

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

P2007/000091

SOLICITUD DE:

1

☐

Corrección de Error Material.

☒

Modificación a una Solicitud.

2

SOLICITANTE
(71)

Nombre: MERCK SHARP & DOHME CORP.

Dirección: 126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907 E.U.A

Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: ESTADOS UNIDOS DE
AMERICA

Teléfono: _____ Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: Diagonal 34 No. 5-28 Bogotá

Teléfono: 601-7700 Fax: 601-7799

E-mail: _____

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747 Bta
TP 74.295

4

Número de expediente:

07055540

5

Descripción de la corrección o modificación solicitada Me permito solicitar el
cambio de nombre del solicitante de MERCK & CO., INC. por el de MERCK SHARP &
DOHME CORP.

QUEDANDO COMO SOLICITANTES: MERCK SHARP & DOHME CORP. y INSTITUTO DI
RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI S.P.A.

6

Comprobante de pago No. _____

Fecha Mayo de 2010

7

Anexos

☒ Comprobante de pago de la tasa.

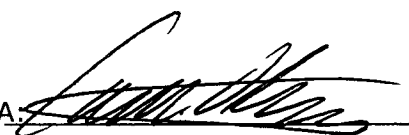
☒ Copia auténtica del Poder y copia auténtica del documento que soporta la cesión
de derechos. (ver expedientes 07-055.540)

☐ Documento que acredita la existencia y representación legal de las partes, cuando
sean personas jurídicas.

8

NOMBRE: CARLOS R. OLARTE

FIRMA



C.C. 79.782.747 Bta T.P. 74.295

2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

MIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 40,799
FECHA : MAYO 19 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-055540- -00004-0000

Fecha: 2010-05-21 12:12:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 329 CTOINFORMACION Folios: 29

**** CONSIGNACION ****

PROPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CLARTE RAISEBY	CONSIGNACION	BANCO DE BOGOTA	060754387	6238702	18/05/2010	2,052,000.00

**** CONCEPTO ****

CONCEPTO	CONCEPTO	TOTAL CONCEPTO
50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	114,000.00
	TOTAL :	\$ 114,000.00

SON: DIENTO CATORCE MIL PESOS

RECEPCIONABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

3

CERTIFICADO DE ADOPCIÓN DE
CERTIFICADO DE CONSTITUCIÓN REPLANTEADO DE
MERCK & CO., INC.

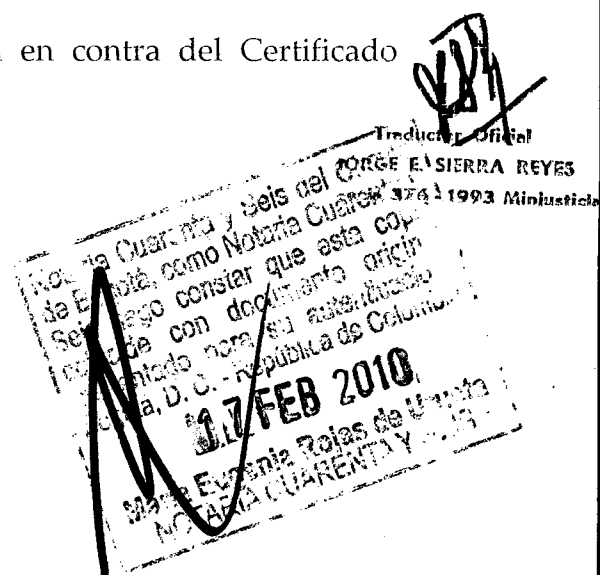
(Identificación: 5934701000)

Merck & Co., Inc., una compañía organizada y vigente según las leyes del Estado de New Jersey (la "Compañía"), para enmendar y replantear su Certificado de Constitución de acuerdo con la Sección 14A:9-5 de la Ley de Compañías Comerciales de New Jersey (la "NJBCA"), certifica por el presente lo siguiente:

PRIMERO: El nombre de la Compañía es Merck Sharp & Dohme Corp.

SEGUNDO: El Certificado de Constitución Replanteado adjunto a éste (el "Certificado Replanteado") fue adoptado por los accionistas de la Compañía el 7 de agosto de 2009 como parte de su aprobación del Acuerdo y Plan de Fusión fechado el 8 de marzo de 2009 entre la Compañía, Schering-Plough Corporation, SP Merger Subsidiary One, Inc. (conocida anteriormente como Blue, Inc.) y SP Merger Subsidiary Two, Inc. (conocida anteriormente como Purple, Inc.) y de acuerdo con la Sección 14A:10-1 y la Sección 14A:10-4.1 de la NJBCA.

TERCERO: El número de acciones autorizadas para votar acerca de la adopción del Certificado Replanteado fue 2.108.708.449 acciones ordinarias, de las cuales 1.399.114.521 votaron por el Certificado Replanteado como parte de su aprobación del Acuerdo y Plan de Fusión, y 5.686.148 votaron en contra del Certificado



Replanteado. Ninguna acción de ninguna clase o serie fue autorizada para votar sobre ese asunto como clase.

CUARTO: Este Certificado de Adopción entrará en vigencia el 3 de noviembre de 2009 a las 4:02 p.m.

En constancia de lo anterior, la Compañía ha hecho que este Certificado se ejecute de la debida forma el día 2 de noviembre de 2009.

MERCK & CO., INC.

Por: (firmado)

Nombre: Celia A. Colbert.

Cargo: Vicepresidente, Secretario y Representante Legal Asistente.

Sello: "Radicado. 2 de noviembre de 2009. Secretario de Hacienda del Estado."

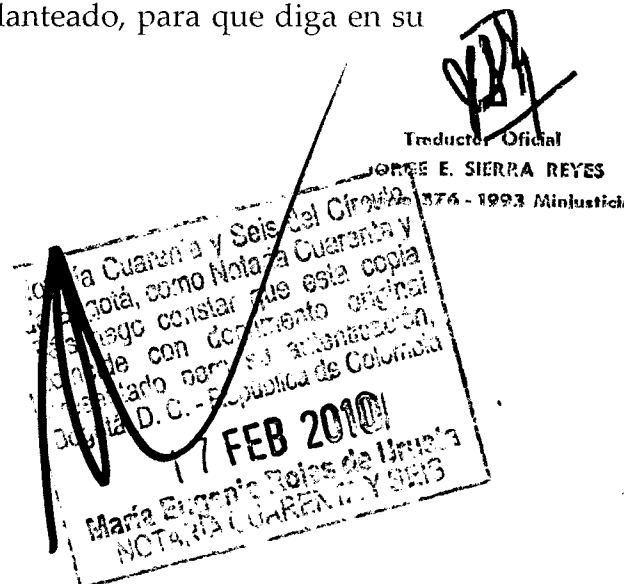
CERTIFICADO DE CONSTITUCIÓN REPLANTEADO

de

MERCK & CO., INC.

