

As. 84.420

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Tra. 2 PATENTES
Eve 1 REGDEPOSITO
Act 444 RESPUESTAREQUE Folio: 15

Señora

JEFE DE DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

REF: Expediente No. 01 018 857 – solicitud de patente de invención a favor
de BRISTOL-MYERS SQUIBB COMPANY

Respuesta a oficio No. 12659 del 2 de noviembre de 2006

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad BRISTOL-MYERS SQUIBB COMPANY según lo acredita el documento de poder anexo, me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 1686 notificado por fijación en lista de fecha 2 de noviembre de 2006.

En atención a las objeciones del señor examinador, se presenta un nuevo capítulo reivindicatorio anexo a la presente con 1 – 23 reivindicaciones, las cuales no adicionan materia nueva ni extienden el alcance de la solicitud como se presentó originalmente, y reemplazan completamente el capítulo reivindicatorio presentado anteriormente.

El nuevo capítulo reivindicatorio subsana las objeciones presentadas por el señor examinador relacionadas con la claridad del mismo. El señor examinador objeta la excesiva amplitud de lo divulgado por dicha anterioridad, la nueva reivindicación 1 subsana dicha objeción especificando la naturaleza de los sustituyentes respecto al número de carbonos o anillos presentes en dichos sustituyentes. Con esta corrección se supera también la objeción presentada por el señor examinador relacionada con la extrema sencillez de la fórmula I en relación con el grado de complejidad que podía alcanzar la molécula al realizar las sustituciones más complejas posibles, ya que los sustituyentes ahora no pueden exceder un grado de complejidad definido.

El señor examinador objeta la reivindicación de mezclas terapéuticas, argumentando que la descripción no presenta pruebas que demuestren el desempeño mejorado de dichas combinaciones en presencia del agente de la solicitud. Se le recuerda al señor examinador que el agente de la presente solicitud es un inhibidor DP4 nuevo, el cual se está probando de manera experimental y aun no existen datos definitivos sobre su eficacia mejorada en presencia de otros agentes antidiabéticos o anti-obesidad. Las mezclas propuestas obedecen al deseo del solicitante de proteger el potencial de las mismas una vez se demuestre su eficacia. Por lo tanto respetuosamente solicitamos al señor examinador un poco de laxitud en este respecto, ya que los resultados definitivos que podrían ser anexados como prueba aun no han sido proporcionados.

El señor examinador objeta también la claridad de las reivindicaciones 12, 15, 16 y 21. En el nuevo capítulo reivindicatorio anexo se ha revisado la redacción de las mismas y se han corregido en concordancia.

En cuanto a la objeción del señor examinador relacionada con la falta de unidad de invención de la presente solicitud, originada en la infinidad de posibles sustituyentes reivindicados en la reivindicación 1, dicha objeción queda subsanada con la nueva reivindicación 1 en la cual, como se dijo

anteriormente, se realiza un delimitación más específica de los sustituyentes propuestos.

Prosigue el señor examinador objetando la falta de unidad de invención en las combinaciones farmacológicas propuestas. Al respecto cabe mencionar que la unidad inventiva de dichas combinaciones yace en que todas se relacionan con enfermedades que pueden ser influenciadas por un inhibidor DP4 como el de la presente solicitud. Aun más, las combinaciones propuestas se centran particularmente en el tratamiento de enfermedades como la diabetes y la obesidad, por lo tanto existe unidad de invención.

En vista de lo anterior, respetuosamente solicitamos el retiro de las objeciones a la presente solicitud, en base al nuevo capítulo reivindicatorio presentado y a los argumentos anteriores ya que, en opinión del solicitante, la presente invención cumple con los requisitos de claridad y además los de novedad, altura inventiva y aplicabilidad industrial de la Decisión 486.

De la Señora Jefe,

Atentamente,



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.SJ.

C.C. 80.410.337 de Usaquén

Carrera 7 No. 71-21, Torre B, Of. 402

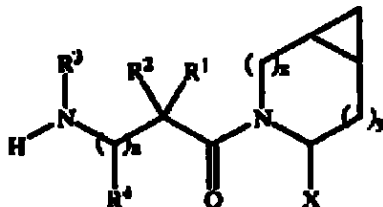
Bogotá, Enero 31 de 2007

CH/JCN

anexos

REIVINDICACIONES

1. Un compuesto inhibidor de DP4 que tiene la estructura



caracterizado porque x es 0 ó 1 e y es 0 ó 1 siempre que

x = 1 cuando y = 0 y

x = 0 cuando y = 1; y en donde

n es 0 ó 1;

X es CN o H;

R¹, R², R³ y R⁴ son los mismos o diferentes y se seleccionan en forma independiente de hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, bicicloalquilo, tricicloalquilo, alquilocicloalquilo, hidroxialquilo, hidroxialquilocicloalquilo, hidroxicicloalquilo, hidroxibicicloalquilo, hidroxitricicloalquilo, bicicloalquilalquilo, alquiltioalquilo, arilalquiltioalquilo, cicloalquenilo, arilo, aralquilo, heteroarilo, heteroarilalquilo, cicloheteroalquilo y cicloheteroalquilalquilo; todos substituidos opcionalmente a través de átomos de carbono disponibles con 1, 2, 3, 4 ó 5 grupos seleccionados de hidrógeno, halo, alquilo, polihaloalquilo, alcoxi, haloalcoxi, polihaloalcoxi, alcóxicarbonilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, policicloalquilo, heteroarilamino, arilamino, cicloheteroalquilo, cicloheteroalquilalquilo, hidroxil, hidroxialquilo, nitro, ciano, amino, amino substituido, alquilamino, dialquilamino, tior, alquiltio, alquilcarbonilo, acilo, alcóxicarbonilo, aminocarbonilo, alquilaminocarbonilo, alquilaminocarbonilo, alquilaminocarbonilo, alquilcarbonilo, alquilcarbonilamino, arilcarbonilamino, alquilsulfonilamino, alquilaminocarbonilamino, alcóxicarbonilamino, alquilsulfonilo, aminosulfonilo, aminosulfonilo, alquilsulfonilo, sulfonamido o sulfonilo;

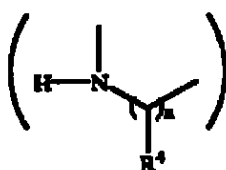
y R¹ y R³ se pueden tomar opcionalmente de manera conjunta para formar -(CR⁵R⁶)_m- en donde m es 2 a 6, y R⁵ y R⁶ son los mismos o diferentes y se seleccionan en forma independiente a partir de hidroxil, alcoxi, H, alquilo, alquenilo, alquinilo, cicloalquilo, halo, amino, amino substituido, cicloalquilalquilo, cicloalquenilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, alquilcarbonilamino,

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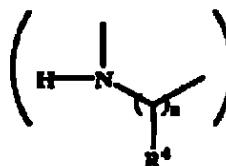
arilcarbonilamino, alcoxicarbonilamino, ariloxicarbonilamino, alcoxicarbonilo, ariloxicarbonilo, o alquilaminocarbonilamino, o R^1 y R^4 se pueden tomar opcionalmente de manera conjunta para formar $-(CR^7R^8)_p-$ en donde p es 2 a 6, y R^7 y R^8 son los mismos o diferentes y se seleccionan independientemente de hidroxí, alcoxi, ciano, H, alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquilalquilo, cicloalquenilo, halo, amino, amino sustituido, arilo, arilalquilo, heteroarilo, heteroarilalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, alquilcarbonilamino, arilcarbonilamino, alcoxicarbonilamino, ariloxicarbonilamino, alcoxicarbonilo, ariloxicarbonilo, o alquilaminocarbonilamino, u

opcionalmente R^1 y R^3 junto con



forman un anillo de 5 a 7 elementos que contienen un total de 2 a 4 heteroátomos seleccionados de N, O, S, SO, o SO₂;

u opcionalmente R^1 y R^3 junto con



forman un anillo cicloheteroalquilo de 4 a 8 elementos en donde el anillo cicloheteroalquilo tiene un anillo arilo opcional fusionado a éste o un anillo cicloalquilo de 3 a 7 elementos, opcional, fusionado a éste;

con la condición que donde x es 1 e y es 0, n es 0, y uno de R^1 y R^2 es H y el otro es alquilo, donde R^3 es diferente de piridilo o piridilo sustituido;

que incluyen todos los estereoisómeros de los mismos;

Con la condición de que cuando X es H, x es 1 e y es 0, n es 0, y uno de R^1 y R^2 es H y el otro es alquilo, luego R^3 es diferente a piridilo.

En donde:

Los términos "alquil" o "alqu", solos o como partes de otro grupo, se refieren a grupos de hidrocarburos que tienen de 1 a 20 átomos;

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El término "cicloalquilo", solo o como parte de otro grupo, se refiere a un grupo de hidrocarburos cíclicos que contienen de 1 a 3 anillos y de 3 a 20 átomos de carbono;

El término "cicloalquenilo", solo o como parte de otro grupo, se refiere a un grupo de hidrocarburos cíclicos que contiene de 3 a 12 átomos de carbono;

El término "alquenilo", solo o como parte de otro grupo, se refiere a un grupo de hidrocarburos que tiene de 2 a 20 átomos de carbono;

El término "alquinilo", solo o como parte de otro grupo, se refiere a un grupo de hidrocarburos que tiene de 2 a 20 átomos de carbono;

El término "arilo", solo o como parte de otro grupo, se refiere a un grupo aromático monocíclico o bicíclico que tiene de 6 a 10 átomos de carbono;

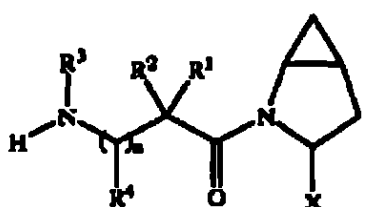
El término "cicloheteroarilo", solo o como parte de otro grupo, se refiere a un anillo de 5, 6 o 7 miembros que tiene 1 o 2 heteroátomos seleccionados de nitrógeno oxígeno y azufre;

El término "heteroarilo", solo o como parte de otro grupo, se refiere a un anillo aromático de 5 o 6 miembros que tiene de 1 a 4 heteroátomos seleccionados de nitrógeno, oxígeno y azufre, y

El término "amino sustituido" se refiere a un grupo amino sustituido con uno o dos sustituyentes, los cuales pueden ser el mismo o diferentes, seleccionados de alquilo, arilo, aralquilo, heteroarilo, heteroarilalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, cicloalquilo, cicloalquilalquilo, haloalquilo, hidroxialquilo, alcoxialquilo y tioalquilo, o dichos sustituyentes pueden tomarse junto con el átomo de nitrógeno al que están unidos para formar 4-morfolinilo, 1-piperazinilo, 4-alkil-1-piperazinilo, 4-diarilalkil-1-piperazinilo, 1-pirrolidinilo, 1-piperidinilo y 1-azepinilo.

y una sal de los mismos farmacéuticamente aceptable, o un éster profármaco de los mismos, y todos los estereoisómeros de los mismos;

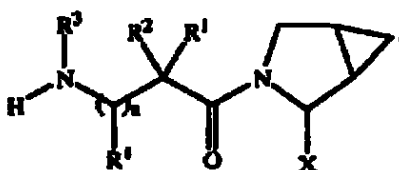
2. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la estructura:



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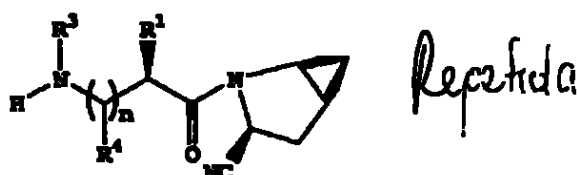
donde R^1 , R^2 , R^3 , R^4 , n , y X son como se definen en la reivindicación 1.

3. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la estructura:



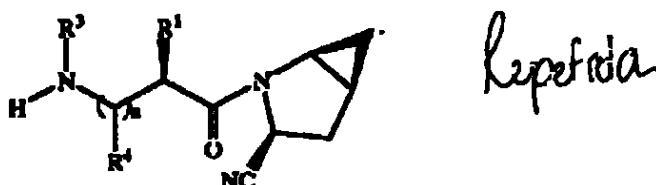
donde R^1 , R^2 , R^3 , R^4 , n , y X son como se definen en la reivindicación 1.

4. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la estructura:



donde R^1 , R^3 , R^4 , y n son como se definen en la reivindicación 1.

5. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la estructura:



donde R^1 , R^3 , R^4 , y n son como se definen en la reivindicación 1.

6. El compuesto de conformidad con la reivindicación 1, caracterizado porque:

R^3 es H, R^1 es H, alquilo, cicloalquilo, bicicloalquilo, tricicloalquilo, alquilocicloalquilo, hidroxialquilo, hidroxialquilocicloalquilo, hidroxicicloalquilo, hidroxibicicloalquilo, o hidroxitricicloalquilo,

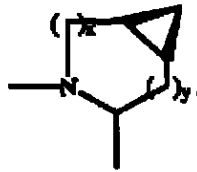
R^2 es H o alquilo, n es 0,

X es CN.

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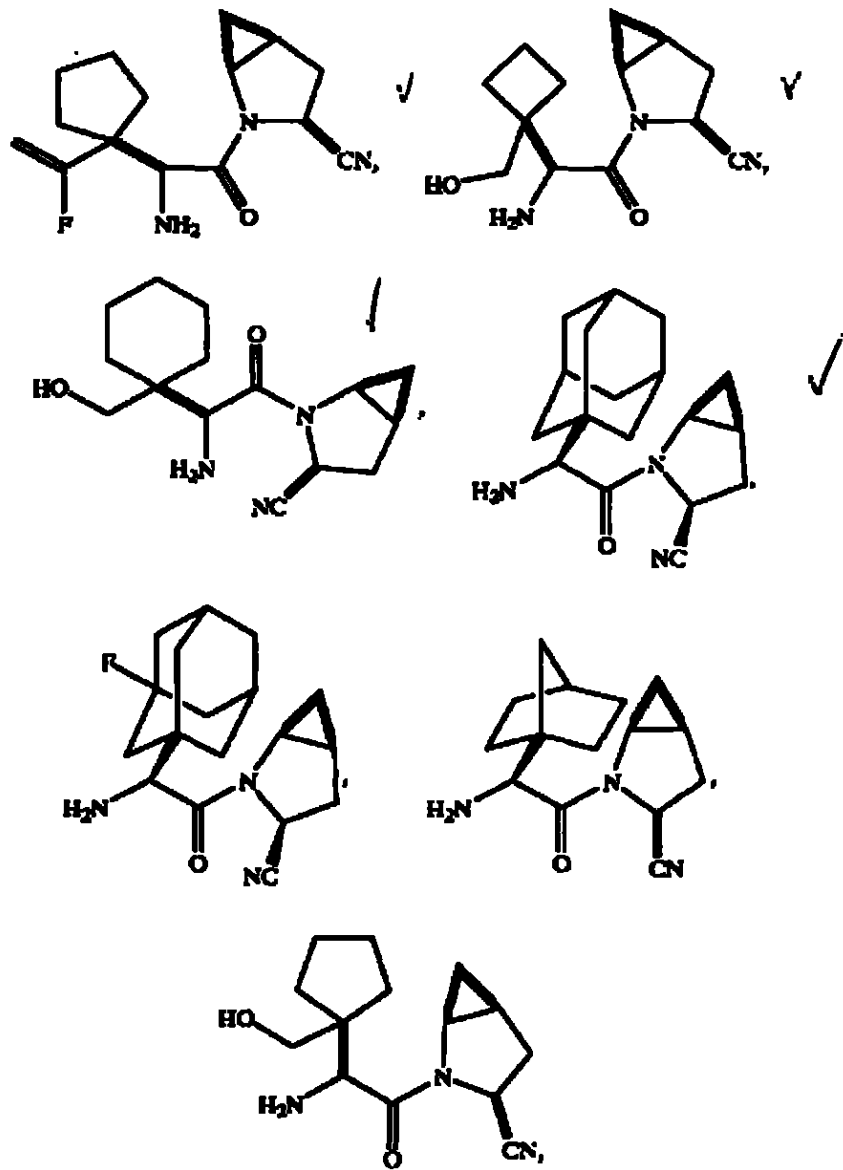
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7. El compuesto de conformidad con la reivindicación 1, caracterizado porque el ciclopropilo fusionado a la pirrolidina tiene la configuración:



donde x e y son como se definen en la reivindicación 1.

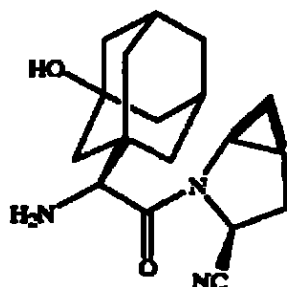
8. El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la estructura:



o una sal farmacéuticamente aceptable de los mismos.

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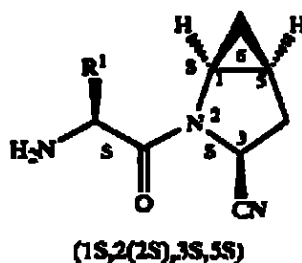
9 El compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la estructura:



o una sal farmacéuticamente aceptable del mismo.

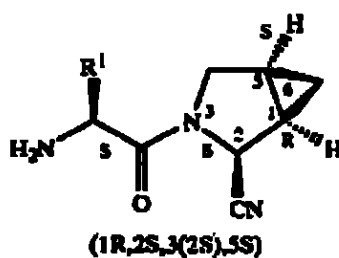
10. El compuesto de conformidad con la reivindicación 8, caracterizado porque la sal farmacéuticamente aceptable es la sal de clorhidrato o la sal del ácido trifluoroacético.

11. El compuesto de conformidad con la reivindicación 1, el cual es



caracterizado porque R^1 es alquilo, cicloalquilo, bicicloalquilo, tricicloalquilo, alquilocicloalquilo, hidroxialquilo, hidroxicicloalquilo, hidroxialquilocicloalquilo, hidroxibicicloalquilo, o hidroxitricicloalquilo,

o



en donde R^1 es alquilo, cicloalquilo, bicicloalquilo, tricicloalquilo, alquilocicloalquilo, hidroxialquilo, hidroxicicloalquilo, hidroxialquilocicloalquilo, hidroxibicicloalquilo, o hidroxitricicloalquilo.

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12. Una composición farmacéutica caracterizada porque comprende un compuesto de conformidad con la reivindicación 1 y un portador del mismo farmacéuticamente aceptable.

13. Una combinación farmacéutica caracterizada porque comprende un compuesto inhibidor de DP4 como se definió en la reivindicación 1 y un agente antidiabético menos un inhibidor de DP4 para el tratamiento de la diabetes y enfermedades relacionadas, un agente antiobesidad y/o un agente modulador de lípidos.

14. La combinación farmacéutica de conformidad con la reivindicación 12, caracterizada porque comprende el compuesto inhibidor de DP4 y un agente antidiabético.

15. La combinación de conformidad con la reivindicación 14, caracterizada porque el agente antidiabético es 1, o más de un segundo ingrediente que es una biguanida, una sulfonilurea, un inhibidor de glucosidasa, un agonista PPAR γ , un agonista dual PPAR α/γ , un inhibidor de SGLT2, un inhibidor de α P2, un inhibidor de glicogen fosforilasa, un inhibidor de AGE, un sintetizador de insulina, un péptido-1 semejante al glucagon (GLP-1) o mimético del mismo, insulina y/o una meglitinida.

16. La combinación de conformidad con la reivindicación 15, caracterizada porque el agente antidiabético es 1 o más de un segundo ingrediente que es metformina, gliburida, glimepirida, glipirida, glipizida, clorpropamida, gliclazida, acarbosa, miglitol, pioglitazona, troglitazona, rosiglitazona, insulina, G1-262570, isaglitazona, JTT-501, NN-2344, L895845, YM-440, R-119702, AJ9677, repaglinida, nateglinida, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, Exendin-4, LY307161, NN2211, y/o LY315902.

17. La combinación de conformidad con la reivindicación 14, caracterizada porque el compuesto está presente en una relación o proporción en peso al agente antidiabético dentro del rango desde aproximadamente 0.01 a en forma aproximada 100:1.

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18. La combinación de conformidad con la reivindicación 13, caracterizada porque el agente antiobesidad es un agonista adrenérgico beta 3, un inhibidor de lipasa, un inhibidor de reabsorción de serotonina (y dopamina), un compuesto beta receptor de la tiroide, un agente anoréctico, y/o un superregulador de la oxidación del ácido graso.

19. La combinación de conformidad con la reivindicación 18, caracterizada porque el agente antiobesidad es orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramina, topiramato, oxacina, dexanfetamina, fentermina, fenilpropanolamina, famoxina, y/o mazindol.

20. La combinación de conformidad con la reivindicación 13, caracterizada porque el agente modulador de lípidos es un inhibidor de MTP, un inhibidor de reductasa de HMG CoA, un inhibidor de escualeno sintetasa, un derivado del ácido fibríco, un superregulador de la actividad del receptor de LDL, un inhibidor de lipoxigenasa, un inhibidor de ACAT, un inhibidor de proteína de transferencia de colesterol éster, o un inhibidor de liasa de citrato de ATP.

21. La combinación de conformidad con la reivindicación 18, caracterizada porque el agente de modulación de lípidos es pravastatina, lovastatina, simvastatina, atorvastatina, cerivastatina, fluvastatina, nisvastatina, visastatina, fenofibrato, gemfibrozil, clofibrato, implitapida, CP-529,414, avasimiba, TS-962, MD-700, y/o LY295427.

22. La combinación de conformidad con la reivindicación 20, caracterizada porque el inhibidor de DP4 está presente en una relación o proporción en peso al agente modulador de lípidos dentro del rango desde aproximadamente 0.01 a en forma aproximada 100:1.

23. Una combinación farmacéutica caracterizada porque comprende un compuesto inhibidor de DP4 como se definió en la reivindicación 1 y un agente para el tratamiento de infertilidad, un agente para tratar el síndrome de ovario poliquístico, un agente para tratar un desorden de crecimiento y/o debilidad, un agente antiartritis, un agente para prevenir la inhibición del rechazo al aloinjerto en el trasplante, un agente para tratar la

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enfermedad autoinmune, un agente antiSIDA, un agente para tratar la enfermedad/síndrome inflamatorio del intestino, un agente para tratar anorexia nerviosa, un agente antiosteoporosis y/o un agente antiobesidad.

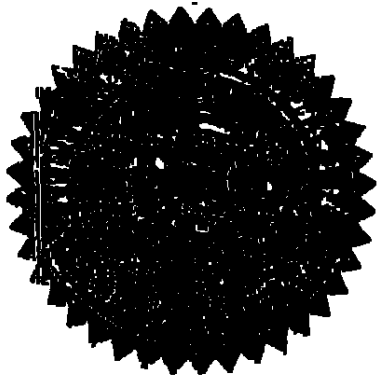
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APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

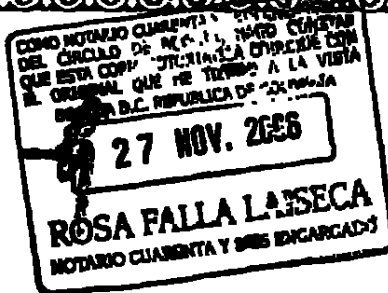
1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MAURA O KNOBL
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
MAURA O KNOBL, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 13TH DAY OF JANUARY 2006
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A248886
9. SEAL/STAMP:
10. SIGNATURE



John E McCormac





Brigard & Castro
BOGOTA - COLOMBIA

Handwritten signature

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PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciliado(s) en

domicled in Princeton, New Jersey, USA

Nombro(amos) a: JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o MARTIN E. TORRES CARDOZO, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales, lemas comerciales y enseñanzas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

Hereby appoints JUAN PABLO CADENA SARMIENTO and/or CARLOS H. PALACIO EASTMAN and/or MARTIN E. TORRES CARDOZO, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names, slogans and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistír a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros) intereses), con todas las demás facultades legales necesarias.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistír, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o MARTIN E. TORRES CARDOZO, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados, judiciales y extrajudiciales.

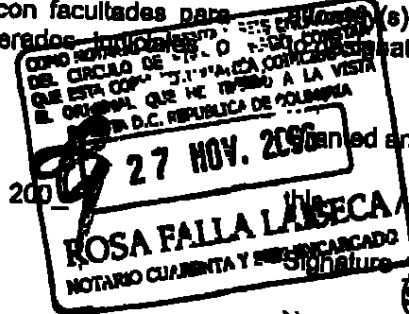
This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints JUAN PABLO CADENA SARMIENTO and/or CARLOS H. PALACIO EASTMAN and/or MARTIN E. TORRES CARDOZO, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) apoderados (s) in fact, with powers to receive notifications and designate judicial and extrajudicial attorneys.

Otorgado y firmado en

hoy de de

Firma

Nombre
Cargo



dated and signed in

day Jan of 2006

Name
Title

Suzanne E. Babajko
Senior Patent Counsel

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Hoy de
personalmente compareció ante mí

On this 11 day of January of 2006 personally
appeared before me SUZANNE E. BABAJKO

a quien conozco, y de quien me consta que firmó el anterior
documento, debidamente juramentado declaró y dijo que él
(ella) es

to me known, and known to me to be the person who
signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the
SENIOR PATENT COUNSEL

de

of BRISTOL-MYERS SQUIBB COMPANY

Sociedad legalmente constituida para un período de
duración que aún no ha terminado; que el declarante está
autorizado por dicha compañía para conferir este poder; que
el sello estampado por él al pie de tal poder, en nombre y
representación de la expresada compañía, es el sello oficial
de ella; y que el objeto para el cual se confiere este
instrumento está comprendido dentro del objeto social de la
sociedad.

Which is legally constituted for a term not yet expired, that
deponent is authorized by said Company to confer this
Power of Attorney; that the seal affixed hereunto by the
deponent in the name and on behalf of said Corporation is
the corporate seal thereof; and that the purpose for which
this instrument is granted is included within the corporate
purpose of company.

