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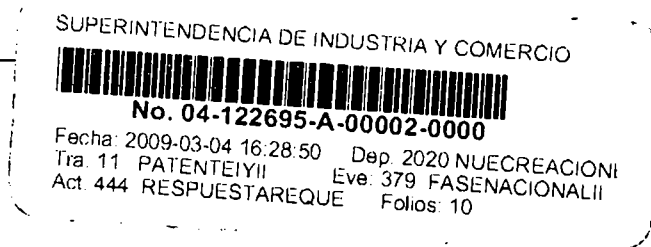
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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____



Re: Expediente No. 04.122.695A

**Solicitud de patente de invención titulada: "PROFARMACOS DE AMINOÁCIDOS
EXCITADORES."**

Solicitante: ELI LILLY AND COMPANY.

N.Ref.: P2004/000142A

RESPUESTA AL OFICIO No. 15558 NOTIFICADO POR FIJACIÓN EN LISTA No. 394,
DE FECHA 5 DE DICIEMBRE DE 2008
(EXAMEN DE FONDO)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486, en los siguientes términos:

1. En primer lugar y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza al Capítulo Reivindicatorio presentado al momento de radicar la solicitud divisional. Para tal efecto, adjunto un recibo de pago que cubre la tasa de modificación correspondiente.

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Así entonces, el Capítulo Reivindicatorio Modificado contiene los siguientes cambios:

Reivindicación original	Modificaciones Solicitud Divisional
1 y 5	Se retira metionil como posible sustituyente de Q.
8 y 14	Eliminadas

Valga anotar que las modificaciones efectuadas cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

2. a- El Examinador argumenta que las Reivindicaciones 5, 7 y 13 reclaman el compuesto reivindicado en la solicitud parental.

b- Con el ánimo de superar la anterior objeción, se han efectuado los siguientes cambios a las reivindicaciones de la presente solicitud divisional.

- En la Reivindicación 1, se incluyó la condición: “Q no puede ser metionil”;
- Se ha removido de la Reivindicación 5, el termino metionil de la definición de Q;
- Se eliminó la Reivindicación 8.

3. a- El Examinador argumenta que la Reivindicación 14 no es patentable, porque caracteriza los compuestos de la invención por su uso. Adicionalmente, el Examinador señala que la Reivindicación en mención contiene materia reivindicada en la solicitud parental.

b- Considero superada la anterior objeción, en tanto que la Reivindicación 14 ha sido eliminada del Capítulo Reivindicatorio Modificado.

4. a- El Examinador argumenta que la patente US5.688.826 (D1) afecta el nivel inventivo de la presente invención, argumentando que la única diferencia entre los compuestos de la presente invención y aquellos divulgados en D1 es el grupo aminoacilo incluido en los compuestos reivindicados como sustituyente en la posición A. Sin embargo, el Examinador anota que dicha diferencia aparentemente no confiere ninguna ventaja o efecto sorprendente e inesperado a los compuestos reivindicados. Adicionalmente, el Examinador señala que para una persona medianamente versada en la materia resulta obvio el diseño de profármacos con el objeto de incrementar la biodisponibilidad de compuestos activos.

b- i) Tal como se establece en la página 1 de la Descripción, la presente invención corresponde a profármacos de los compuestos de D1, los cuales presentan un núcleo biciclo[3.1.0]hexano no sustituido. En el estado de la técnica se vislumbraba la necesidad de mejorar la biodisponibilidad de los compuestos de D1, problema que el solicitante solucionó de manera inventiva mediante la inclusión de un aminoácido en la posición 4 del núcleo biciclo de los compuestos del arte previo (D1).

Claramente, D1 no provee ninguna sugerencia que hubiera motivado a la persona medianamente versada en la materia a incorporar un aminoácido en los compuestos allí divulgados, ni mucho menos a incorporarlo justamente en la posición modificada por el solicitante para desarrollar los compuestos de la invención, con el objeto de obtener profármacos de agonistas mGluR2 con potencia *in vivo* aumentada y mayor biodisponibilidad oral.

En cuanto a que el diseño de profármacos resulta obvio, difiero respetuosamente de la opinión del Examinador en tanto que una persona versada en la materia no concluiría *ab initio* -sin necesidad de experimentación- que una modificación estructural sobre la molécula de un fármaco necesariamente mejoraría su biodisponibilidad. El diseño de un profármaco requiere de trabajo exhaustivo y sobretodo de la intervención de actividad inventiva, para que a pesar de la alteración de las propiedades estéricas y fisicoquímicas, generada por la inclusión de una molécula extraña sobre la estructura de un núcleo farmacofórico, no se afecte su actividad biológica. Por lo tanto, a menos que la anterioridad no indique qué tipo de moléculas pueden ser unidas al núcleo estructural del fármaco sin que se vea afectada su actividad, los profármacos constituyen a todas luces constructos novedosos e inventivos.