(Identificación: 5934701000)

Merck & Co., Inc., una compañía organizada y vigente según las leyes del Estado de New Jersey (la "Compañía"), replantea e integra su Certificado de Constitución Replanteado, como se enmendó previamente, y también enmienda sustantivamente tal Certificado de Constitución Replanteado, para que diga en su totalidad lo que aquí se presenta:



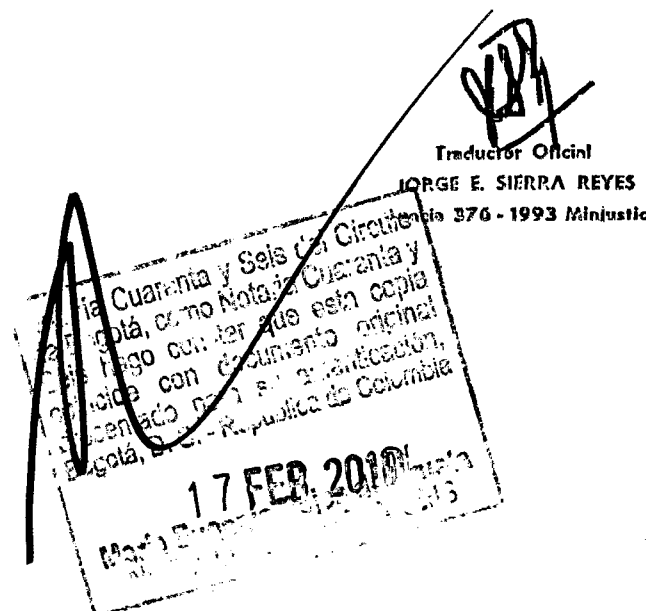
PRIMERO: El nombre de la Compañía es Merck Sharp & Dohme Corp. 

SEGUNDO: El propósito para el cual está organizada la Compañía es comprometerse en cualquier actividad que esté dentro de los objetivos para los cuales pueden organizarse las compañías de acuerdo con la Ley de Compañías Comerciales de New Jersey.

TERCERO: El número total de acciones de capital social que la Compañía tendrá la autoridad de emitir es 100 acciones de capital social, con un valor de \$0.01 por acción. Las acciones de capital social de la Compañía pueden ser emitidas por ésta de vez en cuando según las consideraciones legalmente suficientes que puedan ser fijadas de tanto en tanto por la Junta Directiva.

CUARTO: En fomento y no para limitación de las facultades generales conferidas por el Estado de New Jersey, la Junta Directiva está expresamente autorizada para hacer, alterar o rechazar los estatutos de la Compañía, excepto lo que específicamente aquí se establezca.

QUINTO: La Compañía se reserva el derecho de enmendar, alterar, cambiar o rechazar cualquier disposición contenida en el Certificado de Constitución, de la manera prescrita ahora o posteriormente por estatutos, y todos los derechos conferidos aquí a los accionistas se otorgan sujetos a esta reserva.



SEXTO: La Compañía, hasta donde sea permitido por la Ley de Compañías Comerciales de New Jersey, según pueda ser enmendado de vez en cuando, indemnizará a todas las personas a quienes pueda indemnizar de acuerdo con esto.

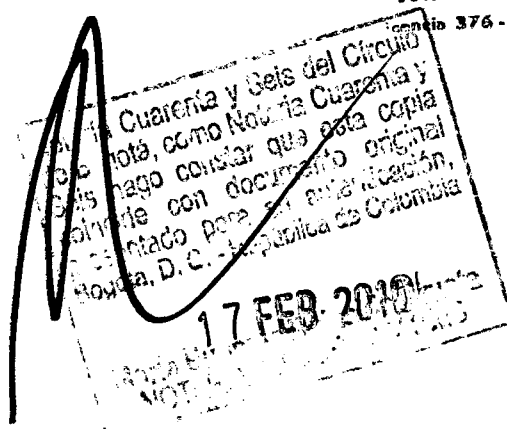
SÉPTIMO: Ningún directivo o funcionario de la Compañía será responsable personalmente ante la Compañía o sus accionistas por daños por infracción de cualquier obligación debida a la Compañía o sus accionistas, excepto si esa disposición no releva a un directivo o funcionario de su responsabilidad por alguna infracción de obligación basada en un acto u omisión (a) en violación de la obligación de lealtad de dicha persona a la Compañía o sus accionistas, (b) no de buena fe o participando de una violación conocida de la ley o (c) que resulta en recibo por parte de dicha persona de cualquier beneficio personal inapropiado. Conforme se usa en este artículo, un acto u omisión en infracción de la obligación de lealtad de una persona significa un acto u omisión que esa persona conoce o cree que es contraria a los mejores intereses de la Compañía o sus accionistas en conexión con un asunto en el cual tiene un conflicto de intereses materiales.

OCTAVO: Excepto si se exige de otra manera por las leyes del Estado de New Jersey, los accionistas y directivos tendrán la facultad de llevar a cabo sus reuniones y guardar los libros, documentos y papeles de la Compañía fuera del Estado de New Jersey y la Compañía tendrá la facultad de tener una o más oficinas dentro o fuera del Estado de New Jersey, en los lugares que puedan ser elegidos de vez en cuando por los estatutos o por resolución de los accionistas o directivos. Las

Traductor Oficial

JORGE E. SIERRA REYES

376 - 1993 Minjusticia

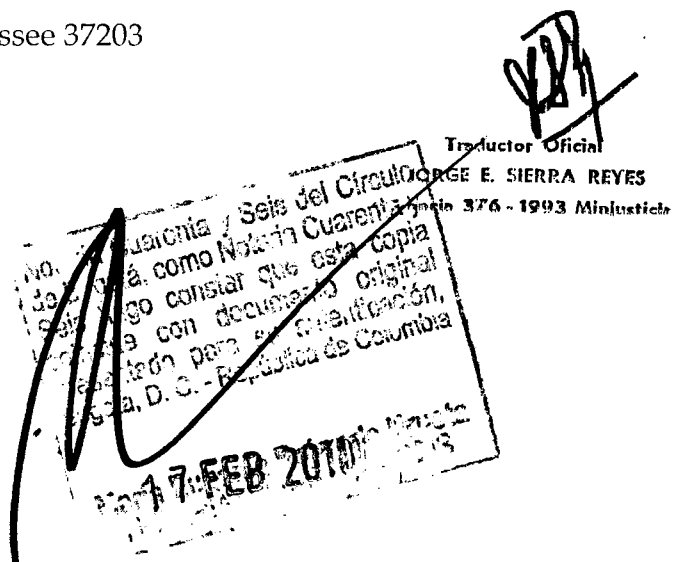


elecciones de directivos no necesitan realizarse por balota a menos que los estatutos de la Compañía lo dispongan de esa manera.

NOVENO: La dirección de la actual oficina registrada de la Compañía en el Estado de New Jersey es 820 Bear Tavern Road, City of West Trenton, County of Mercer, State of New Jersey, 08628 y el nombre del agente registrado de la Compañía en dicha dirección es The Corporation Trust Company.