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad.

The undersigned Notary Public attests that he has seen the
documents that prove the existence of the company.

Estado de
con fecha

State of
under date of

y que quien confiere el presente poder es su representante.

and that he (she) who grants the present power of attorney
is its Representative.

Notario Público (sello)

Public Notary (Seal)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

**NOTARIAL CERTIFICATE
NATURAL PERSON**

Hoy de de , compareció(eron) ante mí

On this 11th day of January of 2006
personally appeared before me

Suzanne E. Babajko

a quien (es) conozco y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede y
quien(es) declara(n) que otorgan el mismo para los fines y
propósitos que en él se expresan.

who is(are) known to me and who I attest executed the
foregoing document and he (they) declared he (they)
grant(s) the document for the uses and purposes therein
expressed

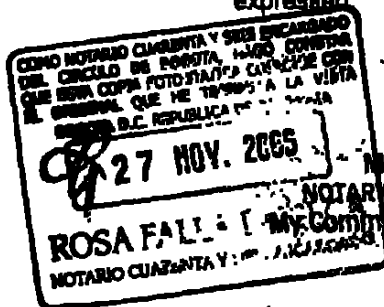
Notario Público (sello)

Notary Public

MAURA O. KNÖBL

NOTARY PUBLIC OF NEW JERSEY

My Commission Expires July 27, 2008



LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

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455

TRADUCCION AL ESPAÑOL del Documento de Poder otorgado por
BRISTOL-MYERS SQUIBB COMPANY domiciliada en Princeton, New
Jersey, Estados Unidos de América.

APOSTILLA
(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PUBLICO HA SIDO FIRMADO POR:
MAURA O KNOBL
3. ACTUANDO EN CAPACIDAD DE:
NOTARIO PUBLICO DE NEW JERSEY
4. LLEVA EL SELLO/TIMBRE DE:
MAURA O KNOBL, NOTARIO

CERTIFICADO

5. EN TRENTON, NEW JERSEY
6. EL 13 DE ENERO DE 2006
7. POR: John E. McCormac, CPA, TESORERO DE NEW JERSEY
8. NO. A248886
9. SELLO/TIMBRE:
10. FIRMA



456
45T

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

D ctor
Juan Pablo Cadena Sarmiento
Apoderado
BRISTOL MYERS SQUIBB COMPANY

Oficio N°

REFERENCIA	Radicación	01 18857
	Trámite	002
	Evento	001
	Actuación	430
	Folios	002

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 01 18857, realizado según el artículo 46 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El art. 46 de la Decisión 486 establece que *"La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más documentos relativos a una o más solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ...b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera...Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente"*

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente solicitud, se determinó que existe en el estado de la técnica los siguientes documentos que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- 1) HANESSIAN S ET AL: "Probing the importance of spatial and conformational domains in captopril analogs for angiotensin converting enzyme activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 16, 18 August 1998 (1998-08-18), pages 2123-2128, XP004137231. ISSN: 0960-894X.
- 2) TVEREZOVSKY V V ET AL: "Synthesis of (2S,3R,4S)-3,4-methanoprolin and analogues by cyclopropylidene insertion" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 53, no. 43, 27 october 1997 (1997-10-27), pages 14773-14792, XP004106307. ISSN: 0040-4020.

3) SAGNARD I ET AL: "Enantioselective syntheses of cyclopropane alpha-amino acids: Synthesis of N-Boc-cis-(2S,3R,4S)-3,4-methanoprolin and N-Boc-(2S,3R,4S)-3,4-methanoprolin and N-Boc-(2S,3R,4S)-3,4-methanoglutamic acid" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 36, no. 18, 1 May 1995 (1995-05-01), pages 3149-3152, XP004028212. ISSN: 0040-4039.

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO 0168603, equivalente a la solicitud colombiana aquí estudiada, y no siendo viable la consecución de dicho artículo por este despacho, se requiere que el solicitante, en virtud de lo establecido en el art. 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione la publicación completa, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001.

Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

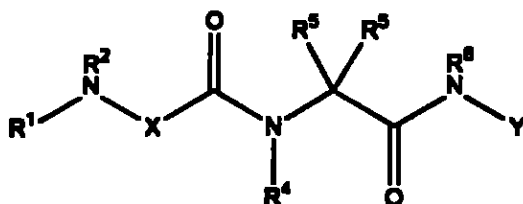
CONCEPTO TÉCNICO Número 0385	EXAMINADOR TÉCNICO Código 202044
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(51) International Patent Classification ⁶ : C07K 5/023, A61K 38/04, 31/47, 38/03, C07D 401/12	A2	(11) International Publication Number: WO 99/47545 (43) International Publication Date: 23 September 1999 (23.09.99)
(21) International Application Number: PCT/US99/05919 (22) International Filing Date: 19 March 1999 (19.03.99) (30) Priority Date: 60/078,770 19 March 1998 (19.03.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/078,770 (CON) Filed on 19 March 1998 (19.03.98) (71) Applicant (for all designated States except US): VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 130 Waverly Street, Cambridge, MA 02139-4242 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): WANNAMAKER, Mar- ion, W. [US/US]; 375 Harvard Road, Stow, MA 01775 (US). HEMIS, Guy, W. [US/US]; 256 Appleton Street, Arlington, MA 01572 (US). CHARPSON, Paul, S. [US/US]; 7 Dart- mouth Drive, Framingham, MA 01701 (US). LAUFFER, David, J. [US/US]; 254 Taylor Road, Stow, MA 01775 (US). MULLICAN, Michael, D. [US/US]; 110 Parker Road, Needham, MA 02194 (US). MURCKO, Mark, A. [US/US];	520 Marshall Street, Holliston, MA 01746 (US). WILSON, Kath, P. [US/US]; 6 Longwood Drive, Hopkinton, MA 01748 (US). JANETKA, James, W. [US/US]; 3612 Stearns Hill Road, Waltham, MA 02451 (US). DAVIES, Robert, J. [GB/US]; Apartment 2K, 225 Weldon Street, Cambridge, MA 02109 (US). GRILLOT, Anne-Laure [FR/US]; Apart- ment #3R, 31 Regent Street, Cambridge, MA 02140 (US). SHI, Zhan [CN/US]; Apartment 7, 15 Sheridan Drive, Shrewsbury, MA 01545 (US). FORSTER, Cornelia, J. [US/US]; 8 Nancy Avenue, Pelham, NH 03076 (US). (74) Agents: HALBY, James, F., Jr.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US) et al. (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, EE, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	
(54) Title: INHIBITORS OF CASPASES (57) Abstract The present invention relates to novel classes of compounds which are caspase inhibitors, in particular interleukin-1β converting enzyme ("ICE") inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting caspase activity and consequently, may be advantageously used as agents against interleukin-1- ("IL-1"), apoptosis-, interferon-γ inducing factor- (IGIF), or interferon-γ- ("IFN-γ") mediated diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases. This invention also relates to methods for inhibiting caspase activity and decreasing IGIF production and IFN-γ production and methods for treating interleukin-1, apoptosis-, and interferon-γ- mediated diseases using the compounds and compositions of this invention. This invention also relates to methods of preparing the compounds of this invention.		

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What is claimed is:

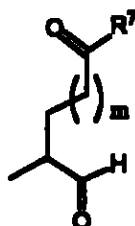
1. A compound represented by formula I:



wherein:

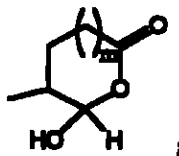
Y is:

(a)



provided that when R⁷ is -OH then Y can also be:

(b)



X is -C(R³)₂- or -N(R³)-;

m is 0 or 1;

R¹ is H, -R⁸, -C(O)R⁸, -C(O)C(O)R⁸, -S(O)₂R⁸,
 -S(O)R⁸, -C(O)OR⁸, -C(O)N(H)R⁸, -S(O)₂N(H)-R⁸,
 -S(O)N(H)-R⁸, -C(O)C(O)N(H)R⁸, -C(O)CH=CHR⁸,

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$-\text{C}(\text{O})\text{CH}_2\text{OR}^8$, $-\text{C}(\text{O})\text{CH}_2\text{N}(\text{H})\text{R}^8$, $-\text{C}(\text{O})\text{N}(\text{R}^8)_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^8)_2$,
 $-\text{S}(\text{O})\text{N}(\text{R}^8)_2$, $-\text{C}(\text{O})\text{C}(\text{O})\text{N}(\text{R}^8)_2$, $-\text{C}(\text{O})\text{CH}_2\text{N}(\text{R}^8)_2$, $-\text{CH}_2\text{R}^8$,
 $-\text{CH}_2\text{-alkenyl-R}^8$, or $-\text{CH}_2\text{-alkynyl-R}^8$;

5 R^2 is $-\text{H}$ and each R^3 is independently $-\text{H}$, an
amino acid side chain, $-\text{R}^8$, alkenyl- R^9 , or alkynyl- R^9 ,
or each R^3 , together with the atom to which they are
bound, form a 3 to 7 membered cyclic or heterocyclic
cyclic ring system, or R^2 and one R^3 together with the
10 atoms to which they are bound, form a 3 to 7 membered
cyclic or heterocyclic ring system, wherein a hydrogen
atom bound to any -alkyl or -cycloalkyl carbon atom is
optionally replaced by $-\text{R}^{10}$, a hydrogen atom bound to
any -aryl or -heteroaryl carbon atom is optionally
15 replaced by $-\text{R}^{11}$, a hydrogen atom bound to any nitrogen
atom of the ring system is optionally replaced by $-\text{R}^1$;

R^4 is $-\text{H}$ and each R^5 is independently $-\text{H}$, an
amino acid side chain, $-\text{R}^8$, -alkenyl- R^9 , or -alkynyl-
20 R^9 , or R^4 and one R^5 together with the atoms to which
they are bound form a 3 to 7 membered cyclic or
heterocyclic ring system, wherein a hydrogen atom bound
to any -alkyl or -cycloalkyl carbon atom is optionally
replaced by R^{10} , a hydrogen atom bound to any -aryl or
25 -heteroaryl carbon atom is optionally replaced by R^{11} ,
and a hydrogen atom bound to any nitrogen atom of the
ring system is optionally replaced with R^1 ;

R^6 is $-\text{H}$;

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R^7 is $-\text{OH}$, $-\text{OR}^8$, or $-\text{N}(\text{H})\text{OH}$;

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each R⁸ is independently -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl, -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R¹⁰, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R¹¹, and a hydrogen atom bound to any nitrogen atom is optionally replaced by R¹;

each R⁹ is independently -aryl, -heteroaryl, cycloalkyl, or -heterocyclyl, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R¹⁰, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R¹¹, and a hydrogen atom bound to any nitrogen atom is optionally replaced by R¹;

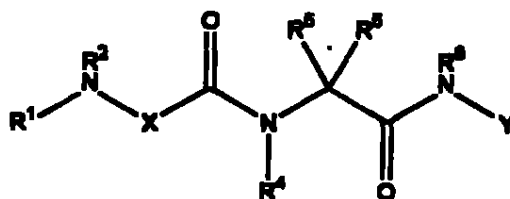
each R¹⁰ is independently -OH, -SH, -F, -Cl, -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H, -N(H)C(O)NH₂, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)alkyl, -N(H)C(O)aryl, -N(H)C(O)alkylaryl, -N(H)C(O)oheteroaryl, -N(H)C(O)alkylheteroaryl, -N(H)C(O)ocycloalkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂, -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)heteroaryl, -N(H)C(O)N(H)alkylheteroaryl, -N(H)C(O)N(H)cycloalkyl, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂, -alkyl,

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-cycloalkyl, -aryl, -heteroaryl, -heterocyclyl,
 -alkylcycloalkyl -alkylaryl, -alkylheteroaryl, or
 -alkylheterocyclyl, wherein a hydrogen atom bound to
 any -aryl or -heteroaryl carbon atom is optionally
 5 replaced by R^{11} and a hydrogen atom bound to any
 nitrogen atom is optionally replaced by R^1 ; and

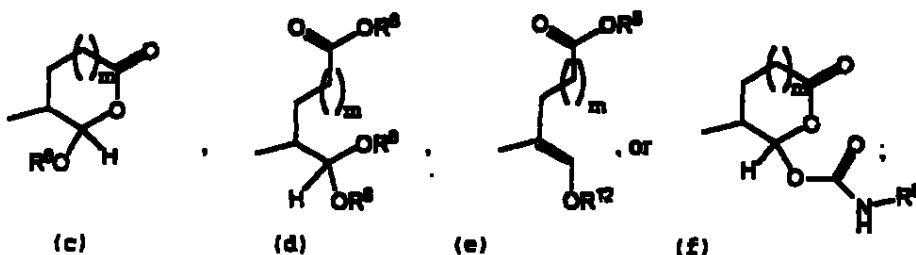
each R^{11} is independently -OH, -SH, -F, -Cl,
 -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H,
 10 -N(H)C(O)NH₂, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-
 alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl,
 -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl,
 -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,
 -N(H)C(O)N(alkyl)₂, -S-alkyl, -S-aryl, -S-alkylaryl,
 15 -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂,
 -CH₂N(H)alkyl, or -CH₂N(alkyl)₂.

2. A compound represented by formula I:

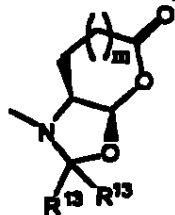


wherein:

Y is:



provided that when R^6 is not hydrogen, R^6 and Y, together with the nitrogen to which they are bound, form a ring (g):



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(g)

X is $-C(R^3)_2-$ or $-N(R^3)-$;

m is 0 or 1;

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R^1 is H, $-R^8$, $-C(O)R^8$, $-C(O)C(O)R^8$, $-S(O)_2R^8$, $-S(O)R^8$, $-C(O)OR^8$, $-C(O)N(H)R^8$, $-S(O)_2N(H)-R^8$, $-S(O)N(H)-R^8$, $-C(O)C(O)N(H)R^8$, $-C(O)CH=CHR^8$, $-C(O)CH_2OR^8$, $-C(O)CH_2N(H)R^8$, $-C(O)N(R^8)_2$, $-S(O)_2N(R^8)_2$, $-S(O)N(R^8)_2$, $-C(O)C(O)N(R^8)_2$, $-C(O)CH_2N(R^8)_2$, $-CH_2R^8$, $-CH_2$ -alkenyl- R^8 , or $-CH_2$ -alkynyl- R^8 ;

15

R^2 is $-R$ and each R^3 is independently $-H$, an amino acid side chain, $-R^8$, alkenyl- R^9 , or alkynyl- R^9 , or each R^3 , together with the atom to which they are bound, form a 3 to 7 membered cyclic or heterocyclic cyclic ring system, or R^2 and one R^3 together with the atoms to which they are bound, form a 3 to 7 membered cyclic or heterocyclic ring system, wherein a hydrogen atom bound to any $-alkyl$ or $-cycloalkyl$ carbon atom is optionally replaced by $-R^{10}$, a hydrogen atom bound to any $-aryl$ or $-heteroaryl$ carbon atom is optionally

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replaced by -R¹¹, a hydrogen atom bound to any nitrogen atom of the ring system is optionally replaced by -R¹;

5 R⁴ is -H and each R⁵ is independently -H, an amino acid side chain, -R⁸, -alkenyl-R⁹, or -alkynyl-R⁹, or R⁴ and one R⁵ together with the atoms to which they are bound form a 3 to 7 membered cyclic or heterocyclic ring system, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R¹⁰, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R¹¹, and a hydrogen atom bound to any nitrogen atom of the ring system is optionally replaced with R¹;

15 R⁶ is -H;

each R⁸ is independently -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl, -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R¹⁰, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R¹¹, and a hydrogen atom bound to any nitrogen atom is optionally replaced by R¹;

25

each R⁹ is independently -aryl, -heteroaryl, cycloalkyl, or -heterocyclyl, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R¹⁰, a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R¹¹, and a hydrogen atom bound to any nitrogen atom is optionally replaced by R¹;

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each R¹⁰ is independently -OH, -SH, -F, -Cl, -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H, -N(H)C(O)NH₂, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)Oalkyl, -N(H)C(O)Oaryl, -N(H)C(O)Oalkylaryl, -N(H)C(O)Oheteroaryl, -N(H)C(O)Oalkylheteroaryl, -N(H)C(O)Ocycloalkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂, -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)heteroaryl, -N(H)C(O)N(H)alkylheteroaryl, -N(H)C(O)N(H)cycloalkyl, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂, -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl, -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R¹¹ and a hydrogen atom bound to any nitrogen atom is optionally replaced by R¹; and

each R¹¹ is independently -OH, -SH, -F, -Cl, -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H, -N(H)C(O)NH₂, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂;

R¹² is -C(O)alkyl, -C(O)cycloalkyl, -C(O)alkenyl, -C(O)alkylaryl, -C(O)alkylheteroaryl, -C(O)heterocyclyl, or -C(O)alkylheterocyclyl; and

The polyetherester amide is a block copolymer. A block copolymer is especially a polyether ester amide in which the polyether segments consist of polyethylene glycol units having a molecular weight M_n of from 200 to 6000 daltons and the polyamide segments consist of polyamide (x) or polyamide (x,y) having a molecular weight M_n of from 200 to 6000 daltons, x and y being a number from 4 to 14.

Particularly preferred is a composition containing a polyetherester amide.

These compositions comprise a fibre-forming or fibrous organic polymeric material, such as a polyamide fibre, together with the polyetherester amide, which can be so incorporated into the polyolefin film that the polyetherester amide is substantially adsorptively bound to the fibre or dissolved in it and together with it forms a network in the polyolefin film in which the fibre is not soluble. A portion of the polyetherester amide has polar groups that are capable of complexing or solvating a salt of an inorganic or organic protonic acid.

The fibrous or fibre-forming organic polymeric material must be so selected that it does not dissolve in the thermoplastic or elastomeric substrate but is able to form a net-like structure of contiguous fibres. Polyamide fibres are most useful in this respect.

Typical examples for a suitable polyamide are:

Polyamides and copolyamides derived from diamines and dicarboxylic acids and/or from aminocarboxylic acids or the corresponding lactams, for example polyamide 4, polyamide 6, polyamide 6/6, 6/10, 6/9, 6/12, 4/6, 12/12, polyamide 11, polyamide 12, aromatic polyamides starting from m-xylene diamine and adipic acid; polyamides prepared from hexamethylenediamine and isophthalic or/and terephthalic acid and with or without an elastomer as modifier, for example poly-2,4,4'-trimethylhexamethylene terephthalamide or poly-m-phenylene isophthalamide.

If material that is already fibrous is used, then the material may be selected in various fibre thicknesses. Fibre thicknesses are usually quoted in dtex (g/10000 m). Fibre thicknesses of from 0.5 to 500 dtex are typical, with the use of fibre thicknesses of from 1 to 100 dtex being preferred.

Especially preferred are the following salts LiClO_4 , LiCF_3SO_3 , NaClO_4 , LiBF_4 , NaBF_4 , KBF_4 , NaCF_3SO_3 , KClO_4 , KPF_6 , KCF_3SO_3 , $\text{KC}_4\text{F}_9\text{SO}_3$, $\text{Ca}(\text{ClO}_4)_2$, $\text{Ca}(\text{PF}_6)_2$, $\text{Mg}(\text{ClO}_4)_2$, $\text{Mg}(\text{CF}_3\text{SO}_3)_2$, $\text{Zn}(\text{ClO}_4)_2$, $\text{Zn}(\text{PF}_6)_2$ and $\text{Ca}(\text{CF}_3\text{SO}_3)_2$.

A preferable method is wherein the polyolefin film additionally contains a UV absorber and/or a light stabilizer selected from the class of sterically hindered amines. Examples for UV-absorbers and sterically hindered amines are given above.

The production of the polyolefin film may be carried out in a manner known per se by mixing the said components and, if desired, further additives with the polymer using devices known per se, such as calenders, mixers, kneaders, extruders and the like. The additives may be added individually or in admixture with one another. It is also possible to use so-called master batches.

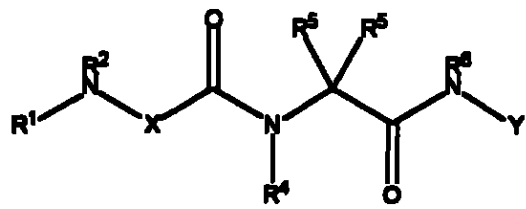
A polyolefin film according to the present invention can be made into the desired form in known manner. Such processes include, for example blown extrusion or cast extrusion.

More preferred is the use of a polyetherester amide composition, which composition comprises

- a) 20-80 parts of a fibrous polyamide
- b) 80-20 parts of a polyetherester amide and
- c) 1-5 parts of NaClO_4 ; wherein the total of components a), b) and c) being 100 parts, for reducing dust deposition on polyolefin films.

R^{13} is -H, -alkyl, -aryl, -alkylaryl or -alkylheteroaryl.

5 3. A compound represented by formula I:

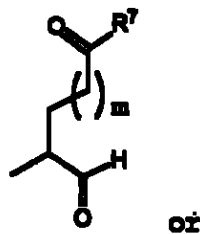


wherein:

Y is:

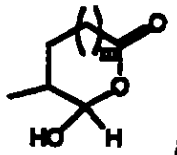
10

(a)



or

(b)



15

m is 0 or 1;

X is $-C(R^3)_2-$

CLAIMS

1. A method for reducing dust deposition on polyolefin films, comprising, incorporating into the polyolefin film a polyetherester amide or a composition containing a polyetherester amide, whereas the composition is:
 - a) 20-80 parts of a fibrous polyamide
 - b) 80-20 parts of a polyetherester amide and
 - c) 1-5 parts of NaClO_4 ; wherein the sum of components a), b) and c) being 100 parts.
2. A method according to claim 1, wherein the polyolefin is polyethylene (PE), a L- or LLDPE, a L- or LL-DPE/ethylene-vinyl acetate copolymer (EVA) or a L- or LL-DPE/ethylenebutylacrylate copolymer (EBA).
3. A method according to claim 1, wherein the polyolefin film is a coextruded film with three to 5 layers wherein at least one outer layer contains a polyetherester amide or a composition containing a polyetherester amide.
4. A method according to claim 1, wherein the polyetherester amide or the composition containing the polyetherester amide is added in an amount of from 0.5 to 100 % by weight, based on the polyolefin film.
5. A method according to claim 1, wherein the polyolefin film additionally contains a UV absorber and/or a light stabilizer selected from the class of sterically hindered amines.

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R^1 is H, $-R^8$, $-C(O)R^8$, $-C(O)C(O)R^8$, $-S(O)_2R^8$,
 $-S(O)R^8$, $-C(O)OR^8$, $-C(O)N(H)R^8$, $-S(O)_2N(H)-R^8$,
 $-S(O)N(H)-R^8$, $-C(O)C(O)N(H)R^8$, $-C(O)CH=CHR^8$,
 $-C(O)CH_2OR^8$, $-C(O)CH_2N(H)R^8$, $-C(O)N(R^8)_2$, $-S(O)_2N(R^8)_2$,
5 $-S(O)N(R^8)_2$, $-C(O)C(O)N(R^8)_2$, $-C(O)CH_2N(R^8)_2$, $-CH_2R^8$,
 $-CH_2$ -alkenyl- R^8 , or $-CH_2$ -alkynyl- R^8 ;

R^2 is -H and each R^3 is independently -H, an
 amino acid side chain, $-R^8$, alkenyl- R^8 , or alkynyl- R^8 ,
 10 or each R^3 together with the atom to which they are
 bound, form a 3 to 7 membered cyclic or heterocyclic
 ring system, wherein a hydrogen atom bound to any
 -alkyl or -cycloalkyl carbon atom is optionally
 replaced by $-R^{10}$, a hydrogen atom bound to any -aryl or
 15 -heteroaryl carbon atom is optionally replaced by $-R^{11}$,
 a hydrogen atom bound to any nitrogen atom of the ring
 system is optionally replaced by $-R^1$;

R^4 is -H and each R^5 is independently -H, an
 20 amino acid side chain, $-R^8$, -alkenyl- R^8 , or
 -alkynyl- R^8 , or R^4 and one R^5 together with the atoms
 to which they are bound form a 3 to 7 membered cyclic
 or heterocyclic ring system, wherein a hydrogen atom
 bound to any -alkyl or -cycloalkyl carbon atom is
 25 optionally replaced by R^{10} , a hydrogen atom bound to
 any -aryl or -heteroaryl carbon atom is optionally
 replaced by R^{11} , and a hydrogen atom bound to any
 nitrogen atom of the ring system is optionally replaced
 with R^1 ;

30

R^6 is -H;

DESCRIPTION OF THE INVENTION

The present invention provides a method for reducing dust deposits on polyolefin films by incorporating therein a polyetherester amide or a composition containing a polyetherester amide.

Dust deposition on plastic foils is not only an esthetic but also a hygienic and safety problem. In packaging and subsequent storage of food, germs can be deposited together with the dust and may cause severe diseases. This must also be avoided in medical and pharmaceutical packaging.

In packaging of electronic parts, dust may cause malfunctions and consequently considerable damages may occur during use.

One of the major problems in agricultural applications such as in greenhouses, made from transparent polyolefin films, is dust deposition on the interior or exterior side of the film which sticks to the film and cannot easily be removed by simple rinsing with water. Already small amounts of dust reduce the light transmission of the film significantly which results in less plant growth. The effect of dust deposition on the light transmission of greenhouse foils is for example described by A. Jaffrin et al. in *Plasticulture*, No.101, 1994, page 33-44.

Several attempts have been made to reduce dust deposition on polyolefin films for packaging and particularly for agricultural applications, such as greenhouse, mulch, silage or bale wrap. Typical antistatic agents such as alkylamine ethoxylates, polyethyleneglycol sorbitan monooleate or sorbitan stearate have been used with limited success.