Por lo tanto, solicito respetuosamente al Examinador señalar, más que el simple deseo general de intentar sintetizar innumerables variaciones de una molécula, los apartes específicos en el arte previo citado, que hubieran conducido a la persona medianamente versada en la materia a incluir un grupo aminoácido en la posición 4 del núcleo farmacofórico de los compuestos divulgados en D1. Adicionalmente, solicito indique las sugerencias que en D1 hubiesen llevado generar una expectativa razonable, que al incluir los aminoácidos definidos en la Reivindicación 1, los fármacos de D1, presentarían una mejor biodisponibilidad oral y una *in vivo* potencia aumentada.

5. Por todo lo anterior, considero que las objeciones presentadas por el Examinador en su examen de fondo No. 3189 han sido resueltas y por consiguiente solicito respetuosamente que el

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Despacho tengan por cumplidos los requisitos de patentabilidad, en tanto no se logró desvirtuar ninguno de ellos por parte del Despacho, y se proceda con la concesión de la patente.

Atentamente,



CARLOS R. OLARTE

C.C. No. 79.782.747 de Bogotá

T.P. 74.295

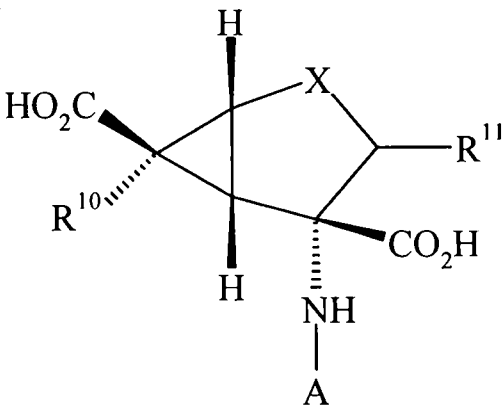
Anexos:

- Capítulo Reivindicatorio Modificado.
- Recibo de pago correspondiente a la tasa de modificación.

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CAPITULO REIVINDICATORIO MODIFICADO
(EXAMEN DE FONDO)

1. Un compuesto de Fórmula I



(I),

en la que:

A es H-(Q)_p⁻;

Q se selecciona independientemente, cada vez que aparece, del grupo

10 aminoacilo derivado de un aminoácido seleccionado del grupo consistente en aminoácidos naturales y aminoácidos no naturales seleccionados de isómeros tipo D de los aminoácidos naturales; Aib (ácido aminobutírico), Nva(norvalina), β-Ala, Aad (ácido aminoadípico), β Aad (ácido 3-aminoadípico), Abu(ácido 2- aminobutírico), Gaba (ácido γ aminobutírico), Acp

15 (ácido 6-aminocaproico), Dbu (ácido 2,4-diaminobutírico), ácido α aminopimelico, TMSA (trimetilsilil-Ala), alle(allo-isoleucina), Nle (Norleucina), tert-Leu, Cit (Citrulina), orn, Dpm, (ácido 2,2'-diaminopimelico), Dpr (ácido 2,3- diaminopropionico), Nal α ó β, Cha (ciclohexil Ala), hidroxiprolina, Sar (sarcosina), O-metil tirosina, fenilglicina; aminoácidos cíclicos; aminoácidos

20 N^o alquilados, donde los aminoácidos N^o alquilados son N^o (1-10C) alquil

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aminoácidos tales como MeGly (N^{α} - metilglicina), EtGly (N^{α} etilglicina) y Et Asn (N^{α} etilasparagina) y aminoácidos en los cuales el carbono α presenta sustituyentes de cadena en dos lados; con la condición que Q no puede ser metionil.

5 p es un número entero de 1 a 10;

X es SO_2 ;

R^{10} es hidrógeno o fluoro; y

R^{11} es hidrógeno, fluoro, o hidroxil;

o una de sus sales farmacéuticamente aceptables.

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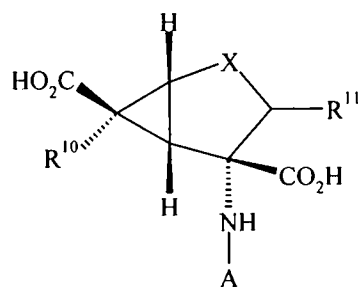
2. El compuesto o sal según la Reivindicación 1, en el que p es un número entero de 1 a 3.