DÉCIMO: El número de directivos que constituyen la actual Junta Directiva de la Compañía es quince (15). Los nombres y direcciones de dichos directivos son los siguientes:

Leslie A. Brun	435 Devon Park Drive, 700 Building Wayne, Pennsylvania 19087
Thomas R. Cech, Ph.D.	University of Colorado, Boulder Boulder, Colorado 80309-0215
Richard T. Clark	One Merk Drive Whitehouse Station, New Jersey 08889-0100
Thomas H. Glocer	3 Times Square, 30 th Floor New York, New York 10036
Steven F. Goldstone	570 Lexington Avenue, 37 th Floor New York, New York 10022
William B. Harrison, Jr.	277 Park Avenue, 35th Floor New York, New York 10172
Harry R. Jacobson, M.D.	3401 West End Avenue, Suite 300 Nashville, Tennessee 37203



William N. Kelley, M.D.

421 Curie Boulevard

Philadelphia, Pennsylvania 19104-6160

Rochelle B. Lazarus

636 11th Avenue

New York, New York 10036

Carlos E. Represas

Av. Ejercito Nacional No. 453

Colonia Granada,, 11520 Mexico, D.F. Mexico

Thomas E. Sheak, Ph.D.

Washington Road

Princeton, New Jersey 08544-1014

Anne M. Tatlock

One Merck Drive

Whitehouse Station, New Jersey 08889-0100

Samuel O. Thier, M.D.

55 Fruit Street, Bulfinch 370

Boston, Massachusetts, 02114-2606

Wendell P. Weeks

1 Riverfront Plaza

Corning, New York 14831

Peter C. Wendell

2884 Sand Hill Road, Suite 100

Menlo Park, California 94025

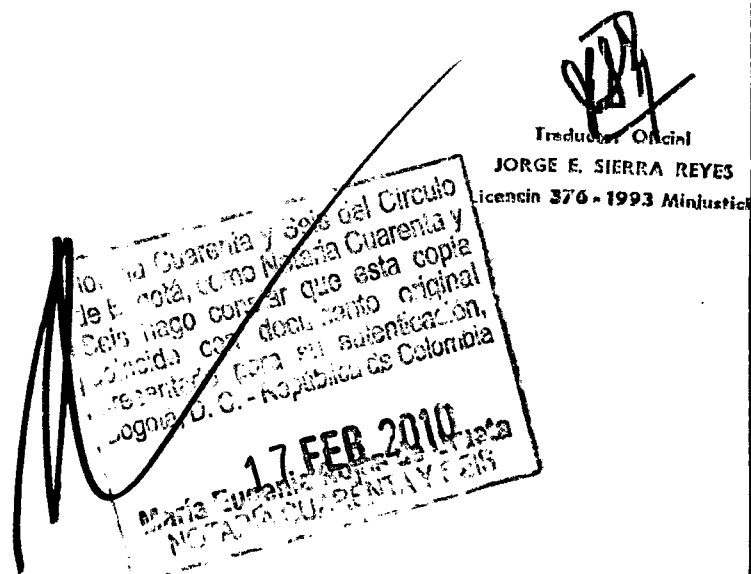
En testimonio de lo anterior, Merck & Co., Inc. hizo que este Certificado de Constitución Replanteado fuera debidamente ejecutado el día 2 de noviembre de 2009.

MERCK & CO., INC.

Por (firmado)

Nombre: Celia A. Colbert

Cargo: Vicepresidente, Secretario y Representante Legal Asistente.



ESTADO DE NEW JERSEY
DEPARTAMENTO DE HACIENDA
RADICACIÓN DE CERTIFICACIÓN (COPIA CERTIFICADA)

MERCK SHARP & DOHME CORP.

Yo, Secretario de Hacienda del Estado de New Jersey, certifico por el presente que el negocio mencionado anteriormente radicó y registró en este departamento los documentos especificados más adelante y que la anterior es una copia auténtica del Certificado Replanteado con un Cambio de Nombre puesto que el mismo fue tomado del original y comparado con dicho original, el cual fue archivado en esta oficina en la fecha establecida en cada instrumento y ahora permanece archivado y registrado en mi oficina.

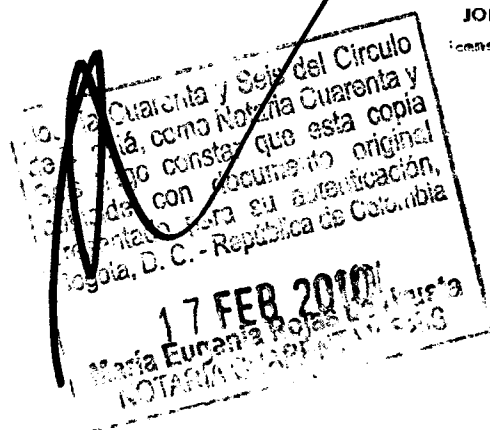
En testimonio de lo anterior he puesto mi firma y estampado mi sello oficial en Trenton, este día 23 de noviembre de 2009. (Firmado) R. David Rousseau, Secretario de Hacienda del Estado.

Sello: "El Gran Sello del Estado de New Jersey"

No. del Certificado: 115810389

Verifique este certificado por internet en:

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




Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

CERTIFICACIÓN NOTARIAL

Estados Unidos de América

Estado de New York, Condado de New York

Yo, Scott J. Lebson, Abogado del Estado de New York, certifico por el presente, de acuerdo con la Norma 2105 C.P.L.R., que he comparado lo anterior con el original y he encontrado que es una copia verdadera y completa.

(Firmado) Scott J. Lebson

Suscrito y juramentado ante mí este día 28 de diciembre de 2009.

(Firmado) Notario Público

Primer sello: "Lanning Gerald Bryer, Notario Público del Estado de New York, No. 31-4827394, calificado en el Condado de New York. Mi nombramiento vence el 31 de enero de 2011".

Segundo sello: "Lanning Gerald Bryer, Notario Público del Estado de New York, No. 02BR4827394, calificado en el Condado de New York. Mi nombramiento vence el 31 de enero de 2011".

Nota adjunta al certificado:

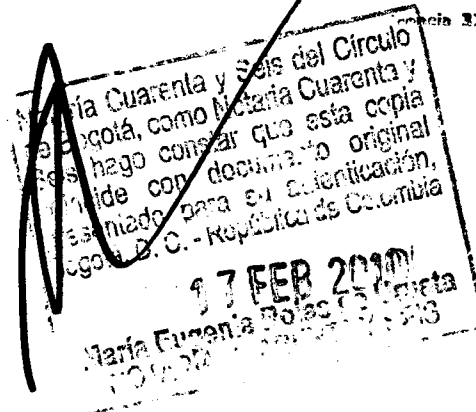
751923 - Estado de New York - Condado de New York.