It has now been found that dust deposition can be significantly reduced by incorporating polyetherester amides or compositions containing polyetherester amides into the films. The films remain essentially transparent. A further advantage is, that even if small amounts of dust are deposited, it can be easily washed away, since the dust particles adhere only loosely to the polymer film.

Alongside with dust deposition the formation of algae is observed on polyolefin films used in greenhouses. This is highly undesirable since it further decreases transmitted light and in addition can lead to plant diseases.

One subject of the present invention is a method for reducing dust deposition on polyolefin films, comprising, incorporating into the polyolefin film a polyetherester amide or a composition containing a polyetherester amide.

Examples for polyolefins from which films can be made are given below.

1. Polymers of monoolefins and diolefins, for example polypropylene, polyisobutylene, polybut-1-ene, poly-4-methylpent-1-ene, polyisoprene or polybutadiene, as well as polymers of cycloolefins, for instance of cyclopentene or norbornene, polyethylene (which optionally can be crosslinked), for example high density polyethylene (HDPE), high density and high molecular weight polyethylene (HDPE-HMW), high density and ultrahigh molecular weight polyethylene (HDPE-UHMW), medium density polyethylene (MDPE), low density polyethylene (LDPE), linear low density polyethylene (LLDPE), (VLDPE) and (ULDPE).

2. Mixtures of the polymers mentioned under 1), for example mixtures of polypropylene with polyisobutylene, polypropylene with polyethylene (for example PP/HDPE, PP/LDPE) and mixtures of different types of polyethylene (for example LDPE/HDPE).

The polyolefin film may be of a single layer or be a multilayer construction, which has been manufactured by co-extrusion with up to 20 layers, preferably up to 7 layers, most preferably up to 5 layers.

A preferred embodiment of the present invention is a coextruded film with three to five layers wherein at least one outer layer contains a polyetherester amide or a composition containing a polyetherester amide.

The polyetherester amide is a block copolymer. A block copolymer is especially a polyether ester amide in which the polyether segments consist of polyethylene glycol units having a molecular weight M_n of from

R^7 is -OH, -OR⁸, -N(H)OH, or -N(H)S(O)₂R⁸;

each R⁸ is independently -alkyl, -cycloalkyl,
5 -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl
-alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl,
wherein a hydrogen atom bound to any -alkyl or
-cycloalkyl carbon atom is optionally replaced by R¹⁰,
a hydrogen atom bound to any -aryl or -heteroaryl
10 carbon atom is optionally replaced by R¹¹, and a
hydrogen atom bound to any nitrogen atom is optionally
replaced by R¹;

each R⁹ is independently -aryl, -heteroaryl,
15 cycloalkyl, or -heterocyclyl, wherein a hydrogen atom
bound to any -alkyl or -cycloalkyl carbon atom is
optionally replaced by R¹⁰, a hydrogen atom bound to
any -aryl or -heteroaryl carbon atom is optionally
replaced by R¹¹, and a hydrogen atom bound to any
20 nitrogen atom is optionally replaced by R¹;

each R¹⁰ is independently -OH, -SH, -F, -Cl,
-Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H,
-N(H)C(O)NH₂, -perfluoroalkyl, -O-alkyl, -O-aryl,
25 -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl,
-N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂,
-N(H)C(O)alkyl, -N(H)C(O)Oalkyl, -N(H)C(O)Oaryl,
-N(H)C(O)Oalkylaryl, -N(H)C(O)Oheteroaryl,
-N(H)C(O)Oalkylheteroaryl, -N(H)C(O)Ocycloalkyl,
30 -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂,
-N(H)C(O)N(H)aryl, -N(H)C(O)N(H)alkylaryl,
-N(H)C(O)N(H)heteroaryl, -N(H)C(O)N(H)alkylheteroaryl,
-N(H)C(O)N(H)cycloalkyl, -S-alkyl, -S-aryl,
-S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl,

200 to 6000 daltons and the polyamide segments consist of polyamide (x) or polyamide (x,y) having a molecular weight M_n of from 200 to 6000 daltons, x and y being a number from 4 to 14.

Particularly preferred is a composition containing a polyetherester amide.

These compositions comprise a fibre-forming or fibrous organic polymeric material, such as a polyamide fibre, together with the polyetherester amide, which can be so incorporated into the polyolefin film that the polyetherester amide is substantially adsorptively bound to the fibre or dissolved in it and together with it forms a network in the polyolefin film in which the fibre is not soluble. A portion of the polyetherester amide has polar groups that are capable of complexing or solvating a salt of an inorganic or organic protonic acid.

The fibrous or fibre-forming organic polymeric material must be so selected that it does not dissolve in the thermoplastic or elastomeric substrate but is able to form a net-like structure of contiguous fibres. Polyamide fibres are most useful in this respect.

Typical examples for a suitable polyamide are:

Polyamides and copolyamides derived from diamines and dicarboxylic acids and/or from aminocarboxylic acids or the corresponding lactams, for example polyamide 4, polyamide 6, polyamide 6/6, 6/10, 6/9, 6/12, 4/6, 12/12, polyamide 11, polyamide 12, aromatic polyamides starting from m-xylene diamine and adipic acid; polyamides prepared from hexamethylenediamine and isophthalic or/and terephthalic acid and with or without an elastomer as modifier, for example poly-2,4,4-trimethylhexamethylene terephthalamide or poly-m-phenylene isophthalamide.

If material that is already fibrous is used, then the material may be selected in various fibre thicknesses. Fibre thicknesses are usually quoted in dtex (g/10000 m). Fibre thicknesses of from 0.5 to 500 dtex are typical, with the use of fibre thicknesses of from 1 to 100 dtex being preferred.

Especially preferred are the following salts LiClO_4 , LiCF_3SO_3 , NaClO_4 , LiBF_4 , NaBF_4 , KBF_4 , NaCF_3SO_3 , KClO_4 , KPF_6 , KCF_3SO_3 , $\text{KC}_4\text{F}_9\text{SO}_3$, $\text{Ca}(\text{ClO}_4)_2$, $\text{Ca}(\text{PF}_6)_2$, $\text{Mg}(\text{ClO}_4)_2$, $\text{Mg}(\text{CF}_3\text{SO}_3)_2$, $\text{Zn}(\text{ClO}_4)_2$, $\text{Zn}(\text{PF}_6)_2$ and $\text{Ca}(\text{CF}_3\text{SO}_3)_2$.

A preferable method is wherein the polyolefin film additionally contains a UV absorber and/or a light stabilizer selected from the class of sterically hindered amines. Examples for UV-absorbers and sterically hindered amines are given above.

The production of the polyolefin film may be carried out in a manner known per se by mixing the said components and, if desired, further additives with the polymer using devices known per se, such as calenders, mixers, kneaders, extruders and the like. The additives may be added individually or in admixture with one another. It is also possible to use so-called master batches.

A polyolefin film according to the present invention can be made into the desired form in known manner. Such processes include, for example blown extrusion or cast extrusion.

More preferred is the use of a polyetherester amide composition, which composition comprises

- a) 20-80 parts of a fibrous polyamide
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- c) 1-5 parts of NaClO_4 ; wherein the total of components a), b) and c) being 100 parts, for reducing dust deposition on polyolefin films.

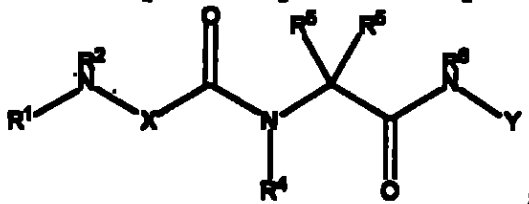
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-CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂, -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R¹¹ and a hydrogen atom bound to any nitrogen atom is optionally replaced by R¹; and

each R¹¹ is independently -OH, -SH, -F, -Cl, -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H, -N(H)C(O)NH₂, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂, -S-alkyl, -S-aryl, -S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂;

provided that if one R³ is -H, then the other R³ is not -H.

4. A compound represented by formula I:



wherein:

Y is:

en el foro "Venezuela y Ecuador, nuevo entorno económico y comercial", que realizó LA REPUBLICA.

» **TLC: el clima en EE. UU. es cada vez más advers**

En el seno de las comisiones Segundas de Senado y Cámara se escucharon ayer a representantes de instituciones, agremiaciones y asociaciones que se presentaron para dar su opinión sobre el Tratado de Libre Comercio (TLC).

» **ISA alcanzó utilidades por 150.469 millones de pesos**

La expansión de Interconexión Eléctrica S.A. (ISA) al mercado externo empieza a reflejarse en sus resultados. Según el último balance de la compañía al finalizar el 2006 alcanzó utilidades netas por 150.469 millones de pesos e ingresos operacionales de 2.016.322 millones de pesos, frente a los 1.076.495 millones de pesos de 2005.

» **Cerca de 700 contactos en macrorrueda de turismo**

Un total de 656 contactos efectivos entre empresas internacionales de turismo y hombres de negocios colombianos, se generaron durante la primera jornada de negocios de la segunda Macrorrueda de Turismo, que finalizó ayer en Bogotá.

» **Desempleo no da tregua en el país**

El desempleo en el país volvió a crecer en el primer mes del año a 13,8 por ciento, desde 13,4 por ciento en diciembre pasado, pero esta vez el Dane dejó de publicar los valores absolutos que indican a cuánto asciende el número de personas sin un puesto de trabajo.



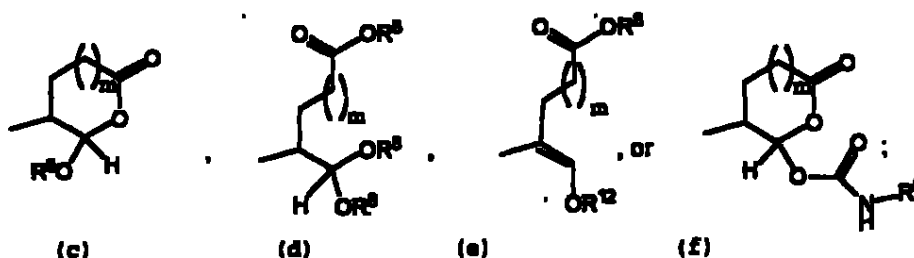
Sociedad técnica - Suplementos y comentarios

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Wuu. . . .
Morr
J49pl
Ww.6029nVotik, can

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m is 0 or 1;

5 X is $-C(R^3)_2-$

R^1 is H, $-R^8$, $-C(O)R^8$, $-C(O)C(O)R^8$, $-S(O)_2R^8$,
 $-S(O)R^8$, $-C(O)OR^8$, $-C(O)N(H)R^8$, $-S(O)_2N(H)-R^8$,
 $-S(O)N(H)-R^8$, $-C(O)C(O)N(H)R^8$, $-C(O)CH=CHR^8$,
 10 $-C(O)CH_2OR^8$, $-C(O)CH_2N(H)R^8$, $-C(O)N(R^8)_2$, $-S(O)_2N(R^8)_2$,
 $-S(O)N(R^8)_2$, $-C(O)C(O)N(R^8)_2$, $-C(O)CH_2N(R^8)_2$, $-CH_2R^8$,
 $-CH_2$ -alkenyl- R^8 , or $-CH_2$ -alkynyl- R^8 ;

R^2 is $-H$ and each R^3 is independently $-H$, an
 15 amino acid side chain, $-R^8$, alkenyl- R^9 , or alkynyl- R^9 ,
 or each R^3 together with the atom to which they are
 bound, form a 3 to 7 membered cyclic or heterocyclic
 ring system, wherein a hydrogen atom bound to any
 $-alkyl$ or $-cycloalkyl$ carbon atom is optionally
 20 replaced by $-R^{10}$, a hydrogen atom bound to any $-aryl$ or
 $-heteroaryl$ carbon atom is optionally replaced by $-R^{11}$,
 a hydrogen atom bound to any nitrogen atom of the ring
 system is optionally replaced by $-R^1$;

25 R^4 is $-H$ and each R^5 is independently $-H$, an
 amino acid side chain, $-R^8$, $-alkenyl-R^9$, or
 $-alkynyl-R^9$, or R^4 and one R^5 together with the atoms

RECIBO DE CASH APLICADO AL EFECTUANTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 200174089-2

RECIBO OFICIAL DE CASH : 07 - 16.146
FECHA : FEBRERO 22 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PASO	BANCO	CUENTA	No. PASO	FECHA PASO	Vr. PASO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO POPULAR	050-00110-6	57757121	22/02/2007	2,300,000.0

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

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 53005-01-03 CAMBIO DE REGALIDAD Y MODIFICA	12 MARCAS Y LETRAS COMERCIALES	77,990.00
	TOTAL :	77,990.00

CON: NOVENTA Y NUEVE MIL PESOS

PASABLE : _____

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to which they are bound form a 3 to 7 membered cyclic or heterocyclic ring system, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R^{10} , a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R^{11} , and a hydrogen atom bound to any nitrogen atom of the ring system is optionally replaced with R^1 ;

10 R^6 is -H;

each R^8 is independently -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R^{10} , a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R^{11} , and a hydrogen atom bound to any nitrogen atom is optionally replaced by R^1 ;

each R^9 is independently -aryl, -heteroaryl, cycloalkyl, or -heterocyclyl, wherein a hydrogen atom bound to any -alkyl or -cycloalkyl carbon atom is optionally replaced by R^{10} , a hydrogen atom bound to any -aryl or -heteroaryl carbon atom is optionally replaced by R^{11} , and a hydrogen atom bound to any nitrogen atom is optionally replaced by R^1 ;

30 each R^{10} is independently -OH, -SH, -F, -Cl, -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H, -N(H)C(O)NH₂, -perfluoroalkyl, -O-alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl, -N(H)-alkylaryl,

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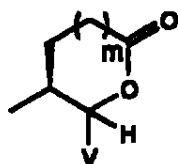
-N(alkyl)₂, -C(O)N(H)alkyl, -C(O)N(alkyl)₂,
 -N(H)C(O)alkyl, -N(H)C(O)Oalkyl, -N(H)C(O)Oaryl,
 -N(H)C(O)Oalkylaryl, -N(H)C(O)Oheteroaryl,
 -N(H)C(O)Oalkylheteroaryl, -N(H)C(O)Ocycloalkyl,
 5 -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)₂,
 -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)alkylaryl,
 -N(H)C(O)N(H)heteroaryl, -N(H)C(O)N(H)alkylheteroaryl,
 -N(H)C(O)N(H)cycloalkyl, -S-alkyl, -S-aryl,
 -S-alkylaryl, -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl,
 10 -CH₂NH₂, -CH₂N(H)alkyl, or -CH₂N(alkyl)₂, -alkyl,
 -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl,
 -alkylcycloalkyl, -alkylaryl, -alkylheteroaryl, or
 -alkylheterocyclyl, wherein a hydrogen atom bound to
 any -aryl or -heteroaryl carbon atom is optionally
 15 replaced by R¹¹ and a hydrogen atom bound to any
 nitrogen atom is optionally replaced by R¹; and

each R¹¹ is independently -OH, -SH, -F, -Cl,
 -Br, -I, -NO₂, -CN, -NH₂, -CO₂H, -C(O)NH₂, -N(H)C(O)H,
 20 -N(H)C(O)NH₂, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-
 alkyl, -O-aryl, -O-alkylaryl, -N(H)alkyl, -N(H)aryl,
 -N(H)-alkylaryl, -N(alkyl)₂, -C(O)N(H)alkyl,
 -C(O)N(alkyl)₂, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,
 -N(H)C(O)N(alkyl)₂, -S-alkyl, -S-aryl, -S-alkylaryl,
 25 -S(O)₂alkyl, -S(O)alkyl, -C(O)alkyl, -CH₂NH₂,
 -CH₂N(H)alkyl, or -CH₂N(alkyl)₂; and

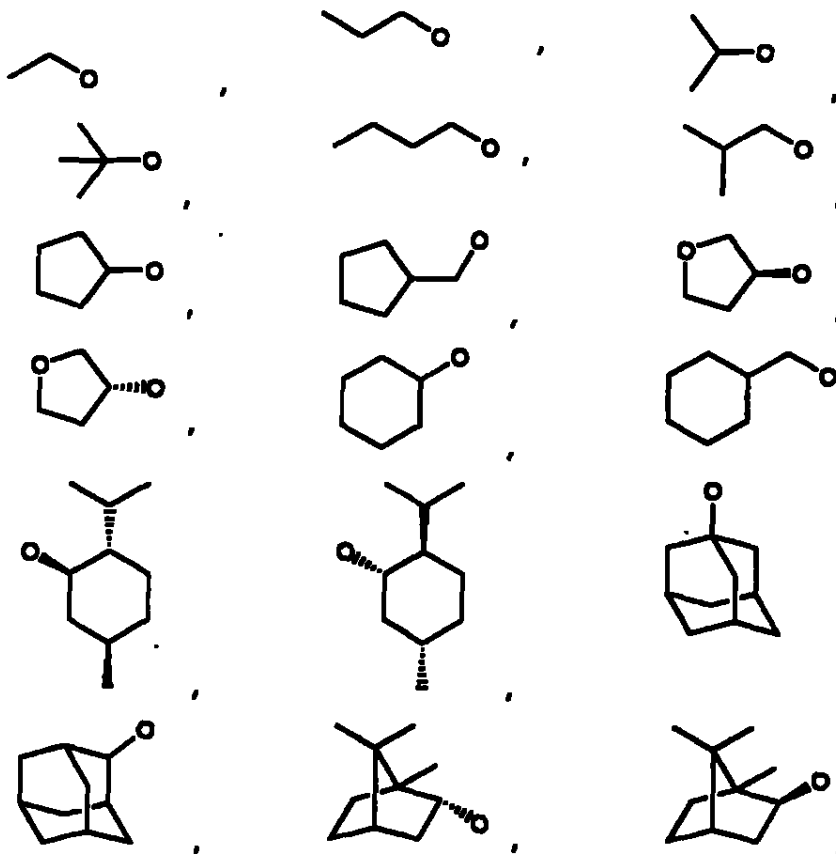
R¹² is -C(O)alkyl, -C(O)cycloalkyl,
 -C(O)alkenyl, -C(O)alkylaryl, -C(O)alkylheteroaryl,
 30 -C(O)heterocyclyl, or -C(O)alkylheterocyclyl.

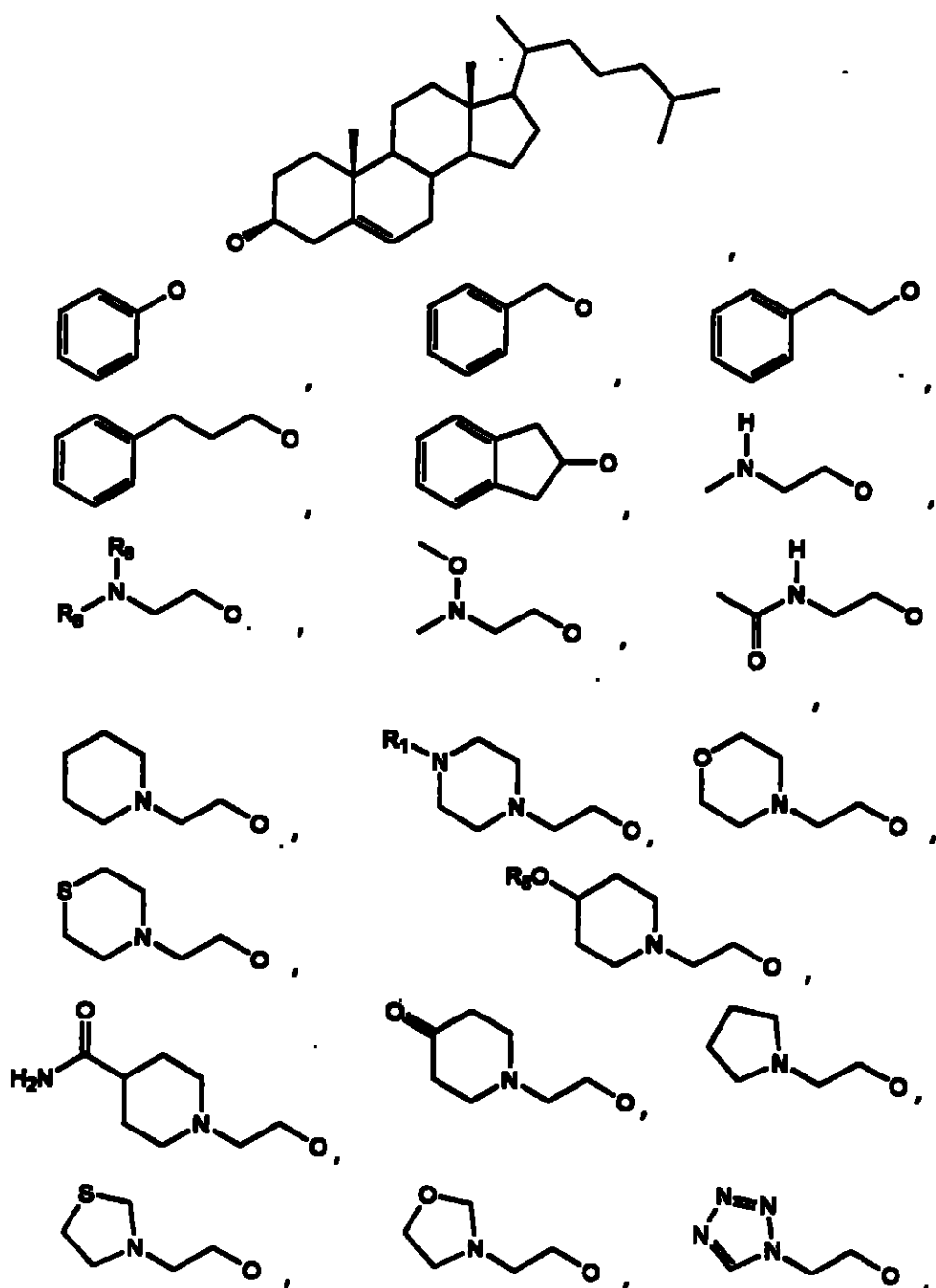
5. The compound according to claim 2 or claim 4 wherein Y is:

10



and V is: CH₃O,

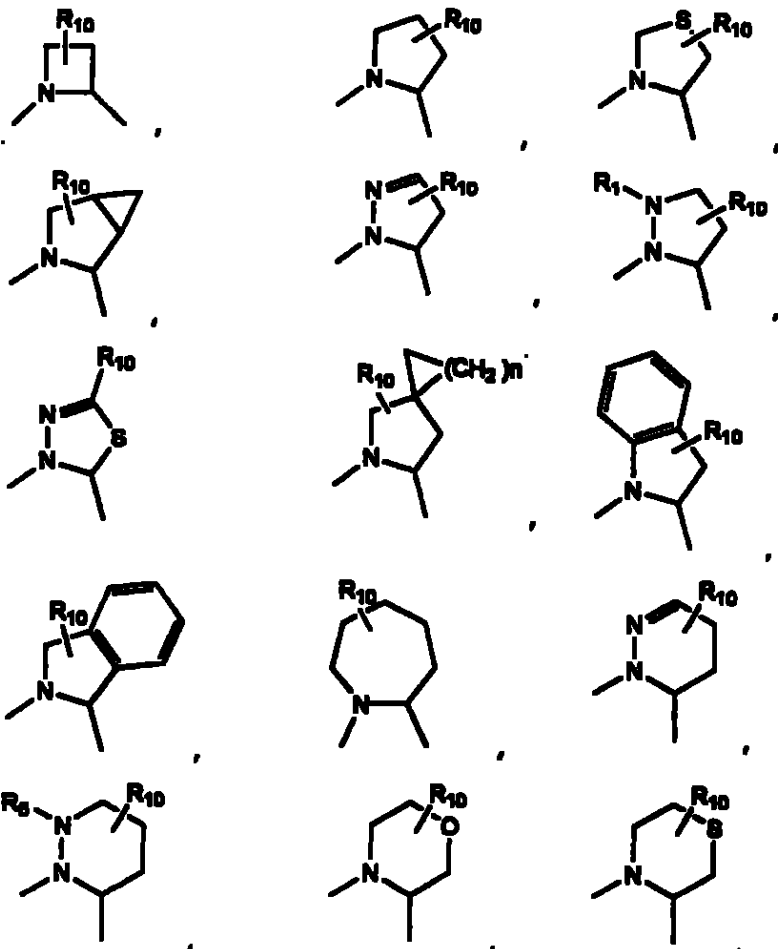




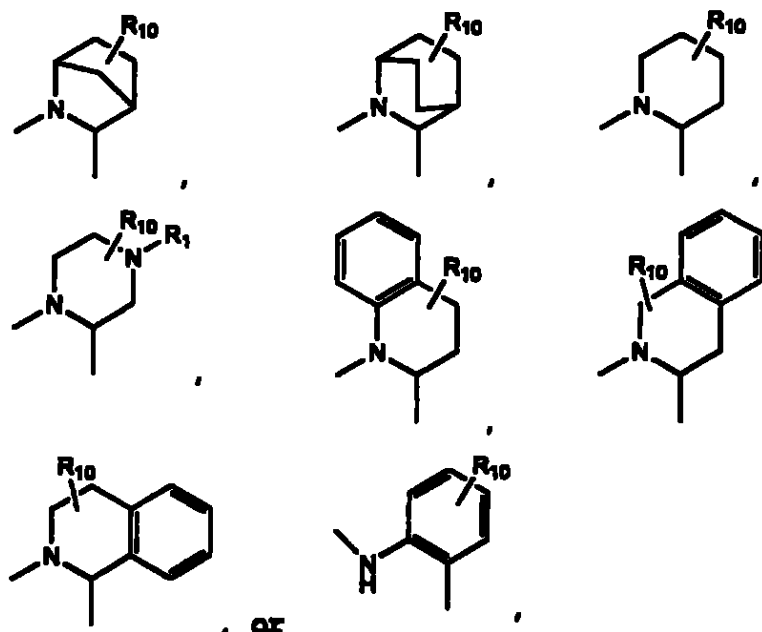


6. The compound according to any one of claims 1-5 wherein R^4 and one R^5 together with the atoms to which they are bound form a ring system selected from:

5



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7. The compound according to claim 6
wherein:

5 one R^3 is -H and the other R^3 is methyl,
isopropyl, tert-butyl, $-\text{CH}_2\text{SR}^8$, $-\text{CH}_2\text{SO}_2\text{R}^8$, $-\text{CH}_2\text{CH}_2\text{SR}^8$, or
 $-\text{CH}_2\text{CH}_2\text{SO}_2\text{R}^8$.

