



FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

P2006/000025

SOLICITUD DE:

1

☐

Corrección de Error Material.

☒

Modificación a una Solicitud.

2

SOLICITANTE
(71)

Nombre: WISCONSIN ALUMINI RESEARCH FOUNDATION

Dirección: 614 Walnut Street, Madison, Wisconsin 53726, 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: World Trade Center Torre A Calle 100 No. 8A-37 Piso 10. 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:

06-021.161

5

Descripción de la corrección o modificación solicitada Me permito presentar la cesión de derechos del solicitante de PFIZER PRODUCTS INC al solicitante **WISCONSIN ALUMINI RESEARCH FOUNDATION**

6

Comprobante de pago No. 08-5.441

Fecha 21 de Enero de 2008

7

Anexos

☒

Comprobante de pago de la tasa.

☒

Poderes, si fuere el caso. Documento que soporta la cesión de Derechos.

☐

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

8

NOMBRE: CARLOS R. OLARTE

FIRMA:

[Firma manuscrita]

C.C. 79.782.747 Bta T.P. 74.295

168
3/168

BOGOTA D.C. ENERO 22, 2008

TRADUCCION OFICAL LEGALIZACION NOTARIA Y APOSTILLE 2007-15339 (2
PAGINAS)
(VERIFIQUE ANTES DE PROCEDER)

NOTA DE TRADUCCION: SE TRATA DE UN DOCUMENTO, EN DOS COLUMNAS, TITULADO "CERTIFICACION NOTARIAL" EN IDIOMA CASTELLANO E INGLES, DE FECHA NOV-02, 2007, EN RELACION CON PFIZER PRODUCDS INC, CON EL SIGUIENTE TEXTO, Y APOSTILLA EN INGLES:

SUSCRITO Y JURAMENTADO ANTE MI HOY NOVIEMBRE 02, 2007 EN EL CONDADO DE NEW LONDON, ESTADO DE CONNECTICUT, ESTADOS UNIDOS DE AMERICA.

(FIRMADO Y SELLADO) LAURA M. MAZUREK, NOTRARIO PUBLICO, ESTADO DE CONNECTICUT NR 146617. MI COMISION EXPIRA 10/3/2011.

PÁGINA 2 DE 2

APOSTILLE

(Convención de la Haya, Octubre 5, 1961)

1. PAIS: **ESTADOS UNIDOS DE AMERICA**
ESTE DOCUMENTO PUBLICO
2. HA SIDO FIRMADO POR LAURA M. MAZUREK
3. ACTUANDO EN SU CALIDAD DE NOTARIO PUBLICO
4. EN EL ESTADO DE CONNECTICUT POR EL TERMINO DE OCTUBRE 23, 2006 A OCTUBRE 31, 2011.

CERTIFICADO

5. EN HARTFORD, CONNECTICUT
6. EL DIA NOVIEMBRE 21, 2007
7. POR SUSAN BYSIEWIOCZ, SECRETARIO DE ESTADO DE CONNECTICUT.
8. NR. **2007-15339.**
9. SELLO/ESTAMPILLA: HAY SELLO DORADO DE CONNECTICUT
10. FIRMADO

(HAY UNA FIRMA)

CERTIFICADO DE AUTENTICIDAD El suscrito Traductor e Interprete Oficial juramentado, debidamente registrado ante en Ministerio de Relaciones Exteriores de Colombia, con el presente certifica que esta es una traducción auténtica, verdadera, y precisa al Idioma Español del documento en Ingles, **anexo.**

FIDEL ANTONIO MURCIA MURCIA
Traductor e Interprete Oficial
Resolución No. 488/94 Ministerio de Justicia



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

49
A 169

1. Country: The United States of America

THIS PUBLIC DOCUMENT

2. has been signed by **LAURA M. MAZUREK**

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

4. in the State of Connecticut for the term of **October 23, 2006 to October 31, 2011**

CERTIFIED

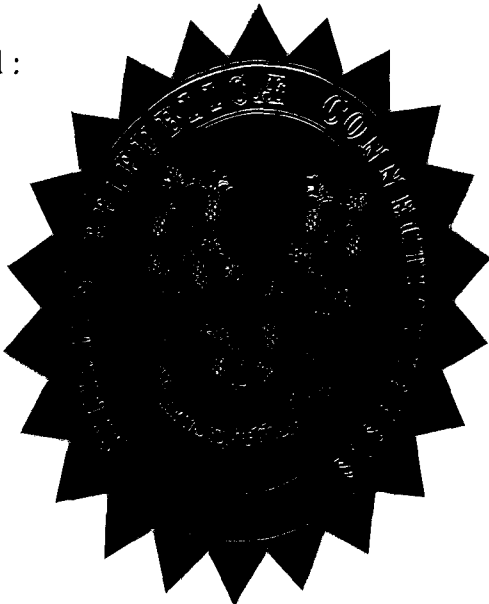
5. at Hartford, Connecticut

6. on **November 21, 2007**

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

8. Number : **2007-15339**

9. Seal :



10. Signature

Susan Bysiewicz

Secretary of the State

ASSIGNMENT

PFIZER PRODUCTS INC.

by means of this document and in consideration of the payment by the Assignee to the Assignor of a good and valuable consideration, assign(s) to

**WISCONSIN ALUMNI RESEARCH
FOUNDATION**

A company organized under the laws of
**The State of Wisconsin,
United States of America**

Domiciled in

**614 Walnut Street
Madison, Wisconsin 53726
United States of America**

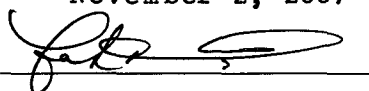
(hereinafter referred to as the "ASSIGNEE").
All my (our) rights, title and interest in and to my (our) invention for a new and useful improvement entitled and as fully set forth and described in:

**Colombian Patent Application No. 06-021.161
Colombian Patent Application No. 06-026.305
Colombian Patent Application No. 06-026.309**

Name: **Frank Maldari**
Title: **Vice President, Corporate Counsel**

Place and date: **Groton, CT., USA**
November 2, 2007

Assignor(s)



CESION

PFIZER PRODUCTS INC.

por medio de la presente y a cambio del pago de una contraprestación económica, cedo (cedemos) a

**WISCONSIN ALUMNI RESEARCH
FOUNDATION**

una compañía organizada bajo las leyes de
**The State of Wisconsin,
United States of America**

domiciliada en

**614 Walnut Street
Madison, Wisconsin 53726
United States of America**

(de ahora en adelante el "CESIONARIO").
todos mis (nuestros) derechos, título e interés sobre mi (nuestra) invención tal como describe en:

**Solicitud de Patente No. 06-021.161
Solicitud de Patente No. 06-026.305
Solicitud de Patente No. 06-026.309**

Name:
Title:

Place and date:

Assignee(s)

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6

NOTARIAL CERTIFICATION

Notarial Certification

Certificación Notarial

On this date, **November 2, 2007**

En esta fecha,

The undersigned Notary Public certifies:

el Notario Público suscrito certifica:

1. That **Frank Maldari**

1. Que

of legal age and domiciled in

mayor de edad y domiciliado

Groton, CT., USA
signed the foregoing document.

suscribió el documento que antecede.

2. That the grantor has executed the foregoing document as
of **PFIZER PRODUCTS INC**

2. Que el otorgante ha suscrito el referido documento en su carácter de
de

3. That **PFIZER PRODUCTS INC**
having its principal place of business located in
Eastern Point Road, Groton, Connecticut, 06340, U.S.A.

4. Que
con sede principal ubicada en

is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

Written Consent of the Directors
April 11, 2006

NOTARY PUBLIC (Signature):
Name and Particulars:
SEAL (optional)

Subscribed to and sworn before me this 2 day of
November 2007. In the County of New London,
State of Connecticut, United States of America.
Laura M. Mazurek
Notary Public

Laura M Mazurek
Notary Public
State of Connecticut
No. 146617
My Commission Expires 10/3/2011

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BOGOTA D.C. ENERO 22, 2008

TRADUCCION OFICIAL
(VERIFIQUE ANTES DE PROCEDER)

ESTADO DE WISCONSIN
OFICINA DEL SECRETARIO DE ESTADO
APOSTILLE

Convención de la Haya, Octubre 5, 1961

1. PAIS: **ESTADOS UNIDOS DE AMERICA**
2. ESTE DOCUMENTO PUBLICO HA SIDO FIRMADO POR **JACQUELINE S. BECKER**
3. ACTUANDO EN SU CALIDAD DE **NOTARIO PUBLICO DE WISCONSIN**
4. LLEVA EL SELLO/ESTAMPILLA DE **NOTARY PUBLICO, ESTADO DE WISCONSIN**
5. CERTIFICADO: EN MADISON, WISCONSIN
6. EL DIA **DICIEMBRE 14, 2007**
7. POR EL SECRETARIO DE ESTADO, ESTADO DE WISCONSIN
8. NR. **160267**
9. SELLO/ESTAMPILLA
10. FIRMADO (HAY FIRMA) **DOUGLAS LA FOLLETTE**
SECRETARIO DE ESTADO

ESTA APOSTILLA SOLAMENTE CONFIRMA LA AUTORIDAD DE LA PERSONA CITADA EN EL NUMERAL 2. NO SIGNIFICA QUE LOS CONTENIDOS DEL DOCUMENTO ANEXO SEAN CORRECTOS, O QUE EL SECRETARIO DE ESTADO APRUEBE LOS CONTENIDOS.