Yo, Norman Goodman, Registrador del Condado y Registrador de la Corte Suprema, del Estado de New York, en y para el Condado de New York, una Corte de Registro, poseedor por ley de un sello, certifico por medio del presente

Traductor Oficial

JORGE E. SIERRA REYES

Matrícula 376 - 1993 Minjusticia



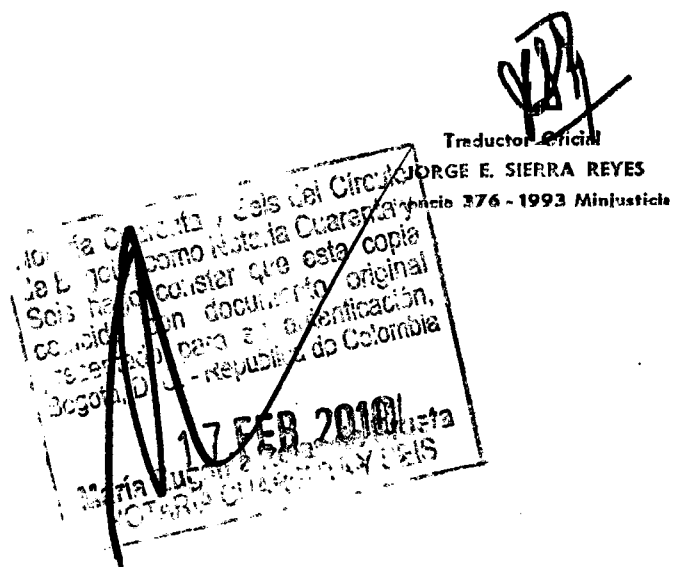
documento, según la Ley Ejecutiva del Estado de New York que Lanning Gerald Bryer, cuyo nombre está suscrito a la declaración, certificado de reconocimiento o prueba adjunta, era en el momento de tomar dicho documento un Notario Público en y para el Estado de New York, debidamente comisionado, juramentado y calificado para actuar como tal; que de acuerdo con la ley, una comisión o un certificado de su carácter oficial, con su firma autógrafa ha sido archivado en mi oficina; que al momento de tomar dicha prueba, reconocimiento o juramento, estaba debidamente autorizado para tomarlo; que estoy bien familiarizado con la firma de dicho Notario Público o he comparado su firma en el instrumento adjunto con la depositada en mi oficina por lo cual creo que la firma en el registro adjunto es genuina.

Como constancia de lo anterior, he puesto aquí mi firma y el sello oficial este día 8 de enero de 2010.

(Firmado): Norman Goodman – Registrador del Condado y Registrador de la Corte Suprema, Condado de New York.

Sello redondo sobre esta nota: "Registrador del Condado - Condado de New York"

Apostilla adjunta:



APOSTILLA:
(Convention de La Haye du 5 octobre 1961)

1. País: Estados Unidos de América

El presente documento público

Norman Goodman

Registrador del Condado

Condado de New York

Certificado

New York, New York

8 de enero de 2010

Secretario del Estado, Estado de New York

NYC-10734498A

9. Sello / estampilla: (en relieve)

10. Firma:

(Firmado) Lorraine Cortes Vasquez

Secretario del Estado

FIN DE LA TRADUCCIÓN

Certificación:

Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.

Documento: "Wreck Co., Inc. - Certificado de Adopción de Constitución"

Fecha: 4 de enero de 2010.

Traductor: Jorge Enrique Sierra Reyes (Sello y Firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia)

Excepción # 876 de 1998, expedida por el Ministerio de Justicia.

Dirección: Cuneu 15 # 99-18 Of. 411, Bogotá, D.C.

Teléfonos: (571) 218 2308, (571) 628 2925.

E-mail: travercil@lyghoo.com

Traducción # 14499

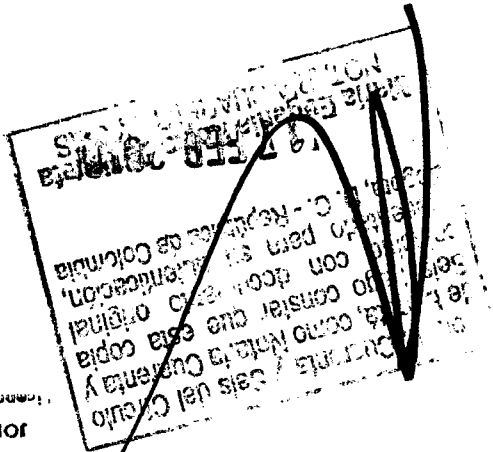
100 FEB 12 P. 41
JEFES DE LEGALIZACIONES
BOGOTÁ D.C.

NO ASUME
RESPONSABILIDAD
DEL TEXTO

Traductor Oficial

JORGE E. SIERRA REYES

Documento 376 - 1993 Ministerio



Apostille

(Convention de La Haye du 5 Octobre 1961)

13

1. Country: United States of America
This public document
2. has been signed by **Norman Goodman**
3. acting in the capacity of **County Clerk**
4. bears the seal/stamp of the county of **New York**

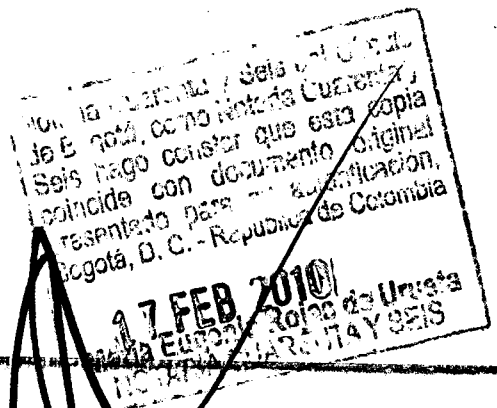
Certified

5. At New York, New York
6. the 08th day of January 2010
7. by Secretary of State, State of New York
8. No. NYC-10734498A
9. Seal/Stamp
10. Signature

Lorraine Cortes Vazquez

Lorraine Cortes Vazquez
Secretary of State

04135595.RSL (REV: 11/24/09)



14



State of New York
County of New York, } ss.

754125 Form 1

I, NORMAN GOODMAN, County Clerk and Clerk of the Supreme Court of the State of New York, in and for the County of New York, a Court of Record, having by law a seal, DO HEREBY CERTIFY pursuant to the Executive Law of the State of New York, that

Larry Gerald Beyer

whose name is subscribed to the annexed affidavit, deposition, certificate of acknowledgment or proof, was at the time of taking the same a NOTARY PUBLIC in and for the State of New York duly commissioned, sworn and qualified to act as such; that pursuant to law, a commission or a certificate of his official character, with his autograph signature has been filed in my office; that at the time of taking such proof, acknowledgment or oath, he was duly authorized to take the same; that I am well acquainted with the handwriting of such NOTARY PUBLIC or have compared the signature on the annexed instrument with his autograph signature deposited in my office, and I believe that such signature is genuine.

