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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-038081- -00003-0000

Fecha: 2008-06-09 16:21:20 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 538 PETICION Folios: 2

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

Trámite : 011

Evento : 379

Actuación : 538

Referencia : Expediente No. 06.038.081
Asunto : Solicitud de patente para: **NUEVOS DERIVADOS
DE CETO-OXADIAZOL COMO INHIBIDORES DE LAS
CATEPSINAS**
Solicitante : **AVENTIS PHARMACEUTICALS INC.**
Publicada en : Gaceta No. 583 del 18 de diciembre de 2007
Fecha solicitud: 21 de abril de 2006

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo II del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$210.000.00, que corresponde a la tasa fijada según lo dispuesto en la Resolución No. 44372 del 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,

EMILIO FERRERO

T.P.A. No. 31.929

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166/ No. M-2008-127729\JGG

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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FECHA : MAYO 27 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	766113	27/05/2008	47,547,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	210,000.00
	TOTAL :	\$ 210,000.00

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Boleto 15896 - 841005-6

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-38081

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **14 DE MARZO DE 2008**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

PCT

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International Bureau
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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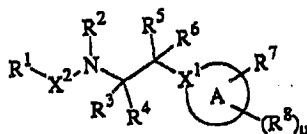
(74) Agents: MONTGOMERY, Wayne, W. et al.; Axys Pharmaceuticals, Inc., 180 Kimball Way, South San Francisco, CA 94080 (US).

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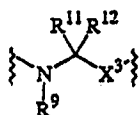
Published

With international search report.

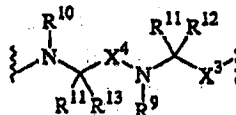
(54) Title: AMINE DERIVATIVES AS PROTEASE INHIBITORS.



(1)



(a)



(b)

(57) Abstract

The present invention relates to novel alkanoyl-substituted heterocyclic derivatives which are cysteine protease inhibitors; the pharmaceutically acceptable salts and *N*-oxides thereof; their uses as therapeutic agents and the methods of their making; according to Formula (I) in which: A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains 5 to 7 ring member atoms, X¹ is a ring member carbon atom and each ring member atom other than X¹ is a carbon atom or a heteroatom, with the proviso that (i) at least one ring member atom is a heteroatom and (ii) when A is a heteromonocyclic radical containing 5 ring member atoms, no more than two of the ring member atoms comprising A are heteroatoms; n is 0, 1, 2 or 3; X¹ is =C- or -CH-; X² is a bond or a divalent group of Formula (a) or (b); R¹ - R⁸ = as in the application.

AMINE DERIVATIVES AS PROTEASE INHIBITORS

THE INVENTION

This application relates to compounds and compositions for treating diseases associated
5 with cysteine protease activity, particularly diseases associated with activity of cathepsins B, K,
L or S.

DESCRIPTION OF THE FIELD

Cysteine proteases represent a class of peptidases characterized by the presence of a
cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the
10 normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g.
as a result of increased expression or enhanced activation, however, may have pathological
consequences. In this regard, certain cysteine proteases are associated with a number of
disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion,
glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others. For
15 example, increased cathepsin B levels and redistribution of the enzyme are found in tumors;
thus, suggesting a role for the enzyme in tumor invasion and metastasis. In addition, aberrant
cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteo arthritis,
pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint
disorders.

20 The prominent expression of cathepsin K in osteoclasts and osteoclast-related
multinucleated cells and its high collagenolytic activity suggest that the enzyme is involved in
osteoclast-mediated bone resorption and, hence, in bone abnormalities such as occurs in
osteoporosis. In addition, cathepsin K expression in the lung and its elastinolytic activity suggest
that the enzyme plays a role in pulmonary disorders as well.

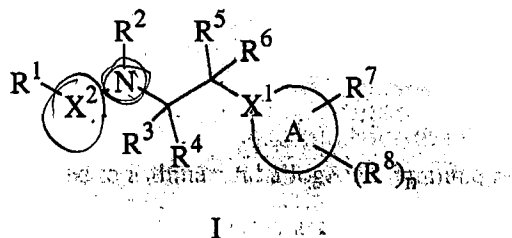
25 Cathepsin L is implicated in normal lysosomal proteolysis as well as several disease
states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in
Alzheimer's disease and certain autoimmune disorders, including, but not limited to juvenile
onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis,
systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic

disorders, including, but not limited to asthma, and allogeneic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts.