(SELLO): GRAN SELLO DEL ESTADO DE WISCONSIN

CERTIFICADO DE AUTENTICIDAD El suscrito Traductor e Interprete Oficial juramentado, debidamente registrado ante el Ministerio de Relaciones Exteriores de Colombia, con el presente certifica que esta es una traducción al Idioma Castellano, del documento en Inglés anexo para efectos de verificación. En caso de controversia en interpretación, el documento fuente en inglés prevalecerá.

FIDEL ANTONIO MURCIA MURCIA
Traductor e Interprete Oficial
Resolución No. 488/94 Ministerio de Justicia

Traductor e Interprete Oficial
Fidel Antonio Murcia Murcia
8 ENE 2008



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**ESTATUTOS DE CONSTITUCION MODIFICADOS
DE WISCONSIN ALUMINI RESEARCH FOUNDATION
(Corporación No de Acciones)**

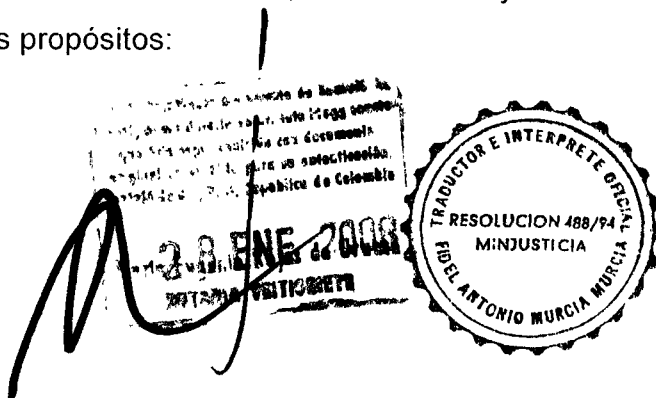
Los siguientes Estatutos Modificados debidamente adoptados en cumplimiento a la autoridad y las estipulaciones del Capítulo 181 de los Estatutos de Wisconsin derogan y toman el lugar de los artículos existentes de constitución y enmienda de los mismos:

Artículo 1. El nombre de la Corporación es Wisconsin Alumni Research Foundation

Artículo 2. El periodo de existencia será perpetuo

Artículo 3. El objeto para el cual la corporación es formada es el siguiente:

- A. Sujeto a las limitaciones establecidas en el presente, esta corporación es organizada y será operada exclusivamente para beneficio de la Universidad de Wisconsin-Madison, una parte del Sistema Universitario de Wisconsin, una universidad pública organizada bajo las leyes del Estado de Wisconsin, y el Instituto para el Desarrollo Morgridge, Inc, una afiliada de caridad pública exenta de impuestos, con la Universidad de Wisconsin, Madison.
- B. Esta corporación está organizada y tiene que ser operada exclusivamente para propósitos de caridad, científicos y educacionales, incluyendo para tales propósitos:



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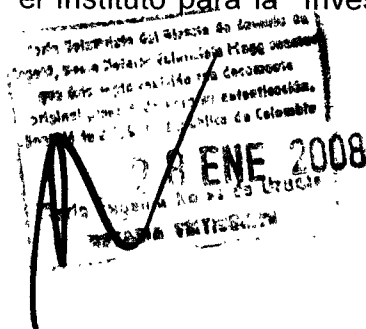
(1) Promover, estimular, y ayudar a la investigación científica y la investigación en y dentro de la universidad de Wisconsin-Madison, y el Instituto para la Investigación Morgridge, Inc, por la facultad, directivos y estudiantes de alumini, y proveer y ayudar en la provisión de medios y maquinaria mediante los cuales sus descubrimientos, inventos y procesos científicos puedan ser desarrollados, aplicados y patentados para beneficio de la humanidad y mediante los cuales se pueda hacer la utilización y disposición pueda ser hecha de tales descubrimientos, inventos y procesos y derechos de patentes o intereses en los mismos que tiendan a proveer fondos para y para estimular y promover más investigación e investigación dentro de dicha Universidad de Wisconsin-Madison y el Instituto para la Investigación Morgridge Inc.

(2) Desembolsar y distribuir los fondos de la corporación para promover y estimular y ayudar en la realización de los antes citados propósitos.

(3) usar y administrar regalos, donaciones, legados y aparatos para beneficio de la Universidad de Wisconsin-Madison y el Instituto para la Investigación Morgridge Inc.

(4) comprometerse en cualquiera y todas las actividades legales incidentales a los propósitos antes citados excepto como se limite en el presente.

La corporación será en todo momento operada en relación con la Universidad de Wisconsin-Madison y el Instituto para la Investigación Morgridge Inc. O ambos



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Artículo 4. La corporación no tendrá miembros. La administración y control de la corporación residirá en la Junta de Depositarios. En número de Depositarios puede ser fijado por los Estatutos pero no será menor de siete.

Artículo 5. Se intenta que esta corporación continúe teniendo el estatus de una corporación exenta de impuestos de renta federales y estatales.

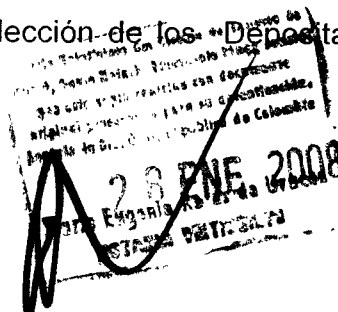
Artículo 6. la corporación será sin capital de acciones, y ningunos dividendos o lucros pecuniarios serán declarados, pagados ni redundaran en beneficio de los Depositarios en su capacidad privada.

Artículo 7 La oficina principal de la corporación es en la ciudad de Madison, Condado de Dane, Madison, Wisconsin. La dirección de la oficina principal es 614 Walrus St., Madison, Wisconsin, 53726.

Artículo 8 El nombre del agente registrado es Carl B. Gulbrandsen.

Artículo 9 La dirección del agente registrado es 614 Walrus St., 13th Floor, Madison, Wisconsin, 53726.

Artículo 10 Solamente serán Depositarios aquellas personas que (1) hayan asistido a la Universidad de Wisconsin.Madison por un periodo no menor de dos años, o (2) que sean graduados de la Universidad de Wisconsin.Madison. los Depositarios serán aquellas personas calificadas que sean Depositarias al momento de la adopción de estos Estatutos Modificados, y las otras personas que sean elegidas en cualquier tiempo por los Depositarios. Los términos y condiciones que rigen los requisitos y selección de los Depositarios serán fijados por los Estatutos.

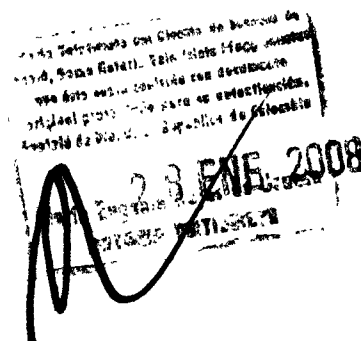


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Artículo 11. En caso de disolución de la corporación, los Depositarios después de pagar y hacer las apropiaciones para el pago de todas las responsabilidades de la corporación, distribuirán todos los activos de la corporación exclusivamente para los antes mencionados propósitos de la corporación, como lo determinen los Depositarios, a la Universidad de Wisconsin.Madison, o a la organización u organizaciones, incluyendo depósitos organizados y operados exclusivamente para propósitos de caridad, educacionales o científicos, y al momento de clasificar como una organización u organizaciones descritas en la Sección 501(cc)(3) del Código 1954 de Renta Interna, sobre la condición de que tal organización u organizaciones que reciban las distribuciones aplicarán y dedicarán tales activos exclusivamente para beneficio de la Universidad de Wisconsin.Madison para los mencionados propósitos de la corporación, asumiendo, sin embargo, que cualquier transferencia o disposición de tales activos netos estarán sujetos a la ejecución y realización de cualquier fiducia bajo la cual su propiedad o parte de la misma sea recibida o mantenida.

Artículo 12 Estos estatutos pueden ser enmendados mediante dos tercios de los votos de los Depositarios, pero ninguna enmienda cambiarán substancialmente el propósito original de la corporación o las estipulaciones del Artículo 11 del presente.