8. The compound according to claim 7
10 wherein one R^3 is -H and the other R^3 is methyl.

9. The compound according to claim 8
 wherein R^1 is $-\text{C}(\text{O})\text{R}^8$ or $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^8$.

10. The compound according to claim 6
 wherein:

R^4 and one R^5 together with the atoms to
which they are bound form the ring system:

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10 11. The compound according to claim 10
wherein one R³ is -H and the other R³ is methyl.

12. The compound according to claim 11
wherein R¹ is -C(O)R⁸ or -C(O)C(O)R⁸.
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13. The compound according to claim 10
wherein R¹⁰ is 4-fluoro or 4,4-difluoro.

14. The compound according to claim 13
20 wherein one R³ is -H and the other R³ is methyl.

15. The compound according to claim 14
wherein R¹ is -C(O)R⁸ or -C(O)C(O)R⁸.

25 16. The compound according to claim 1 or
claim 3 selected from the group consisting of: 5a-5bd,
7a-7at, 9a-9g, 15a-15f, 16a-16b, 17a-17a, 18a-18f, 20a-
20t, 23a-23i, 24a-24a, 25a-25a, 26a-26h, 27a-27n, 28a-
28c, 29a-29s, 32a-32e, 34, 42, 46, 52, 57, 61, 65, 69,
30 73, 121, 122 a-v, and 123 a-c.

17. The compound according to claim 4
selected from the group consisting of: 41, 45, 51, 56,
60, 64, 68, 72, 76-93, 98a-z, aa-az, ba and bb, 101,
35 102a, 102b, 108a-d, 110, 111, 116a-h, and 120a and b.

18. A pharmaceutical composition comprising:
a) a compound according to any one of claims 1-17; and

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b) a pharmaceutically acceptable carrier, adjuvant or vehicle.

19. A method for treating or preventing a
- 5 disease selected from an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a necrotic disease, an excess
- 10 dietary alcohol intake disease, a viral mediated disease, inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic
- 15 thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease,
- 20 psoriasis, atopic dermatitis, graft vs host disease, osteoporosis, leukemias and related disorders, myelodysplastic syndrome, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's
- 25 sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, neurological
- 30 damage due to stroke, ulcerative colitis, traumatic brain injury, organ transplant rejection, hepatitis-B, hepatitis-C, hepatitis-G, yellow fever, dengue fever, or Japanese encephalitis, in a patient comprising the step of administering to said patient a compound



US006011155A

United States Patent [19]
Vilhauer**[11] Patent Number: 6,011,155**
[45] Date of Patent: Jan. 4, 2000**[54] N-(SUBSTITUTED GLYCYL)-2-CYANOPYRROLIDINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN INHIBITING DIPEPTIDYL PEPTIDASE-IV****[75] Inventor: Edwin Bernard Vilhauer, Morristown, N.J.****[73] Assignee: Novartis AG, Basle, Switzerland****[21] Appl. No.: 08/962,168****[22] Filed: Oct. 31, 1997****Related U.S. Application Data****[60] Provisional application No. 60/030,570, Nov. 7, 1996.****[51] Int. Cl.⁷ C07D 207/34; C07D 207/42; C07D 401/06; C07D 405/10; C07D 409/06****[52] U.S. Cl. 544/333; 544/326; 544/330; 546/208; 546/276.4; 546/279.1; 548/530; 548/540****[58] Field of Search 548/530, 540, 548/517; 546/276.4, 279.1, 208; 544/516, 330, 328, 333****[56] References Cited****U.S. PATENT DOCUMENTS**

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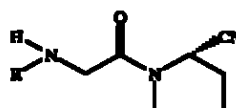
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Primary Examiner—Floyd D. Higel**Attorney, Agent, or Firm—Joseph J. Borovian****[57] ABSTRACT****N-(N'-substituted glycyI)-2-cyanopyrrolidines of formula I**

Compounds of formula I inhibit DPP-IV (dipeptidyl-peptidase-IV) activity. They are therefore indicated for use as pharmaceuticals in inhibiting DPP-IV and in the treatment of conditions mediated by DPP-IV, such as non-insulin-dependent diabetes mellitus, arthritis, obesity, osteoporosis and further conditions of impaired glucose tolerance.

11 Claims, No Drawings

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preferably $\geq 99\%$) or together with the *R* enantiomer, e.g., in racemic form. The above dosage ranges are based on the compounds of formula I (excluding the amount of the *R* enantiomer).

Prior US Provisional Application number 60/030,570, filed on Nov. 7, 1996 is incorporated by reference herein, in its entirety.

The following examples show representative compounds encompassed by this invention and their synthesis. However, it should be clearly understood that they are for purposes of illustration only.

EXAMPLE 1

1-[2-[(5-chloropyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine dihydrochloride

A. Preparation of 2-carbamoylpyrrolidine-carboxymethylene-(S)-bromide

22.37 g (196 mmol) of (S)-2-carbamoylpyrrolidine, 30.1 ml (216 mmol) of triethylamine and 30.0 mg of dimethylaminopyridine (DMAP) are dissolved in 200 ml of methylene chloride and the solution is then added, dropwise, to an ice-cold solution of 18.8 ml (216 mmol) of bromoacetyl-bromide in 192 ml of methylene chloride, over a period of 60 minutes under a calcium sulfate drying tube. The resultant solution is then stirred for 2 hours at ice-water temperature under a calcium sulfate drying tube, after which time it is poured into 3.5 liters of ethyl acetate. The resultant precipitate is filtered, washed with ethyl acetate, and the filtrate is concentrated to obtain the desired compound as a hard yellow taffy.

B. Preparation of 2-Cyanopyrrolidino-Carboxymethylene-(S)-Bromide

50.0 g (213 mmol) of the bromide compound prepared in a) above is dissolved in 300 ml of methylene chloride and the solution is cooled in an ice water bath under a calcium sulfate drying tube. The cooled solution is then poured into 60.2 ml (426 mmol) of trifluoroacetic anhydride over a 2 minute period and the resultant solution is then stirred at ice-water temperature under a calcium sulfate drying tube for 4 hours and partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The product is then extracted into the methylene chloride layer and the aqueous layer is then washed twice with methylene chloride. The combined organic layers are then washed successively with water and brine and then dried over sodium sulfate. The solution is then filtered and the solvent is removed by rotovaping and high vacuum pumping to obtain the desired compound as a dark yellow solid.

C. Preparation of the Title Compound in Free Base Form

To a 500 ml flask is added 16.6g (97.2 mmol) of 2-[(5-chloropyridin-2-yl)amino]ethylamine and 100 ml of tetrahydrofuran and the mixture is cooled in an ice bath. To the cooled mixture is added 7.0 g (32.4 mmol) of the bromide compound prepared in b) above dissolved in 30 ml of tetrahydrofuran. The resultant mixture is stirred for 2 hours at 0° C., the solvent is removed by rotovaping and the mixture is partitioned between ethyl acetate and water. The product is then extracted into the ethyl acetate layer and the aqueous layer is then washed twice with ethyl acetate. The combined organic layers are then washed successively with water and brine, dried over sodium sulfate and concentrated to obtain the desired compound in crude form. The crude form is then purified on silica gel employing a mixture of 5% methanol in methylene chloride as the eluent to yield the desired compound as a light brown oil.

D. Preparation of the Title Compound

After dissolving the free base compound prepared in c) above in 30 ml of dry tetrahydrofuran, hydrogen chloride

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gas is bubbled into the solution for five seconds. The off-white precipitate that forms is then filtered, washed with dry tetrahydrofuran and the solvent is removed by high vacuum pumping to obtain the title compound as an off-white solid, m.p. 265°-267° C.

EXAMPLE 2

1-[2-[(5-trifluoromethylpyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine

To a 25 ml. flask is added 1.15 g (5.61 mmol) of 2-[(5-trifluoromethylpyridin-2-yl)amino]ethylamine and 10 ml of tetrahydrofuran and the mixture is cooled in an ice bath. To the cooled mixture is added 0.404 g (1.87 mmol) of the bromide compound of Example 1b) dissolved in 5 ml of tetrahydrofuran. The resultant mixture is stirred for 2 hours at 0° C., the solvent is removed by rotovaping and the mixture is partitioned between ethyl acetate and water. The product is then extracted into the ethyl acetate layer and the aqueous layer is then washed twice with ethyl acetate. The combined organic layers are then washed successively with water and brine, dried over sodium sulfate and concentrated to obtain the desired compound in crude form. The crude form is then purified on silica gel employing a mixture of 5% methanol in methylene chloride as the eluent to yield the title compound as a golden oil.

EXAMPLE 3

1-[2-[(5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine dihydrochloride

A. Preparation of the Title Compound in Free Base Form

Following essentially the procedure of Example 1c), and using in place of the amine therein, an equivalent amount of 2-[(5-cyanopyridin-2-yl)amino]ethylamine, the desired compound is obtained as a golden oil.

B. Preparation of the Title Compound

Following essentially the procedure of Example 1d), and using in place of the free base compound prepared in Example 1c), an equivalent amount of the free base compound prepared in a) above, the title compound is obtained as an off-white precipitate, m.p. 155°-157° C.

EXAMPLE 4

1-[2-[(pyrimidin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine

Following essentially the procedure of Example 2, and using in place of the amine therein, an equivalent amount of 2-[(pyrimidin-2-yl)amino]ethylamine, and using in place of the eluent therein, a mixture of 10% methanol in methylene chloride, the title compound is obtained as a golden oil.

EXAMPLE 5

1-[(1-hydroxymethyl)cyclopent-1-yl]amino]acetyl-2-cyano-(S)-pyrrolidine

To 1.5 g of (1-hydroxymethyl)cyclopentylamine in 40 ml of anhydrous tetrahydrofuran is added, dropwise via an addition funnel over 40 minutes, 0.93 g (4.35 mmol) of the bromide compound of Example 1b) under a calcium sulfate drying tube. The resultant mixture is then stirred at room temperature for 18 hours under a calcium sulfate drying tube, after which time hydrogen chloride gas is bubbled in for ~5 seconds. The resultant gum is then separated from the solution by decanting and washed with 25 ml of tetrahydrofuran.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 14,674
FECHA : FEBRERO 19 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO POPULAR	050-00110-6	55017201	19/02/2007	5,046,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE NOMINALIDAD Y MODIFICA	
		12 MARCAS Y LEYAS COMERCIALES	77,000.00
		TOTAL :	6 77,000.00

SEX: NOVENTA Y NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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drofuran. The solution is then decanted and the gum is partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The product is then extracted into the methylene chloride layer and the aqueous layer is then washed twice with methylene chloride. The combined organic layers are then washed successively with water and brine and then dried over sodium sulfate. The solution is then filtered and the solvent is removed by rotovaping and high vacuum pumping to obtain the title compound as a clear yellow oil which solidifies to a yellow solid, m.p. 65°-67° C.

EXAMPLE 6

1-[2-[(pyridin-2-yl)amino]ethylamino]acetyl-2-cyano(S)-pyrrolidine

Following essentially the procedure of Example 2, and using in place of the amine therein, an equivalent amount of 2-[(pyridin-2-yl)amino]ethylamine, and using in place of the eluent therein, a 90:10:0.5 mixture of methylene chloride, methanol and ammonium hydroxide, the title compound is obtained as a golden oil.

EXAMPLE 7

Following essentially the procedure of Example 2, and using in place of the amine therein, an equivalent amount of:

- a) 2-[(4-chloropyrimidin-2-yl)amino]ethylamine;
 - b) 2-[(3-chloropyridin-2-yl)amino]ethylamine;
 - c) 2-[(4-trifluoromethylpyrimidin-2-yl)amino]ethylamine;
 - d) (2-chlorophenyl)ethylamine; and
 - e) (3,3-biphenyl)propylamine;
- there is obtained:
- A) 1-[2-[(4-chloropyrimidin-2-yl)amino]ethylamino]acetyl-2-cyano(S)-pyrrolidine as a tan solid;
 - B) 1-[2-[(3-chloropyridin-2-yl)amino]ethylamino]acetyl-2-cyano(S)-pyrrolidine as a golden oil;
 - C) 1-[2-[(4-trifluoromethylpyrimidin-2-yl)amino]ethylamino]acetyl-2-cyano(S)-pyrrolidine as a golden oil;
 - D) 1-[2-(2-chlorophenyl)ethylamino]acetyl-2-cyano(S)-pyrrolidine; and
 - E) 1-[2-(3,3-diphenyl)propylamino]acetyl-2-cyano(S)-pyrrolidine, respectively.

EXAMPLE 8

1-[2-[(5-nitropyridin-2-yl)amino]ethylamino]acetyl-2-cyano(S)-pyrrolidine

To 83.6 ml of anhydrous tetrahydrofuran is added 4.54 g (24.9 mmol) of 2-[(5-nitropyridin-2-yl)amino]ethylamine, and the resultant mixture is heated slightly then stirred at room temperature under a calcium sulfate drying tube. 1.80 g (8.3 mmol) of the bromide compound of Example 1b) in 20 ml of anhydrous tetrahydrofuran is then added, over a period of 30 minutes, under a calcium sulfate drying tube. The resultant mixture is then stirred at room temperature for 2 hours under a calcium sulfate drying tube and concentrated via rotovaping. The resultant paste is then partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The product is then extracted into the methylene chloride layer and the aqueous layer is then washed twice with methylene chloride. The combined organic layers are then washed successively with water and brine and then

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dried over sodium sulfate. The solution is then filtered and the solvent is removed by rotovaping and high vacuum pumping to obtain the crude form of the title compound as a dark yellow-orange clear thick oil. The crude form is then flash chromatographed employing a mixture of 5% methanol in methylene chloride as the eluent to obtain the title compound as a bright yellow thick oil.

EXAMPLE 9

Following essentially the procedure of Example 2, and using in place of the amine therein, an equivalent amount of:

- a) 2-[(3-chloro-5-trifluoromethylpyridin-2-yl)amino]ethylamine;
 - b) 2-[(3-trifluoromethylpyridin-2-yl)amino]ethylamine; and
 - c) 2-[(3,5-dichloropyridin-2-yl)amino]ethylamine;
- and using in place of the eluent therein, a mixture of 3% methanol in methylene chloride, there is obtained:
- A) 1-[2-[(3-chloro-5-trifluoromethylpyridin-2-yl)amino]ethylamino]acetyl-2-cyano(S)-pyrrolidine as a golden oil;
 - B) 1-[2-[(3-trifluoromethylpyridin-2-yl)amino]ethylamino]acetyl-2-cyano(S)-pyrrolidine as a golden oil; and
 - C) 1-[2-[(3,5-dichloropyridin-2-yl)amino]ethylamino]acetyl-2-cyano(S)-pyrrolidine as a golden oil.

EXAMPLE 10

1-[(cyclopent-1-yl)amino]acetyl-2-cyano(S)-pyrrolidine monohydrochloride

A. Preparation of the Title Compound in Free Base Form

Following essentially the procedure of Example 2, and using in place of the amine therein, an equivalent amount of (cyclopent-1-yl)amine, the desired compound is obtained as a tan solid.

B. Preparation of the Title Compound

Following essentially the procedure of Example 1d), and using in place of the free base compound therein, an equivalent amount of the compound prepared in a) above, the title compound is obtained as a white solid.

EXAMPLE 11

1-[2-(2-bromo-4,5-dimethoxyphenyl)ethylamino]acetyl-2-cyano(S)-pyrrolidine

To 15 ml of anhydrous tetrahydrofuran is added 1.44 g (5.52 mmol) of 2-(2-bromo-4,5-dimethoxyphenyl)ethylamine, and the resultant mixture is heated slightly under a calcium sulfate drying tube. 0.4 g (1.84 mmol) of the bromide compound of Example 1b) is then added, dropwise, over a period of 10 minutes. The resultant mixture is then stirred at room temperature for 18 hours under a calcium sulfate drying tube, concentrated via rotovaping and partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The product is then extracted into the methylene chloride layer and the aqueous layer is then washed twice with methylene chloride. The combined organic layers are then washed successively with water and brine and then dried over sodium sulfate. The solution is then filtered and the solvent is removed by rotovaping and high vacuum pumping to obtain the crude form of the title compound as a clear yellow oil. The crude form is then flash chromatographed employing a mixture of 5% methanol in methylene chloride as the eluent to obtain the title compound as a clear, light yellow, thick oil.



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Dirección Cra. 10a. No. 24-78 Of. 308

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DATOS DE LA PATENTE DE MODELO DE UTILIDAD

(84) Título JUEGO DE MINITEJO EN ESTRUCTURA PLASTICA,
RELLENO DE PLASTILINA.

PRIORIDAD REIVINDICADA SI ☐ NO ☐ TIPO DE PRIORIDAD ANDINA ☐ UNIONISTA ☐

(30) País _____ (32) Fecha _____ (31) No. Solicitud _____

Para Publicar a los ☐ 6 meses ☐ 12 meses ☐ 18 meses a partir de la fecha de la presente solicitud

(51) CLASIFICACION INTERNACIONAL A63F 7/00

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EXAMPLE 12

1-[3-(isopropoxy)propylamino]acetyl-2-cyano-(S)-pyrrolidine monohydrochloride

A. Preparation of the Title Compound in Free Base Form
Following essentially the procedure of Example 1c), and using in place of the amine therein, an equivalent amount of 3-(isopropoxy)propylamine, the desired compound is obtained as a brown oil.

B. Preparation of the Title Compound

Following essentially the procedure of Example 1d), and using in place of the free base compound therein, an equivalent amount of the compound prepared in a) above, the title compound is obtained as a white solid, m.p. 174°-176° C.

EXAMPLE 13

1-[2-hydroxy-1,1-dimethylethylamino]acetyl-2-cyano-(S)-pyrrolidine monohydrochloride

A. Preparation of the Title Compound in Free Base Form
Following essentially the procedure of Example 2, and using in place of the amine therein, an equivalent amount of 2-hydroxy-1,1-dimethylethylamine, and using in place of the eluent therein, an 80:20:1 mixture of methylene chloride, methanol and ammonium hydroxide, the title compound is obtained as a golden oil.

B. Preparation of the Title Compound

Following essentially the procedure of Example 1d), and using in place of the free base compound therein, an equivalent amount of the compound prepared in a) above, the title compound is obtained as a brown solid.

EXAMPLE 14

1-[3-(2-oxo-pyrrolidin-1-yl)propylamino]acetyl-2-cyano-(S)-pyrrolidine monohydrochloride

A. Preparation of the Title Compound in Free Base Form
Following essentially the procedure of Example 2, and using in place of the amine therein, an equivalent amount of 3-(2-oxo-pyrrolidin-1-yl)propylamine, and using in place of the eluent therein, a 90:10:1 mixture of methylene chloride, methanol and ammonium hydroxide, the desired compound is obtained as a golden oil.

B. Preparation of the Title Compound

Following essentially the procedure of Example 1d), and using in place of the free base compound therein, an equivalent amount of the compound prepared in a) above, the title compound is obtained as a tan solid.

Below are the ¹³C NMR signals for the nitrile functionalities of the specific synthesized compounds described above:

Compound #	¹³ C NMR (MHz, solvent) δ ppm (CN)
Ex. 5	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.64 ppm (CN)
Ex. 12	¹³ C NMR (75 MHz, D ₂ O) δ 121.63 ppm (CN)
Ex. 1	¹³ C NMR (75 MHz, D ₂ O) δ 121.60 ppm (CN)
Ex. 3	¹³ C NMR (75 MHz, D ₂ O) δ 120.42 ppm (CN)
Ex. 8	¹³ C NMR (75 MHz, DMSO) δ 119.13 ppm (CN)
Ex. 7B	¹³ C NMR (75 MHz, CDCl ₃) δ 118.23 ppm (CN)
Ex. 9A	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.66 ppm (CN)
Ex. 9B	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.66 ppm (CN)
Ex. 9C	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.66 ppm (CN)
Ex. 6	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.84 ppm (CN)
Ex. 7C	¹³ C NMR (75 MHz, CDCl ₃) δ 118.23 ppm (CN)
Ex. 2	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.66 ppm (CN)
Ex. 7A	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.66 ppm (CN)

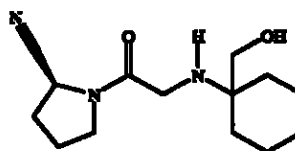
16

-continued

Compound #	¹³ C NMR (MHz, solvent) δ ppm (CN)
Ex. 4	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.66 ppm (CN)
Ex. 10	¹³ C NMR (75 MHz, D ₂ O) δ 121.69 ppm (CN)
Ex. 11	¹³ C NMR (75 MHz, CDCl ₃) δ 118.31 ppm (CN)
Ex. 7D	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.63 ppm (CN)
Ex. 7E	¹³ C NMR (75 MHz, CD ₃ OD) δ 119.64 ppm (CN)
Ex. 13	¹³ C NMR (75 MHz, D ₂ O) δ 121.52 ppm (CN)
Ex. 14	¹³ C NMR (75 MHz, D ₂ O) δ 121.52 ppm (CN)

EXAMPLE 15

1-[(1-hydroxymethylcyclohexyl)amino]acetyl-2-cyano-(S)-pyrrolidine



A. Preparation of 1-chloroacetyl-2-cyanopyrrolidine
To a mechanically stirred solution of 20.0 g (180.0 mmol) of chloroacetylchloride and 97 g (0.70 mmol) of potassium carbonate in 150 ml of tetrahydrofuran was added a solution of L-prolinamide 20.0 g (180.0 mmol) in 500 ml of tetrahydrofuran in a dropwise fashion over 45 minutes. This reaction was then mechanically stirred for an additional two hours. The reaction was then filtered to remove potassium salts and the filtrate was dried over Na₂SO₄. The Na₂SO₄ was then removed via filtration and to this colorless filtrate was added trifluoroacetic anhydride (25.0 ml, 0.180 mmol) in one portion. The reaction is then magnetically stirred for 1 hour and the resulting clear yellow/orange solution is concentrated via rotovap. The excess trifluoroacetic anhydride is chased by adding ethyl acetate to the concentrated oil and reconcentrating via rotovap. This operation is performed three times.

The resulting oil is partitioned between ethyl acetate and water. The product is then extracted into the ethyl acetate and the aqueous layer is then washed twice with ethyl acetate. The combined organic layers are then washed successively with water and brine dried over magnesium sulfate, filtered and concentrated to obtain 17.0 g (98.6 mmol) of 1-chloroacetyl-2-cyanopyrrolidine as a yellow solid.

B. Preparation of the Title Compound

To a 100 ml flask is dissolved 1.2 g (8.70 mmol) of 1-amino-1-cyclohexanemethanol (amine nucleophile; preparation described above) into 20 ml of tetrahydrofuran. Potassium carbonate (1.60 g, 11.6 mmol) is then added and the solution is cooled in an ice-water bath. To this cooled mixture is added a solution of 0.50 g (2.89 mmol) of 1-chloroacetyl-2-cyanopyrrolidine in 10 ml of tetrahydrofuran over 20 minutes. The reaction is then stirred at ice-water temperature for two hours under a calcium sulfate drying tube and then allowed to stir at room temperature for 18 hours. The reaction is then filtered with THF washing to remove the potassium salts and concentrated via rotovap to provide an opaque, light-yellow oil. The crude form is then purified on silica gel employing a mixture of 5% methanol in methylene chloride as the eluent to yield the free base of the title compound as a yellow waxy solid. Melting point-softens at 93° C. ¹³C NMR(ppm)=118.1.

2020
Bogotá DC

Señor(a)
ALEJANDRO VELASQUEZ SALGADO

REFERENCIA:	Radicación No.	00-34403
	Trámite	003
	Evento	001
	Actuación	416
	Oficio No.	2658
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente de modelo de utilidad que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión del Acuerdo de Cartagena, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486 del Acuerdo de Cartagena, en concordancia con el artículo 85 de la misma decisión.

Cúmplase
Dado en Bogotá DC, a los 15 OCT. 2001


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

Bogotá, DC, Junio/2002 El extracto de esta solicitud fue publicado en el número 510 de la Gaceta de Propiedad Industrial, de fecha 27/11/2001. El término hábil señalado por la ley expiró el 11/11/2002 y SI ☐ NO ☒ se presentaron oposiciones por parte de terceros.

202027

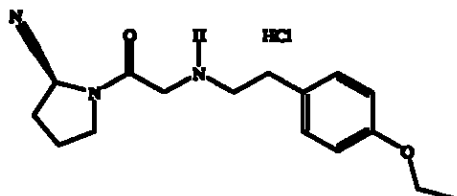
Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 382 2695
E-mail: Info@slc.gov.co
Bogotá, D.C., Colombia

17

Using the procedures described in the above examples, and/or with minor modifications thereto as noted below, the following additional compounds were prepared:

EXAMPLE 16

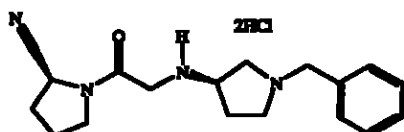
Pyrrolidine, 1-[[2-(4-ethoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-, monohydrochloride



4-Ethoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=182°-184° C. ¹³C NMR (ppm)=121.4.

