCl (pH 1). La capa de ácido acuosa se basificó hasta pH 8 utilizando NaOH acuoso al 10%, dando como resultado la separación de una capa oleosa que cristalizó lentamente con trituración. Después de reposar a lo largo de 2 días, el producto sólido se recogió y se secó en vacío a 50°C para proporcionar 21,40 g del compuesto del título en forma de un sólido castaño.

REIVINDICACIONES

1.- Un procedimiento para preparar nevirapina, que comprende las siguientes etapas:

(a) hacer reaccionar un 2-halo-3-piridincarbonitrilo de la fórmula



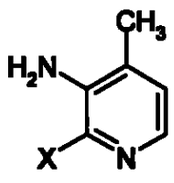
en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo, con ciclopropilamina para proporcionar 2-(ciclopropilamino)-3-piridincarbonitrilo;

(b) hidrolizar el 2-(ciclopropilamino)-3-piridincarbonitrilo para proporcionar ácido 2-(ciclopropilamino)-3-piridina-carboxílico;

(c) aislar el ácido 2-(ciclopropilamino)-3-piridina-carboxílico a partir del medio de reacción;

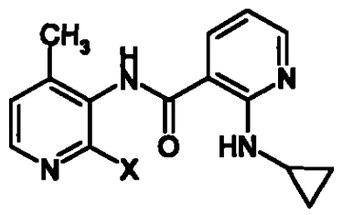
(d) tratar el ácido 2-(ciclopropilamino)-3-piridina-carboxílico con un agente clorante para proporcionar cloruro de 2-(ciclopropilamino)-3-piridincarbonilo;

(e) hacer reaccionar el cloruro de 2-(ciclopropilamino)-3-piridincarbonilo con una 2-halo-4-metil-3-piridinamina de la fórmula



en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo, para producir una N-(2-halo-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxa-

mida de la fórmula



en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo; y

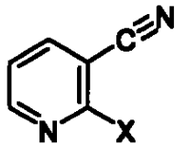
(f) ciclar la N-(2-halo-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida mediante tratamiento con una base fuerte, para proporcionar nevirapina.

2.- Ácido 2-(ciclopropilamino)-3-piridina-carboxílico [BI49].

3.- Cloruro de 2-(ciclopropilamino)-3-piridincarbonilo [BI50].

4.- Un procedimiento para preparar ácido 2-(ciclopropilamino)-3-piridina-carboxílico, procedimiento que comprende las siguientes etapas:

(a) hacer reaccionar un 2-halo-3-piridincarbonitrilo de la fórmula

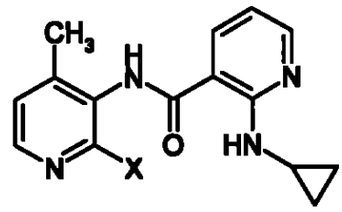


en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo, con ciclopropilamina para proporcionar 2-(ciclopropilamino)-3-piridincarbonitrilo; y

(b) hidrolizar el 2-(ciclopropilamino)-3-piridincarbonitrilo para proporcionar ácido 2-(ciclopropilamino)-3-piridina-carboxílico.

5.- Un procedimiento para preparar una N-(2-halo-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida

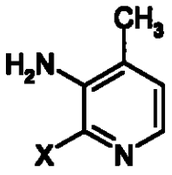
de la fórmula



en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo, que comprende las siguientes etapas:

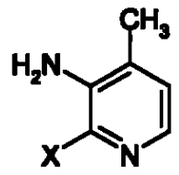
(a) tratar ácido 2-(ciclopropilamino)-3-piridina-carboxílico con un agente clorante para proporcionar cloruro de 2-(ciclopropilamina)-3-piridincarbonilo;

(b) hacer reaccionar el cloruro de 2-(ciclopropilamino)-3-piridincarbonilo con una 2-halo-4-metil-3-piridinamina de la fórmula



en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo, para producir una N-(2-halo-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida.

6.- Un procedimiento para preparar una N-(2-halo-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida, que comprende hacer reaccionar cloruro de 2-(ciclopropilamino)-3-piridincarbonilo con una 2-halo-4-metil-3-piridinamina de la fórmula



en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo.

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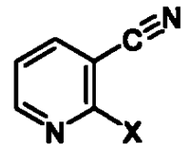
RESUMEN

Un procedimiento para preparar nevirapina, que comprende las siguientes etapas:

(a) hacer reaccionar un 2-halo-3-piridincarbonitrilo de la fórmula



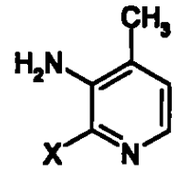
en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo, con ciclopropilamina para proporcionar 2-(ciclopropilamino)-3-piridincarbonitrilo;

(b) hidrolizar el 2-(ciclopropilamino)-3-piridincarbonitrilo para proporcionar ácido 2-(ciclopropilamino)-3-piridina-carboxílico;

(c) aislar el ácido 2-(ciclopropilamino)-3-piridina-carboxílico a partir del medio de reacción;

(e) tratar el ácido 2-(ciclopropilamino)-3-piridina-carboxílico con un agente clorante para proporcionar cloruro de 2-(ciclopropilamino)-3-piridincarbonilo;

(f) hacer reaccionar el cloruro de 2-(ciclopropilamino)-3-piridincarbonilo con una 2-halo-4-metil-3-piridinamina de la fórmula



en donde X es un átomo de flúor, cloro, bromo o yodo, preferiblemente cloro o bromo, para producir una N-(2-halo-4-metil-3-piridinil)-2-(ciclopropilamino)-3-piridincarboxamida; y

(g) ciclar la N-(2-halo-4-metil-3-piridinil)-2-(ciclopropil-amino)-3-piridincarboxamida mediante tratamiento con una base fuerte, para proporcionar nevirapina.

PRP/WPC14468/ID-000003

[redacted]

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

Item	Expediente No	05007450 No de unidades	No de Folio
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	1	✓
10	OTROS:		

Observaciones: aite final.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176009-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05007438 [illegible] Folios: 86
Fecha (AMD): 2005-01-28 17:08:23
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 05 - 4,988
FECHA : ENERO 24 DE 2005

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	32758706	24/01/2005	33,330,000.00

C O N C E P T O

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

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 14468-841-001-4

87

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05007438 00000000 Folios: 05
Fecha (AMD): 2005-01-28 17:00:23
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ **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. ✗	( )	(✓)
- 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 Neva

Fecha:

88

Industria y Comercio
SUPERINTENDENCIA

Folio 88

2020
Bogotá DC

Doctor
EMILIO FERRERO
Apoderado
BOEHRINGER INGELHEIM CHEMICALS, INC

REFERENCIA:		
	Radicación No.	05-7450
	Solicitud Internacional	PCT/US2003/017376
	Fecha inicio fase nacional	28-01-2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	011
	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 CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202027

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