La corporación no tiene miembros con derecho a voto, y la modificación que antecede de los estatutos de constitución fue adoptada en una reunión de la Junta de Depositarios el día 09 de Mayo, 2007, por dos tercios o más de los Depositarios activos.



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El actual nombre corporativo (previo a cualquier cambio efectuado por esta enmienda) es Wisconsin Alumini Research Foundation, y la oficina principal está en la ciudad de Madison, Condado de Dane, Wisconsin.

Ejecutado en duplicado y sello (si hay) hoy Mayo 09, 2007.

Por (HAY FIRMA)

Presidente o Vicepresidente

Por (HAY FIRMA)

Patricia Lipton, Secretaria

CERTIFICADO DE AUTENTICIDAD El suscrito Traductor e Interprete Oficial juramentado, debidamente registrado ante el Ministerio de Relaciones Exteriores de Colombia, con el presente certifica que esta es una traducción al Idioma Castellano, del documento en Inglés anexo para efectos de verificación. En caso de controversia en interpretación, el documento fuente en inglés prevalecerá.

TRAINING AND EDUCATION SERVICES Cra 15 # 99 13 of 411 telefonos 2182308 6232925 e-mail teseser1@yahoo.com

FIDEL ANTONIO MURCIA MURCIA

Traductor e Interprete Oficial

Resolución No. 488/94 Ministerio de Justicia

28 ENE 2008
Fidel Murcia



The State of Wisconsin

Office of the
Secretary of State

CERTIFIED

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America
2. This public document has been signed by Jacqueline S Becker
3. acting in the capacity of Notary Public, State of Wisconsin
4. bears the seal/stamp of Notary Public, State of Wisconsin

CERTIFIED for Colombia

5. at Madison, Wisconsin
6. December 14, 2007
7. by the Secretary of State of Wisconsin
8. No. 160267

9. Seal/stamp:

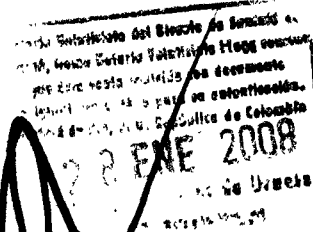


10. Signature

Douglas La Follette

DOUGLAS LA FOLLETTE
Secretary of State

This Apostille only confirms the authority of the person named in Number 2. It does not mean that the contents of the attached document are correct, or that the Secretary of State approves of the contents.





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Carlos R. Olarte
J. Ian Raisbeck
Ana María Friery
Juan Guillermo Moure
Natalia Castro
Zayde Chacón
Simón Salazar
Alexander Agudelo
Lina Mosquera
Catalina Barbastefano
Ángela Corrales
Erika Ríos
Carlos A. Prieto
Carolina Romo
Of Counsel
Guillermo Chacón
Graciela M. Cruz
Jacqueline Chapa
Cruz E. de Moncalca

Power of Attorney

The undersigned,

domiciled in

WISCONSIN ALUMNI RESEARCH FOUNDATION

614 Walnut Street; Madison, Wisconsin 53726; United States of America

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Friery and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents for Inventions, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Obtainer's Certificates, Copyrights, Domain Names, or any other intellectual property right in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications, collect refunds, desist, settle, conciliate or negotiate. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

El suscrito,

domiciliado en

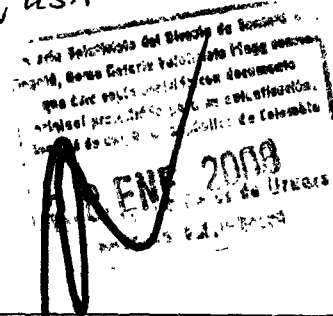
por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Friery y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las Patentes de Invención, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Certificados de Obtentor, Derechos de Autor, Nombres de Dominio, o cualquier otro bien de propiedad intelectual de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Date/Fecha:

19, November, 2007

City/Country/Ciudad,País: Madison, Wisconsin, USA



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NOTARIAL CERTIFICATION

Notarial Certification

Certificación Notarial

On this date, 19, November, 2007

En esta fecha,

The undersigned Notary Public certifies:

el Notario Público suscrito certifica:

1. That Michael Falk

1. Que

of legal age and domiciled in
Wisconsin Alumni Research Foundation. 614 Walnut Street, Madison, Wisconsin 53726
signed the foregoing document.

mayor de edad y domiciliado
Street, Madison, Wisconsin 53726
suscribió el documento que antecede.

2. That the grantor has executed the foregoing
document as General Counsel
of Wisconsin Alumni Research Foundation

2. Que el otorgante ha suscrito el referido
documento en su carácter de
de

3. That Wisconsin Alumni Research
Foundation
having its principal place of business located in
614 Walnut Street; Madison, WI 53726;
United States of America
is duly incorporated, is currently in existence, and
that the purposes for which the Power of Attorney is
granted are within the scope of its corporate
purposes.

4. Que

con sede principal ubicada en

4. That the grantor has the authority to execute the
Power of Attorney and that his/her representation is
legal.

está legalmente constituida, que tiene existencia
legal vigente y que los propósitos para los cuales
se otorga el poder se encuentra dentro de los que
comprenden su objeto social.

4. Que el otorgante tiene la representación para
suscribir el poder, y que ésta es legítima.

5. The foundation for my certifications contained in
points 2, 3 and 4 was the exhibition of the following
authentic document(s):

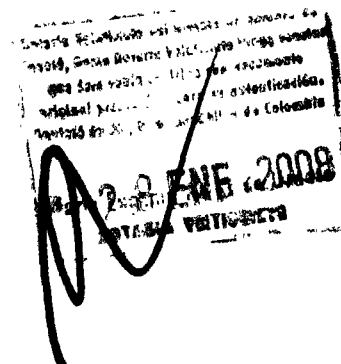
5. El fundamento de mis certificaciones
contenidas en los puntos 2, 3 y 4 fue la exhibición
de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

Name and Particulars:

SEAL (optional)

Jacqueline S. Becker, Notary Public
My Commission Expires 3-16-08



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RESTATED ARTICLES OF INCORPORATION
OF THE WISCONSIN ALUMNI RESEARCH FOUNDATION
(Non-Stock Corporation)

The following Restated Articles duly adopted pursuant to the authority and provisions of Chapter 181 of the Wisconsin Statutes supersede and take the place of existing articles of incorporation and amendments thereto:

- Article 1. The name of the corporation is Wisconsin Alumni Research Foundation.
- Article 2. The period of existence shall be perpetual.
- Article 3. The purposes for which the corporation is formed are as follows:
- A. Subject to the limitations herein, this corporation is organized and shall be operated exclusively for the benefit of the University of Wisconsin-Madison, a part of the University of Wisconsin System, a public university organized under the laws of the State of Wisconsin, and The Morgridge Institute for Research, Inc., a tax-exempt public charity affiliated with the University of Wisconsin – Madison.
- B. This corporation is organized and is to be operated exclusively for charitable, scientific or educational purposes, including for such purposes:
- (1) To promote, encourage and aid scientific investigation and research at and within the University of Wisconsin-Madison, and The Morgridge Institute for Research, Inc., by the faculty, staff, alumni and students, and to provide or assist in providing means and machinery by which their scientific discoveries, inventions and processes may be developed, applied and patented for the overall benefit of humankind and by which such utilization or disposition may be made of such discoveries, inventions and processes and patent rights or interest therein as may tend to provide funds for and to stimulate and promote further investigation and research within said University of Wisconsin-Madison and The Morgridge Institute for Research, Inc.
 - (2) To pay out and distribute the corporation's funds to promote, encourage and aid in the performance of the foregoing purposes.
 - (3) To use and administer gifts, grants, bequests and devises for the benefit of the University of Wisconsin-Madison and The Morgridge Institute for Research, Inc.

Notary Public for the State of Wisconsin
My Comm. Expires 12/31/2008
JAN 2009

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(4) To engage in any and all lawful activities incidental to the foregoing purposes except as limited herein.

C. This corporation shall at all times be operated in connection with the University of Wisconsin-Madison or The Morgridge Institute for Research, Inc., or both.

Article 4. The corporation shall have no members. The management and control of the corporation shall reside in the Board of Trustees. The number of Trustees may be fixed by By-Law but shall not be less than seven.

Article 5. It is intended that this corporation shall continue to have the status of a corporation which is exempt from federal and state income taxation.

Article 6. The corporation shall be without capital stock, and no dividends or pecuniary profits shall be declared, paid to, or inure to the benefit of the Trustees thereof in their private capacity.

Article 7. The principal office of the corporation is in the City of Madison, Dane County, Madison, Wisconsin. The address of the principal office is 614 Walnut St, Madison, Wisconsin 53726.

Article 8. The name of the registered agent is Carl E. Gulbrandsen.

Article 9. The address of the registered agent is 614 Walnut St., 13th Floor, Madison, Wisconsin 53726.