EXAMPLE 17

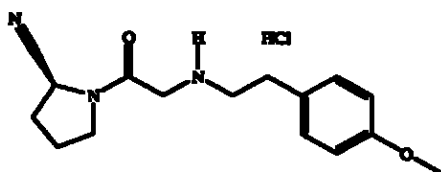
Pyrrolidine, 1-[(1-phenylmethyl-3-pyrrolidinyl)amino]acetyl-2-cyano-(S)-(R)-, dihydrochloride



(3R)-(-)-1-Benzyl-3-aminopyrrolidine (commercially available) was used as the amine nucleophile. The title compound was an off white solid. Melting point=175° C.-177° C. ¹³C NMR (ppm)=121.5.

EXAMPLE 18

Pyrrolidine, 1-[[2-(4-methoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-, monohydrochloride

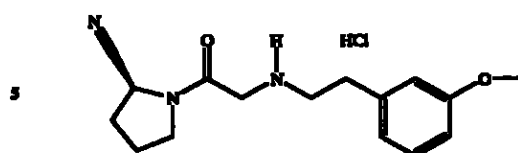


4-Methoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=185° C.-187° C. ¹³C NMR (ppm)=121.4.

EXAMPLE 19

Pyrrolidine, 1-[[2-(3-methoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-, monohydrochloride

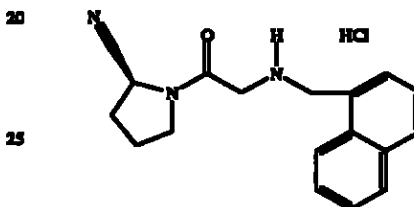
18



3-Methoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a light yellow solid. Melting point=172° C.-174° C. ¹³C NMR (ppm)=119.25.

EXAMPLE 20

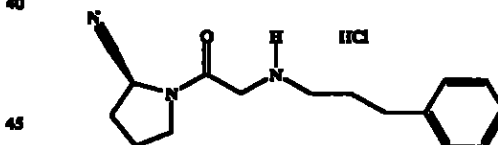
Pyrrolidine, 1-[(1-naphthalenyl)methyl]amino]acetyl-2-cyano-(S)-, monohydrochloride



1-Naphthalenemethylamine (commercially available) was used as the amine nucleophile. The title compound was a light yellow solid. Melting point=130° C.-135° C. ¹³C NMR (ppm)=119.29.

EXAMPLE 21

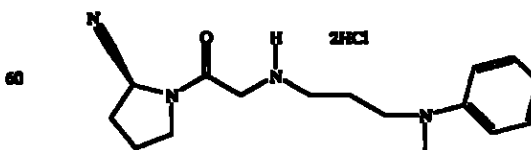
Pyrrolidine, 1-[(3-phenylpropyl)amino]acetyl-2-cyano-(S)-, monohydrochloride



3-Phenyl-1-propylamine (commercially available) was used as the amine nucleophile. The title compound was an off-white fluffy solid. ¹³C NMR (ppm)=119.26.

EXAMPLE 22

Pyrrolidine, 1-[[3-[(phenyl)(methyl)amino]propyl]amino]acetyl-2-cyano-(S)-, dihydrochloride



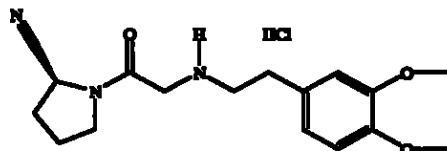
N-(3-Aminopropyl)-N-methylaniline (commercially available) was used as the amine nucleophile. The title

19

compound was a white solid. Melting point=96° C.-98° C. (foams). ¹³C NMR (ppm)=121.6.

EXAMPLE 23

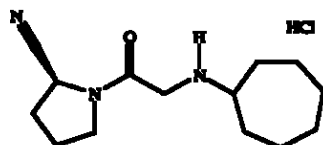
Pyrrolidine, 1-[2-[(3,4-dimethoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



3,4-Dimethoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=170° C.-172° C. ¹³C NMR (ppm)=121.5.

EXAMPLE 24

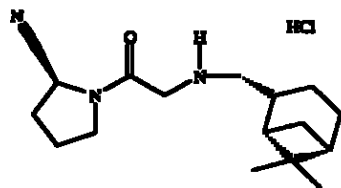
Pyrrolidine, 1-(cycloheptylamino)acetyl-2-cyano-, (S)-, monohydrochloride



Cycloheptylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=68° C.-70° C. ¹³C NMR (ppm)=121.4.

EXAMPLE 25

Pyrrolidine, 1-[(6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl]amino]acetyl-2-cyano-[1S[1α,2α(S*),5α]]-(S)-, monohydrochloride

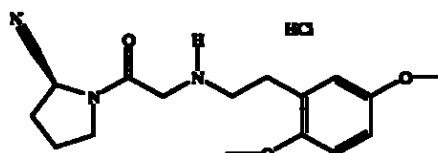


(-)-Cis-myrtanylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=275° C.-279° C., decomposed. ¹³C NMR (ppm)=119.17.

20

EXAMPLE 26

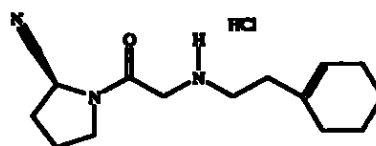
Pyrrolidine, 1-[2-(2,5-dimethoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



2,5-Dimethoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. Melting point=65° C.-67° C. ¹³C NMR (ppm)=119.25.

EXAMPLE 27

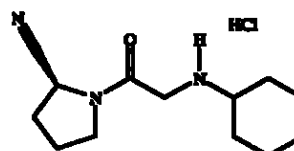
Pyrrolidine, 1-[2-(1-cyclohexan-1-yl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



2-(1-Cyclohexenyl) ethylamine (commercially available) was used as the amine nucleophile. The title compound was an off-white fluffy solid. Melting point=162° C.-164° C. ¹³C NMR (ppm)=119.27.

EXAMPLE 28

Pyrrolidine, 1-(cyclohexylamino)acetyl-2-cyano-, (S)-, monohydrochloride

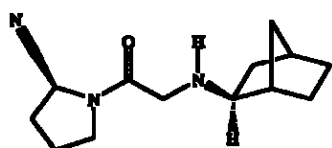


Cyclohexylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. Melting point=182° C.-184° C. ¹³C NMR (ppm)=119.28.

EXAMPLE 29

Pyrrolidine, 1-[(bicyclo[2.2.1]hept-2-yl)amino]acetyl-2-cyano-[1S[1α,2α(S*),5α]]-(S)-, monohydrochloride

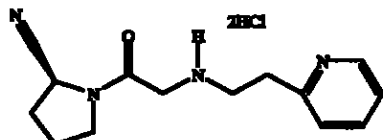
21



(±)-Exo-2-aminonorbormane (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=98° C.-100° C. ¹³C NMR (ppm)=118.36.

EXAMPLE 30

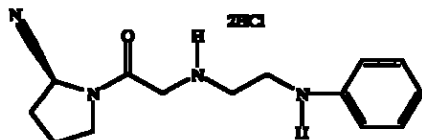
Pyrrolidine, 1-[[2-(2-pyridinyl)ethyl]amino]acetyl-2-cyano-, (S)-, dihydrochloride



2-(2-Aminoethyl) pyridine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=95° C.-97° C. ¹³C NMR (ppm)=121.5.

EXAMPLE 31

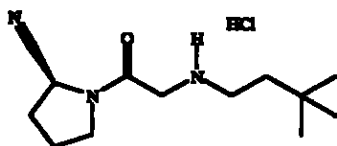
Pyrrolidine, 1-[[2-(2-phenylamino)ethyl]amino]acetyl-2-cyano-, (S)-, dihydrochloride



N-phenylethylenediamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=124° C.-126° C. ¹³C NMR (ppm)=121.4.

EXAMPLE 32

Pyrrolidine, 1-[(3,3-dimethylbutyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride

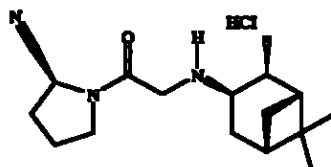


3,3-Dimethylbutylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=164° C.-166° C. ¹³C NMR (ppm)=121.5.

22

EXAMPLE 33

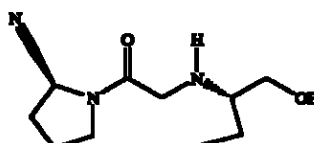
Pyrrolidine, 1-[(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)amino]acetyl-2-cyano-, (S)-[1S [1α,2β,3α(S*),5α]]-monohydrochloride



(1R,2R,3R,5S)-(-)-Isopinocampheylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=82° C.-84° C. ¹³C NMR (ppm)=121.5.

EXAMPLE 34

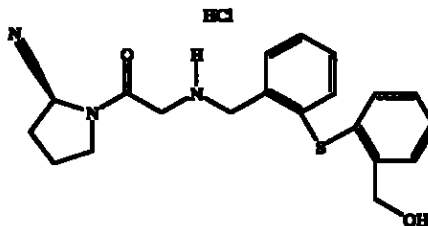
Pyrrolidine, 1-[[1-(1-hydroxymethyl)propyl]amino]acetyl-2-cyano-[S,S]-



(S)-(+)-2-Amino-1-butanol (commercially available) was used as the amine nucleophile. The title compound was an off-white solid. Melting point=80° C.-82° C. ¹³C NMR (ppm)=118.2.

EXAMPLE 35

Pyrrolidine, 1-[[2-[(2-hydroxymethyl)phenyl]thio]phenylmethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



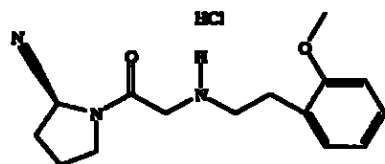
2-(2-(Aminomethyl) phenylthio) benzyl alcohol (commercially available) was used as the amine nucleophile. The title compound was a yellow solid. Melting point=65° C.-67° C. ¹³C NMR (ppm)=121.4.

44
486

6,011,155

23
EXAMPLE 36

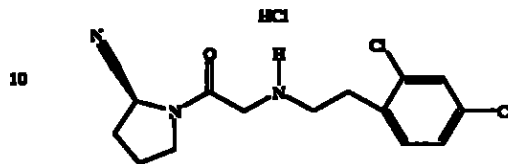
Pyrrolidine, 1-[[2-(2-methoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



2-Methoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was an off white solid. Melting point=174° C. -176° C. ¹³C NMR (ppm)=121.7.

24
EXAMPLE 39

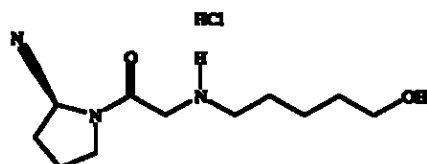
Pyrrolidine, 1-[[2-(2,4-dichlorophenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride



2,4-Dichlorophenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. Melting point=154° C.-156° C. ¹³C NMR (ppm)=121.48.

EXAMPLE 37

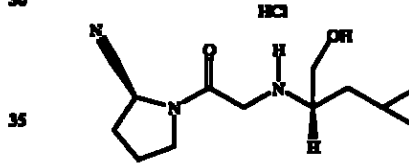
Pyrrolidine, 1-[(5-hydroxypentyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride



5-Amino-1-pentanol (commercially available) was used as the amine nucleophile. The title compound was a sticky light-green solid. ¹³C NMR (ppm)=121.67.

EXAMPLE 40

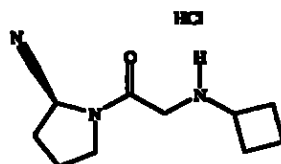
Pyrrolidine, 1-[(1-hydroxymethyl)-3-methylbutyl]amino]acetyl-2-cyano-, O-, (S)-,



(S)-(+)-Leucinol (commercially available) was used as the amine nucleophile. The title compound was a light yellow solid. Melting point=65° C.-66° C. ¹³C NMR (ppm)=117.99.

EXAMPLE 38

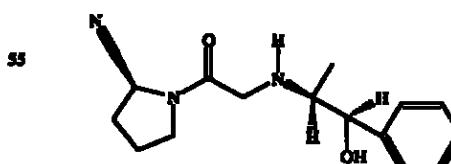
Pyrrolidine, 1-(cyclobutylamino)acetyl-2-cyano-, (S)-, monohydrochloride



Cyclobutylamine (commercially available) was used as the amine nucleophile. The title compound was an off-white solid. Melting point=274° C.-278° C. decomposed. ¹³C NMR (ppm)=121.64.

EXAMPLE 41

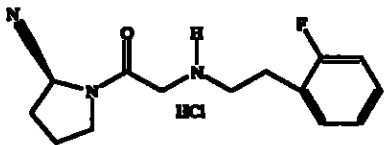
Pyrrolidine, 1-[(2-hydroxy-2-phenylethyl)amino]acetyl-2-cyano-[2S-[1R*,2S*]-monohydrochloride



(1R,2S)-(-)-Norephedrine (commercially available) was used as the amine nucleophile. The title compound was a light yellow solid. Melting point=82° C.-83° C. ¹³C NMR (ppm)=118.35.

25
EXAMPLE 42

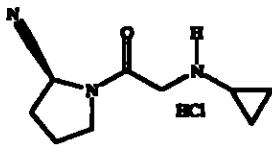
Pyrrolidine, 1-[[2-(2-fluorophenyl)ethyl]amino]acetyl-2-cyano-(S)-, monohydrochloride



2-Fluorophenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. Melting point=160° C.-162° C. ¹³C NMR (ppm)=121.70.

EXAMPLE 43

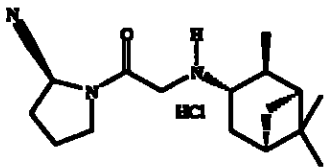
Pyrrolidine, 1-(cyclopropylamino)acetyl-2-cyano-(S)-, monohydrochloride



Cyclopropylamine (commercially available) was used as the amine nucleophile. The title compound was an off-white solid. Melting point=170° C.-172° C. ¹³C NMR (ppm)=121.62.

EXAMPLE 44

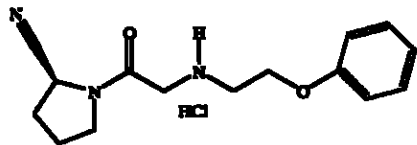
Pyrrolidine, 1-[(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)amino]acetyl-2-cyano-[1S[1α,2α,3β(S*),5α]]-monohydrochloride



(1S,2S,3S,5R)-(+)-Isopinocampheylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=84° C.-86° C. ¹³C NMR (ppm)=121.8.

26
EXAMPLE 45

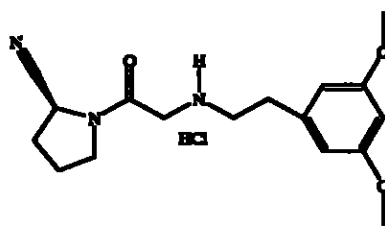
Pyrrolidine, 1-[[2-(2-phenoxy)ethyl]amino]acetyl-2-cyano-(S)-, monohydrochloride



2-Phenoxyethylamine (commercially available) was used as the amine nucleophile. The title compound was a sticky golden solid. ¹³C NMR (ppm)=121.7.

EXAMPLE 46

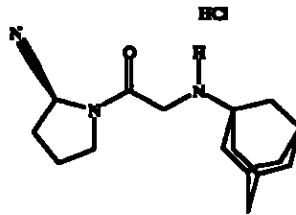
Pyrrolidine, 1-[2-[(3,5-dimethoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-, monohydrochloride



3,5-Dimethoxyphenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. Melting point=74° C.-76° C. ¹³C NMR (ppm)=121.66.

EXAMPLE 47

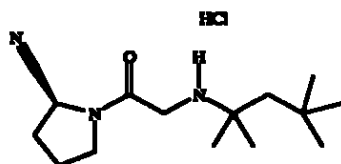
Pyrrolidine, 1-[(1-adamantyl)amino]acetyl-2-cyano-(S)-, monohydrochloride



1-Adamantanamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=240° C.-242° C. ¹³C NMR (ppm)=121.80.

27
EXAMPLE 48

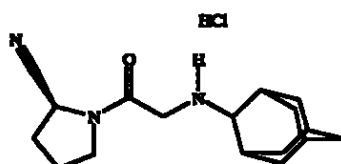
Pyrrolidine, 1-[(1,1,3,3-tetramethylbutyl)amino]acetyl-2-cyano-(S)-,monohydrochloride



1,1,3,3-Tetramethylbutylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. Melting point=68° C.-70° C. ¹³C NMR (ppm)=121.55.

EXAMPLE 49

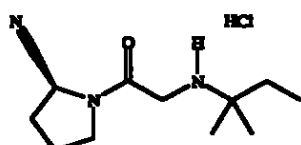
Pyrrolidine, 1-[(2-adamantyl)amino]acetyl-2-cyano-(S)-,monohydrochloride



2-Adamantanamine (commercially available) was used as the amine nucleophile. The title compound was an off-white fluffy solid. Melting point=122° C.-124° C. ¹³C NMR (ppm)=121.69.

EXAMPLE 50

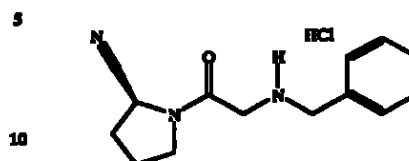
Pyrrolidine, 1-[(1,1-dimethylpropyl)amino]acetyl-2-cyano-(S)-,monohydrochloride



1,1-Dimethylpropylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. Melting point=62° C.-64° C. ¹³C NMR (ppm)=121.53.

28
EXAMPLE 51

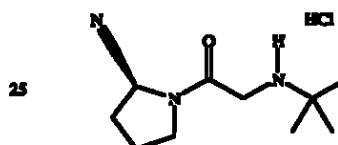
Pyrrolidine, 1-[(phenylmethyl)amino]acetyl-2-cyano-(S)-,monohydrochloride



Benzylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=58° C.-60° C. ¹³C NMR (ppm)=121.38.

EXAMPLE 52

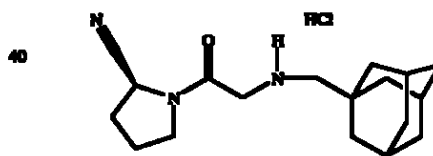
Pyrrolidine, 1-[(1,1-dimethylethyl)amino]acetyl-2-cyano-(S)-,monohydrochloride



Tert-butylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=226° C.-228° C. ¹³C NMR (ppm)=121.56.

EXAMPLE 53

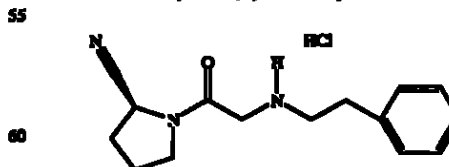
Pyrrolidine, 1-[(2-adamantyl)methyl]amino]acetyl-2-cyano-(S)-,monohydrochloride



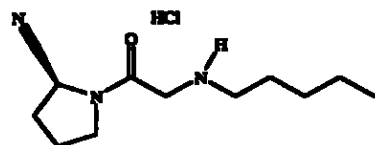
1-Adamantanamethylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=158° C.-160° C. ¹³C NMR (ppm)=121.56.

EXAMPLE 54

Pyrrolidine, 1-[(2-phenylethyl)amino]acetyl-2-cyano-(S)-,monohydrochloride

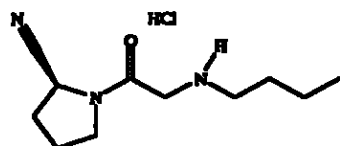


Phenethylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=275° C.-280° C. decomposed. ¹³C NMR (ppm)=121.52.

29
EXAMPLE 55Pyrrolidine, 1-(pentylamino)acetyl-2-cyano-(S)-,
monohydrochloride

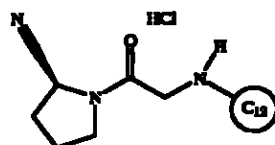
Pentylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=176° C.-178° C. ¹³C NMR (ppm)=121.67.

EXAMPLE 56

Pyrrolidine, 1-(butylamino)acetyl-2-cyano-(S)-,
monohydrochloride

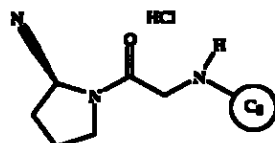
Butylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=180° C.-182° C. ¹³C NMR (ppm)=121.56.

EXAMPLE 57

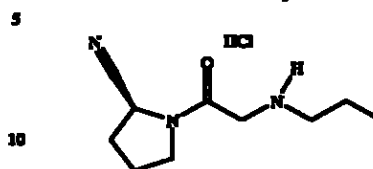
Pyrrolidine, 1-(cyclododecylamino)acetyl-2-cyano-,
(S)-monohydrochloride

Cyclododecylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. ¹³C NMR (ppm)=121.52.

EXAMPLE 58

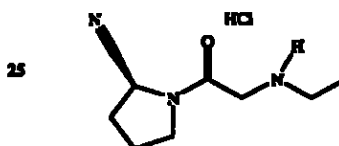
Pyrrolidine, 1-(cyclooctylamino)acetyl-2-cyano-,
(S)-monohydrochloride

Cyclooctylamine (commercially available) was used as the amine nucleophile. The title compound was a white fluffy solid. ¹³C NMR (ppm)=121.64.

30
EXAMPLE 59Pyrrolidine, 1-(propylamino)acetyl-2-cyano-(S)-,
monohydrochloride

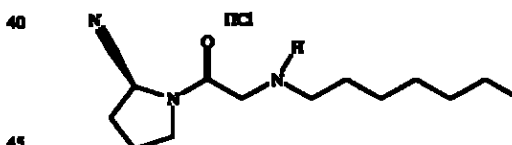
Propylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=193° C.-194° C. ¹³C NMR (ppm)=121.57.

EXAMPLE 60

Pyrrolidine, 1-(ethylamino)acetyl-2-cyano-(S)-,
monohydrochloride

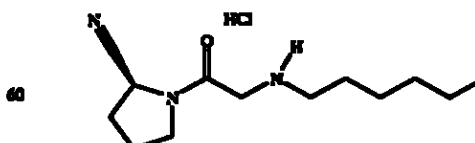
Ethylamine (commercially available) was used as the amine nucleophile. The title compound was an off-white stick solid. ¹³C NMR (ppm)=121.67.

EXAMPLE 61

Pyrrolidine, 1-(heptylamino)acetyl-2-cyano-(S)-,
monohydrochloride

Heptylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=170° C.-172° C. ¹³C NMR (ppm)=121.7.

EXAMPLE 62

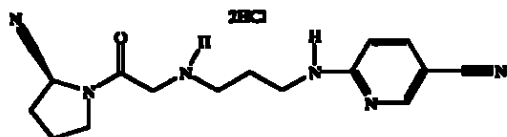
Pyrrolidine, 1-(hexylamino)acetyl-2-cyano-(S)-,
monohydrochloride

Hexylamine (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=174° C.-176° C. ¹³C NMR (ppm)=121.75.

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EXAMPLE 63

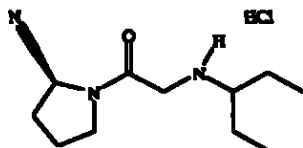
Pyrrolidine, 1-[[3-[(5-cyano-2-pyridinyl)amino]propyl]amino]acetyl-2-cyano-(S)-, dihydrochloride



2(3-Aminopropylamino)-5-cyanopyridine (preparation described above) was used as the amine nucleophile. The title compound was a white sticky solid. Melting point=210° C.-212° C. ¹³C NMR(ppm)=119.33.

EXAMPLE 64

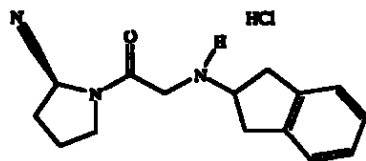
Pyrrolidine, 1-[(1-ethylpropyl)amino]acetyl-2-cyano-(S)-, monohydrochloride



3-Aminopentane (commercially available) was used as the amine nucleophile. The title compound was a white fluffy sticky solid. ¹³C NMR ppm)=119.35.

EXAMPLE 65

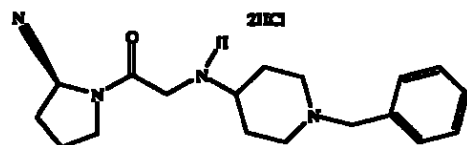
Pyrrolidine, 1-[(2,3-dihydro-1H-inden-2-yl)amino]acetyl-2-cyano-(S)-, monohydrochloride



2-Aminoindan (commercially available) was used as the amine nucleophile. The title compound was a white solid. Melting point=182° C.-184° C. ¹³C NMR (ppm)=121.38.

EXAMPLE 66

Pyrrolidine, 1-[(1-phenylmethyl-4-piperidinyl)amino]acetyl-2-cyano-(S)-, monohydrochloride



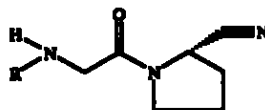
4-Amino-1-benzylpiperidine (commercially available) was used as the amine nucleophile. The title compound was

32

a white solid. Melting point=280° C.-283° C. decomposed. ¹³C NMR (ppm)=121.39.