In view of the number of diseases wherein it is recognized that an increase in cysteine protease activity contributes to the pathology and/or symptomatology of the disease, molecules which are shown to inhibit the activity of this class of enzymes, in particular molecules which are inhibitors of cathepsins B, K, L and/or S, will be useful as therapeutic agents.

SUMMARY OF THE INVENTION

In one particular embodiment, the present invention relates to protease inhibitors of Formula I:



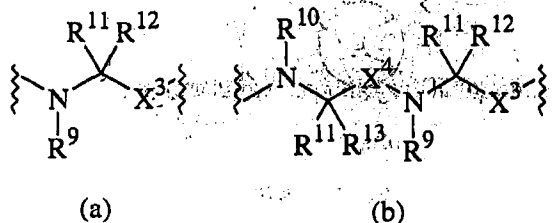
in which:

A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains 5 to 7 ring member atoms, X¹ is a ring member carbon atom and each ring member atom other than X¹ is a carbon atom or a heteroatom, with the proviso that (i) at least one ring member atom is a heteroatom and (ii) when A is a heteromonocyclic radical containing 5 ring member atoms, no more than two of the ring member atoms comprising A are heteroatoms;

n is 0, 1, 2 or 3;

X¹ is =C- or -CH-;

X² is a bond or a divalent group of Formula (a) or (b):



wherein:

X^3 and X^4 independently are $-C(O)-$ or $-CH_2S(O)_2-$
 R^9 and R^{10} independently are hydrogen, (C_{1-6}) alkyl or as defined below;
 R^{11} at each occurrence independently is hydrogen or (C_{1-6}) alkyl;
 R^{12} and R^{13} independently are (i) (C_{1-6}) alkyl optionally substituted with cyano, halo, nitro, $-NR^{14}R^{14}$, $-NR^{14}C(O)OR^{14}$, $-NR^{14}C(O)NR^{14}R^{14}$, $-NR^{14}C(NR^{14})NR^{14}R^{14}$,
 $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-S(O)_2NR^{14}R^{14}$, $-P(O)(OR^{14})OR^{14}$,
 $-OP(O)(OR^{14})OR^{14}$, $-NR^{14}C(O)R^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-OR^{16}$, $-SR^{16}$,
 $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-NR^{16}R^{17}$, $-NR^{17}C(O)R^{16}$,
 $-NR^{17}C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-S(O)_2NR^{16}R^{17}$, $-NR^{17}C(O)NR^{16}R^{17}$ or
 $-NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein R^{14} at each occurrence independently is hydrogen,
 (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl, R^{15} is (C_{1-6}) alkyl or halo-substituted
 (C_{1-3}) alkyl, halo, (C_{1-6}) alkyl or R^{16} is (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl,
hetero (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl, (C_{6-12}) aryl, (C_{0-6}) alkyl, hetero (C_{5-12}) aryl, (C_{0-6}) alkyl,
 (C_{9-12}) polycycloaryl, (C_{0-6}) alkyl or hetero (C_{8-12}) polycycloaryl, (C_{0-6}) alkyl and R^{17} is
hydrogen or (C_{1-6}) alkyl, and wherein within R^{16} said cycloalkyl, heterocycloalkyl, aryl,
heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$,
 $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$,
 $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or
 $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5 is a bond or (C_{1-6}) alkylene, R^{18} is hydrogen or
 (C_{1-6}) alkyl and R^{19} is (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl,
 (C_{6-12}) aryl, (C_{0-6}) alkyl, hetero (C_{5-12}) aryl, (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl, (C_{0-6}) alkyl or
hetero (C_{8-12}) polycycloaryl, (C_{0-6}) alkyl, or (ii) a group selected from
 (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl, hetero (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl, (C_{6-12}) aryl, (C_{0-6}) alkyl,
hetero (C_{5-12}) aryl, (C_{0-6}) alkyl, (C_{9-12}) polycycloaryl, (C_{0-6}) alkyl and
hetero (C_{8-12}) polycycloaryl, (C_{0-6}) alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$,
 $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$,
 $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or
 $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5 , R^{18} and R^{19} are as defined above; wherein
within R^{12} and/or R^{13} any alicyclic or aromatic ring system present may be substituted

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further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴,
 5 -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; or

R¹² together with R⁹ and/or R¹³ together with R¹⁰ form trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted
 10 (C₁₋₄)alkyl, nitro, oxo, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; and