3. El compuesto o sal según la Reivindicación 1, en el que p es 1.

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4. El compuesto o sal según una cualquiera de las Reivindicaciones 1 a 3, en el que Q es un aminoácido derivado de un aminoácido natural.

20 5. Un compuesto de Fórmula I



(I)

2/10/23

en el que:

A es $H-(Q)_p^-$;

Q es glicil, alanil, valil, leucil, isoleucil, prolil, fenilalanil, tirosil, triptofil,

5 lisil ó serinil.

p es un entero de 1 a 10;

X es SO_2 ;

R^{10} es hidrógeno o flúor; y

R^{11} es hidrógeno, flúor o hidroxil;

10 o la sal farmacéuticamente aceptable del mismo.

6. El compuesto o sal según la Reivindicación 5, en el que p es un número entero de 1 a 3.

15 7. El compuesto o sal según la Reivindicación 5, en el que p es 1.

8. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 7, donde R^{10} es hidrógeno.

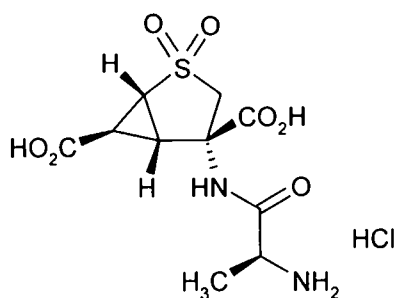
20 9. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 8, donde R^{11} es hidrógeno.

10. Una sal farmacéuticamente aceptable según las Reivindicaciones 1 a 5, que es una sal de adición de ácidos preparada con un
25 ácido que proporciona un anión farmacéuticamente aceptable; una sal de

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adición de bases preparada con una base que proporciona un anión farmacéuticamente aceptable para un compuesto que contiene un dominio ácido; o un compuesto bipolar que contiene grupos con carga opuesta.

- 5 **11.** Un compuesto según las Reivindicaciones 1 a 5, en el que
- A es $H-(Q)_p$;
- Q es L-alanil;
- p es 1;
- X es SO_2 ;
- 10 R^{10} es hidrógeno; y
- R^{11} es hidrógeno;
- o la sal clorhidrato, sal tosilato, sal mesilato, sal esilato, sal besilato o sal monosódica del mismo.
- 15 **12.** El compuesto según la Reivindicación 11 que es clorhidrato del ácido (1R,4S,5S,6S)-4-(2'S-aminopropionil)amino]-2,2-dioxo-2 λ^6 -tia-biciclo[3.1.0.]hexano-4,6-dicarboxílico o tosilato del ácido (1R,4S,5S,6S)-4-(2'S-2'-aminopropionil)amino-2,2-dioxo-2 λ^6 -tia-biciclo[3.1.0.]hexano-4,6-dicarboxílico.



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13. Una formulación farmacéutica que comprende, en asociación con un vehículo, diluyente o excipiente farmacéuticamente aceptable, un compuesto de acuerdo con las Reivindicaciones 1 a 12.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 16,262
FECHA : FEBRERO 27 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-122695-A-00002-0000

Fecha: 2009-03-04 16:28:50 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 10

***** CONSIGNACION *****

POSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105276194	26/02/2009	2,389,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
12		MARCAS Y LEMAS COMERCIALES	111,000.00
TOTAL :			\$ 111,000.00

SON: CIENTO ONCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



US005998412A

United States Patent [19][11] **Patent Number:** **5,998,412****Broka et al.**[45] **Date of Patent:** **Dec. 7, 1999****[54] SULFAMIDE-METALLOPROTEASE INHIBITORS**

[75] Inventors: **Chris Allen Broka**, Foster City; **Jeffrey Allen Campbell**, Fremont, both of Calif.; **Arlindo Lucas Castelhamo**, New City, N.Y.; **Jian Jeffrey Chen**, Santa Clara, Calif.; **Robert Than Hendricks**, Palo Alto, Calif.; **Michael Joseph Melnick**, San Diego, Calif.; **Kelth Adrian Murray Walker**, Los Altos Hills, Calif.

[73] Assignees: **Syntex (U.S.A.) Inc.**, Palo Alto; **Agouron Pharmaceuticals, Inc.**, San Diego, both of Calif.

[21] Appl. No.: **09/009,951**

[22] Filed: **Jan. 21, 1998**

Related U.S. Application Data

[60] Provisional application No. 60/036,714, Jan. 23, 1997, and provisional application No. 60/062,209, Oct. 16, 1997.