IN WITNESS WHEREOF, I have hereunto set my hand affixed my official seal this

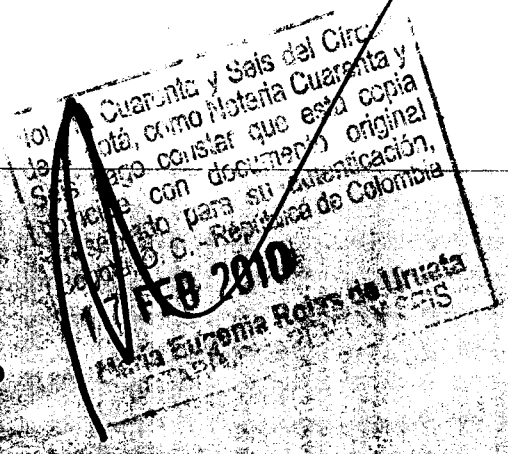
JAN 08 2010

FEE PAID \$3.00

Norman Goodman

County Clerk and Clerk of the Supreme Court, New York County

LADAS & PARRY LLP

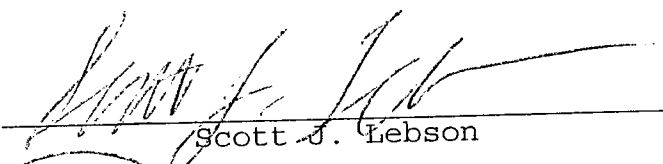


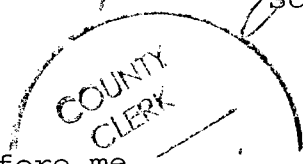
15

CERTIFICATION

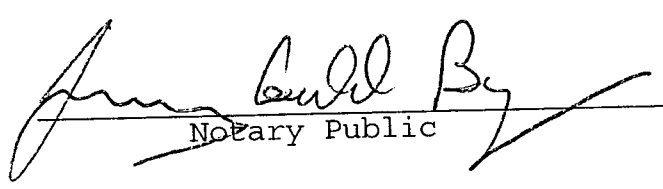
UNITED STATES OF AMERICA]
STATE OF NEW YORK] ss:
COUNTY OF NEW YORK]

I, Scott J. Lebson, an Attorney-At-Law of the State of New York, do hereby certify, pursuant to Rule 2105, C.P.L.R., that I have compared the foregoing with the original and have found it to be a true and complete copy.


Scott J. Lebson



Subscribed and sworn to before me
this 28th day of December 2009.


Notary Public

[SEAL]

LANNING GERALD BRYER
Notary Public, State of New York
No. 31-4827394
Qualified in New York County
Commission Expires January 31, 2011

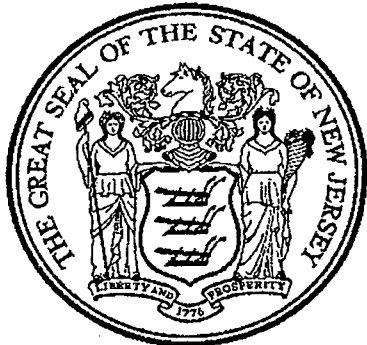
LANNING GERALD BRYER
Notary Public, State of New York
No. 02BR4827394
Qualified in New York County
Commission Expires January 31, 2011

Notaria Cuarenta y Seis del Circulo
de Bogotá, como Notaria Cuarenta y
Seis, hago constar que esta copia
con documento original
firmado para su autenticación,
31-01-2010, D.C. República de Colombia
17 FEB 2010
Escritorio de Ladas & Parry LLP

STATE OF NEW JERSEY
DEPARTMENT OF TREASURY
FILING CERTIFICATION (CERTIFIED COPY)

MERCK SHARP & DOHME CORP.

I, the Treasurer of the State of New Jersey,
do hereby certify, that the above named business
did file and record in this department the below
listed document(s) and that the foregoing is a
true copy of the
Restated Certificate With A Name Change
as the same is taken from and compared with the
original(s) filed in this office on the date set
forth on each instrument and now remaining on file
and of record in my office.



Certificate Number: 115810389

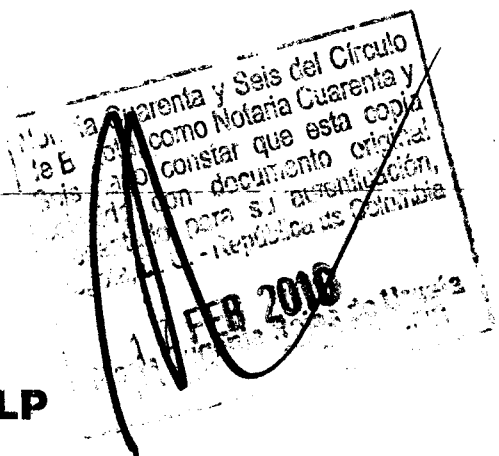
Verify this certificate online at

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

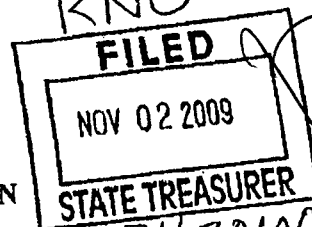
IN TESTIMONY WHEREOF, I have
hereunto set my hand and affixed
my Official Seal at Trenton, this
23rd day of November, 2009

A handwritten signature in black ink, appearing to read "R. David Rousseau".

R. David Rousseau
State Treasurer



CERTIFICATE OF ADOPTION
OF
RESTATED CERTIFICATE OF INCORPORATION
OF
MERCK & CO., INC.
(ID Number: 5934701000)



Merck & Co., Inc., a corporation organized and existing under the laws of the State of New Jersey (the "Corporation"), to amend and restate its Certificate of Incorporation pursuant to Section 14A:9-5 of the New Jersey Business Corporation Act (the "NJBCA"), hereby certifies as follows:

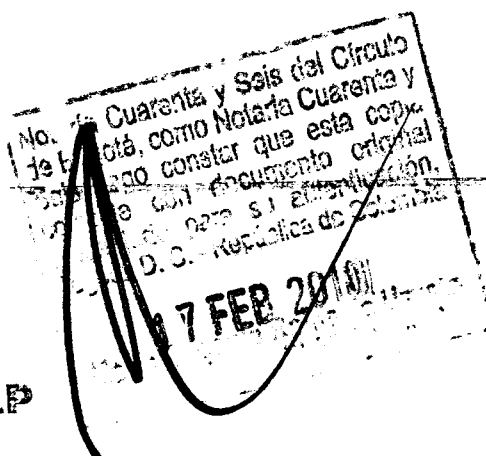
FIRST: The name of the Corporation is Merck Sharp & Dohme Corp.

SECOND: The Restated Certificate of Incorporation attached hereto (the "Restated Certificate") was adopted by the shareholders of the Corporation on August 7, 2009 as part of their approval of the Agreement and Plan of Merger, dated as of March 8, 2009, by and among the Corporation, Schering-Plough Corporation, SP Merger Subsidiary One, Inc. (formerly known as Blue, Inc.), and SP Merger Subsidiary Two, Inc. (formerly known as Purple, Inc.), and pursuant to Section 14A:10-1 and Section 14A:10-4.1 of the NJBCA.

THIRD: The number of shares entitled to vote on the adoption of the Restated Certificate was 2,108,780,449 shares of Common Stock, of which 1,399,114,521 voted for the Restated Certificate as part of their approval of the Agreement and Plan of Merger, and 5,686,148 voted against the Restated Certificate. No shares of any class or series were entitled to vote thereon as a class.

FOURTH: This Certificate of Adoption shall become effective on November 3, 2009 at 4:02 p.m.

5 2222357
✓ 4050605
✓ 4050606
✓ 4050607
✓ 4050608
✓ 4050609



LADAS & PARRY LLP

18

IN WITNESS WHEREOF, the Corporation has caused this Certificate to be duly executed as of the 2nd day of November, 2009.

MERCK & CO., INC.