15 ~~R¹~~ is -X⁶X⁷R²⁰, wherein X⁶ is -C(O)-, -C(O)C(O)- or -S(O)₂-, X⁷ is a bond, -O- or -NR²¹-, wherein R²¹ is hydrogen or (C₁₋₆)alkyl, and R²⁰ is (i) (C₁₋₆)alkyl optionally substituted by cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵, -C(O)R¹⁵, -OR²², -SR²², -S(O)R²²,
 20 -S(O)₂R²², -C(O)R²², -C(O)OR²², -C(O)NR²²R²³, -NR²²R²³, -NR²³C(O)R²², -NR²³C(O)OR²², -NR²³C(O)NR²²R²³ or -NR²³C(NR²³)NR²²R²³, wherein R¹⁴ and R¹⁵ are as defined above, R²² is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²³ at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or
 25 (ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl or
 (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by -R²⁴, -X⁵OR²⁴, -X⁵SR²⁴, -X⁵S(O)R²⁴, -X⁵S(O)₂R²⁴, -X⁵C(O)R²⁴, -X⁵C(O)OR²⁴,
 30 -X⁵C(O)NR²⁴R²⁵, -X⁵NR²⁴R²⁵, -X⁵NR²⁵C(O)R²⁴, -X⁵NR²⁵C(O)OR²⁴, -X⁵NR²⁵C(O)NR²⁴R²⁵ or -X⁵NR²⁵C(NR²⁵)NR²⁴R²⁵, wherein X⁵ is as defined above, R²⁴ is (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²⁵ at each

occurrence independently is hydrogen or (C₁₋₆)alkyl; wherein within R¹ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴,
 5 -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; or when X² is a divalent group of formula (a) or (b) then R¹ may also represent hydrogen, carboxy, oxalo or carbamoyl;

R² is hydrogen or (C₁₋₆)alkyl;

10 R³ is (i) (C₁₋₆)alkyl optionally substituted with cyano, halo, nitro, -SR²⁶, -C(O)OR²⁶, -C(O)NR²⁶R²⁶, -P(O)(OR²⁶)OR²⁶, -OP(O)(OR²⁶)OR²⁶, -S(O)R²⁷, -S(O)₂R²⁷ or -C(O)R²⁷, wherein R²⁶ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R²⁷ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, or (ii) (C₃₋₆)cycloalkyl(C₂₋₃)alkyl, hetero(C₃₋₆)cycloalkyl(C₂₋₃)alkyl, (C₆₋₁₂)aryl(C₂₋₃)alkyl or hetero(C₃₋₆)aryl(C₂₋₃)alkyl, wherein
 15 said cycloalkyl, heterocycloalkyl, aryl or heteroaryl optionally is substituted further with 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein
 20 X⁵, R¹⁴ and R¹⁵ are as defined above, provided that when R³ is unsubstituted (C₁₋₃)alkyl and R⁴ is hydrogen or unsubstituted (C₁₋₃)alkyl, then X² may not represent (i) a bond when R¹ is -C(O)R²⁰, -C(O)₂R²⁰ or -S(O)₂R²⁰ in which R²⁰ is (C₁₋₆)alkyl, phenyl(C₁₋₄)alkyl, phenyl, (C₃₋₇)cycloalkyl, camphan-10-yl, naphth-1-yl, naphth-2-yl, phenyl substituted by one or more of (C₁₋₄)alkyl, perfluoro(C₁₋₄)alkyl, (C₁₋₄)alkoxy, hydroxy, halo, amido, nitro, amino,
 25 (C₁₋₄)alkylamino, (C₁₋₄)dialkylamino, carboxy or (C₁₋₄)alkoxycarbonyl, or naphth-1-yl or naphth-2-yl substituted by one or more of (C₁₋₄)alkyl, perfluoro(C₁₋₄)alkyl, (C₁₋₄)alkoxy, hydroxy, halo, amido, nitro, amino, carboxy or (C₁₋₄)alkoxycarbonyl or (ii) a divalent group of formula (a) or (b) in which the moiety R¹² is methyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, 1-methylpropyl, benzyl, naphth-1-ylmethyl, naphth-2-ylmethyl, thien-2-ylmethyl, thien-3-ylmethyl, or wherein R⁹
 30 and R¹² form ethylene, trimethylene, hydroxy-substituted trimethylene, tetramethylene or phenylene-1,2-dimethylene; or