[51] Int. Cl.⁶ **A61K 31/435**; **A61K 31/495**; **C07D 491/048**; **C07D 495/04**

[52] U.S. Cl. **514/250**; **514/255**; **514/300**; **514/301**; **514/302**; **514/318**; **514/330**; **514/331**; **514/562**; **544/350**; **544/360**; **544/380**; **546/113**; **546/114**; **546/115**; **546/193**; **546/225**; **546/235**; **562/556**

[58] Field of Search **562/556**; **514/562**, **514/250**, **300**, **301**, **302**; **544/350**; **546/113**, **114**, **115**

[56] References Cited**U.S. PATENT DOCUMENTS**

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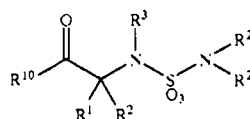
von Geldern, et al., *Journal of Medicinal Chemistry*, vol. 39:4, (1996), pp. 968-981, "Azole Endothelin Antagonists".
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 Patt, et al., *J. Med. Chem.*, vol. 35:14, 1992, pp. 2562-2572, "Structure-Activity Relationships of a Series of 2-Amino-4-thiazole-Containing Renin Inhibitors".

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Rohan Perics; Rekha Bansal

[57] ABSTRACT

This invention relates to sulfamides of formula (I)

(I)



that are inhibitors of metalloproteases, pharmaceutical compositions containing them, methods for their use and methods for preparing these compounds.

15 Claims, No Drawings

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SULFAMIDE-METALLOPROTEASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit under 35 U.S.C. 119(c) of U.S. Provisional Application No. 60/036,714, filed Jan. 23, 1997 and U.S. Provisional Application No. 60/062,209, filed Oct. 16, 1997.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to compounds that inhibit metalloproteases such as matrix metalloproteases, particularly interstitial collagenases, as well as TNF α -convertase and related sheddases and are therefore useful in the treatment of mammals having disease states alleviated by the inhibition of such metalloproteases.

2. Background Information and Related Disclosures

Matrix metalloproteases ("MMPs") are a family of proteases (enzymes) involved in the degradation and remodeling of connective tissues. Members of this family of endopeptidase enzymes are present in various cell types that reside in or are associated with connective tissue, such as fibroblasts, monocytes, macrophages, endothelial cells, and invasive or metastatic tumor cells. MMP expression is stimulated by growth factors and cytokines in the local tissue environment, where these enzymes act to specifically degrade protein components of the extracellular matrix, such as collagen, proteoglycans (protein core), fibronectin and laminin. These ubiquitous extracellular matrix components are present in the linings of joints, interstitial connective tissues, basement membranes, and cartilage. Excessive degradation of extracellular matrix by MMPs is implicated in the pathogenesis of many diseases, including rheumatoid arthritis, osteoarthritis, multiple sclerosis, bone resorptive diseases (such as osteoporosis), chronic obstructive pulmonary disease, restenosis, cerebral hemorrhaging associated with stroke, periodontal disease, aberrant angiogenesis, tumor invasion and metastasis, corneal and gastric ulceration, ulceration of skin, aneurysmal disease, and in complications of diabetes. MMP inhibition is, therefore, recognized as a good target for therapeutic intervention.

The MMPs share a number of properties, including zinc and calcium dependence, secretion as zymogens, and 40-50% amino acid sequence homology. The MMP family currently consists of at least fifteen enzymes, and includes collagenases, stromelysins, gelatinases, matrilysin, metalloelastase, and membrane-type MMP, as discussed in greater detail below.

Interstitial collagenases catalyze the initial and rate-limiting cleavage of native collagen types I, II, and III. Collagen, the major structural protein of mammals, is an essential component of the matrix of many tissues, for example, cartilage, bone, tendon and skin. Interstitial collagenases are very specific matrix metalloproteases which cleave these collagens to give two fragments which spontaneously denature at physiological temperatures and therefore become susceptible to cleavage by less specific enzymes. Cleavage by the collagenases results in the loss of structural integrity of the target tissue, essentially an irreversible process. There are currently three known human collagenases. The first is human fibroblast-type collagenase (HFC, MMP-1, or collagenase-1) that is produced by a wide variety of cells including fibroblasts and macrophages. The

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second is human neutrophil-type collagenase (HNC MMP-8, or collagenase-2) which has so far only been demonstrated to be produced by neutrophils. The most recently discovered member of this group of MMPs is human collagenase-3 (MMP-13) which was originally found in breast carcinomas, but has since shown to be produced by chondrocytes. The only collagenase known to exist in rodents is the homolog of human collagenase-3.

The gelatinases include two distinct, but highly related, enzymes: a 72-kD enzyme (gelatinase A, HFG, MMP-2) secreted by fibroblasts and a wide variety of other cell types, and a 92-kD enzyme (gelatinase B, HNG, MMP-9) released by mononuclear phagocytes, neutrophils, corneal epithelial cells, tumor cells, cytotrophoblasts and keratinocytes. These gelatinases have been shown to degrade gelatins (denatured collagens), collagen types IV (basement membrane) and V, fibronectin and insoluble elastin.