By: Celia A. Colbert
Name: Celia A. Colbert
Title: Senior Vice President, Secretary
and Assistant General Counsel

Signature Page to Certificate of Adoption of Restated Certificate of Incorporation

Yo, la Cuarenta y Seis del Circulo
de 5, notó, como Notaria Cuarenta y
Seis, hago constar que esta copia
concluye un documento original
presentado para su autenticación,
por el Sr. [illegible] República de Colombia
17 FEB 2010

LADAS & PARRY LLP

9

**RESTATED CERTIFICATE OF INCORPORATION
OF**

**MERCK & CO., INC.
(ID Number: 5934701000)**

Merck & Co., Inc., a corporation organized and existing under the laws of the State of New Jersey (the "Corporation"), restates and integrates its Restated Certificate of Incorporation, as heretofore amended, and also substantively amends such Restated Certificate of Incorporation, to read in full as herein set forth:

FIRST: The name of the Corporation is Merck Sharp & Dohme Corp.

SECOND: The purpose for which the Corporation is organized is to engage in any activity within the purposes for which corporations may be organized under the New Jersey Business Corporation Act.

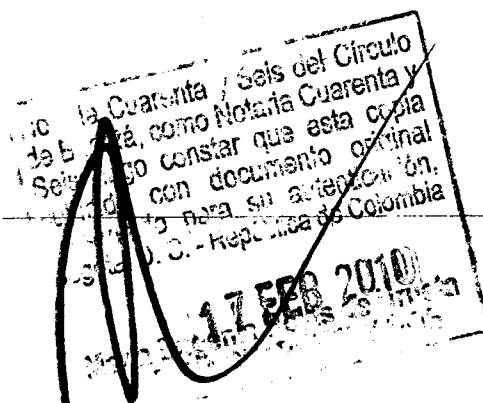
THIRD: The total number of shares of capital stock which the Corporation shall have authority to issue is 100 shares of common stock, \$0.01 par value per share. Shares of capital stock of the Corporation may be issued by the Corporation from time to time for such legally sufficient consideration as may be fixed from time to time by the Board of Directors.

FOURTH: In furtherance and not in limitation of the general powers conferred by the laws of the State of New Jersey, the Board of Directors is expressly authorized to make, alter or repeal the bylaws of the Corporation, except as specifically stated therein.

FIFTH: The Corporation reserves the right to amend, alter, change or repeal any provision contained in the Certificate of Incorporation, in the manner now or hereafter prescribed by statute, and all rights conferred upon shareholders herein are granted subject to this reservation.

SIXTH: The Corporation shall, to the full extent permitted by the New Jersey Business Corporation Act, as it may be amended from time to time, indemnify all persons whom it may indemnify pursuant thereto.

SEVENTH: No director or officer of the Corporation shall be personally liable to the Corporation or its shareholders for damages for breach of any duty owed to the Corporation or its shareholders, except that such provision shall not relieve a director or officer from liability for any breach of duty based upon an act or omission (a) in breach of such person's duty of loyalty to the Corporation or its shareholders, (b) not in good faith or involving a knowing violation of law or (c) resulting in receipt by such person of any improper personal benefit. As used in this article, an act or omission in breach of a person's duty of loyalty means an act or omission which that person knows or believes to be contrary to the best interests of the Corporation or its shareholders in connection with a matter in which he has a material conflict of interest.



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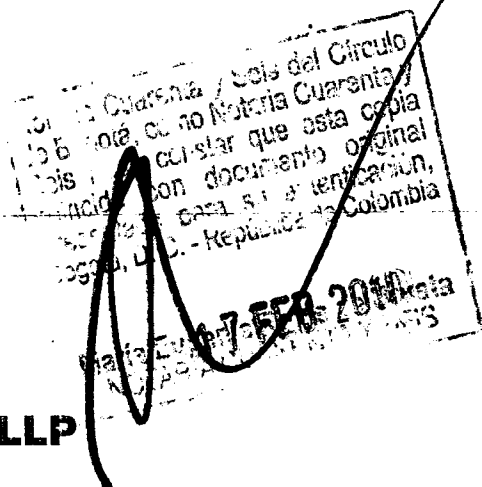
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EIGHTH: Except as otherwise required by the laws of the State of New Jersey, the shareholders and directors shall have the power to hold their meetings and to keep the books, documents, and papers of the Corporation outside of the State of New Jersey, and the Corporation shall have the power to have one or more offices within or without the State of New Jersey, at such places as may be from time to time designated by the bylaws or by resolution of the shareholders or directors. Elections of directors need not be by ballot unless the bylaws of the Corporation shall so provide.

NINTH: The address of the Corporation's current registered office in the State of New Jersey is 820 Bear Tavern Road, City of West Trenton, County of Mercer, State of New Jersey, 08628, and the name of the Corporation's registered agent at such address is The Corporation Trust Company.

TENTH: The number of directors constituting the current Board of Directors of the Corporation is fifteen (15). The names and addresses of said directors are as follows:

Leslie A. Brun	435 Devon Park Drive, 700 Building Wayne, Pennsylvania 19087
Thomas R. Cech, Ph.D.	University of Colorado, Boulder Boulder, Colorado 80309-0215
Richard T. Clark	One Merck Drive Whitehouse Station, New Jersey 08889-0100
Thomas H. Glocer	3 Times Square, 30 th Floor New York, New York 10036
Steven F. Goldstone	570 Lexington Avenue, 37 th Floor New York, New York 10022
William B. Harrison, Jr.	277 Park Avenue, 35 th Floor New York, New York 10172
Harry R. Jacobson, M.D.	3401 West End Avenue, Suite 300 Nashville, Tennessee 37203
William N. Kelley, M.D.	421 Curie Boulevard Philadelphia, Pennsylvania 19104-6160
Rochelle B. Lazarus	636 11 th Avenue New York, New York 10036
Carlos E. Represas	Av. Ejercito Nacional No. 453 Colonia Granada, 11520 Mexico, D.F. Mexico
Thomas E. Shenk, Ph.D	Washington Road Princeton, New Jersey 08544-1014
Anne M. Tatlock	One Merck Drive Whitehouse Station, New Jersey 08889-0100
Samuel O. Thier, M.D.	55 Fruit Street, Bulfinch 370 Boston, Massachusetts 02114-2606



Peter C. Wendell

2884 Sand Hill Road, Suite 100
Menlo Park, California 94025



LLP

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IN WITNESS WHEREOF, Merck & Co., Inc. caused this Restated Certificate of Incorporation to be duly executed as of November 2nd, 2009.

MERCK & CO., INC.

By:

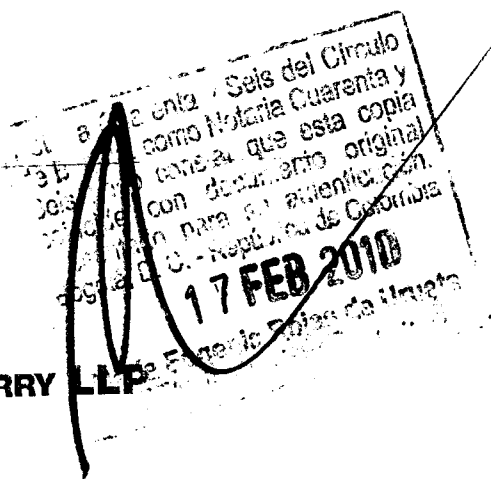
Celia A. Colbert

Name: Celia A. Colbert

Title: Senior Vice President, Secretary
and Assistant General Counsel

Signature Page to Restated Certificate of Incorporation of Merck & Co., Inc.