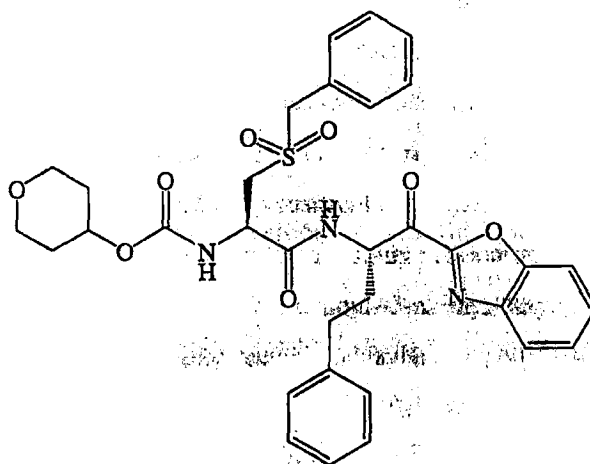
R³ and R⁴ taken together with the carbon atom to which both R³ and R⁴ are attached

- form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above;
- R⁴ is hydrogen, (C₁₋₆)alkyl or as defined above;
- R⁵ is hydrogen and R⁶ is hydroxy or R⁵ and R⁶ together form oxo;
- 10 R⁷ is a group selected from cyano, halo, nitro, -R²⁹, -X⁵NR²⁹R³⁰, -X⁵NR³⁰C(O)OR²⁹, -X⁵NR³⁰C(O)NR²⁹R³⁰, -X⁵NR³⁰C(NR³⁰)NR²⁹R³⁰, -X⁵OR²⁹, -X⁵SR²⁹, -X⁵C(O)OR²⁹, -X⁵C(O)NR²⁹R³⁰, -X⁵S(O)₂NR²⁹R³⁰, -X⁵P(O)(OR³⁰)OR²⁹, -X⁵OP(O)(OR²⁹)OR²⁹, -X⁵NR³⁰C(O)R³¹, -X⁵S(O)R³¹, -X⁵S(O)₂R³¹ and -X⁵C(O)R³¹, wherein X⁵ is as defined above, R²⁹ is hydrogen or -R³¹, R³⁰ at each occurrence is hydrogen or (C₁₋₆)alkyl and R³¹ is (C₁₋₆)alkyl,
- 15 (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₃₋₁₂)aryl(C₀₋₆)alkyl, wherein within R⁷ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; and
- 20 R⁸ at each occurrence independently is selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof; but
- 30 excluding compounds selected from the group consisting of

((S)-1-{(S)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-3-methyl-butylcarbamoyl]-3-methyl-butylcarbamoyl}-3-methyl-butyl)-carbamamic acid benzyl ester, [1-[1-(1H-imidazol-2-yl-

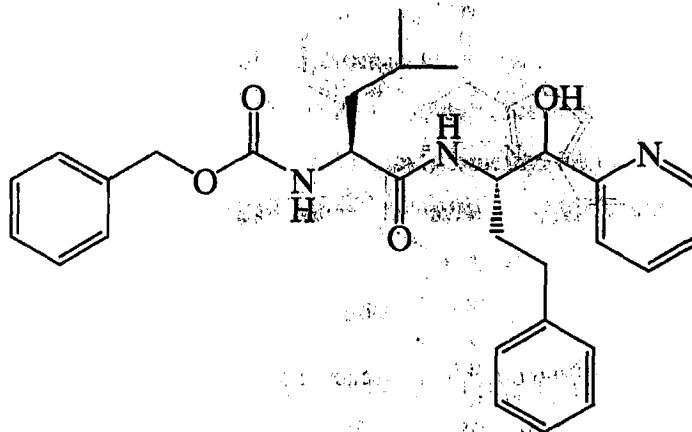
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phenylmethanesulfonyl)-ethyl]-amide; and a compound of Formula I in which A is benzoxazol-2-yl; X² is a group of Formula (a), wherein R⁹ is hydrogen and R¹² is benzylsulfonylmethyl; R¹ is tetrahydropyran-4-yloxycarbonyl; R² is hydrogen; R³ is phenethyl; R⁴ is hydrogen; and R⁵ and R⁶ together form oxo; that is, a compound having the following structure:



is named tetrahydropyran-4-yl 1R-(1S-benzoxazol-2-ylcarbonyl-3-phenylpropylcarbamoyl)-2-benzylsulfonylethylcarbamate or {(R)-1-[(S)-1-(1-benzoxazol-2-yl-methanoyl)-3-phenylpropylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tetrahydro-pyran-4-yl ester.