Article 10. Only those persons shall be Trustees who (1) have attended the University of Wisconsin-Madison for a period of not less than two years, or (2) who are graduates of the University of Wisconsin-Madison. The Trustees shall be those qualified persons who are Trustees at the time of the adoption of these Restated Articles, and such other persons as may be elected from time to time by the Trustees. The terms and conditions governing the qualifications and selection of Trustees shall be fixed by the By-Laws.

Article 11. In case of the dissolution of the corporation, the Trustees after paying or making provision for payment of all of the liabilities of the corporation, shall distribute all assets of the corporation exclusively for the aforesaid purposes of the corporation, as the Trustees shall determine, to the University of Wisconsin-Madison or to such organization or organizations, including trusts, organized and operated exclusively for charitable, educational, scientific purposes, and shall at the time qualify as an organization

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or organizations described in Section 501(c)(3) of the Internal Revenue Code of 1954, upon the condition that such organization or organizations receiving such distributions shall apply and devote such assets exclusively for the benefit of the University of Wisconsin-Madison for the aforesaid purposes of the corporation, provided, however, that any transfer or disposition of such net assets shall be subject to the execution and performance of any trust under which its property or any part thereof may have been received or may be held.

Article 12. These articles may be amended upon a two-thirds vote of the Trustees, but no such amendment shall change substantially the original purpose of the corporation or the provisions of Article II hereof.

The corporation has no members having voting rights, and the foregoing restatement of the articles of incorporation was adopted at a meeting of the Board of Trustees on May 9, 2007, by a two-thirds or more vote of the Trustees in office.

The present corporate name (prior to any change effected by this restatement) is Wisconsin Alumni Research Foundation, and the principal office is in the City of Madison, Dane County, Wisconsin.

Executed in duplicate and seal (if any) affixed this 9th day of May, 2007.

AFFIX SEAL
(or state that
there is none)

By: [Signature]
President or Vice-President

By: [Signature]
Patricia Lipton, Secretary

23 ENE 2008
Eugenia Rojas de Ovaco
NOTARIA PUBLICA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-21161

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **567** DE

FECHA **31 DE AGOSTO DE 2006** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **28 DE NOVIEMBRE DE 2006**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X



US005843928A

185
185**United States Patent** [19][11] **Patent Number:** **5,843,928****Deluca et al.**[45] **Date of Patent:** **Dec. 1, 1998**[54] **2-ALKYLIDENE-19-NOR-VITAMIN D COMPOUNDS**[75] Inventors: **Hector F. Deluca**, Deerfield, Wis.;
Slcinski R. Rafal, Warsaw, Poland[73] Assignee: **Wisconsin Alumni Research Foundation**, Madison, Wis.[21] Appl. No.: **819,693**[22] Filed: **Mar. 17, 1997**[51] Int. Cl.⁶ **A61K 31/59; C07C 401/00**[52] U.S. Cl. **514/167; 552/653**[58] Field of Search **552/653; 514/167**[56] **References Cited****U.S. PATENT DOCUMENTS**

4,666,634	5/1987	Miyamoto et al.	260/397
5,086,191	2/1992	Deluca et al.	552/653
5,237,110	8/1993	Deluca et al.	568/665
5,246,925	9/1993	Deluca et al.	514/167
5,428,029	6/1995	Doran et al.	514/167
5,484,782	1/1996	Deluca et al.	514/167
5,536,713	7/1996	Deluca et al.	514/167
5,587,497	12/1996	Deluca et al.	552/653

FOREIGN PATENT DOCUMENTS

0184206	12/1985	European Pat. Off.
0387077	9/1990	European Pat. Off.
0516410	12/1992	European Pat. Off.

OTHER PUBLICATIONS

Posner et al., "Stereocontrolled Synthesis of a Trihydroxylated A Ring as an Immediate Precursor to 1 α ,2 α ,25-Trihydroxyvitamin D₃", J. Org. Chem. 56, pp. 4339-4341, Apr. 15, 1991.

"Chemistry of Synthetic High Polymers", Chemical Abstracts, vol. 110, No. 10, Mar. 6, 1989.

Okano et al., "Regulatory Activities of 2 β -(3-Hydroxypropoxy)-1 α ,25-Dihydroxy-Vitamin D₃. A Novel Synthetic Vitamin D₃ Derivative, on Calcium Metabolism", Biochemical and Biophysical Research Communications, vol. 163, No. 3, pp. 1444-1449, Sep. 29, 1989.

Bouillon et al., "Biologic Activity of Dihydroxylated 19-Nor-(Pre)Vitamin D₃", Bioactivity of 19-Nor-Pre D, vol. 8, No. 8, pp. 1009-1015, 1993.

Sarandeses et al., "Synthesis of 1 α ,25-Dihydroxy-19-Norprevitamin D₃", Tetrahedron Letters, pp. 5445-5448, Apr. 1992.

Perlman et al., "1 α ,25-Dihydroxy-19-Nor-Vitamin D₃. A Novel Vitamin D-Related Compound with Potential Therapeutic Activity", Tetrahedron Letters, vol. 31, No. 13, pp. 1823-1824, Feb. 1990.

Baggiolini et al., "Stereocontrolled Total Synthesis of 1 α ,25-Dihydroxycholecalciferol and 1 α ,25-Dihydroxyero-calciferol", J. Org. Chem., 51, pp. 3098-3108, 1986.

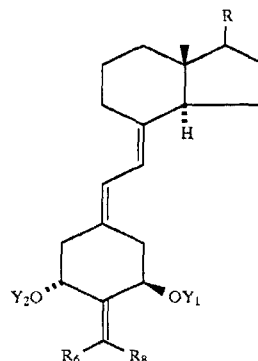
Kiegiel et al., "Chemical Conversion of Vitamin D₃ to its 1,25-Dihydroxy Metabolite", Tetrahedron Letters, vol. 31, No. 43, pp. 6057-6060, 1991.

Primary Examiner—Deborah C. Lambkin

Attorney, Agent, or Firm—Andrus, Sceales, Starke & Sawall

[57] **ABSTRACT**

This invention provides a novel class of vitamin D related compounds, namely, the **2-alkylidene-19-nor-vitamin D derivatives**, as well as a general method for their chemical synthesis. The compounds have the formula:



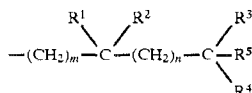
where Y₁ and Y₂, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R₆ and R₈, which may be the same or different, are each selected from hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or when taken together represent the group —(CH₂)_x— where x is an integer from 2 to 5, and where the group R represents any of the typical side chains known for vitamin D type compounds. These 2-substituted compounds are characterized by low intestinal calcium transport activity and high bone calcium mobilization activity resulting in novel therapeutic agents for the treatment of diseases where bone mobilization is desired, particularly low bone turnover osteoporosis. These compounds also exhibit pronounced activity in arresting the proliferation of undifferentiated cells and inducing their differentiation to the monocyte thus evidencing use as anti-cancer agents and for the treatment of diseases such as psoriasis.

33 Claims, 2 Drawing Sheets

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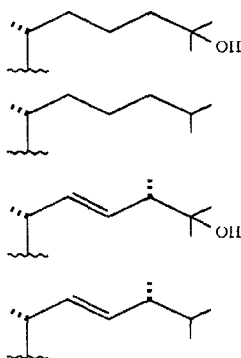
where the stereochemical center (corresponding to C-20 in steroid numbering) may have the R or S configuration, (i.e. either the natural configuration about carbon 20 or the 20-epi configuration), and where Z is selected from Y, —OY, —CH₂OY, —C≡CY and —CH=CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR⁵ and a radical of the structure:



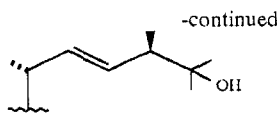
where m and n, independently, represent the integers from 0 to 5, where R¹ is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C₁₋₅-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R², R³, and R⁴, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C₁₋₅ alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R¹ and R², taken together, represent an oxo group, or an alkylidene group, =CR³R⁴, or the group —(CH₂)_p—, where p is an integer from 2 to 5, and where R³ and R⁴, taken together, represent an oxo group, or the group —(CH₂)_q—, where q is an integer from 2 to 5, and where R⁵ represents hydrogen, hydroxy, protected hydroxy, or C₁₋₅ alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —CH(CH₃)—, —CH(R³)—, or —CH(R⁴)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

The wavy line to the methyl substituent at C-20 indicates that carbon 20 may have either the R or S configuration.