Stromelysins 1 and 2 have been shown to cleave a broad range of matrix substrates, including laminin, fibronectin, proteoglycans, and collagen types IV and IX in their non-helical domains.

Matrilysin (MMP-7, PUMP-1) has been shown to degrade a wide range of matrix substrates including proteoglycans, gelatins, fibronectin, elastin, and laminin. Its expression has been documented in mononuclear phagocytes, rat uterine explants and sporadically in tumors. Other less characterized MMPs include macrophage metalloelastase (MME, MMP-12), membrane type MMP (MMP-14), and stromelysin-3 (MMP-11).

Inhibitors of MMPs provide useful treatments for diseases associated with the excessive degradation of extracellular matrix, such as arthritic diseases (rheumatoid arthritis and osteoarthritis), multiple sclerosis, bone resorptive diseases (such as osteoporosis), the enhanced collagen destruction associated with diabetes, chronic obstructive pulmonary disease, cerebral hemorrhaging associated with stroke, periodontal disease, corneal or gastric ulceration, ulceration of the skin, tumor invasion and metastasis, aneurysmal disease such as abdominal aortic aneurysm disease, and aberrant angiogenesis. The involvement of individual collagenases in the degradation of tissue collagens probably depends markedly on the tissue. The tissue distribution of human collagenases suggests that collagenase-3 is the major participant in the degradation of the collagen matrix of cartilage, while collagenase-1 is more likely to be involved in tissue remodeling of skin and other soft tissues. Thus, inhibitors selective for collagenase-3 over collagenase-1 are preferred for treatment of diseases associated with cartilage erosion, such as arthritis, etc.

Some inhibitors of MMP also are known to substantially inhibit the release of tumor necrosis factor (TNF) from cells and therefore may be used in the treatment of conditions mediated by TNF. Such uses include, but are not limited to, the treatment of inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, restenosis, graft versus host reactions and autoimmune disease. Compounds of this invention may inhibit TNF release without inhibiting the MMPs.

In addition to these effects on the release of TNF from cells, MMP inhibitors and related compounds have also been shown to inhibit the release of other biologically active molecules from cells, including soluble receptors (CD30 and receptors for TNF (p55 and p75), IL-6, IL-1 and TSH), adhesion molecules (e.g., L-selectin, ICAM-1, fibronectin) and other growth factors and cytokines, including Fas

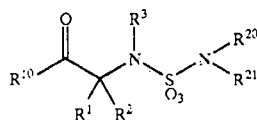
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ligand, TGF- α , EGF, HB-EGF, SCF and M-CSF. The release of such molecules is facilitated by several proteolytic proteins known as sheddases. Inhibition of the release or shedding of such molecules by inhibiting the sheddases may be of benefit in a number of disease states, including rheumatoid arthritis, multiple sclerosis, vascular disease, Type II diabetes, HIV, cachexia, psoriasis, allergy, hepatitis, inflammatory bowel disease, and cancer. Since non-specific inhibition of the shedding enzymes (sheddases) may have opposite pharmacological effects, selectivity will be a particular advantage, e.g., the inhibition of TNF release without the concurrent inhibition of TNF receptor release.

The design and uses of MMP inhibitors is described, for example, in *J. Enzyme Inhibition*, 2, 1-22 (1987); *Drug News & Prospectives*, 3(8), 453-458 (1990); *Arthritis and Rheumatism*, 36(2), 181-189 (1993); *Arthritis and Rheumatism*, 34(9), 1073-1075 (1991); *Seminars in Arthritis and Rheumatism*, 19(4), Supplement 1 (February), 16-20 (1990); *Drugs of the Future*, 15(5), 495-508 (1990); *Annals N.Y. Acad. Sci.*, 157, (1996), and *J. Enzyme Inhibition*, 2, 1-22 (1987). MMP inhibitors are also the subject of various patents and patent applications, for example, U.S. Pat. Nos. 5,189,178 and 5,183,900, European Published Patent Applications 438 223, 606 426, and 276 436, and Patent Cooperation Treaty International Applications 92/21360, 92/06966, 92/09563, and 94/25434.