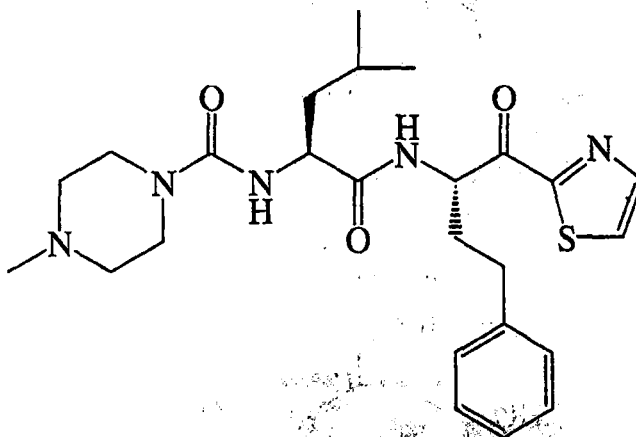
A compound of Formula I in which A is pyrid-2-yl; X² is a group of Formula (a), wherein R⁹ is hydrogen and R¹¹ is 2-methylpropyl; R¹ is benzyloxycarbonyl; R², R⁴ and R⁵ each are hydrogen; R³ is phenethyl; and R⁶ is hydroxy; that is, a compound having the following structure:



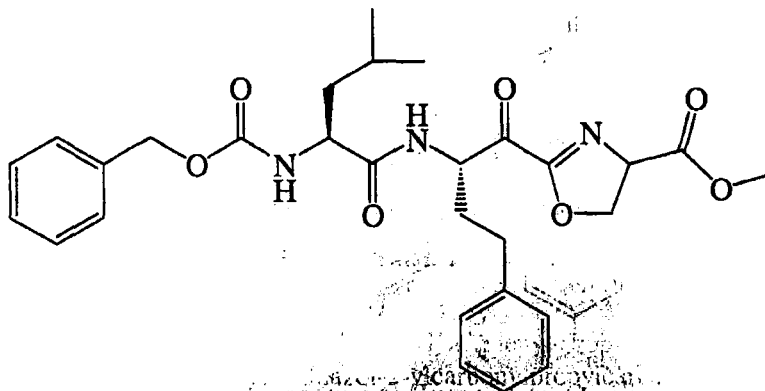
is named benzyl 1S-(1S-pyrid-2-ylcarbonyl-3-phenylpropylcarbamoyl)-3-methylbutylcarbamate

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- or {(S)-1-[(S)-1-(1-hydroxy-1-pyridin-2-yl-methyl)-3-phenyl-propylcarbamoyl]-3-methyl-butyl}-carbamic acid benzyl ester; and a compound of Formula I in which A is thiazol-2-yl; X² is a group of Formula (a), wherein R⁹ is hydrogen and R¹¹ is 2-methylpropyl; R¹ is 4-methylpiperazin-1-ylcarbonyl; R² and R⁴ each are hydrogen; R³ is phenethyl; and R⁵ and R⁶ together form oxo; that is, a compound having the following structure:



- is named *N*-[3-methyl-1*S*-(3-phenyl-1-thiazol-2-ylcarbonylpropylcarbamoyl)butyl]-4-methylpiperazine-1-carboxamide or 4-methyl-piperazine-1-carboxylic acid or {(S)-3-methyl-1-[(S)-3-phenyl-1-(1-thiazol-2-yl-methanoyl)-propylcarbamoyl]-butyl}-amide; and a compound of Formula I in which A is 4,5-tetrahydro-4-methoxycarbonyloxazol-2-yl; X² is a group of Formula (a), wherein R⁹ is hydrogen and R¹¹ is 2-methylpropyl; R¹ is benzyloxycarbonyl; R² and R⁴ each are hydrogen; R³ is phenethyl; and R⁵ and R⁶ together form oxo; that is, a compound having the following structure:



- is named methyl 2*S*-(2*S*-benzyloxycarbonylamino-4-methylvaleryl-amino)-4-phenylbutyryl-4,5-dihydrooxazole-4-carboxylate or 2-[(S)-2-[(S)-2-benzyloxycarbonylamino-4-methyl-

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pentanoylamino)-4-phenyl-butanoyl]-4,5-dihydro-oxazole-4-carboxylic acid methyl ester.

Certain compounds of Formula I exist in tautomeric equilibrium. Compounds of Formula I which exist as tautomers are named, illustrated or otherwise described in this application as one possible tautomer. However, it is to be understood that the all possible
5 tautomers are meant to be encompassed by such names, illustrations and descriptions.