Specific important examples of side chains with natural 20R-configuration are the structures represented by formulas (a), (b), (c), (d) and (e) below. i.e. the side chain as it occurs in 25-hydroxyvitamin D₃ (a); vitamin D₃ (b); 25-hydroxyvitamin D₂ (c); vitamin D₂ (d); and the C-24 epimer of 25-hydroxyvitamin D₂ (e):



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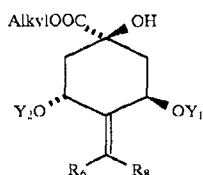
(e)

The above novel compounds exhibit a desired, and highly advantageous, pattern of biological activity. These compounds are characterized by little, if any intestinal calcium transport activity, as compared to that of 1α,25-dihydroxyvitamin D₃, while exhibiting relatively high activity, as compared to 1α,25-dihydroxyvitamin D₃, in their ability to mobilize calcium from bone. Hence, **these compounds are highly specific in their calcemic activity.** Their preferential activity on mobilizing calcium from bone and reduced intestinal calcium transport activity allows the in vivo administration of these compounds for the **treatment of metabolic bone diseases where bone loss is a major concern.** Because of their preferential calcemic activity on bone, these compounds would be preferred therapeutic agents for the treatment of diseases where bone formation is desired, such as **osteoporosis**, especially low bone turnover osteoporosis, steroid induced osteoporosis, senile osteoporosis or postmenopausal osteoporosis, as well as osteomalacia and renal osteodystrophy. The treatment may be transdermal, oral or parenteral. The compounds may be present in a composition in an amount from about 0.1 μg/gm to about 50 μg/gm of the composition, and may be administered in dosages of from about 0.1 μg/day to about 50 μg/day.

The compounds of the invention are also especially suited for treatment and prophylaxis of human disorders which are characterized by an imbalance in the immune system, e.g. in autoimmune diseases, including multiple sclerosis, diabetes mellitus, host versus graft reaction, and rejection of transplants; and additionally for the treatment of inflammatory diseases, such as rheumatoid arthritis and asthma, as well as the improvement of bone fracture healing and improved bone grafts. Acne, alopecia, skin conditions such as dry skin (lack of dermal hydration), undue skin slackness (insufficient skin firmness), insufficient sebum secretion and wrinkles, and hypertension are other conditions which may be treated with the compounds of the invention.

The above compounds are also characterized by high cell differentiation activity. Thus, these compounds also provide therapeutic agents for the treatment of psoriasis, or as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer and prostate cancer. The compounds may be present in a composition to treat psoriasis in an amount from about 0.01 μg/gm to about 100 μg/gm of the composition, and may be administered topically, transdermally, orally or parenterally in dosages of from about 0.01 μg/day to about 100 μg/day.

This invention also provides novel intermediate compounds formed during the synthesis of the end products. Structurally, these novel intermediates are characterized by the general formulae V, VI, VII, VIII, IX and X below where Y₁, Y₂, R₆ and R₈ are as previously defined herein.



V

4×SiCH₃), 0.541 (3H, s, 18-H₃), 0.564 (6H, q, J=7.9 Hz, 3×SiCH₃), 0.848 (3H, d, J=6.5 Hz, 21-H₃), 0.864 and 0.896 (9H and 9H, each s, 2×Si-t-Bu), 0.945 (9H, t, J=7.9 Hz, 3×SiCH₂CH₃), 1.188 (6H, s, 26- and 27-H₃), 2.15–2.35 (4H, br m), 2.43–2.53 (3H, br m), 2.82 (1H, br d, J=12.9 Hz, 9β-H), 4.42 (2H, m, 1β- and 3α-H), 4.92 and 4.97 (1H and 1H, each s, =CH₂), 5.84 and 6.22 (1H and 1H, each d, J=11.1 Hz, 7- and 6-H); MS m/z (relative intensity) 758 (M⁺, 33), 729 (M⁺-Et, 7), 701 (M⁺-t-Bu, 5), 626 (100), 494 (25), 366 (52), 75 (82), 73 (69).

Protected vitamin 14 (5.0 mg) was dissolved in benzene (160 μL) and the resin (AG 50W-X4, 70 mg; prewashed with methanol) in methanol (900 μL) was added. The mixture was stirred at room temperature under argon for 19 h, diluted with ethyl acetate/ether (1:1, 4 mL) and decanted. The resin was washed with ether (8 mL) and the combined organic phases washed with brine and saturated NaHCO₃, dried (MgSO₄) and evaporated. The residue was purified by HPLC (6.2 mm×25 cm Zorbax-Sil column, 4 mL/min) using hexane/2-propanol (9:1) solvent system. Analytically pure 2-methylene-19-nor-vitamin 15 (2.6 mg, 95%) was collected at R_V 28 mL [(20R)-analog was eluted at R_V 29 mL and 1α,25-dihydroxyvitamin D₃ at R_V 52 mL in the same system] as a white solid; UV (in EtOH) λ_{max} 243.5, 252.5, 262.5 nm; ¹H NMR (CDCl₃) δ 0.551 (3H, s, 18-H₃), 0.858 (3H, d, J=6.6 Hz, 21-H₃), 1.215 (6H, s, 26- and 27-H₃), 1.95–2.04 (2H, m), 2.27–2.35 (2H, m), 2.58 (1H, dd, J=13.3, 3.7 Hz), 2.80–2.87 (2H, m), 4.49 (2H, m, 1β- and 3α-H), 5.09 and 5.11 (1H and 1H, each s, =CH₂), 5.89 and 6.36 (1H and 1H, each d, J=11.3 Hz, 7- and 6-H); MS m/z (relative intensity) 416 (M⁺, 100), 398 (26), 380 (13), 366 (21), 313 (31).

BIOLOGICAL ACTIVITY OF 2-METHYLENE-SUBSTITUTED 19-NOR-1,25-(OH)₂D₃ COMPOUNDS AND THEIR 20S-ISOMERS

The introduction of a methylene group to the 2-position of 19-nor-1,25-(OH)₂D₃ or its 20S-isomer had little or no effect

order of at least 10 and possible 100–1,000 times more than that of the native hormone. Under identical conditions, twice the dose of 1,25-(OH)₂D₃ gave a serum calcium value of 13.8 mg/100 ml of serum calcium at the 130 pmol dose. When given at 260 pmol/day, it produced the astounding value of 14 mg/100 ml of serum calcium at the expense of bone. To show its selectivity, this compound produced no significant change in intestinal calcium transport at either the 130 or 260 pmol dose, while 1,25-(OH)₂D₃ produced the expected elevation of intestinal calcium transport at the only dose tested, i.e. 260 pmol/day. The 2-methylene-19-nor-1,25-(OH)₂D₃ also had extremely strong bone calcium mobilization at both dose levels but also showed no intestinal calcium transport activity. The bone calcium mobilization activity of this compound is likely to be 10–100 times that of 1,25-(OH)₂D₃. These results illustrate that the 2-methylene and the 20S-2-methylene derivatives of 19-nor-1,25-(OH)₂D₃ are selective for the mobilization of calcium from bone. Table 2 illustrates the response of both intestine and serum calcium to a single large dose of the various compounds; again, supporting the conclusions derived from Table 1.

The results in FIG. 2 illustrate that 2-methylene-19-nor-20S-1,25-(OH)₂D₃ is extremely potent in inducing differentiation of HL-60 cells to the monocyte. The 2-methylene-19-nor compound had activity similar to 1,25-(OH)₂D₃. These results illustrate the potential of the 2-methylene-19-nor-20S-1,25-(OH)₂D₃ and 2-methylene-19-nor-1,25-(OH)₂D₃ compounds as anti-cancer agents, especially against leukemia, colon cancer, breast cancer and prostate cancer, or as agents in the treatment of psoriasis.

Competitive binding of the analogs to the porcine intestinal receptor was carried out by the method described by Dame et al (Biochemistry 25, 4523–4534, 1986).

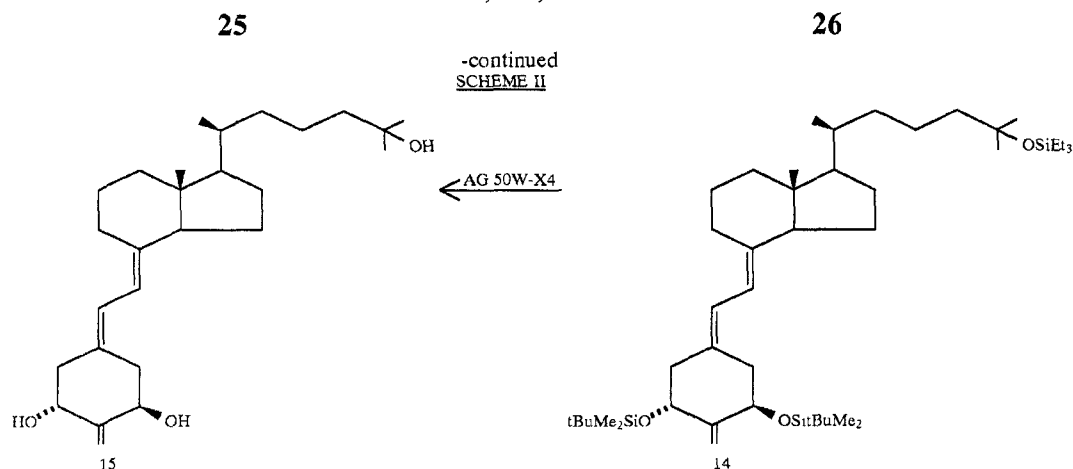
The differentiation of HL-60 promyelocytic into monocytes was determined as described by Ostrem et al (J. Biol. Chem. 262, 14164–14171, 1987).