What is claimed is:

1. A compound of formula I:



wherein

R is a group -(CH₂)_n-N-R₁; an unsubstituted (C₃₋₁₂) cycloalkyl ring; a (C₂₋₁₂) cycloalkyl ring substituted in the 1-position by a hydroxy(C₁₋₃)alkyl group; a group -(CH₂)_n-R₂; a group



a group -(CH₂)_n-R₄; an isopropyl group; an isopropyl group substituted in the i-position by a hydroxy(C₁₋₃)alkyl group; or R₅;

R₁ is an unsubstituted pyridine ring; a pyridine ring mono- or di-substituted by halo, trifluoromethyl, cyano or nitro; an unsubstituted pyrimidine ring; a pyrimidine ring monosubstituted by halo, trifluoromethyl, cyano or nitro; or an unsubstituted phenyl ring;

R₂ is an unsubstituted phenyl ring; a phenyl ring mono-, di- or tri-substituted by halo, (C₁₋₃)alkoxy or a phenyl sulfide (optionally substituted with a (C₁₋₃)alkoxy); phenoxy; (C₁₋₃)alkyl; 3,1,1 bicyclic ring system (optionally substituted with 1 or more (C₁₋₃) alkyl groups); unsubstituted pyridine ring; naphthyl, cyclohexene; or adamantyl;

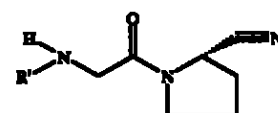
each R₃, independently, is an unsubstituted phenyl ring; or a phenyl ring mono-substituted by halo or (C₁₋₃)alkoxy;

R₄ is a 2-oxopyrrolidine group or a (C₂₋₆)alkoxy group; R₅ is indan; pyrrolidine (unsubstituted or substituted with -CH₂-phenyl); piperidine (unsubstituted or substituted with -CH₂-phenyl); a 2,2,1 bicyclic ring system (unsubstituted or substituted with 1 or more (C₁₋₃) alkyl groups); adamantyl; a straight or branched chain (C₁₋₆) alkyl (unsubstituted or substituted by one or more substituents selected from hydroxy, -CH₂OH and phenyl); or a 3,1,1 bicyclic ring system (unsubstituted or substituted with 1 or more (C₁₋₃)alkyl groups); and m and n independently are integers of 1 to 3;

p is an integer of 2 to 4;

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1 of formula I:



where

R' is a group -(CH₂)_n-N-R₁; an unsubstituted (C₂₋₇) cycloalkyl ring; a (C₂₋₇) cycloalkyl ring substituted in

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 97 - 14,674
FECHA : FEBRERO 19 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Gr. PAGO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO POPULAR	050-00116-6	55017201	19/02/2007	5,046,000.00

***** CONCEPTO *****

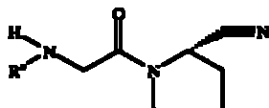
CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEHAS COMERCIALES	77,000.00
	TOTAL :	\$ 77,000.00

GRU: NOVENTA Y NUEVE MIL PESOS

RESPONSABLE : _____

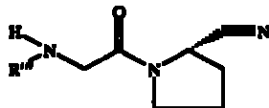
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

the 1-position by a hydroxy(C_{1-3})alkyl group; a group $-(CH_2)_3R_4$; or a group R_5 as defined in claim 1;
 R_1 is an unsubstituted pyridine ring; a pyridine ring mono- or di-substituted by halo, trifluoromethyl, cyano or nitro; or an unsubstituted pyrimidine ring; and
 R_4 is a (C_{1-4})alkoxy group;
 or a pharmaceutically acceptable acid addition salt thereof.
 3. A compound according to claim 2 of formula Ib:



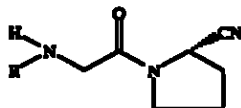
where

R'' is a group $-(CH_2)_3N-R_1''$; a (C_{4-6})cycloalkyl ring substituted in the 1-position by a hydroxy(C_{1-3})alkyl group; a group $CH_2)_3R_4$; or a group R_5 ;
 R_1'' is a pyridine ring mono- or di-substituted by halo, trifluoromethyl, cyano or nitro;
 R_4 is as defined in claim 2; and
 R_5 is a 3,1,1 bicyclic ring system (unsubstituted or substituted with 1 or more (C_{1-3}) alkyl groups; a 2,2,1 bicyclic ring system (optionally substituted with 1 or more (C_{1-3}) alkyl groups; or adamantyl;
 or a pharmaceutically acceptable acid addition salt thereof.
 4. A compound according to claim 3 of formula Ic:



where

R'' is a group $-(CH_2)_3N-R_1''$; a (C_{4-6})cycloalkyl ring substituted in the 1-position by a hydroxymethyl group; a group $-(CH_2)_3R_4$; or a group R_5 ;
 R_1'' is a pyridine ring monosubstituted by halo, trifluoromethyl, cyano or nitro;
 R_4 is as defined in claim 3; and
 R_5 is adamantyl;
 or a pharmaceutically acceptable acid addition salt thereof.
 5. A compound of formula I:



wherein R is:

a) $R_1R_{1a}N(CH_2)_m$ wherein
 R_1 is a pyridinyl or pyrimidinyl moiety unsubstituted or mono- or independently disubstituted with (C_{1-4}) alkyl, (C_{1-4})alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl unsubstituted or- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halo-
 R_{1a} is hydrogen or (C_{1-3})alkyl; and

m is 2 or 3;
 b) (C_{2-12})cycloalkyl unsubstituted or monosubstituted in the 1-position with (C_{1-3})hydroxyalkyl;
 c) $R_2(CH_2)_n$ wherein either
 R_2 is phenyl unsubstituted or mono- or independently di- or independently trisubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen or phenylthio unsubstituted or monosubstituted in the phenyl ring with hydroxymethyl; or is (C_{1-4})alkyl; a [3.1.1]bicyclic carbocyclic moiety unsubstituted or mono- or plurisubstituted with (C_{1-4})alkyl; a pyridinyl or naphthyl moiety unsubstituted or mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen; cyclohexane; or adamantyl; and
 n is 1 to 3; or
 R_2 is phenoxy unsubstituted or mono- or independently disubstituted with (C_{1-4}), (C_{1-4})alkoxy or halogen; and
 n is 2 or 3;
 d) $(R_3)_2CH(CH_2)_2$ wherein each R_3 independently is phenyl unsubstituted or mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;
 e) $R_4(CH_2)_p$ wherein R_4 is 2-oxopyrrolidinyl or (C_{2-4})alkoxy and p is 2 to 4;
 f) isopropyl unsubstituted or monosubstituted in the 1-position with (C_{1-3})hydroxyalkyl;
 g) R_5 wherein R_5 is indanyl; a pyrrolidinyl or piperidinyl moiety unsubstituted or substituted with benzyl; a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety unsubstituted or mono- or plurisubstituted with (C_{1-4})alkyl; adamantyl; or (C_{1-4})alkyl unsubstituted or mono- or independently plurisubstituted with hydroxy, hydroxymethyl or phenyl unsubstituted or mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;
 in free form or in acid addition salt form.
 6. A compound according to claim 5 (a compound Ip) wherein R is R' , which is:
 a) $R_1'NH(CH_2)_2$ wherein R_1' is a pyridinyl or pyrimidinyl moiety unsubstituted or mono- or independently disubstituted with halogen, trifluoromethyl, cyano or nitro;
 b) (C_{2-12})cycloalkyl unsubstituted or the monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;
 c) $R_2'(CH_2)_2$ wherein R_2' is phenyl unsubstituted or mono- or independently di- or independently trisubstituted with halogen or (C_{1-3})alkoxy;
 d) $(R_3')_2CH(CH_2)_2$ wherein each R_3' independently is phenyl substituted or monosubstituted with halogen or (C_{1-3})alkoxy;
 e) $R_4'(CH_2)_2$ wherein R_4' is as defined in claim 5; or
 f) isopropyl unsubstituted or monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;
 in free form or in acid addition salt form.
 7. A compound according to claim 5 (a compound Is), wherein R is R'' , which is:
 a) $R_1''R_{1a}''(CH_2)_m$ wherein R_1'' is pyridinyl unsubstituted or mono- or independently disubstituted with chlorine, trifluoromethyl, cyano or nitro; pyrimidinyl unsubstituted or monosubstituted with chlorine or trifluoromethyl; or phenyl; R_{1a}'' is hydrogen or methyl; and m is 2 or 3;
 b) (C_{2-12})cycloalkyl unsubstituted or monosubstituted in the 1-position with hydroxymethyl;
 c) $R_2''(CH_2)_n$ wherein either R_2'' is phenyl unsubstituted or mono- or independently di- or independently trisub-

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491

RECIBO DE CASH APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CASH : 97 - 16,145
FECHA : FEBRERO 22 DE 2007

==== CONSIGNACION =====

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO POPULAR	050-00110-6	57757121	22/02/2007	2,300,000.00

==== CONCEPTO =====

CANT. CONTABILITICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-03 CAMBIO DE LOCALIDAD Y MODIFICA	12 MARCAS Y LEAS COMERCIALES	77,390.00
	TOTAL :	77,390.00

CON: NOVENTA Y NUEVE MIL PESOS

OTISABLE : _____

stituted with halogen, alkoxy of 1 or 2 carbon atoms or phenylthio monosubstituted in the phenyl ring with hydroxymethyl; (C₁₋₆)alkyl; 6,6-dimethylbicyclo[3.1.1]hept-2-yl; pyridinyl; naphthyl; cyclohexane; or adamantyl; and *m* is 1 to 3; or R₂^a is phenoxy; and *n* is 2;

d) (3,3-diphenyl)propyl;

e) R₃^a(CH₂)_{*m*} wherein R₃^a is 2-oxopyrrolidin-1-yl or isopropoxy and *m* is 2 or 3;

f) isopropyl unsubstituted or monosubstituted in 1-position with hydroxymethyl;

g) R₃^a wherein R₃^a is: indanyl; a pyrrolidinyl or piperidinyl moiety unsubstituted or N-substituted with benzyl; bicyclo[2.2.1]hept-2-yl; 2,6,6-trimethylbicyclo[3.1.1]hept-3-yl; adamantyl; or (C₁₋₆)alkyl optionally mono- or independently disubstituted with hydroxy, hydroxymethyl or phenyl;

in free form or in acid addition salt form.

8. The compound according to claim 5 wherein R is 2-[(5-cyanopyridin-2-yl)amino]ethyl, i.e. 1-[2-[(5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine, in free form or in acid addition salt form, or a compound according to claim 5 which is of formula I wherein R is either

2-[(5-chloropyridin-2-yl)amino]ethyl, or

(1-hydroxymethyl)cyclopent-1-yl, or

2-[(5-nitropyridin-2-yl)amino]ethyl, or

3-(isopropoxy)propyl,

in free form or in acid addition salt form.

9. A compound according to claim 5 which is:

1-[2-[(5-chloropyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine dihydrochloride;

1-[2-[(5-trifluoromethylpyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[2-[(5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine dihydrochloride;

1-[2-[(pyrimidin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[(1-hydroxymethyl)cyclopent-1-yl]amino]acetyl-2-cyano-(S)-pyrrolidine;

1-[2-[(pyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[2-[(4-chloropyrimidin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[2-[(3-chloropyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[2-[(4-trifluoromethylpyrimidin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[(2-chlorophenyl)ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[(3,3-diphenyl)propylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[2-[(5-nitropyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[2-[(3-chloro-5-trifluoromethylpyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[2-[(3-trifluoromethylpyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[2-[(3,5-dichloropyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[(cyclopent-1-yl)amino]acetyl-2-cyano-(S)-pyrrolidine monohydrochloride;

1-[2-(2-bromo-4,5-dimethoxyphenyl)ethylamino]acetyl-2-cyano-(S)-pyrrolidine;

1-[3-(isopropoxy)propylamino]acetyl-2-cyano-(S)-pyrrolidine monohydrochloride;

1-[(2-hydroxy-1,1-dimethylethylamino)]acetyl-2-cyano-(S)-pyrrolidine monohydrochloride;

1-[3-(2-oxo-pyrrolidin-1-yl)propylamino]acetyl-2-cyano-(S)-pyrrolidine monohydrochloride;

1-[(1-hydroxymethylcyclohexyl)amino]acetyl-2-cyano-(S)-pyrrolidine;

5 Pyrrolidine, 1-[2-(4-ethoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[(1-phenylmethyl-3-pyrrolidinyl)amino]acetyl-2-cyano-(S)-(R)-dihydrochloride;

Pyrrolidine, 1-[2-(4-methoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

10 Pyrrolidine, 3-[2-(3-methoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[(1-naphthalenyl)methyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[(3-phenylpropyl)amino]acetyl-2-cyano-(S)-monohydrochloride;

15 Pyrrolidine, 1-[3-[(phenyl)(methyl)amino]propyl]amino]acetyl-2-cyano-(S)-dihydrochloride;

Pyrrolidine, 1-[2-[(3,4-dimethoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

20 Pyrrolidine, 1-(acycloheptylamino)acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[(6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl]amino]acetyl-2-cyano-[1S[1 α ,2 α (S*),5 α]]-(S)-monohydrochloride;

25 Pyrrolidine, 1-[2-(2,5-dimethoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[2-(1-cyclohexen-1-yl)ethyl]amino]acetyl-2-cyano-(S)-;

Pyrrolidine, 1-(cyclohexylamino)acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[(bicyclo[2.2.1]hept-2-yl)amino]acetyl-2-cyano-[1S[1 α ,2 α (S*),5 α]]-(S)-monohydrochloride;

Pyrrolidine, 1-[2-(2-pyridinyl)ethyl]amino]acetyl-2-cyano-(S)-dihydrochloride;

35 Pyrrolidine, 1-[(2-phenylamino)ethyl]amino]acetyl-2-cyano-(S)-dihydrochloride;

Pyrrolidine, 1-[(3,3-dimethylbutyl)amino]acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)amino]acetyl-2-cyano-(S)[1S[1 α ,2 β ,3 α (S*),5 α]]-monohydrochloride;

40 Pyrrolidine, 1-[(1-hydroxymethyl)propyl]amino]acetyl-2-cyano-(S)-;

Pyrrolidine, 1-[(2-[(2-hydroxymethyl)phenyl]thio)phenylmethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

45 Pyrrolidine, 1-[2-(2-methoxyphenyl)ethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[(5-hydroxypentyl)amino]acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-(cyclobutylamino)acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[2-(2,4-dichlorophenyl)ethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

55 Pyrrolidine, 1-[(1-hydroxymethyl)-3-methylbutyl]amino]acetyl-2-cyano-(S)-;

Pyrrolidine, 1-[(2-hydroxy-2-phenylethyl)amino]acetyl-2-cyano-[2S-1R*,2S*]-monohydrochloride;

Pyrrolidine, 1-[2-(2-fluorophenyl)ethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

60 Pyrrolidine, 1-(cyclopropylamino)acetyl-2-cyano-(S)-monohydrochloride;

Pyrrolidine, 1-[(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)amino]acetyl-2-cyano-[1S[1 α ,2 α ,3 β (S*),5 α]]-monohydrochloride;

65 Pyrrolidine, 1-[(2-phenoxy)ethyl]amino]acetyl-2-cyano-(S)-monohydrochloride;

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RECIBO DE CAJA AFILIADO AL EFICIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 16.146
CHA : FEBRERO 22 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO POPULAR	050-00110-6	57757121	22/02/2007	2,500,000.00

***** CONCEPTO *****

CANT. CONTABILITICO	CONCEPTO	TOTAL CONCEPTO
1 53005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEHAS COMERCIALES	77,000.00
	TOTAL :	77,000.00

CON: NOVENTA Y NUEVE MIL PESOS

USABLE : _____

4

Pyrrolidine, 1-[2-[(3,5-dimethoxyphenyl)ethyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[(1-adamantyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[(1,1,3,3-tetramethylbutyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[(2-adamantyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[(1,1,1-trimethylpropyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[(phenylmethyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[(1,1-dimethylethyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[(2-adamantyl)methyl]amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[(2-phenylethyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-(pentylamino)acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-(butylamino)acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-(cyclododecylamino)acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-(cyclooctylamino)acetyl-2-cyano-, (S)-, monohydrochloride;

Pyrrolidine, 1-(propylamino)acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-(ethylamino)acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-(heptylamino)acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-(hexylamino)acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[[3-[(5-cyano-2-pyridinyl)amino]propyl]amino]acetyl-2-cyano-, (S)-, dihydrochloride;
 Pyrrolidine, 1-[(1-ethylpropyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-1(2,3-dihydro-1H-inden-2-yl)amino]acetyl-2-cyano-, (S)-, monohydrochloride;
 Pyrrolidine, 1-[(1-phenylmethyl-4-piperidinyl)amino]acetyl-2-cyano-, (S)-, monohydrochloride; or a pharmaceutically acceptable salt of any of the above compounds which are in free form.
 10. A pharmaceutical composition comprising a compound according to claim 5 in free form or in pharmaceutically acceptable acid addition salt form, together with at least one pharmaceutically acceptable carrier or diluent.
 11. A compound according to claim 8 which is 1-[2-[(5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-, (S)-pyrrolidine dihydrochloride.

* * * * *

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT: 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 16.146
CHA : FEBRERO 22 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARDENAS Y CARDENAS P.I. CONSIGNACION		BANCO POPULAR	050-00110-6	57757121	22/02/2007	2,300,000.00

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

CANT. SENTISFICO	CONCEPTO	TOTAL CONCEPTO
1 50003-01-05 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEHAS COMERCIALES	99,000.00
	TOTAL :	99,000.00

CON: NOVENTA Y NUEVE MIL PESOS

OTRO : _____



Altanzzeichen: P 33 24 263.1
Anmeldetag: 8. 7. 83
Offenlegungstag: 17. 1. 85

Int. Cl. 3:
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C 07 D 403/08
C 07 D 401/08
C 07 D 401/12
C 07 D 405/08
C 07 D 413/08
C 07 D 417/08
A 61 K 31/40

DE 3324263 A1

D3 494
499

⑦ Anmelder:

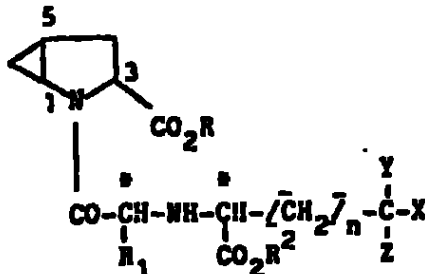
Hoechst AG, 65926 Frankfurt, DE

⑧ Erfinder:

Urbech, Hansjörg, Dr., 6243 Kronberg, DE; Henning,
Rainer, Dr., 6234 Hattersheim, DE; Becker, Reinhard,
Dr., 6200 Wiesbaden, DE

Derivate der 2-Azabicyclo[3.1.0]hexan-3-carbonsäure, Verfahren zu ihrer Herstellung, diese enthaltende Mittel und deren Verwendung sowie 2-Azabicyclo[3.1.0]hexan-Derivate als Zwischenprodukte und Verfahren zu deren Herstellung

Die Erfindung betrifft Verbindungen der Formel I



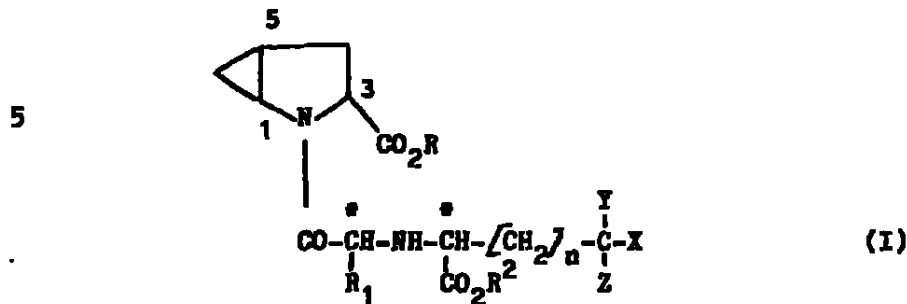
durch Alkyl, Alkoxyl, Hydroxyl, Halogen, Nitro, Amino, Arylamino, Alkylamino, Dialkylamino und/oder Methylendioxy mono-, di- oder trisubstituiert sein kann, oder Indol-3-yl bedeuten, Verfahren zu ihrer Herstellung, diese enthaltende Mittel und deren Verwendung sowie 2-Azabicyclo[3.1.0]hexan-Derivate als Zwischenprodukte und Verfahren zu deren Herstellung.

DE 3324263 A1

n = 0 oder 1, R = Wasserstoff, Alkyl, Alkanyl oder Aryl, R¹ = Wasserstoff oder Alkyl, das gegebenenfalls durch Amino, Alkylamino oder Benzoylamino substituiert sein kann, Alkanyl, Cycloalkyl, Cycloalkanyl, Cycloalkylalkyl, Aryl oder teilhybrisiertes Aryl, das jeweils durch Alkyl, Alkoxyl oder Halogen substituiert sein kann, Aryl oder Arylalkyl, die beide wie vorstehend definiert im Arylrest substituiert sein können, ein mono- bzw. bicyclischer S- oder O- und/oder N-Heterocyclus-Rest oder eine Seitenkette einer Aminosäure, R² = Wasserstoff, Alkyl, Alkanyl oder Aryl, Y = Wasserstoff oder Hydroxyl, Z = Wasserstoff oder Y und Z = zusammen Wasserstoff, X = Alkyl, Alkanyl, Cycloalkyl, Aryl, das

PATENTANSPRÜCHE:

① Verbindung der Formel I,



in der die Wasserstoffatome an den Brückenknopf-C-Atomen
zueinander cis- konfiguriert sind und die COOR-Gruppe am
C-Atom 3 exo- oder endoständig zum bicyclischen Ringsy-
stem orientiert ist, in der

15 $n = 0$ oder 1,

$R =$ Wasserstoff, (C_1-C_6) -Alkyl, (C_2-C_6) -Alkyl oder
 (C_6-C_{12}) -Aryl- (C_1-C_4) -Alkyl,

$R^1 =$ Wasserstoff oder $(C_1$ bis $C_6)$ -Alkyl, das gegebenen-
falls durch Amino, $(C_1$ bis $C_6)$ -Acylamino oder Benzoyl-
20 amino substituiert sein kann, $(C_2$ bis $C_6)$ -Alkenyl,
 $(C_5$ bis $C_9)$ -Cycloalkyl, $(C_5$ bis $C_9)$ - Cycloalkenyl,
 $(C_5$ bis $C_7)$ -Cycloalkyl- $(C_1$ bis $C_4)$ -alkyl, $(C_6$ bis
 $C_{12})$ -Aryl oder teilhydriertes $(C_6$ bis $C_{12})$ -Aryl, das
jeweils durch $(C_1$ bis $C_4)$ -Alkyl, $(C_1$ oder $C_2)$ -Alkoxy
25 oder Halogen substituiert sein kann, $(C_6$ bis $C_{12})$ -Aryl-
 $(C_1$ bis $C_4)$ -alkyl oder $(C_7$ bis $C_{13})$ -Aroyl- (C_1-C_2) alkyl
die beide wie vorstehend definiert im Arylrest
substituiert sein können, ein mono- bzw. bicycli-
scher Heterocyclen-Rest mit 5 bis 7 bzw. 8 bis 10
30 Ringatomen, wovon 1 bis 2 Ringatome Schwefel- oder
Sauerstoffatome und/oder wovon 1 bis 4 Ringatome
Stickstoffatome darstellen, oder eine gegebenenfalls
geschützte Seitenkette einer natürlich vorkommenden
 α -Aminosäure $R^1-CH(NH_2)-COOH$,

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R^2 = Wasserstoff (C_1-C_6 -Alkyl, (C_2-C_6)-Alkenyl oder (C_6-C_{12})-Aryl- (C_1-C_4) -alkyl,

Y = Wasserstoff oder Hydroxy,

5 Z = Wasserstoff oder

Y und Z = zusammen Sauerstoff,

10 X = (C_1-C_6)-Alkyl, (C_2-C_6)-Alkenyl, (C_5-C_9)-Cyclo-
alkyl, (C_6-C_{12})-Aryl, das durch (C_1-C_4)-Alkyl,
(C_1-C_4)-Alkoxy, Hydroxy, Halogen, Nitro, Amino, Acyl-
amino, (C_1-C_4)-Alkylamino, Di- (C_1-C_4) -alkyl-amino
und/oder Methylendioxy mono-, di- oder trisubstitu-
iert sein kann,

oder Indol-3-yl bedeuten,

15 sowie deren physiologisch unbedenkliche Salze.

2. Verbindung der Formel I gemäß Anspruch 1, dadurch gekenn-
zeichnet, daß das C-Atom in Position 3 des bicyclischen
Ringsystems sowie die mit einem Stern markierten C-Atome
20 der Seitenkette jeweils S-Konfiguration aufweisen.

3. Verbindung der Formel I gemäß einem der Ansprüche 1 oder
2, in welcher

25 n = 1 ist,

R^1 = Wasserstoff, Allyl, Vinyl oder eine gegebenenfalls
geschützte Seitenkette einer natürlich vorkommenden
L-Aminosäure bedeutet und

30 R, R^2 , Y, Z und X die in Anspruch 1 definierten Bedeu-
tungen haben.

4. Verbindung der Formel I gemäß einem der Ansprüche 1 bis
3, in welcher

35

n = 1,

R = Wasserstoff

R^1 = Methyl, die gegebenenfalls acylierte Seitenkette von Lysin oder die O-(C₁-C₆)-alkylierte Seitenkette des Tyrosin,

5 R^2 = Wasserstoff, Methyl, Ethyl, Benzyl oder tert. Butyl

X = Phenyl oder mit Fluor und/oder Chlor mono- oder disubstituiertes Phenyl,

10 Y = Wasserstoff oder Hydroxy

Z = Wasserstoff oder

Y und Z zusammen Sauerstoff bedeuten.