SUMMARY OF THE INVENTION

In a first aspect, this invention provides hydroxamic acids and their derivatives selected from the group of compounds represented by formula (I):



wherein:

R^1 and R^2 are independently selected from hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclo, heterocycloalkyl, heteroalkyl, or -(alkylene)-C(O)-X where X is alkyl, haloalkyl, alkoxy, haloalkyloxy, amino, monosubstituted amino, disubstituted amino, aryl, aralkyl, aryloxy, heteroaryloxy, hydroxy, aralkyloxy, heteroaralkyloxy, or heteroaryl; or R^1 and R^2 together with the carbon atom to which they are attached form a carbocycle or a heterocycle;

R^3 is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heterocycloalkyl, heteroalkyl, (diphenylmethyl)alkyl, or -(alkylene)-C(O)-X where X is alkyl, haloalkyl, alkoxy, haloalkyloxy, amino, monosubstituted amino, disubstituted amino, aryl, aralkyl, aryloxy, heteroaryloxy, hydroxy, aralkyloxy, heteroaralkyloxy, or heteroaryl; or R^3 together with either R^1 or R^2 and the atoms to which they are attached forms a heterocycloamino group;

R^{10} is -NR¹¹OR¹² wherein:

R^{11} and R^{12} are independently selected from hydrogen, alkyl, or aralkyl;

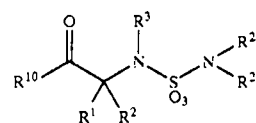
R^{20} and R^{21} are independently selected from hydrogen, alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaralkyl, or heteroaralkenyl;

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or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a heterocycloamino group or an optionally substituted tetrahydropyridine or hexahydroazepine ring; or either of R^{20} or R^{21} together with R^3 forms an alkylene group; and their pharmaceutically acceptable salts, prodrugs, individual isomers, and mixtures of isomers, provided that R^{20} and R^{21} together with the nitrogen atom to which they are attached do not form a morpholino ring either:

- (i) when R^1 and R^3 are hydrogen and R^2 is aralkyl; or
- (ii) when R^1 and R^3 together with the atoms to which they are attached form a tetrahydroisoquinoline ring and R^2 is hydrogen.

In a second aspect, this invention provides carboxylic acids selected from the group of compounds represented by formula (I):



wherein:

R^1 and R^2 are independently selected from hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclo, heterocycloalkyl, heteroalkyl, or -(alkylene)-C(O)-X where X is alkyl, haloalkyl, alkoxy, haloalkyloxy, amino, monosubstituted amino, disubstituted amino, aryl, aralkyl, aryloxy, heteroaryloxy, hydroxy, aralkyloxy, heteroaralkyloxy, or heteroaryl; or R^1 and R^2 together with the carbon atom to which they are attached form a carbocycle or a heterocycle;

R^3 is hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heterocycloalkyl, heteroalkyl, (diphenylmethyl)alkyl, or -(alkylene)-C(O)-X where X is alkyl, haloalkyl, alkoxy, haloalkyloxy, amino, monosubstituted amino, disubstituted amino, aryl, aralkyl, aryloxy, heteroaryloxy, hydroxy, aralkyloxy, heteroaralkyloxy, or heteroaryl; or R^3 together with either R^1 or R^2 and the atoms to which they are attached form a heterocycloamino group;

R^{10} is -OH;

R^{20} is hydrogen or alkyl; and

R^{21} is cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaralkyl or heteroaralkenyl; or

R^{20} and R^{21} together with the nitrogen atom to which they are attached form either:

- (i) a heterocycloamino group substituted with at least one substituent selected from cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl-Q-, aryl-Q-, or heteroaryl-Q- where Q is an alkylene chain in which a methylene group is optionally replaced by -C(O)-, -O-, -S(O)n- (where n is an integer from 0 to 2), -NR- (where R is hydrogen or alkyl), -NR^aC(O)-, -C(O)NR^a- (where R^a is hydrogen or alkyl), -NR^bSO₂- or -SO₂NR^b- (where R^b is hydrogen or alkyl);
- (ii) a heterocycloamino group that is fused to a cycloalkyl, aryl or heteroaryl ring; or
- (iii) an optionally substituted tetrahydropyridine or hexahydroazepine ring;

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or either of R²⁰ or R²¹ together with R³ forms an alkylene group; and their pharmaceutically acceptable salts, prodrugs, individual isomers, and mixtures of isomers, provided that:

- (i) R¹, R², and R³ are not all hydrogen; and
- (ii) when R¹ and R³ are hydrogen and R² is alkyl, then R²¹ is not pyridylalkyl.

In a third aspect, this invention provides pharmaceutical compositions containing a therapeutically effective amount of a compound of formula (I) or its pharmaceutically acceptable salt and a pharmaceutically acceptable excipient.

In a fourth aspect, this invention provides a method of treatment of a disease in a mammal treatable by administration of a metalloproteinase inhibitor, comprising administration of a therapeutically effective amount of a compound of formula (I) or its pharmaceutically acceptable salt.