TABLE 1

Response of Intestinal Calcium Transport and Serum Calcium (Bone Calcium Mobilization) Activity to Chronic Doses of 2-Methylene Derivatives of 19-Nor-1,25-(OH) ₂ D ₃ and its 20S Isomers			
Group	Dose (pmol/day/7 days)	Intestinal Calcium Transport (S/M)	Serum Calcium (mg/100 ml)
Vitamin D Deficient	Vehicle	5.5 ± 0.2	5.1 ± 0.16
1,25-(OH) ₂ D ₃ Treated	260	6.2 ± 0.4	7.2 ± 0.5
2-Methylene-19-Nor-1,25-(OH) ₂ D ₃	130	5.3 ± 0.4	9.9 ± 0.2
	260	4.9 ± 0.6	9.6 ± 0.3
2-Methylene-19-Nor-20S-1,25-(OH) ₂ D ₃	130	5.7 ± 0.8	13.8 ± 0.5
	260	4.6 ± 0.7	14.4 ± 0.6

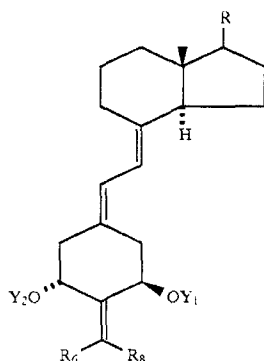
on binding to the porcine intestinal vitamin D receptor. All compounds bound equally well to the porcine receptor including the standard 1,25-(OH)₂D₃ (FIG. 1). It might be expected from these results that all of these compounds would have equivalent biological activity. Surprisingly, however, the 2-methylene substitutions produced highly selective analogs with their primary action on bone. When given for 7 days in a chronic mode, the most potent compound tested was the 2-methylene-19-nor-20S-1,25-(OH)₂D₃ (Table 1). When given at 130 pmol/day, its activity on bone calcium mobilization (serum calcium) was of the

Male weanling rats were obtained from Sprague Dawley Co. (Indianapolis, Ind.) and fed a 0.47% calcium, 0.3% phosphorus vitamin D-deficient diet for 1 week and then given the same diet containing 0.02% calcium, 0.3% phosphorus for 2 weeks. During the last week they were given the indicated dose of compound by intraperitoneal injection in 0.1 ml 95% propylene glycol and 5% ethanol each day for 7 days. The control animals received only the 0.1 ml of 95% propylene glycol, 5% ethanol. Twenty-four hours after the last dose, the rats were sacrificed and intestinal calcium transport was determined by everted sac technique as pre-



We claim:

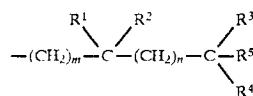
1. A compound having the formula:



where Y_1 and Y_2 , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R_6 and R_8 , which may be the same or different, are each selected from hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group $-(CH_2)_x-$ where x is an integer from 2 to 5, and where the group R is represented by the structure:



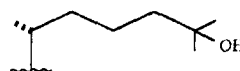
where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y , $-OY$, $-CH_2OY$, $-C\equiv CY$ and $-CH=CHY$, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $-COR^5$ and a radical of the structure:



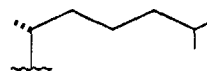
where m and n , independently, represent the integers from 0 to 5, where R^1 is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C_{1-5} -alkyl, which may be straight chain or branched and,

optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2 , R^3 , and R^4 , independently, is selected from deuterium, deuterioalkyl, hydrogen, fluoro, trifluoromethyl and C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R^1 and R^2 , taken together, represent an oxo group, or an alkylidene group, $=CR^3R^4$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, and where R^3 and R^4 , taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $-CH(CH_3)-$, $-CH(R^3)-$, or $-CH(R^2)-$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

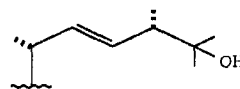
2. The compound of claim 1 where R is a side chain of the formula



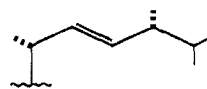
3. The compound of claim 1 where R is a side chain of the formula



4. The compound of claim 1 where R is a side chain of the formula

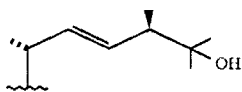


5. The compound of claim 1 where R is a side chain of the formula

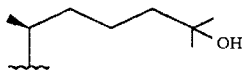


6. The compound of claim 1 where R is a side chain of the formula

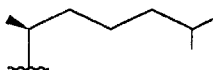
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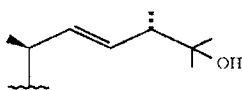
7. The compound of claim 1 where R is a side chain of the formula



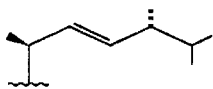
8. The compound of claim 1 where R is a side chain of the formula



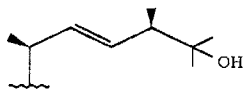
9. The compound of claim 1 where R is a side chain of the formula



10. The compound of claim 1 where R is a side chain of the formula



11. The compound of claim 1 where R is a side chain of the formula



12. 2-methylene-19-nor-1 α ,25-dihydroxyvitamin D₃.

13. 2-methylene-19-nor-20(S)-1 α ,25-dihydroxyvitamin D₃.

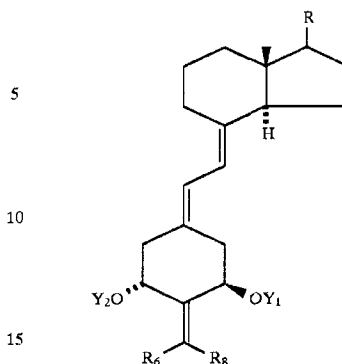
14. A pharmaceutical composition containing at least one compound as claimed in claim 1 together with a pharmaceutically acceptable excipient.

15. The pharmaceutical composition of claim 14 containing 2-methylene-19-nor-1 α ,25-dihydroxyvitamin D₃ in an amount from about 0.1 μ g to about 50 μ g.

16. The pharmaceutical composition of claim 14 containing 2-methylene-19-nor-20(S)-1 α ,25-dihydroxyvitamin D₃ in an amount from about 0.1 μ g to about 50 μ g.

17. A method of treating metabolic bone disease where it is desired to maintain or increase bone mass comprising administering to a patient with said disease an effective amount of a compound having the formula:

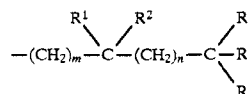
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where Y₁ and Y₂, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R₆ and R₈, which may be the same or different, are each selected from hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group —(CH₂)_x— where x is an integer from 2 to 5, and where the group R is represented by the structure:



where the stereochemical center at carbon 20 may have the R or S configuration, and where Z is selected from Y, —OY, —CH₂OY, —C≡CY and —CH=CHY, where the double bond may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, —COR³ and a radical of the structure:



where m and n, independently, represent the integers from 0 to 5, where R¹ is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C₁₋₅-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R², R³, and R⁴, independently, is selected from deuterium, deuterioalkyl, hydrogen, fluoro, trifluoromethyl and C₁₋₅ alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R¹ and R², taken together, represent an oxo group, or an alkylidene group, =CR²R³, or the group —(CH₂)_p—, where p is an integer from 2 to 5, and where R³ and R⁴, taken together, represent an oxo group, or the group —(CH₂)_q—, where q is an integer from 2 to 5, and where R⁵ represents hydrogen, hydroxy, protected hydroxy, or C₁₋₅ alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —CH(CH₃)—, —CH(R³)—, or —CH(R²)— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

18. The method of claim 17 where the disease is senile osteoporosis.

19. The method of claim 17 where the disease is postmenopausal osteoporosis.

20. The method of claim 17 where the disease is steroid-induced osteoporosis.

(19) World Intellectual Property Organization
International Bureau



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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, 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.



WO 02/091993 A2

(54) Title: ESTROGEN RECEPTOR MODULATORS

(57) Abstract: The present invention relates to compounds and derivatives thereof, their synthesis, and their use as estrogen receptor modulators. The compounds of the instant invention are ligands for estrogen receptors and as such may be useful for treatment or prevention of a variety of conditions related to estrogen deficiency including: bone loss, bone fractures, osteoporosis, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of LDL cholesterol, cardiovascular disease, impairment of cognitive functioning, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity, incontinence, and cancer, in particular of the breast, uterus and prostate.