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

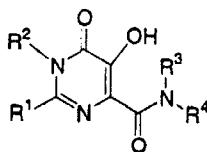
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Published:

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

(54) Title: N-SUBSTITUTED HYDROXYPYRIMIDINONE CARBOXAMIDE INHIBITORS OF HIV INTEGRASE



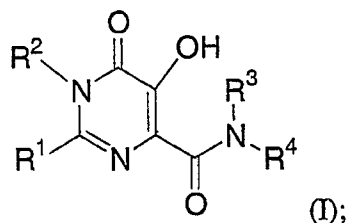
(I)

(57) Abstract: N-substituted 5-hydroxypyrimidin-6-one-4-carboxamides of formula (I): are described as inhibitors of HIV integrase and inhibitors of HIV replication, wherein R¹, R², R³ and R⁴ are defined herein. These compounds are useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS. The compounds are employed against HIV infection and AIDS as compounds per se or in the form of pharmaceutically acceptable salts. The compounds and their salts can be employed as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of preventing, treating or delaying the onset of AIDS and methods of preventing or treating infection by HIV are also described.

diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhibitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The inhibition of integrase in vitro and HIV replication in cells is a
 5 direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase in vitro in HIV infected cells. The particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication.

SUMMARY OF THE INVENTION

10 The present invention is directed to novel hydroxypyrimidinone carboxamides. These compounds are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS and/or ARC, either as compounds or their pharmaceutically acceptable salts or hydrates (when appropriate),
 15 or as pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention includes a compound of Formula (I):



20 wherein

R¹ is

- (1) -H,
- (2) -C₁₋₆ alkyl, which is optionally substituted with one or more
 25 substituents (e.g., optionally from 1 to 6, or 1 to 5, or 1 to 4, or 1 to 3, or 1 or 2 substituents; or is optionally mono-substituted) each of which is independently halogen, -OH, -CN, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -C(=O)R^a, -CO₂R^a, -SR^a, -S(=O)R^a, -N(R^aR^b), -C(=O)-C₀₋₆ alkyl-N(R^aR^b), N(R^a)-C(=O)-C₀₋₆ alkyl-N(R^bR^c),

- 2-(1-acetylpyrrolidin-2-yl)-N-[2-(dimethylamino)benzyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide;
- 5 2-[(2S)-1-acetylpyrrolidin-2-yl]-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide;
- N-(4-fluorobenzyl)-5-hydroxy-2-[4-hydroxy-1-(pyrazin-2-ylcarbonyl)pyrrolidin-2-yl]-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide;
- 10 N-[1-(4-{{(4-fluorobenzyl)amino}carbonyl})-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-1-methylethyl]imidazo[2,1-b][1,3]thiazole-6-carboxamide;
- 2-[(2S,4S)-1-acetyl-4-fluoropyrrolidin-2-yl]-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-
- 15 6-oxo-1,6-dihydropyrimidine-4-carboxamide;
- N-(4-fluorobenzyl)-5-hydroxy-1-methyl-2-{1-methyl-4-[(1-methyl-1H-imidazol-2-yl)carbonyl]piperazin-2-yl}-6-oxo-1,6-dihydropyrimidine-4-carboxamide;
- 20 N-(4-fluorobenzyl)-5-hydroxy-1-methyl-2-(1-methyl-1-{{(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl}amino}ethyl)-6-oxo-1,6-dihydropyrimidine-4-carboxamide;
- N1-{1-[4-{{(4-fluoro-2-(methylsulfonyl)benzyl)amino}carbonyl})-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-1-methylethyl}-N2,N2-
- 25 dimethylethanediamide;
- 2-(4-acetyl-1,2-dimethylpiperazin-2-yl)-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide;
- 30 N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-2-[1-(pyrimidin-4-ylcarbonyl)pyrrolidin-2-yl]-1,6-dihydropyrimidine-4-carboxamide;
- N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-2-[1-(pyrimidin-5-ylcarbonyl)pyrrolidin-2-yl]-1,6-dihydropyrimidine-4-carboxamide;
- 35

the monocyclic or bicyclic heterocycle defined in R^m is optionally substituted with one or more substituents (e.g., optionally from 1 to 6, or 1 to 5, or 1 to 4, or 1 to 3, or 1 or 2 substituents; or is optionally mono-substituted) each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, oxo, aryl, $-C_{1-6}$ alkyl-aryl, $-C(=O)$ -aryl, $-CO_2$ -aryl, $-CO_2-C_{1-6}$ alkyl-aryl, a 5- or 6-membered saturated heterocyclic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, or a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; and

10

each n is independently an integer equal to zero, 1 or 2;

or a pharmaceutically acceptable salt thereof.

15

The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of preventing AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV.

20

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

25

The present invention includes the N-substituted hydroxypyrimidinone carboxamides of Formula (I) above. These compounds and pharmaceutically acceptable salts thereof are HIV integrase inhibitors.

30

An embodiment of the present invention is a compound of Formula (I) exactly as defined above, except that in the definition of R^k , R^k is optionally substituted with one or more substituents each of which is independently one of the substituents (1) to (18), and is optionally mono-substituted with one of the substituents (19) to (34).

Another embodiment of the present invention is a compound of Formula (I) as originally defined above, except that the definition of R^2 includes a

using an alkaline phosphatase conjugated anti-FITC antibody and a chemiluminescent alkaline phosphatase substrate. Representative compounds (e.g., the compounds set forth in Table 1 below) tested in the integrase assay demonstrated IC₅₀'s of about 5 micromolar or less.

5 Further description on conducting the assay using preassembled complexes is found in Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al., *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

10 Certain compounds representative of the present invention have also been tested in an assay for inhibition of acute HIV infection of T-lymphoid cells, conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. These compounds demonstrated IC₉₅'s of about 20 micromolar or less.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. When the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

For the purpose of preventing or treating HIV infection or preventing, treating or delaying the onset of AIDS, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing a therapeutically effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the

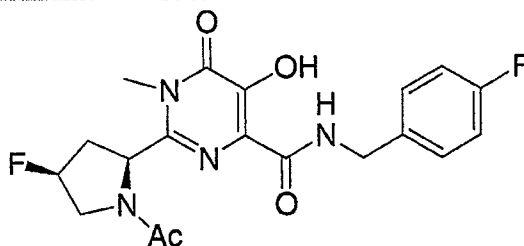
3h. The title compound was obtained as its trifluoroacetate salt by RP-HPLC purification (gradient of CH₃CN/H₂O + 0.01% TFA).

¹H-NMR (DMSO-d₆ +TFA, 400 MHz, 340K) δ 9.27 (bt, 1H), 7.94 (s, 1H), 7.40-7.36 (m, 2H), 7.15-7.11 (m, 2H), 4.48 (d, J= 6.4 Hz, 2H), 4.30-4.36, (m, 1H), 4.09 (dd, J= 13.6, 4.0 Hz, 1H), 3.91-3.86 (m, 5H), 3.34-3.30 (m, 5H), 3.18 (dd, J= 13.6, 4.0 Hz, 1H).