Certain compounds of Formulae I and II exist in tautomeric equilibrium. Compounds of Formulae I and II which exist as tautomers are named, illustrated or otherwise described in this application as one possible tautomer. However, it is to be understood that the all possible tautomers are meant to be encompassed by such names, illustrations and descriptions.

10 Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the
15 potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I may range from 0.1 micrograms per kilogram body weight ($\mu\text{g/kg}$) per day to 10 milligram per kilogram body weight (mg/kg) per day, typically 1 $\mu\text{g/kg/day}$ to 1 mg/kg/day . Therefore, a therapeutically effective amount for a 80 kg human patient may range from 10 $\mu\text{g/day}$ to 100 mg/day , typically 0.1 mg/day to 10 mg/day . In general, one of
20 ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given disease.

The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or
25 parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect
30 the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available

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A11-B12-C4-D86	A75-B12-C4-D86	A128-B12-C4-D86	A11-B5-C4-D123
A75-B5-C4-D123	A128-B5-C4-D123	A11-B6-C4-D123	A75-B6-C4-D123
A128-B6-C4-D123	A11-B12-C4-D123	A75-B12-C4-D123	A128-B12-C4-D123

EXAMPLE 28

Cathepsin B Assay

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Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-FR-AMC (20 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

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Compounds of the invention were tested by the above-described assay and observed to exhibit cathepsin B inhibitory activity with a K_i of less than or equal to 10 μ M.

EXAMPLE 29

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

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Compounds of the invention were tested by the above-described assay and observed to

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exhibit cathepsin K inhibitory activity with a K_i of less than or equal to 10 μ M.

EXAMPLE 30

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of
5 dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM
(pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 μ L of
assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a
shaker plate, covered and incubated for 30 minutes at room temperature. Z-Phe-Arg-AMC (1
nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed
10 spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were
calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to
exhibit cathepsin L inhibitory activity with a K_i of less than or equal to 10 μ M.

EXAMPLE 31

Cathepsin S Assay

15 Solutions of test compounds in varying concentrations were prepared in 10 μ L of
dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM
(pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM). Human cathepsin S (0.158 pMoles in 25 μ L of
assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a
shaker plate, covered and incubated for 30 minutes at room temperature. Z-Val-Val-Arg-AMC
20 (9 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was
followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i)
were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested by the above-described assay and observed to
25 exhibit cathepsin S inhibitory activity with a K_i of less than or equal to 10 μ M.

EXAMPLE 32

Ovalbumin Challenge Mouse

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C57 mice (female) were sensitised with ovalbumin (10 μ g, i.p.) administered together with aluminium hydroxide adjuvant (20 mg, i.p.) on days 0 and 12. Mice are challenged on either day 22, 23 or 24 by exposure for 60 minutes to an aerosol of ovalbumin (10 g/l) twice, 4 hours apart. Mice are dosed p.o. with either vehicle 5 ml/kg (0.5%MC/0.2 % Tween 80 in H₂O) or test compound at 0, 8, 23, 29, 33, 48 and 56 hours.

Mice were euthanized with pentobarbitone i.p. after 86 hours (72 hours after the first challenge). The lungs were insufflated for histological examination as soon as possible after euthanization. Lungs were insufflated with 10% neutral buffered formalin (NBF), at 30 cm water pressure. The lungs were removed and placed in pots of 10% NBF. After fixation in 10% NBF for a minimum of 24 hours the lungs were processed through graded alcohols to wax. The lungs were blocked longitudinally and one 2 μ m section for each animal was cut at the level of the main bronchi. Sections then were stained with haematoxylin and eosin. Pathological assessment of sections is performed and a grading is assigned.

Histopathological evaluation of the lung tissue demonstrate a dose dependant anti-inflammatory effect on vascular and mucosal beds after treatment with compounds of the invention between 0.03 and 30 mg/kg.

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

2020
Bogotá, D.C.,

Abogado:
✓ **EMILIO FERRERO**

ASUNTO:	Radicación No.	06 038 081
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	1 6 4 2 7

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

Documentos estudiados:

Descripción: Folios 84 a 161 como se radicó inicialmente.
Folios 295 a 298 modificada en fase Internacional.

Reivindicaciones: Folios 162 a 176 como se radicó inicialmente.
Folios 299 a 308 modificada en fase Internacional.