In a fifth aspect, this invention provides processes for preparing compounds of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, pentyl, and the like.

"Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g., methylene, ethylene, propylene, 2-methylpropylene, pentylen, and the like.

"Alkenyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, e.g., ethenyl, propenyl, and the like.

"Alkenylene" means a linear divalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, e.g., ethenylene, 2-propenylene, and the like.

"Acyl" means a radical —C(O)R where R is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, heteroaralkenyl, or heterocyclo, e.g., acetyl, benzoyl, thenoyl, and the like.

"Acyloxy" means a radical —OC(O)R where R is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or haloalkyl, e.g., acetoxy, 3,3,3-trifluoroacetoxy and the like.

"Acylamino" means a radical —NRC(O)R' where R is hydrogen or alkyl and R' is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, haloalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkenyl, or heteroaralkyl, e.g., acetylamino, trifluoroacetyl amino, benzoylamino, methylacetylamino, and the like.

"Sulfonylamino" means a radical —NRSO₂R' where R is hydrogen or alkyl and R' is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, haloalkyl, amino, monosubstituted amino, disubstituted amino, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkenyl, or heteroaralkyl, e.g., methylsulfonylamino, benzylsulfonylamino, N-methylaminosulfonylamino, and the like.

"Halo" means fluoro, chloro, bromo, or iodo, preferably fluoro and chloro.

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"Haloalkyl" means alkyl substituted with one or more same or different halo atoms, e.g., —CH₂Cl, —CF₃, —CH₂CF₃, —CH₂CCl₃, and the like.

"Cycloalkyl" means a saturated monovalent cyclic hydrocarbon radical of three to six ring carbons, e.g., cyclopropyl, cyclopentyl, cyclohexyl, and the like.

"Carbocycle" means a saturated, cyclic group of 3 to 8 ring atoms in which all the ring atoms are carbon, e.g., cyclopentyl, cyclohexyl, and the like.

"Monosubstituted amino" means a radical —NHR where R is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or an amino protecting group, e.g., methylamino, (1-methylethyl) amino, phenylamino, and the like.

"Disubstituted amino" means a radical —NRR' where R and R' are independently alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or an amino protecting group. Representative examples include, but are not limited to dimethylamino, methylethylamino, di(1-methylethyl) amino, methylbenzylamino, and the like.

"Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 10 ring atoms and optionally substituted independently with one or more substituents, preferably one or two substituents selected from alkyl, haloalkyl, halo, nitro, acyloxy, cyano, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, heteroaralkyl, —OR (where R is hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, heteroaryl, optionally substituted phenylalkyl, or heteroaralkyl), —NRR' (where R and R' are independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenylalkenyl, heteroaryl, or heteroaralkyl), —C(O)R (where R is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, haloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenylalkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl), —S(O)_nR (where n is an integer from 0 to 2 and R is hydrogen (provided that n is 0), alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, heteroaryl, optionally substituted phenylalkyl, or heteroaralkyl), —SO₂NRR' (where R and R' are independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenylalkenyl, heteroaryl or heteroaralkyl), —COOH, —(alkylene)—COOH, —(alkenylene)—COOH, —COOR^a, —(alkenylene)—COOR^a, —(alkylene)—COOR^a (where R^a is alkyl, optionally substituted phenylalkyl, or heteroaralkyl), —CONR^bR^c, —(alkylene)—CONR^bR^c, (where R^b and R^c are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, and heteroaralkyl), —NRC(O)R' (where R is hydrogen or alkyl and R' is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, haloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenylalkenyl, heteroaryl, heteroaralkenyl, or heteroaralkyl), —NRSO₂R' (where R is hydrogen or alkyl and R' is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, haloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenylalkenyl, heteroaryl, heteroaralkenyl, or heteroaralkyl), or —NRSO₂NR^bR^c (where R is hydrogen or alkyl and R^b and R^c are independently hydrogen, alkyl, alkenyl, haloalkyl,

cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, or optionally substituted phenylalkenyl). More specifically the term aryl includes, but is not limited to, phenyl, 1-naphthyl and 2-naphthyl, and the derivatives thereof.