15 5. N-(1-S-Carbethoxy-3-phenyl-propyl)-S-alanyl-cis-2-azabicyclo-
[3.1.0]hexan-endo-3-S-carbonsäure

6. N-(1-S-Carboxy-3-phenyl-propyl)-S-alanyl-cis-2-azabicyclo-
[3.1.0]hexan-endo-3-S-carbonsäure

7. N-(1-S-Carbethoxy-3-phenyl-propyl)-S-lysyl-cis-2-azabi-
20 cyclo[3.1.0]hexan-endo-3-S-carbonsäure

8. N-(1-S-Carboxy-3-phenyl-propyl)-S-lysyl-cis-2-azabicyclo-
[3.1.0]hexan-endo-3-S-carbonsäure

9. N-(1-S-Carbethoxy-3-phenyl-propyl)-O-ethyl-S-tyrosyl-cis-
2-azabicyclo[3.1.0]hexan-endo-3-S-carbonsäure

25 10. N-(1-S-Carbethoxy-3-phenyl-propyl)-O-methyl-S-tyrosyl-cis-
2-azabicyclo[3.1.0]hexan-endo-3-S-carbonsäure

11. N-(1-S-Carbethoxy-3-phenyl-propyl)-S-alanyl-cis-2-azabi-
cyclo[3.1.0]hexan-exo-3-S-carbonsäure

12. N-(1-S-Carboxy-3-phenyl-propyl)-S-alanyl-cis-2-azabicyclo-
30 [3.1.0]hexan-exo-3-S-carbonsäure

13. N-(1-S-Carbethoxy-3-phenyl-propyl)-S-lysyl-cis-2-azabicyclo-
[3.1.0]hexan-exo-3-S-carbonsäure

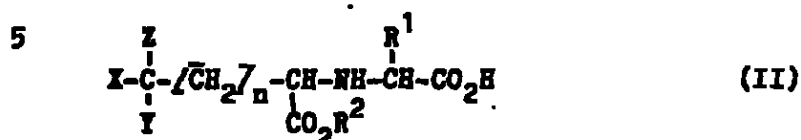
14. N-(1-S-Carboxy-3-phenyl-propyl)-S-lysyl-cis-2-azabicyclo-
[3.1.0]hexan-endo-3-S-carbonsäure

35 15. N-(1-S-Carbethoxy-3-phenyl-propyl)-O-ethyl-S-tyrosyl-cis-
2-azabicyclo[3.1.0]hexan-exo-3-S-carbonsäure

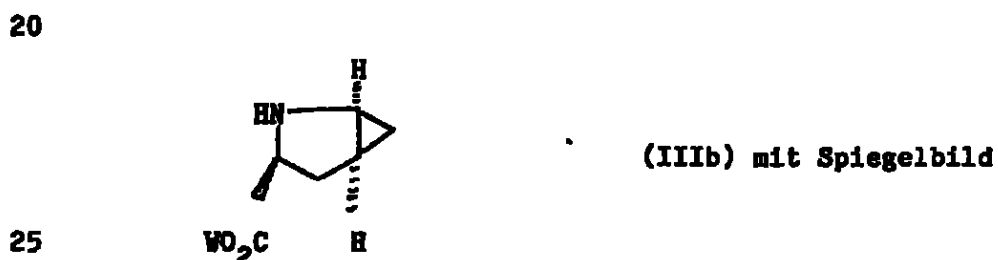
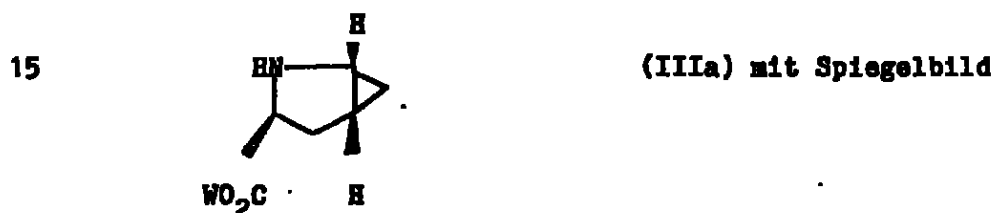
16. N-(1-S-Carbethoxy-3-phenyl-propyl)-O-methyl-S-tyrosyl-cis-
2-azabicyclo[3.1.0]hexan-exo-3-S-carbonsäure

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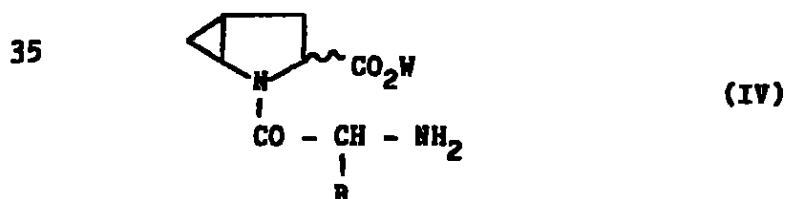
17. Verfahren zur Herstellung von Verbindungen gemäß den Ansprüchen 1 bis 16, dadurch gekennzeichnet,
a) daß man eine Verbindung der Formel II



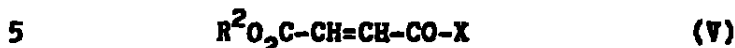
- 10 in der n, X, Y, Z, R¹ und R² die in Anspruch 1 definierten Bedeutungen mit Ausnahme von R² = Wasserstoff haben, mit einer Verbindung der Formeln IIIa oder IIIb oder dem Stereoisomerengemisch



- in denen W eine Carboxy veresternde Gruppe bedeutet, umsetzt und anschließend das Produkt hydriert oder mit einer Säure oder einer Base behandelt, oder
- 30 b) daß man zur Herstellung der Verbindungen der Formel I, in der Y und Z zusammen Sauerstoff bedeuten,
- b¹) eine Verbindung der Formel IV

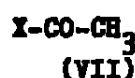


in welcher R^1 die Bedeutung wie in Formel I und W die Bedeutung wie in den Formeln III a und b besitzen, mit einer Verbindung der Formel V,



worin R^2 und X die Bedeutungen wie in Formel I haben, umgesetzt und anschließend gegebenenfalls W und/oder R^2 unter Bildung der freien Carboxygruppen abgespalten, 10 oder

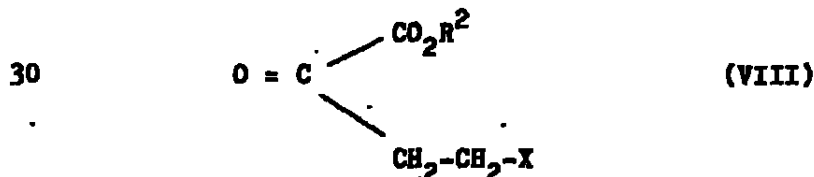
b₂) eine Verbindung der unter b₁) genannten Formel IV mit einer Verbindung der allgemeinen Formel VI, worin R^2 die Bedeutung wie in Formel I hat, und mit einer Verbindung der allgemeinen Formel VII, 15



(VI)

20 worin X die Bedeutung wie in Formel I hat, umgesetzt und anschließend gegebenenfalls W und/oder R^2 unter Bildung der freien Carboxygruppen abgespalten, oder

c) daß man zur Herstellung von Verbindungen der Formel I, 25 in der Y und Z jeweils Wasserstoff bedeuten, eine Verbindung der unter b₁) genannten Formel IV mit einer Verbindung der Formel VIII,



worin R^2 und X die Bedeutungen wie in Formel I besitzen. 35 umgesetzt, die erhaltenen Schiff-Basen reduziert und anschließend gegebenenfalls W und/oder R^2 unter Bildung der freien Carboxygruppen abgespalten, oder

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- 5 d) daß man zur Herstellung von Verbindungen der Formel I, in der Y = Hydroxy und Z = Wasserstoff bedeuten, eine Verbindung der Formel I, in der Y und Z zusammen Sauerstoff bedeuten, mit einem komplexen Boranat oder Boran-Amin-Komplex reduziert;

- 10 die nach a) bis d) erhaltenen Verbindungen der Formel I, in welcher R für Wasserstoff steht, gegebenenfalls in Ester der Formel I, worin R (C₁ bis C₆)-Alkyl oder (C₇ bis C₉)-Aralkyl bedeutet, überführt und Verbindungen der Formel I gegebenenfalls in ihre physiologisch verträglichen Salze überführt.

- 15 18. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 16 als Heilmittel.

19. Verbindung gemäß einem der Ansprüche 1 bis 16 zur Verwendung als Heilmittel.

- 20 20. Mittel, enthaltend eine Verbindung gemäß einem der Ansprüche 1 bis 4.

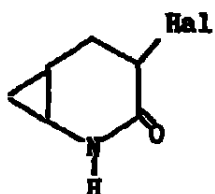
21. Mittel, enthaltend eine Verbindung gemäß einem der Ansprüche 1 bis 4 in Kombination mit einem Diuretikum.

25

22. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 4, in Kombination mit einem Diuretikum als Heilmittel.

- 30 23. Verbindung der Formeln IIIa oder IIIb, in welchen W Wasserstoff oder eine Carboxy veresternde Gruppe bedeutet sowie deren Stereoisomerengemisch.

- 35 24. Verfahren zur Herstellung von Verbindungen der Formel III a oder III b gemäß Anspruch 23, dadurch gekennzeichnet, daß man Verbindungen der Formel XI



(XI)

in welcher Hal für Halogen steht, in Gegenwart einer Base umlagert und die erhaltenen Verbindungen der Formeln III a oder III b (W= Wasserstoff) gegebenenfalls verestert.



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

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D4

(12)

EUROPEAN PATENT APPLICATION

(13) Application number: 7806284.8

(14) Int. Cl.²: C 07 D 209/52
C 07 C 83/04

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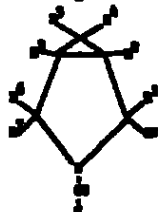
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(24) Derivatives of 2-methyl-2,3,4,5-tetrahydro-2H-pyran and a process for their preparation.

(25) Novel compounds of the general formula:



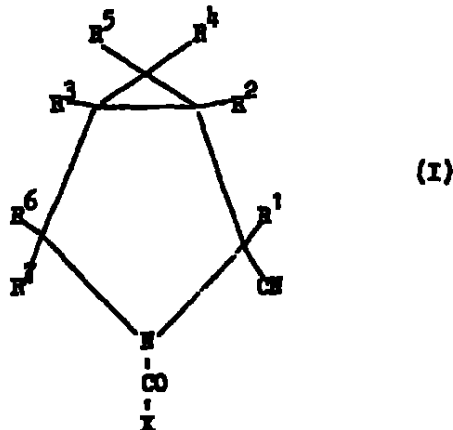
presence of an alpha carboxylic acid, and may be converted by hydrolysis and/or alcoholysis into compounds having valuable biological activity.

EP 0 007 652 A1

wherein R¹ represents a hydrogen atom or an alkyl group of up to 6 carbon atoms, which may be substituted by one or two halogen atoms and/or alkoxy groups having up to 4 carbon atoms; R², R³, R⁴, R⁵, R⁶ and R⁷ each independently represents a hydrogen atom or a halogen atom or an alkyl or alkoxy group of up to 6 carbon atoms which may contain up to 3 halogen atoms, or an aryl, alkaryl or aralkyl group of up to 10 carbon atoms, which may contain up to 3 halogen atoms; or R⁴ and R⁵ or R⁶ and R⁷ together form an alkylenedioxy group of up to 6 methylene groups; and X represents an alkyl group having up to 6 carbon atoms, may be prepared by reacting an ester of a 2-oxocyclopropyl aldehyde with a cyanide in the

CLAIMS

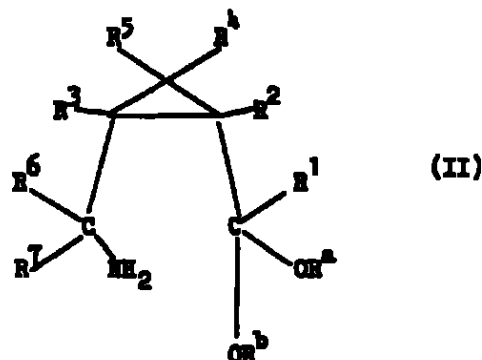
1. A compound of the general formula:



- wherein R¹ represents a hydrogen atom or an alkyl group of up to 6 carbon atoms, which may be substituted by one or two halogen atoms and/or alkoxy groups having up to 4 carbon atoms; R², R³, R⁴, R⁵, R⁶ and R⁷ each independently represents a hydrogen atom or a halogen atom or an alkyl or alkaryl group of up to 6 carbon atoms which may contain up to 3 halogen atoms, or an aryl, alkaryl or aralkyl group of up to 10 carbon atoms, which may contain up to 3 halogen atoms; or R⁴ and R⁵ or R⁶ and R⁷ together form an alkylene moiety of up to 6 methylene groups; and X represents an alkyl group having up to 5 carbon atoms.
2. A compound as claimed in claim 1, in which each of R¹ to R⁷ represents a hydrogen atom.
3. A compound as claimed in either claim 1 or claim 2, in which X represents an ethyl group.
4. A process for the preparation of a compound as claimed in any one of claims 1 to 3, characterized in that it comprises reacting a compound of the general formula:

509
504

9



wherein R^a and R^b each independently represents an alkyl group of up to 4 carbon atoms, R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ have the meanings given for the general formula I and the R₅R₇CH₂ group has a cis-relationship with the group -CH¹(OH^a)(OH^b), with a

5 compound of formula M-CH, wherein M represents a hydrogen atom or an alkali or alkaline earth metal or an ammonium moiety, in the presence of an alkane carboxylic acid having up to 5 carbon atoms.

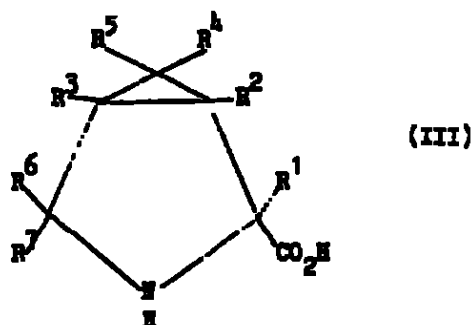
5. A process as claimed in claim 4, characterized in that in
10 the compound of the general formula II, each of R^a and R^b independently represents a methyl or an ethyl group.

6. A process as claimed in either claim 4 or claim 5, characterized in that a cyanide is used in which M represents an alkali metal.

15 7. A process as claimed in claim 4, characterized in that the alkane carboxylic acid used is acetic acid.

8. A process as claimed in any one of claims 4 to 7, characterized in that it is conducted at a temperature in the range of from 40 to 120°C.

20 9. A process for the preparation of a compound of the general formula:



0007038

510 505

in which $R^1 - R^7$ have the meanings given in claim 1, or a salt and/or an ester thereof, characterized in that a compound as claimed in claim 1 is hydrolyzed and/or alcoholised.

10. A compound of the general formula II as defined in claim 4.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

**Doctor
Juan Pablo Cadena Samliento
Apoderado
BRISTOL – MYERS SQUIBB COMPANY**

Oficio-Nº 3431

REFERENCIA	Radicación	01 18857
	Trámite	002
	Evento	001
	Actuación	430
	Folios	014

Como resultado del examen de patentabilidad de la solicitud de patente de invención Nº 01 18857, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

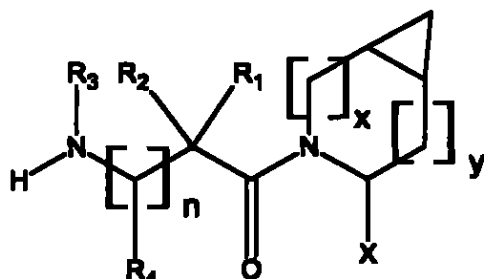
- El resumen y el capítulo descriptivo de la solicitud en los folios 226 a 227 y 1 a 77 respectivamente.
- Los ejemplos que ilustran la invención en los folios 78 a 211.
- Las cláusulas 1 a 11 relacionadas en el capítulo reivindicatorio de la solicitud que se encuentran en los folios 222 a 225.
- La copia de la solicitud original mediante la cual se reivindica prioridad de Estados Unidos US60/188,555 de 10/03/2000 en los folios 229 a 291, junto con su traducción correspondiente en los folios 292 a 395.
- El primer examen de forma realizado a la solicitud de oficio No. 1394, que se encuentra en el folio 403.
- La respuesta al primer examen de forma, allegada mediante memorial de fecha 06/07/2001 que se encuentra en los folios 404 a 409.
- La solicitud de examen de patentabilidad junto con el pago de la tasa correspondiente, allegada mediante memorial de fecha 26/11/2003, que se encuentra en los folios 412 a 413.
- El memorial de fecha 08/06/2005 que contiene un nuevo capítulo reivindicatorio, el cual reemplaza al presentado con anterioridad y que se encuentra en los folios 416 a 427.
- El primer examen de fondo efectuado a la solicitud No. 1686 que se encuentra en los folios 436 a 444.
- El memorial de respuesta allegado en la fecha 31/01/2007 que se encuentra en los folios 445 a 460.
- El nuevo capítulo reivindicatorio que se encuentra en los folios 448 a 456, allegado mediante memorial de fecha 31/01/2007.

2. OBJETO DE LA INVENCION

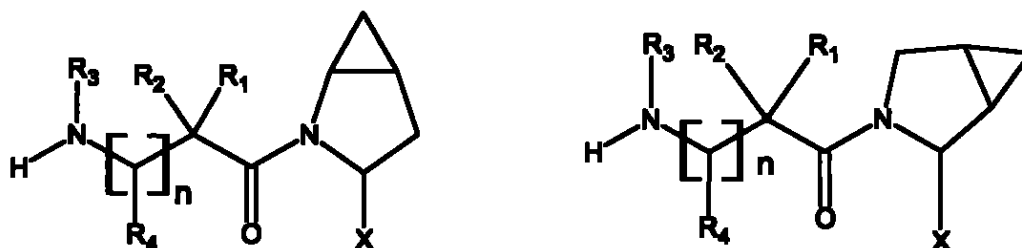
La solicitud hace referencia a un **"Inhibidores a base de pirrolidina fusionada con ciclopropilo de dipeptidilpeptidasa IV y método"**

- **Reivindicaciones 1 a 11:**

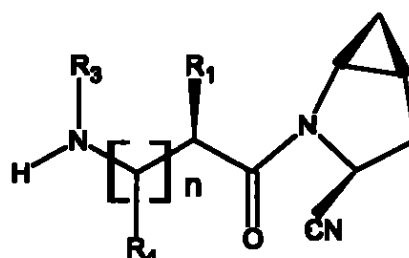
Se reivindica un compuesto que presenta la estructura:



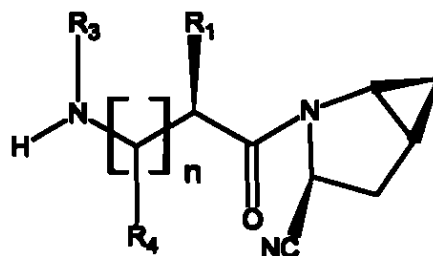
Se reivindica en las cláusulas (2) y (3) un compuesto que tiene la estructura:



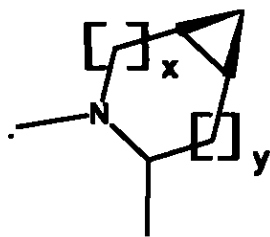
En la cláusula (4) se reivindica la estructura:



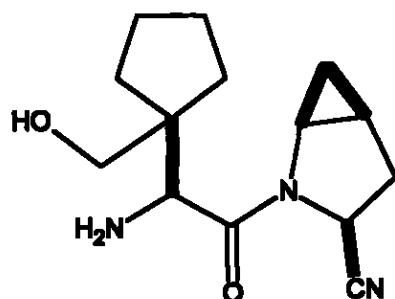
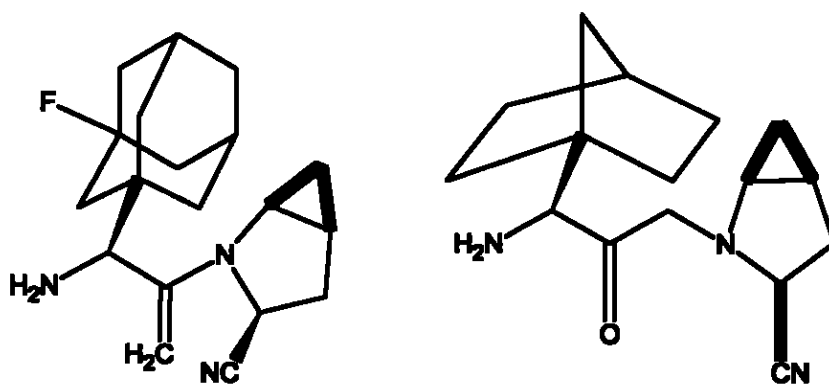
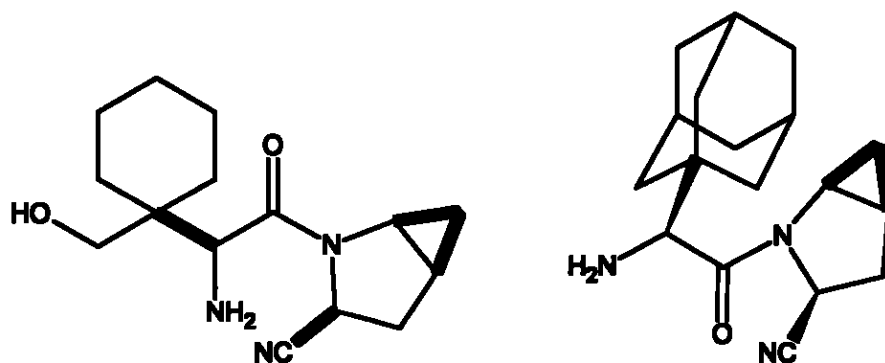
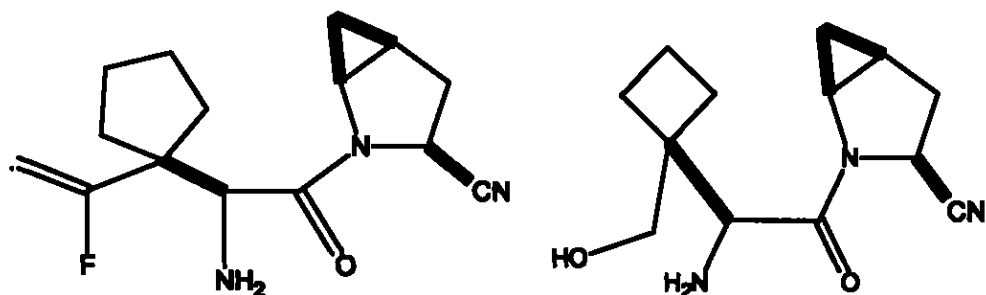
En la cláusula (5) se reivindica la estructura:



En la cláusula (7) se reivindica el compuesto que se caracteriza porque el ciclopropilo fusionado a la pirrolidina tiene la configuración:

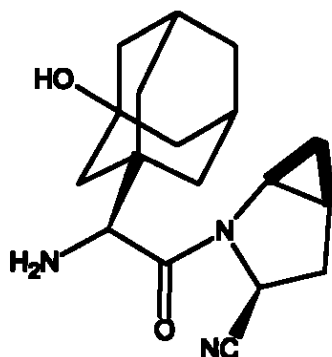


En la cláusula (8) se reivindican en particular los compuestos:

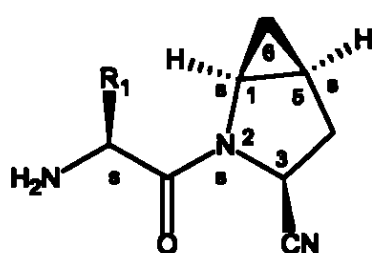


O una sal farmacéuticamente aceptable de los mismos como clorhidrato o sal de ácido trifluoroacético.

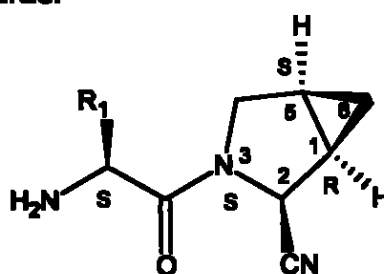
En la cláusula (9) se reivindica el compuesto:



En la cláusula (11) se reclaman las estructuras:



(1S,2(2S),3S,5S)



(1R,2S,3(2S),5S)

• **Reivindicación 12:**

Se reivindica una composición farmacéutica caracterizada porque comprende un compuesto conforme a la cláusula 1 y un portador del mismo farmacéuticamente aceptable.

• **Reivindicaciones 13 a 16:**

Se reivindica una combinación farmacéutica caracterizada porque comprende un compuesto inhibidor de DP4 como se definió en la cláusula 1 y un agente antidiabético para el tratamiento de la diabetes y enfermedades relacionadas, un agente antiobesidad y/o un agente modulador de lípidos.

En particular se reivindica una combinación farmacéutica en la que se asocia el compuesto inhibidor de DP4 y un agente antidiabético, y el agente antidiabético se selecciona entre: biguanida, sulfonilúrea, un inhibidor de glucosidasa, un agonista PPAR γ , un agonista dual PPAR α/γ , un inhibidor SGLT₂, un inhibidor de α P2, un inhibidor de glicógeno fosforilasa, un inhibidor de AGE, un sintetizador de insulina, un péptido-1 semejante al glucagón (GLP-1) o mimético del mismo, insulina y/o meglitinida.

Se reivindica la combinación que se caracteriza porque el agente antidiabético es metformina, gliburida, glimepirida, glipirida, glipizida, clorpropamida, gliclazida, acarbosa, miglitol, pioglitazona, troglitazona, rosiglitazona, insulina, G1-262570, isaglitazona, JTT-501, NN-2344, L895845, YM-440, R-119702, AJ9677, repaglinida, nateglinida, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, Exendin-4, LY307161, NN2211, y/o LY315902.

• **Reivindicaciones 17 a 22:**

Se reivindica una combinación caracterizada porque el compuesto está presente en una relación o proporción en peso al agente antidiabético dentro del rango desde aproximadamente 0.01 a en forma aproximada 100:1.

Además se reivindica la combinación caracterizada porque el agente antiobesidad es un agonista adrenérgico beta-3, un inhibidor de lipasa, un inhibidor de reabsorción de serotonina (y dopamina), un compuesto beta receptor de la tiroide, un agente anoréctico, y/o superregulador de la oxidación del ácido graso.

En particular se reivindica la combinación en la que el agente antiobesidad es orlistat, AT-962, AJ9677, L750355, CP331648, sibutramina, topramato, oxacina, dexanfetamina, fenentermina, fenilpropanolamina, famoxina y/o mazindol.