Prioridad: US 60/541,373 (24.10.2003)

Objeto de la Invención

Título de la invención: "NUEVOS DERIVADOS DE CETO-OXADIAZOL COMO INHIBIDORES DE LAS CATEPSINAS"

Problema Técnico Planteado: Necesidad de nuevos derivados de ceto-oxadiazol para tratar enfermedades asociadas con cisteína y con la actividad de las catepsinas S, K, y B y el proceso para su obtención.

Solución: Proveer Compuestos de acuerdo a la formula I

IPC: C07D 271/06

Excepciones a la Patentabilidad (Art 20 D 486 literal d)

La solicitud estudiada comprende materia excluida de patentabilidad, en las reivindicaciones 44, 45, 46 (f.299), 47, 48, 49, 50, 51, 52, 53 (f.300), 37, 50, 51 (f.306), 52, 53, 57, 58, 59, 60 (f.307), 61, 62 (f.308)

Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

La solicitud estudiada comprende materia relativa a un uso en las reivindicaciones 43 (f.299), 38, 39 (f.306). De acuerdo a D.486 las reivindicaciones relativas a un uso

son no patentables, razón por la cual las que se encuentran presentes en el capítulo reivindicatorio actual deberían ser eliminadas.

Al parecer las reivindicaciones presentadas no están completas, por lo que este Despacho deja de presente que cualquier reivindicación faltante que se relacione con un uso o con una Excepciones a la Patentabilidad y que se adicione más adelante durante el trámite será objetada.

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Se presenta un grupo de reivindicaciones iniciales (f. 162-176) y un grupo posterior (f. 299-308) como fueron presentadas en fase internacional. Se anota que se realiza el presente examen a la luz del último grupo de reivindicaciones presentado (f. 299-308).

Claridad:

Se observa que el último capítulo reivindicatorio no tiene una numeración adecuada y faltan reivindicaciones. Este capítulo debería estar numerado por números arábigos comenzando por el 1 y siguiendo un orden creciente para identificar cada una de las reivindicaciones subsecuentes.

De acuerdo a lo presentado, se observa la siguiente distribución: los folios 299 y 300 contienen las reivindicaciones de la 43 a la 53; y los folios 301- 308 contienen las reivindicaciones 3, 6 a 14, 32 a 39, 50 a 55 y 57 a 62. Como se observa hay reivindicaciones faltantes, y por consiguiente las dependencias presentadas no son claras, pues no es posible saber cual es el contenido de las reivindicaciones independientes.

Dado que la reivindicación 3 (f. 301) parece ser la que encabeza la lista de reivindicaciones, se procede a examinar dicha reivindicación de acuerdo a la D. 486.

Este Despacho solicita la presentación un capítulo reivindicatorio debidamente numerado y atendiendo los requerimientos mencionados en el presente oficio.

Concisión:

Se observa que la reivindicación 3 presenta la estructura I, en donde A puede tener un número altísimo de connotaciones: se representan tres opciones, pero de acuerdo a las definiciones dadas para X2, R4, R3, X4, X5, y R11 se obtienen demasiadas posibilidades para la porción de molécula A.

Se anota que los radicales se definen con una elevada cantidad de funciones posibles (ácidos carboxílicos, cetonas, heteroanillos, cicloalquilos...), un alto número de átomos para cada una de las funciones (alquilo C1-12, heteroarilo C8-12) y tampoco se definen el número, ni el tipo de heteroátomos en los casos en que corresponde. Por lo anterior, el alcance acá reclamado contiene un elevadísimo número de moléculas.

Se sugiere restringir el alcance de las funciones, los átomos de las funciones y especificar los heteroátomos y el número de los mismos en las definiciones para los radicales de la fórmula I reclamada en la reivindicación 3.

10/10/1964

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n (Art 25 D 486)

tes grupos inventivos dentro de

tes grupos inventivos dentro de

Indirizzo 2. 11. Verfolie 1

Técnica

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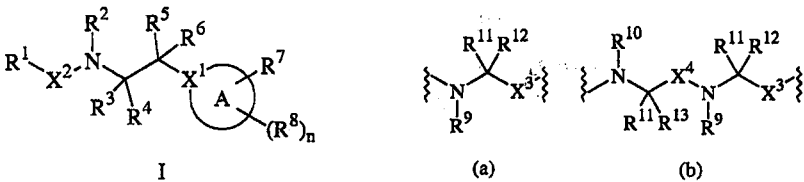
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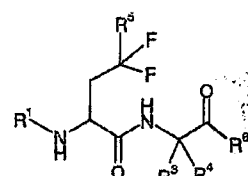
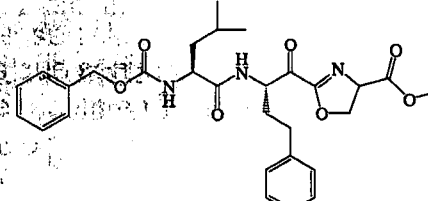
14 D486)