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unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

The instant compounds are also useful in combination with known agents useful for treating or preventing bone loss, bone fractures, osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma, cartilage degeneration, endometriosis, uterine fibroid disease, cancer of the breast, uterus or prostate, hot flashes, cardiovascular disease, impairment of cognitive function, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity and incontinence. Combinations of the presently disclosed compounds with other agents useful in treating or preventing osteoporosis or other bone disorders are within the scope of the invention. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the disease involved. Such agents include the following: an organic bisphosphonate; a cathepsin K inhibitor; an estrogen or an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; calcitonin; Vitamin D or a synthetic Vitamin D analogue; selective serotonin reuptake inhibitors (SSRIs); and the pharmaceutically acceptable salts and mixtures thereof. A preferred combination is a compound of the present invention and an organic bisphosphonate. Another preferred

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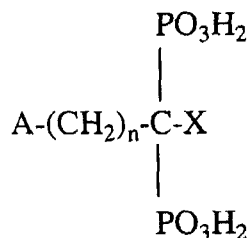
combination is a compound of the present invention and a cathepsin K inhibitor.

Another preferred combination is a compound of the present invention and an

estrogen. Another preferred combination is a compound of the present invention and an androgen receptor modulator. Another preferred combination is a compound of the

5 present invention and an osteoblast anabolic agent.

"Organic bisphosphonate" includes, but is not limited to, compounds of the chemical formula



10 wherein n is an integer from 0 to 7 and wherein A and X are independently selected from the group consisting of H, OH, halogen, NH₂, SH, phenyl, C1-C30 alkyl, C3-C30 branched or cycloalkyl, bicyclic ring structure containing two or three N, C1-C30 substituted alkyl, C1-C10 alkyl substituted NH₂, C3-C10 branched or cycloalkyl substituted NH₂, C1-C10 dialkyl substituted NH₂, C1-C10 alkoxy, C1-C10 alkyl substituted thio, thiophenyl, halophenylthio, C1-C10 alkyl substituted phenyl, pyridyl, 15 furanyl, pyrrolidinyl, imidazolyl, imidazopyridinyl, and benzyl, such that both A and X are not selected from H or OH when n is 0; or A and X are taken together with the carbon atom or atoms to which they are attached to form a C3-C10 ring.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula.

20 The C1-C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, NH₂, C1-C10 alkyl or dialkyl substituted NH₂, OH, SH, and C1-C10 alkoxy.

The foregoing chemical formula is also intended to encompass 25 complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Non-limiting examples of salts include those

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Patent 4,970,335, to Isomura *et al.*, issued November 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent
5 672,205 (1966) and *J. Org. Chem* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).
10 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

1-hydroxy-2-imidazo-(1,2-a)pyridin-3-ethylidene (minodronate).
15 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).
3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).
[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is
20 described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as
25 described in U.S. Patent 4,876,248, to Breliere *et al.*, October 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zoledronate).

Nonlimiting examples of bisphosphonates include alendronate,
30 cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, and zolendronate, and pharmaceutically acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate, especially a sodium, potassium, calcium, magnesium or ammonium salt of alendronic acid. Exemplifying the preferred
35 bisphosphonate is a sodium salt of alendronic acid, especially a hydrated sodium salt

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“Estrogen receptor modulators” refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, estrogen, progestogen, estradiol, droloxifene, raloxifene, ~~nilutamide~~, TSE-424, tamoxifen, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

“Cathepsin K inhibitors” refers to compounds which interfere with the activity of the cysteine protease cathepsin K. Nonlimiting examples of cathepsin K inhibitors can be found in PCT publications WO 00/55126 to Axys Pharmaceuticals and WO 01/49288 to Merck Frosst Canada & Co. and Axys Pharmaceuticals.

“Androgen receptor modulators” refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

“An inhibitor of osteoclast proton ATPase” refers to an inhibitor of the proton ATPase, which is found on the apical membrane of the osteoclast, and has been reported to play a significant role in the bone resorption process. This proton pump represents an attractive target for the design of inhibitors of bone resorption which are potentially useful for the treatment and prevention of osteoporosis and related metabolic diseases. See C. Farina *et al.*, “Selective inhibitors of the osteoclast vacuolar proton ATPase as novel bone antiresorptive agents,” DDT, 4: 163-172 (1999)), which is hereby incorporated by reference in its entirety.

“HMG-CoA reductase inhibitors” refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms “HMG-CoA reductase inhibitor” and “inhibitor of HMG-CoA reductase” have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®;

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amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further

5 examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide,

10 hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

15 Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

As used above, "integrin receptor antagonists" refers to compounds

20 which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or

25 counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. H.N. Lode and coworkers in PNAS USA 96: 1591-1596 (1999) have observed synergistic

30 effects between an antiangiogenic α_v integrin antagonist and a tumor-specific antibody-cytokine (interleukin-2) fusion protein in the eradication of spontaneous tumor metastases. Their results suggested this combination as having potential for the treatment of cancer and metastatic tumor growth. $\alpha_v\beta_3$ integrin receptor antagonists inhibit bone resorption through a new mechanism distinct from that of all currently

35 available drugs. Integrins are heterodimeric transmembrane adhesion receptors that

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dihydroxy vitamin D. When serum calcium decreases, there is an increase in the production of parathyroid hormone (PTH), which regulates calcium homeostasis and increases plasma calcium levels by increasing the conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D.

5 1,25-dihydroxy vitamin D is thought to be responsible for the effects of vitamin D on calcium and bone metabolism. The 1,25-dihydroxy metabolite is the active hormone required to maintain calcium absorption and skeletal integrity. Calcium homeostasis is maintained by 1,25 dihydroxy vitamin D by inducing monocyctic stem cells to differentiate into osteoclasts and by maintaining calcium in
10 the normal range, which results in bone mineralization by the deposition of calcium hydroxyapatite onto the bone surface, see Holick, MF, Vitamin D photobiology, metabolism, and clinical applications, In: DeGroot L, Besser H, Burger HG, et al., eds. *Endocrinology*, 3rd ed., 990-1013 (1995). However, elevated levels of 1,25-dihydroxy vitamin D₃ can result in an increase of calcium concentration in the blood
15 and in the abnormal control of calcium concentration by bone metabolism, resulting in hypercalcemia. ~~1,25-dihydroxy vitamin D₃ also indirectly regulates osteoclastic activity in bone metabolism. Elevated levels may be expected to increase excessive bone resorption in osteoporosis.~~

20 ~~"Synthetic vitamin D analogues" includes non-naturally occurring compounds that act like vitamin D.~~

 Selective Serotonin Reuptake Inhibitors act by increasing the amount of serotonin in the brain. SSRIs have been used successfully for a decade in the United States to treat depression. Non-limiting examples of SSRIs include fluoxetine, paroxetine, sertraline, citalopram, and fluvoxamine. SSRIs are also being used to
25 treat disorders related to estrogen functioning, such as premenstrual syndrome and premenstrual dysmorphic disorder. See Sundstrom-Poromaa I, Bixo M, Bjorn I, Nordh O., "Compliance to antidepressant drug therapy for treatment of premenstrual syndrome," *J Psychosom Obstet Gynaecol* 2000 Dec;21(4):205-11.

 If formulated as a fixed dose, such combination products employ the
30 compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

 The term "administration" and variants thereof (e.g., "administering")

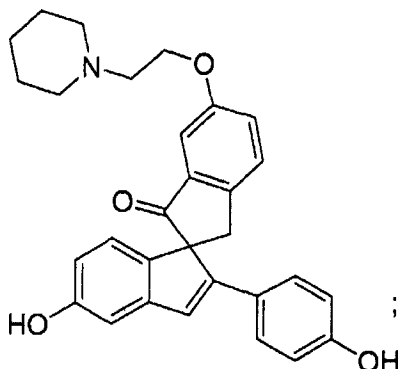
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compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds of the present invention can be used in combination with other agents useful for treating estrogen-mediated conditions. The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating cathepsin-mediated conditions includes in principle any combination with any pharmaceutical composition useful for treating disorders related to estrogen functioning.

The scope of the invention therefore encompasses the use of the instantly **claimed compounds in combination with a second agent selected from:** an organic bisphosphonate; a cathepsin K inhibitor; an estrogen; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent; calcitonin; **Vitamin D; a synthetic Vitamin D analogue;** a selective serotonin reuptake inhibitor; and the pharmaceutically acceptable salts and mixtures thereof.

These and other aspects of the invention will be apparent from the teachings contained herein.

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or a pharmaceutically acceptable salt or stereoisomer thereof.