En particular se reivindica la combinación en la que el agente modulador de lípidos es un inhibidor de MTP, un inhibidor de reductasa de HMG CoA, un inhibidor de escualeno sintetasa, un derivado del ácido fibrótico, un superregulador de la actividad del receptor de LDL, un inhibidor de lipoxigenasa, un inhibidor de ACAT, un inhibidor de proteína de transferencia de colesterol éster, o un inhibidor de liasa de citrato de ATP, y dentro de este grupo se selecciona: pravastatina, lovastatina, simvastatina, atorvastatina, cerivastatina, fluvastatina, nisvastatina, visastatina, fenofibrato, gemfibrozil, clofibrato, implitapida, CP-529,414, avasimiba, TS-962, MD-700, y/o LY295427.

Y se reivindica la combinación caracterizada porque el inhibidor DP4 se encuentra presente en una relación o proporción en peso al agente modulador de lípidos dentro del rango desde aproximadamente 0.01 a en forma aproximada 100:1.

- **Reivindicación 23:**

Se reivindica una combinación farmacéutica que se caracteriza porque comprende un compuesto inhibidor de DP4 y un agente para el tratamiento de la infertilidad, un agente para tratar el síndrome de ovario poliquístico, un agente para tratar un desorden de crecimiento y/o debilidad, un agente antiartritis, un agente para prevenir la inhibición del rechazo al aloinjerto en transplante, un agente para tratar la enfermedad autoinmune, un agente antitSIDA, un agente para tratar la enfermedad/síndrome inflamatorio del intestino, un agente para tratar anorexia nerviosa, un agente antiosteoporosis y/o un agente antiobesidad.

Una vez catalogada la invención ésta se clasificó en la sección: A 61 K ³¹/40 de la Clasificación Internacional de Patentes.

3. CLARIDAD DE LA SOLICITUD:

El artículo 30 de la Decisión 486 contempla que "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción".

En atención a las modificaciones efectuadas por el interesado, esta Dependencia encuentra que continúan existiendo los defectos de precisión, claridad y concisión de la materia reivindicada en el siguiente orden:

- La estructura química de fórmula (I) presenta complejidad química menor que la de los compuestos que resultan de efectuar las correspondientes sustituciones químicas sobre los radicales R₁, R₂, R₃, R₄, -(CR₅R₆)_m.

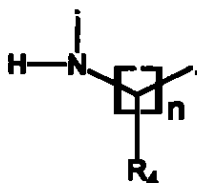
No basta con señalar que las sustituciones de índole heterocíclica (solas o como parte de un grupo) hacen referencia a un anillo aromático de 5, 6 ó 7 miembros que presentan 1 ó 2 heteroátomos seleccionados entre nitrógeno, oxígeno y azufre. O que el término cicloheteroarilo, solo o como parte de un grupo, se refiere a un anillo de 5, 6 ó 7 miembros que tiene de 1 a 2 heteroátomos seleccionados entre nitrógeno, oxígeno y azufre. Porque se están incluyendo una gran variedad de núcleos que no precisan un verdadero alcance de la invención y que no encuentran un sustento real en el aparte descriptivo de la solicitud – ver folios 78 a 211 -.

De esta manera cuando se estudian los diferentes radicales de índole heterocíclica que reivindica la solicitud se evidencia que se incluyen un número amplísimo de posibilidades que, como se señaló, no encuentran sustento en el aparte descriptivo de la solicitud y para demostrar este hecho se remite al interesado a los ejemplos que ilustran la invención, los cuales no comprenden la gran variedad de sistemas heterocíclicos que sustituyen las cinco fórmulas estructurales y que se definen en el alcance de la cláusula (1) para los radicales R_1 , R_2 , R_3 , R_4 , $-(CR_5R_6)_m$ y que incluyen:

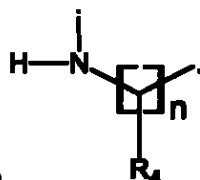
1. **Análogos heterocíclicos del ciclopentadieno con un heteroátomo:** pirrol, furano, tiofeno.
2. **Análogos heterocíclicos del benceno con un heteroátomo:** piridina, sales de pirilio y piranos, pironas.
3. **Compuestos con dos heteroátomos en un anillo de cinco miembros:** pirazol, imidazol, isoxazol, oxazol, isotiazol y tiazol.
4. **Compuestos con dos heteroátomos en su anillo de seis miembros:** piridazina, pirimidina, pirazina, oxazina, tiamina, dioxanos y análogos azufrados.
5. **Compuestos con más de dos heteroátomos:** triazinas, pteridinas, entre otros...
6. **Compuestos heterocíclicos con anillos de siete miembros:** azepina, diazepinas, oxepina, tiepina, entre otros...

En consecuencia, nuevamente se requiere al interesado para que defina con precisión el verdadero alcance de su invención, señalando la frontera existente entre la materia inventada y el estado de la técnica y excluyendo del capítulo reivindicatorio aquella que constituye mera especulación.

- De igual forma, el interesado hace caso omiso a la objeción de claridad en el sentido de que la estructura de fórmula (I) no es la más representativa de la invención (característica esencial) para que defina las demás relacionadas en el aparte reivindicatorio – valga mencionar: fórmulas generales de las cláusulas 2, 3, 4, 5, 7, 11 y 12 – porque si se tiene en cuenta que para ciertos



casos: " R_1 y R_3 conjuntamente con elementos que contienen un total de 2 a 4 heteroátomos seleccionados entre N, O, S, SO, o SO_2 ", o como más adelante se establece que " R_1 y R_3



conjuntamente con R_4 forman un anillo cicloheteroalquilo de 4 a 8 elementos en donde el anillo cicloheteroalquilo tiene un anillo arilo opcional fusionado a éste o un anillo cicloquilo de 3 a 7 elementos, opcional, fusionado a éste", resulta evidente que de las sustituciones en comento se generan: a) compuestos química y estructuralmente más complejos que los definidos bajo el amparo de la característica esencial de fórmula (I) y sus "dependientes" (fórmulas generales de las cláusulas 2, 3, 4, 5, 7, 11 y 12) y b) compuestos que no se encuentran sustentados en la descripción – ver folios 78 a 211 -.

Para corroborar que la complejidad química de los compuestos resultantes de las sustituciones en comento (formación de un anillo heterocíclico entre los radicales R_1 y R_3 de la estructura central y el átomo de carbono 3 de la cadena α -ceto-alquílica) es mayor que la de los compuestos que se derivan de las estructuras generales definidas, se remite al interesado a la clasificación señalada en el aparte anterior para anillos heterocíclicos de 5 a 7 miembros y a la descrita a continuación para ciclos heteroaromáticos – anillos de 3 a 7 elementos fusionados con arilo -:

Sistemas de anillos fusionados que incluyen a los anillos de pirrol, furan y tiofeno: Indol, isoindoles, indolizina y ciclazina, benzofurano, isobenzofurano, benzo[b]tiofeno.

Análogos heterocíclicos del naftaleno con un heteroátomo: quinolina, isoquinolina, quinolizina, acridina y fenantridina, sales de benzopirillo y benzopiranos.

Compuestos con más de dos heteroátomos: purinas, pteridinas, benzotriazoles.

En consecuencia, no cabe duda de la falta de especialidad del lenguaje químico empleado y de la falta de concisión y precisión para definir la materia, por ello se recomienda al interesado verificar el alcance de la invención a la luz de la materia descrita y sustentada en el aparte descriptivo.

- Nuevamente, esta Dependencia señala la falta de representatividad de la característica esencial (fórmula I) para definir con precisión el alcance de la invención.

Si bien es cierto la fórmula (I) reivindicada de manera independiente, comprende una estructura química heterocíclica de seis miembros fusionada en [c] con ciclopropano, a lo largo de las cláusulas dependientes 2 a 5 y 11 se reclama protección para otra clase de núcleo fusionado, que está conformado por un anillo de pirrol fusionado en [b] con ciclopropano – ver cláusula 2 –, un anillo de pirrol fusionado en [c] con ciclopropano – ver cláusula 3 –, un anillo de pirrol sustituido en posición 5 por un grupo clano y fusionado en [b] o en [c] con ciclopropano – ver cláusula 11 -.

En consecuencia, siendo que se afirma en el capítulo reivindicatorio que la estructura de fórmula (I) caracteriza todos los compuestos de la invención solo por la forma como se reivindican los compuestos (de manera dependiente), esta Superintendencia encuentra que la característica esencial no comprende todos los compuestos de la invención y resulta insuficiente para cobijar aquellos núcleos que reclaman anillos heterocíclicos de 5 miembros fusionados con ciclopropano.

Este hecho se vuelve más relevante cuando se aprecia en las cláusulas 8 y 9 los diferentes núcleos que se reclaman bajo la estructura (I), siendo que se trata de anillo de pirrol fusionado en [b] con ciclopropano, demostrando que la fórmula (I): anillo de seis miembros fusionado en [c] con ciclopropano, no es idónea para tal efecto. Y adicionalmente si se tiene en cuenta que los grupos formados entre los radicales R₁ y R₃ son de características estructurales y químicas diversas, se hace palpable que la estructura principal o característica esencial de fórmula (I) no presenta la complejidad requerida para definir las diferentes modalidades de la invención.

- De otro lado y como se había señalado en la oportunidad jurídica, una combinación terapéutica se define en atención a la mezcla farmacológica que presenta un efecto sorprendente frente a la administración individual de los compuestos activos, como esta situación no se aprecia en ningún aparte del capítulo descriptivo, cabría preguntarse nuevamente ¿dónde se encuentra el sustento técnico para que se reivindiquen las mezclas terapéuticas de las cláusulas 13 a 23?

4. EVALUACIÓN DE LA UNIDAD DE INVENCION:

El artículo 25 de la decisión 486 establece que *"La solicitud de patente sólo podrá comprender una invención o grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo"*

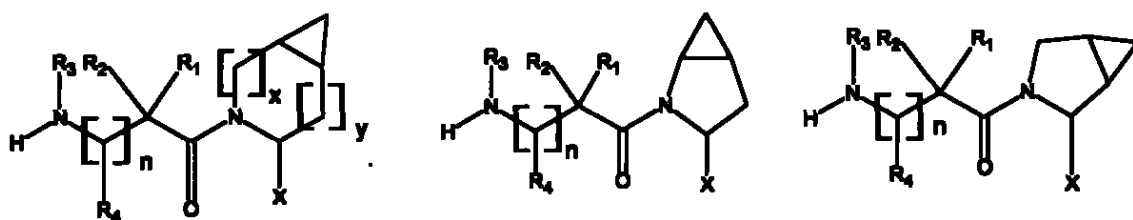
- En atención a las objeciones de claridad relativas a la falta de idoneidad de la fórmula estructural (I) para definir todas las modalidades posibles de la invención, se suma el hecho de la diversidad de núcleos estructurales que constituyen en sí mismos y de manera individual una invención y por ende no pueden cobijarse al amparo de la fórmula estructural (I).

Como ya se había señalado en el aparte de claridad, al amparo de una estructura cíclica de seis miembros condensada con un ciclo de tres miembros no pueden cobijarse compuestos que presentan estructuras diversas y que atienden a fórmulas estructurales que comprenden ciclos de cinco miembros condensados con ciclos de tres miembros.

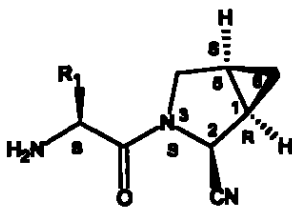
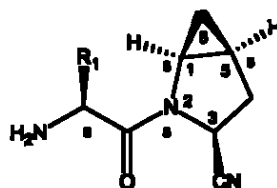
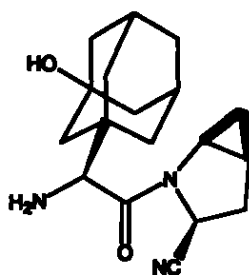
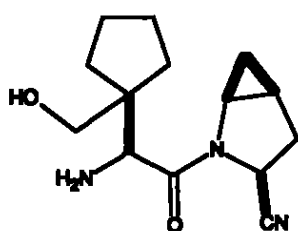
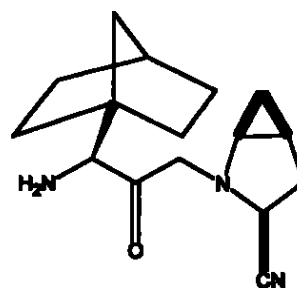
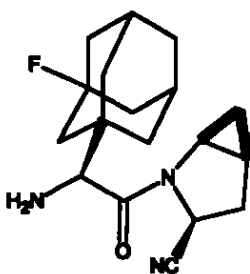
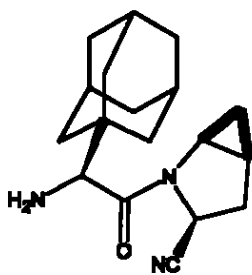
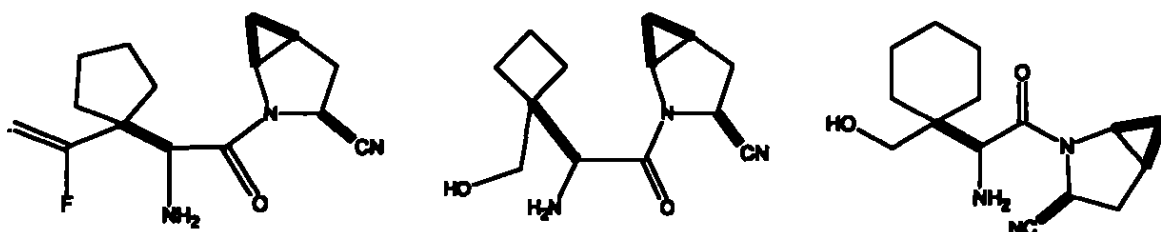
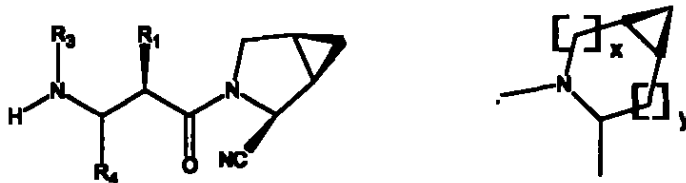
Y por esta razón se reitera lo siguiente: si bien es cierto que la fórmula (I) reivindicada de manera independiente, comprende una estructura química heterocíclica de seis miembros fusionada en [c] con ciclopropano, a lo largo de las cláusulas dependientes 2 a 5 y 11 se reclama protección para otra clase de núcleo fusionado, que está conformado por un anillo de pirrol fusionado en [b] con ciclopropano – ver cláusula 2 –, un anillo de pirrol fusionado en [c] con ciclopropano – ver cláusula 3 –, un anillo de pirrol sustituido en posición 5 por un grupo clavo y fusionado en [b] o en [c] con ciclopropano – ver cláusula 11 –.

Para ilustrar este hecho se compara la fórmula (I) con los diversos núcleos estructurales reclamados a lo largo de las cláusulas 2 a 5 y 11, haciendo evidente la falta de un único concepto inventivo que pueda extrapolarse a todas las modalidades de la invención.

Como ya se había señalado no basta con precisar en la estructura que el núcleo heterocíclico puede convertirse en un ciclo de cinco miembros cuando varía el número de átomos de carbono en el anillo ya que dichas modificaciones generan fórmulas químicas estructuralmente diferentes a la inicialmente definida en la cláusula 1.



Fórmula (I)



De esta forma, cada vez que se modifique el número de átomos en el anillo, o se varíe la posición de fusión entre el heterociclo y el anillo de ciclopropano, o se forme un anillo diferente entre R_1 y R_3 se tendrá un nuevo grupo de compuestos los cuales constituyen en sí mismos una invención, individual e independiente (con un concepto químico definido) química y estructuralmente diferente de otras.

Es importante señalar que no obstante la falta de claridad entorno a la forma como se precisa el alcance del núcleo, es posible identificar tres grupos principales de

Invencciones cuando se ha efectuado la correspondiente revisión del estado de la técnica, es decir tres conceptos Inventivos, un primer grupo relacionado con anillos de cinco miembros condensados en [b] con un anillo de ciclopropano, el segundo grupo correspondiente a los anillos de cinco miembros condensados en [c] con un anillo de ciclopropano y un tercer grupo de anillos de seis miembros fusionados con un anillo de ciclopropano.

- Con respecto a las combinaciones farmacológicas, se objeta la falta de un único concepto Inventivo entorno a las mezclas y asociaciones terapéuticas, por cuanto si no existe unidad de invención frente a los compuestos inhibidores de DP4, tampoco la hay frente a las diferentes mezclas que se generen de estos con compuestos antidiabéticos.

5. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la solicitud en estudio - 10.03.2000-, relacionados con la materia técnica reivindicada:

Nº	Documento	Título	Fecha de Publicación
D1	WO9947545	"Inhibitors of caspases"	23/09/1999
D2	US6011155	"N-(substituted glyceryl)-2-cyanopirrolidines, pharmaceutical compositions containing them and their use in inhibiting dipeptidyl peptidase IV"	04/01/2000
D3	DE3324263	"Derivate der 2-azabicyclo[3.1.0]hexan-3-carbonsäure, Verfahren zu ihrer herstellung, diese enthaltende Mittel und deren verwendung sowie 2-azabicyclo[3.1.0]hexan-derivate als zwischenprodukte und verfahren zu deren herstellung"	17/01/1985
D4	EP0007652	"Derivatives of azabicyclo(3.1.0)hexane and a process for their preparation"	06/02/1980

6. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

6.1 Evaluación del NIVEL INVENTIVO:

El artículo 18 de la decisión 486 dispone *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la Materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese*

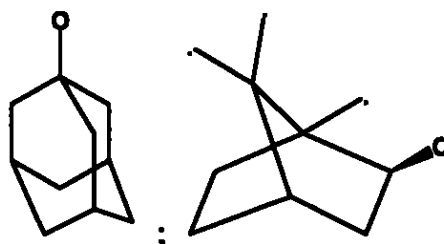
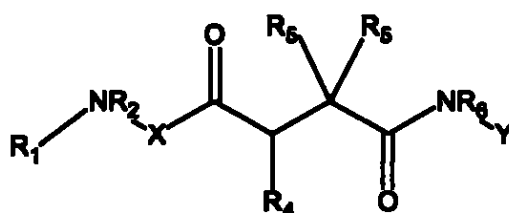
derivado de manera evidente del estado de la técnica"

Una vez efectuada la búsqueda del estado de la técnica fue posible precisar que existen documentos directamente asociados a la materia reclamada que determinan el hecho no sólo de la afectación de nivel inventivo sino de la falta de unidad de invención.

En el aparte "unidad de invención" ya se había señalado que existen tres grupos de invenciones diferenciadas, las que fue posible identificar con la búsqueda del estado del arte más cercano.

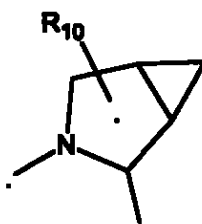
Dentro de los documentos técnicos relevantes se encuentran los siguientes:

- **Publicación D1:** Hace referencia a compuestos que presentan la estructura básica:



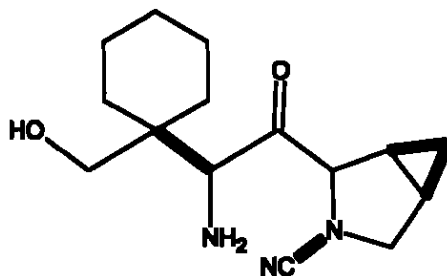
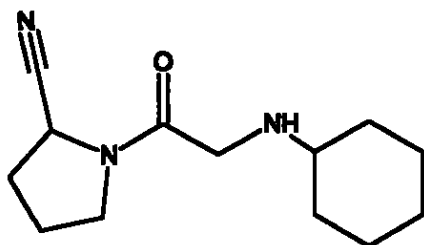
Donde Y puede ser:

Y R₄ y R₅ junto con el átomo al que se enlazan en la cadena pueden formar un sistema cíclico de la siguiente clase:

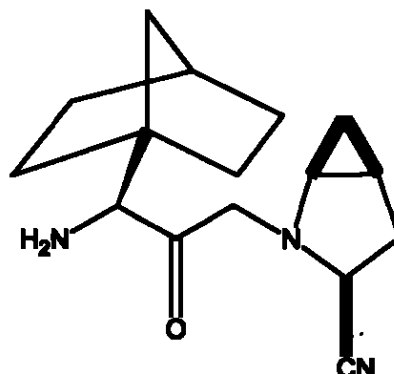
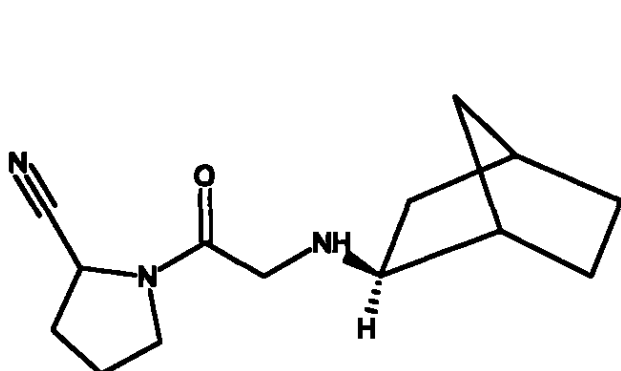


En consecuencia la anterioridad en comento afecta el grupo de invenciones correspondiente a anillos de cinco miembros condensados en [c] con un anillo de ciclopropano, en particular aquellos ejemplos señalados en la cláusula (8) que hacen referencia a sistemas bicíclicos.

- **Publicación D2:** Señala dentro de sus ejemplos, compuestos estructuralmente relacionados con los reivindicados por la solicitud en estudio, tal es el caso del ejemplo 28 que al compararse con uno de los compuestos reclamados por la solicitud en la cláusula (8) evidencia ciertas analogías estructurales:

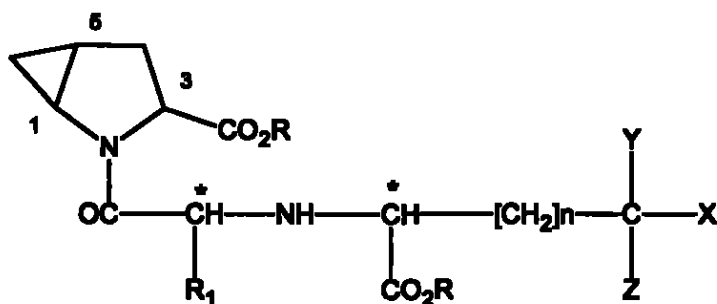


O en el caso del ejemplo 29 cuya estructura también es muy similar a una de las reivindicadas por la solicitud en la cláusula (8):



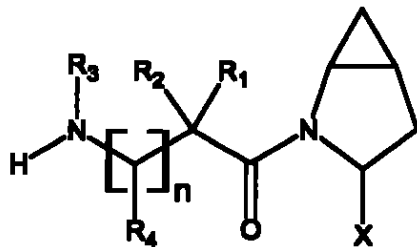
De esta manera si bien la conformación estructural de los compuestos publicados en la anterioridad no es idéntica a la de los compuestos reivindicados se encuentran grandes similitudes y analogías químicas y funcionales que configuran la afectación de nivel inventivo.

- Publicación D3: Revela compuestos que presentan la siguiente estructura química:

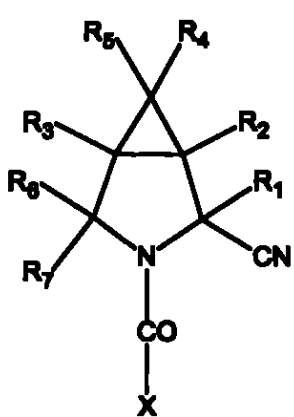


Para los cuales X puede constituir un grupo arilo o indolilo, entre otros.

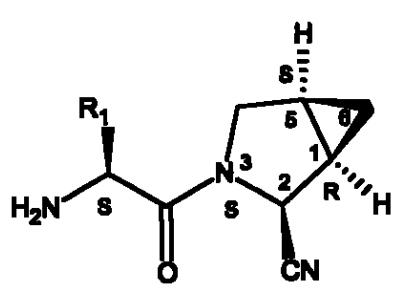
Si esta estructura se compara con los anillos de cinco miembros condensados en [b] con un anillo de ciclopropano reivindicados, tal es el caso de la fórmula de la cláusula (2):



- **Publicación D4:** Este documento enseña compuestos que presentan la fórmula estructural:



Para los cuales X representa una cadena alquilica de 5 átomos de carbono, tal como lo muestra la fórmula (1R,2S,3(2S),5S) de la cláusula (11):



En consecuencia, por permitir la derivación evidente de la materia reivindicada, los documentos en comento (D1, D2, D3 y D4) afectan la altura inventiva de la solicitud además que demuestran la existencia de tres conceptos inventivos diferentes.

En atención a ello los requisitos de patentabilidad se encuentran afectados en el siguiente orden:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO9947545	1 a 23	Nivel Inventivo
D2	US6011155	1 a 23	Nivel Inventivo
D3	DE3324263	1 a 23	Nivel Inventivo
D4	EP0007652	1 a 23	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 sesenta días contados a partir de la fecha de la 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 5 del título primero de la Circular Única N° 10 de 2001.


Álix Carmonza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

15 MAR 2007

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO Número 0398	EXAMINADOR TÉCNICO Código 202044
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EXAMEN TÉCNICO DE F NDO			
Nº Radicación	01-18857	Fecha de presentación	08/03/2001
Nº Prioridad	US60/188.555	Fecha de Prioridad	10/03/2000

Palabras clave	Pirrolidinas fusionadas con ciclopropilo
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CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
A61K31/435

DOCUMENTOS CORRESPONDIENTES EN OTROS PAISES		
Patente Original	EP 1559710	WO 0168603

BASES DE DATOS CONSULTADAS	
ESPACENET	EPOLINE

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Oficina	Fecha	Reivindicaciones
EPO		

ANTERIORIDADES ENCONTRADAS		
Documento	Relevancia	Relvindicaciones afectadas

LITERATURA NO PATENTES		
Documento no Patentes	Relevancia	Relv. Afectadas

Observaciones	Unidad de Invención
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Fecha del examen	27/10/2006