MS *m/z* 407 (M+H)⁺.

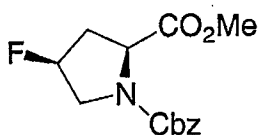
EXAMPLE 16

10 2-[(2S,4S)-1-acetyl-4-fluoropyrrolidin-2-yl]-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide



Step1: 1-Benzyl-2-methyl-(2S,4S)-4-fluoropyrrolidine-1,2-dicarboxylate

15

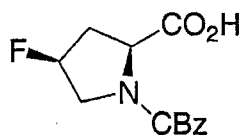


1-benzyl-2-methyl(2S,4R) 4-hydroxypyrrolidine-1,2 dicarboxylate in dichloromethane was added dropwise to a solution, precooled to -78 °C, of N,N-diethylaminosulfur trifluoride (1.0 eq.) in dichloromethane. The reaction was stirred while the temperature was allowed to increase to 25 °C. The solvent was concentrated under vacuum and the crude was purified by flash chromatography (eluent: petroleum ether: EtOAc = 1:1) to give the title compound.

¹H NMR (CDCl₃, 300 MHz, 300 K) δ 7.42-7.30 (m, 5H), 5.35-5.10 (m, 3H), 4.65 (d, J=9.6 Hz, 0.5H), 4.57 (d, J= 9.4Hz, 0.5H), 3.99-3.62 (m, 2H), 3.79 (s, 1.5H), 3.68 (s, 1.5H), 2.62-2.29 (m, 2H).

MS: *m/z* 282 (M+H)⁺.

Step 2: (4S)-1-[(Benzyloxy)carbonyl]-4-fluoro-L-proline



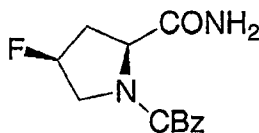
5 1-Benzyl-2-methyl-(2S,4S)-4-fluoropyrrolidine-1,2-dicarboxylate dissolved in methanol was treated with NaOH 1N (2 eq.) and the reaction mixture was stirred at 50 °C for 3 hours. After concentration of the solvent, HCl 1N was added until pH=1 and the aqueous layer was extracted three times with dichloromethane. The organic phase was washed with brine, dried over Na₂SO₄ and filtered to give, after
10 concentration, title compound.

¹H NMR (CDCl₃, 400 MHz, 300 K) δ 7.45-7.30 (m, 5H), 5.33-5.18 (m, 3H), 4.70-4.60 (bm, 1H), 4.00-3.65 (m, 2H), 2.85-2.25 (m, 2H).

MS: m/z 268 (M+H)⁺.

Step 3: Benzyl-(2S,4S)-2-aminocarbonyl-4-fluoropyrrolidine-1-carboxylate

15



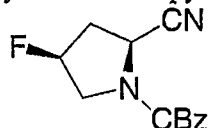
A stirred solution of (4S)-1-[(Benzyloxy)carbonyl]-4-fluoro-L-proline in dioxane was treated with pyridine (0.7 eq.) and Boc₂O (1.3 eq.), then ammonium bicarbonate (1.26
20 eq.) was added and the mixture was stirred at room temperature for 15 hours.

Dioxane was concentrated and the residue was taken up in ethyl acetate, washed with 1 N HCl and brine, dried over Na₂SO₄ to give, after filtration and concentration, title compound.

¹H NMR (DMSO-d₆, 400 MHz, 340 K) δ 7.40-7.28 (m, 5H), 5.25 (dt, J_{H-F} = 53.6 Hz, J = 4.5 Hz, 1H), 5.13-5.06 (m, 2H), 4.28 (d, J = 9.6 Hz, 1H), 3.80-3.63 (m, 2H), 2.45-2.21 (m, 2H).

MS: m/z 267 (M+H)⁺.

Step 4: Benzyl-(2S,4S)-2-cyano-4-fluoropyrrolidine-1-carboxylate



Benzyl-(2S,4S)-2-aminocarbonyl-4-fluoropyrrolidine-1-carboxylate in

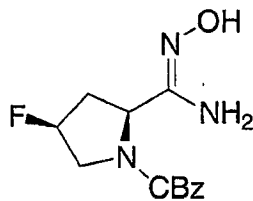
- 5 dichloromethane was treated at 0 °C with Et₃N (2.1 eq.) and trifluoroacetic anhydride was added dropwise.

The reaction mixture was stirred at 0 °C for 0.5 hour and 10 minutes at room temperature. Then, it was diluted with dichloromethane, washed with HCl 1N and brine, dried over Na₂SO₄ and filtered to give, after concentration, title compound.

- 10 ¹H NMR (DMSO-d₆, 400 MHz, 340 K) δ 7.42-7.30 (m, 5H), 5.40 (dbt, J_{H-F}= 52.3 Hz, 1H), 5.20 (d, J=12.7 Hz, 1H), 5.16 (d, J= 12.7 Hz, 1H), 4.94 (d, J= 8.4Hz, 1H), 3.68-3.56 (m, 2H), 2.63-2.41(m, 2H).

MS: m/z 249 (M+H)⁺.

- 15 Step 5: Benzyl-(2S,4S)-2-[amino(hydroxyimino)methyl]-4-fluoropyrrolidine-1-carboxylate



- 20 Benzyl-(2S,4S)-2-cyano-4-fluoropyrrolidine-1-carboxylate dissolved in absolute ethanol was treated with triethyl amine (1.5eq.) and hydroxylamine hydrochloride (1.3 eq.).

- The reaction mixture was stirred at 50 °C for 3 hours and then the solvent was removed under reduced pressure. The residue was partitioned between water and dichloromethane and the aqueous layer was extracted with dichloromethane three
25 times. The organic phase was dried over Na₂SO₄ and filtered. The solid obtained by concentration was then recrystallized from MeOH to give title compound.

185

15		2-(1-acetylpyrrolidin-2-yl)-N-(2,3-dimethoxybenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide	431	1
16		2-(1-acetylpyrrolidin-2-yl)-5-hydroxy-N-(2-methoxybenzyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide	401	1
17		N-[1-(4-fluorobenzyl)amino]carbonyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-1-methylethyl]-N-2~,N-2~-dimethyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide	434	8
18		2-(1-acetylpyrrolidin-2-yl)-N-[2-(dimethylamino)benzyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide	414	4
19		2-[(2S)-1-acetylpyrrolidin-2-yl]-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide	389	1
20		N-(4-fluorobenzyl)-5-hydroxy-2-[4-hydroxy-1-(pyrazin-2-ylcarbonyl)pyrrolidin-2-yl]-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide	469	5*
21		N-[1-(4-[[[4-fluorobenzyl]amino]carbonyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-1-methylethyl]imidazo[2,1-b][1,3]thiazole-6-carboxamide	485	5
22		2-[(2S,4S)-1-acetyl-4-fluoropyrrolidin-2-yl]-N-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide	407	1