- 5 13. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.
14. A pharmaceutical composition made by combining a compound according to Claim 1 and a pharmaceutically acceptable carrier.
- 10 15. A process for making a pharmaceutical composition comprising combining a compound according to Claim 1 and a pharmaceutically acceptable carrier.
- 15 16. A method of eliciting an estrogen receptor modulating effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1.
17. The method according to Claim 16 wherein the estrogen
- 20 receptor modulation effect is an estrogen receptor agonizing effect.
18. The method according to Claim 17 wherein the estrogen receptor agonizing effect is an ER α receptor agonizing effect.
- 25 19. A method of treating or preventing a disease in a mammal in need thereof by administering to the mammal a therapeutically effective amount of a compound according to Claim 1, wherein said disease is selected from: bone loss,

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- bone fractures, osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic bone disease, hypercalcemia of malignancy, multiple myeloma, cartilage
- 5 degeneration, endometriosis, uterine fibroid disease, breast cancer, uterine cancer, prostate cancer, hot flashes, cardiovascular disease, impairment of cognitive function, cerebral degenerative disorders, restenosis, gynecomastia, vascular smooth muscle cell proliferation, obesity or incontinence.
- 10 20. The method of Claim 19 wherein the disease is osteoporosis.
21. The method of Claim 19 wherein the disease is metastatic bone disease.
- 15 22. A method of treating or preventing an estrogen dependent cancer in a mammal in need thereof by administering to the mammal a therapeutically effective amount of a compound according to Claim 1.
- 20 23. ~~A pharmaceutical composition comprising a compound of~~
Claim 1 and another agent selected from: an organic bisphosphonate; a cathepsin K inhibitor; an estrogen; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent; calcitonin; **Vitamin D**; a **synthetic Vitamin D analogue**; or a selective serotonin reuptake
- 25 inhibitor; or a pharmaceutically acceptable salt or mixture thereof.
24. A method of treating osteoporosis comprising administering to a mammal in need thereof a compound of Claim 1 and another agent selected from: an organic bisphosphonate; a cathepsin K inhibitor; an estrogen; an estrogen receptor
- 30 modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent; calcitonin; Vitamin D; a synthetic Vitamin D analogue; or a selective serotonin reuptake inhibitor; or a pharmaceutically acceptable salt or mixture thereof.

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25. A method of treating bone loss comprising administering to a mammal in need thereof a compound of Claim 1 and another agent selected from: an organic bisphosphonate; a cathepsin K inhibitor; an estrogen; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase;
5 an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent; calcitonin; Vitamin D; a synthetic Vitamin D analogue; or a selective serotonin reuptake inhibitor; or a pharmaceutically acceptable salt or mixture thereof.

26. A method of treating metastatic bone disease comprising
10 administering to a mammal in need thereof a compound of Claim 1 and another agent selected from: an organic bisphosphonate; a cathepsin K inhibitor; an estrogen; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent; calcitonin; Vitamin D; a synthetic Vitamin D
15 analogue; or a selective serotonin reuptake inhibitor; or a pharmaceutically acceptable salt or mixture thereof.

27. A method of lowering cholesterol comprising administering to a mammal in need thereof a compound of Claim 1 and another agent selected from: an
20 organic bisphosphonate; a cathepsin K inhibitor; an estrogen; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent; calcitonin; Vitamin D; a synthetic Vitamin D analogue; or a selective serotonin reuptake inhibitor; or a pharmaceutically acceptable salt or mixture thereof.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE
Apoderado

ASUNTO	Radicación	06-021161
	Trámite	011
	Evento	379
	Actuación	430 - 2646
	Oficio	
	Folios	204

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒
No. Sol. Internacional	PCT/IB2004/002900		
Fecha de Presentación Internal.	2004/09/06		

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 51 a 138

Reivindicaciones: Folios 139 a 141 como se radicó inicialmente

Prioridad: Fecha: 2003/09/19, país: US, número: 60/504.521

2. Objeto de la invención

- Título de la solicitud: Composiciones farmacéuticas y procedimientos que comprenden combinaciones de derivados de 2-alkiliden-19-nor-vitamina D y un agonista / antagonista de estrógenos. Número de folio: 1.

El problema planteado en esta solicitud es la necesidad de combinaciones útiles para tratar la osteoporosis senil, osteoporosis postmenopáusica, fracturas de huesos, injertos de huesos, cáncer de mama, de próstata, obesidad, osteopenia, osteoporosis masculina, fragilidad, daño muscular o sarcopenia.

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Para solucionar este problema técnico la solicitud en estudio proporciona una combinación de un derivado de 2-alkiliden-19-nor-vitamina D y un agonista/antagonista de estrógenos

Clasificación Internacional de Patentes (IPC.): A61K 31/593

3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

- El solicitante no es claro cuando incluye en sus reivindicaciones los compuestos: **“profármaco”**. Al realizar la lectura del capítulo reivindicatorio, se encuentra que las frases resultan imprecisas, dado que no especifican con exactitud el(los) compuesto(s) a los cuales se refiere con dichos términos por lo tanto no se aceptan tal como aparecen.

4. Excepción a la patentabilidad (artículo 20 D486 literal a)-d)

Reivindicación 4 - 11: Se refiere a un método de tratamiento de una enfermedad por lo tanto están exceptuadas de patentabilidad según la legislación vigente.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2003/09/19

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	US 5843928	2-ALKYLIDENE-19-NOR-VITAMIN D COMPOUNDS	1998/12/1
D ₂	WO 02/091993	ESTROGEN RECEPTOR MODULATORS	2002/11/21

6. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica:

- 1) Composición que comprende el compuesto 2-metilen-19-nor-20(S)-1 α -25-dihidroxivitamina D₃ y un agonista/antagonista de estrógenos.

Dicha composición está afectada por los siguientes documentos del Estado de la Técnica:

D₁ que enseña una nueva clase de compuestos de vitamina D, llamados derivados de 2-alquiliden-19-nor-vitamina D. son agentes terapéuticos para el tratamiento de enfermedades donde se desea la formación de hueso particularmente en osteoporosis y enfermedades donde la pérdida de hueso es la mayor preocupación. (Ver folio: 185 - 186). Se reivindica específicamente el **2-metilen-19-nor-1 α , 25-dihidroxitamina D₃** (ver folio 189, reiv 15) con la misma utilidad para tratamiento que la del objeto de la presente solicitud.

D₂ que enseña ligandos para **receptores estrogénicos** (ej lasofoxifeno (-)-cis-6-fenil-5-[4-(2-pirrolidin-1-il-etoxi)fenil]-5,6,7,8-tetrahidro-naftalen-2-ol folio 194) que son usadas en el tratamiento y prevención de una variedad de condiciones relacionadas con funcionamiento estrogénico como: pérdida de hueso, fracturas, osteoporosis, degeneración de cartílago, etc. (ver folio 190). Dichos compuestos son útiles en combinación con conocidos agentes para el tratamiento de la pérdida de hueso, fracturas, osteoporosis, y osteoporosis inducida por glucocorticoides. Las combinaciones con otros agentes útiles en la osteoporosis u otros desordenes del hueso están dentro del alcance del documento. Especifica que una persona ordinariamente versada en el arte es capaz de discernir cuales combinaciones serian útiles para lo que desea obtener y tales agentes de combinación pueden incluir: **Vitamina D o un análogo sintético de vitamina D.** (ver folio 191, 196 y reiv 23 folio 199).

La única **diferencia con D₁** es que esta solicitud **especifica el compuesto de vitamina D (2- metilen-19-nor-1 α , 25-dihidroxitamina D₃)** pero esta diferencia no parece conceder un efecto técnico inesperado.

No puede determinarse un efecto técnico que logre la diferencia con la anterioridad encontrada ya que la combinación estaba previamente enseñada por D₂ para lograr el mismo objetivo y utilidad terapéutica tal como la solicitud.

El Problema Técnico Objetivo se puede definir en “como lograr una **combinación** de 2-metilen-19-nor-20(S)-1 α -25-dihidroxitamina D₃ y un agonista/antagonista de estrógenos” **alternativa a las previamente conocidas.**

Por consiguiente resultaría obvio el diseño de este tipo de combinaciones para un experto medio en la materia que conozca el estado de la técnica ya que D₁ enseñaba previamente el análogo de vitamina D reivindicado en la presente solicitud **2- metilen-19-nor-1 α , 25-dihidroxitamina D₃** y además con una utilidad terapéutica era exacta a la de la solicitud en donde se establece la necesidad de combinaciones útiles para tratar la osteoporosis senil, osteoporosis postmenopáusica, fracturas de huesos, injertos de huesos, cáncer de mama, de próstata, obesidad, osteopenia, osteoporosis masculina, fragilidad, daño muscular o sarcopenia, por lo tanto tomaría la sugerencia de combinación de compuestos activos previamente indicada en D₂ junto con el compuesto específico enseñado en D₁ para llegar de tal manera a la propuesta de la presente solicitud.

En conclusión, no se considera que la presente solicitud merezca reconocimiento de nivel inventivo.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D ₁	US 5843928	1-3	NIVEL INVENTIVO
D ₂	WO 02/091993	1-3	NIVEL INVENTIVO

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
2-6 FEB. 2010

CONCEPTO TÉCNICO No. 424	EXAMINADOR TÉCNICO Código No. 202087
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