bilidad del grupo inver

uesto que tiene una e

D1 divulga derivados heterocíclicos sustituidos que son inhibidores de cisteína, de acuerdo a la formula I (D1), en donde A comprende un anillo heteromonociclico que contiene de 5 a 6 miembros, o un anillo fusionado policiclico que contiene de 8 a 14 miembros, donde cada anillo contiene 5 a 7 miembros. X1 corresponde a un carbono miembro del ciclo (p.2, ln. 8-20), n es 0-3; X2 es un enlace o un grupo divalente de formula a o b (ver abajo), en donde X3 y X4 son independientemente CO CH2SO2, R9 y R10 con independientemente H, alquilo C1-6, R11 que puede ser H o alquilo C1-6. (p.3, ln 1-20)



Características esenciales de la Solicitud	D1 WO0055144
 Grupo Ic	 (D1.p45, ln.10-15)
Grupo R1-NH-CH-C(O)- (parte izquierda de la molécula)	X2 es a (p.2, ln.20), X3 es -C(O)- (p.3), R9 es H (p.3, ln.2), R11 es H (p.3, ln.3), R12 es alquilo C1-6 opcionalmente sustituido por ciano, halo (p.3, ln.5-10)
R1 es H, R13SO2, R13OCO, R8R7NCO, R8R7NSO2, R13SO2NCO, R13CONSO2	Si, (D1.p45, ln.10-15)
R5 H, F, Alquilo C1-9, cicloalquil C3-12,-aquilo C0.6, Heteroaril	Si, (D1.p45, ln.10-15)
R3 H, alquilo C1-6, cicloalquil C3-12, cicloalquil C3-12-aquilo C0-6 ...	Si, (D1.p45, ln.10-15)
R4 H, alquilo C1-6, o R3 y R4 forman un cicloalquilo	Si, (D1.p45, ln.10-15)
R6 es arilo C6-12, heteroarilo C5-13, heterocicloalquil C3-12-alquil C0-6	Si, (D1.p45, ln.10-15)
Grupos F	Si, R12 es alquilo C1-6 opcionalmente sustituido por ciano, halo (p.3, ln.5-10)

La diferencia entre D1 y la presente solicitud se observa que reside en que no hay ningún ejemplo en D1 que revele los halógenos sobre el alquilo que está cercano a X1 en la molécula de formula I de la presente solicitud.

El efecto técnico que logra la diferencia es una actividad inhibidora selectiva de Catepsina S, lo cual se presentó en la Descripción en términos de Ensayos de Catepsina S (f.158), B, K, y L, (f.159).

El Problema Técnico Objetivo de esta solicitud es la necesidad de derivados de ceto-oxadiazol alternativos para tratar enfermedades asociadas con cisteína y con la actividad de las catepsinas S, K, y B y el proceso para su obtención.

D1 para R12 sugiere que un halógeno puede sustituir un grupo alquilo de 1 a 6

átomos de carbono.

Se observa que D1 anticipaba parte de la molécula reclamada por la presente solicitud (p.167). Si bien ninguno de los ejemplos presenta grupos F sobre la molécula, la definición que D1 sugiere para R12 si lo incluye. Se considera que D1 sugería al experto la inclusión de un grupo F sobre la porción alquilo como se presenta en la solicitud.

Por otro lado, no se observa que los derivados acá reclamados tengan un efecto diferente al que ya se revelaba por D1: inhibidores de proteasa, más específicamente de cisteína (portada, f.320, D1). Particularmente, D1 revela que estos compuestos poseen actividad inhibidora de catepsinas B, K, L y S (p.167).

Dado que no se observa que los compuestos acá reclamados tengan un efecto inesperado o sorprendente frente a aquellos revelados por el Estado de la Técnica, se considera que los compuestos acá reclamados carecen de nivel inventivo.

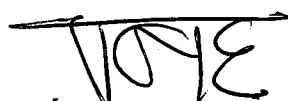
Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO0055144	3-62	Nivel Inventivo

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

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


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 12 de Julio 2010

CONCEPTO TECNICO NUMERO: 4075	EXAMINADOR TÉCNICO Código:202092
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