"Heteroaryl" means a monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. The heteroaryl ring is optionally substituted independently with one or more substituents, preferably one or two substituents, selected from alkyl, haloalkyl, halo, nitro, cyano, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, —OR (where R is hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl or optionally substituted phenylalkyl), —NRR' (where R and R' are independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, or optionally substituted phenylalkenyl), —C(O)R (where R is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, haloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, or optionally substituted phenylalkenyl), —S(O)_nR (where n is an integer from 0 to 2 and R is hydrogen (provided that n is 0), alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, or optionally substituted phenylalkyl), —SO₂NRR' (where R and R' are independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, or optionally substituted phenylalkenyl), —COOH, —(alkylene)—COOH, —(alkenylene)—COOH, —COOR^a, —(alkylene)—COOR^a, —(alkenylene)COOR^a (where R^a is alkyl, heteroalkyl, aralkyl, or heteroaralkyl), —CONR'R", —(alkylene)CONR'R", (where R' and R" are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl), —COCH(R')NH₂ (where R' is a side chain of a natural or unnatural alpha amino acid in which any functional group present may be protected), an amino protecting group, or 1,3-dihydro-2H-1,4-benzodiazepin-2-one wherein the N-1 and C-3 positions may be optionally substituted, independently of each other, with a substituent selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, acyl, and heteroaralkyl. More specifically the term heterocycloamino includes, but is not limited to, pyrrolidino, piperidino, morpholino, piperazino, indolino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, 1,2,3,4-tetrahydro-(α, β, or -γ, -carbolino, tetrahydroisoquinolyl, and 1,3-dihydro-2H-1,4-benzodiazepin-2-one-5-yl, and the derivatives thereof.

"Optionally substituted phenyl" means phenyl ring which is optionally substituted with one or more substituents, preferably one or two substituents selected from alkyl, haloalkyl, halo, nitro, cyano, —NRR' (where R and R' are independently selected from hydrogen or alkyl), —OR (where R is hydrogen, alkyl or haloalkyl), —COOR^a (where R^a is hydrogen or alkyl) or —CONR'R" (where R' and R" are independently selected from hydrogen or alkyl). Representative examples include, but are not limited to, phenyl, 3-chlorophenyl, 4-(methylthio)phenyl, and the like.

"Heterocycloamino" means a saturated monovalent cyclic group of 4 to 8 ring atoms, wherein at least one ring atom is N and optionally contains one or two additional ring heteroatoms selected from the group consisting of N, O, or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl group. The heterocycloamino ring may be fused to a cycloalkyl, aryl or heteroaryl ring, and it may be optionally substituted with one or more substituents, preferably one or two substituents, selected from alkyl, haloalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, diphenylmethyl, (diphenylmethyl)alkyl, halo, cyano, acyl, amino, monosubstituted amino, disubstituted amino, acylamino, sulfonylamino, —OR (where R is hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, acyl, aryl, heteroaryl, aralkyl, or heteroaralkyl), —S(O)_nR [where n is an integer from 0 to 2 and R is hydrogen (provided that n is 0), alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, amino, monosubstituted amino, disubstituted amino, heterocyclo, aryl, heteroaryl, aralkyl, or heteroaralkyl], —P(O)(NR^bR^c)₂ (where R^b and R^c are independently selected from alkyl or aralkyl), —COOH, —(alkylene)—COOH, —(alkenylene)—COOH, —COOR^a, —(alkylene)—COOR^a, —(alkenylene)COOR^a (where R^a is alkyl, heteroalkyl, aralkyl, or heteroaralkyl), —CONR'R", —(alkylene)CONR'R", (where R' and R" are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl), —COCH(R')NH₂ (where R' is a side chain of a natural or unnatural alpha amino acid in which any functional group present may be protected), an amino protecting group, or 1,3-dihydro-2H-1,4-benzodiazepin-2-one wherein the N-1 and C-3 positions may be optionally substituted, independently of each other, with a substituent selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, acyl, and heteroaralkyl. More specifically the term heterocycloamino includes, but is not limited to, pyrrolidino, piperidino, morpholino, piperazino, indolino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, 1,2,3,4-tetrahydro-(α, β, or -γ, -carbolino, tetrahydroisoquinolyl, and 1,3-dihydro-2H-1,4-benzodiazepin-2-one-5-yl, and the derivatives thereof.

"Optionally substituted tetrahydropyridine or hexahydroazepine ring" means a tetrahydropyridine or a hexahydroazepine ring that is optionally substituted with one or two substituents selected from alkyl, haloalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, diphenylmethyl, (diphenylmethyl)alkyl, acyl, hydroxy, —COOH, —(alkylene)—COOH, —(alkenylene)—COOH, —COOR^a, —(alkylene)—COOR^a, —(alkenylene)COOR^a (where R^a is alkyl, heteroalkyl, aralkyl, or heteroaralkyl), —S(O)_nR [where n is an integer from 1 to 2 and R is hydrogen (provided that n is 0), alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, amino, monosubstituted amino, disubstituted amino, aryl, heteroaryl, aralkyl, or heteroaralkyl], —CONR'R", and —(alkylene)—CONR'R" (where R' and R" are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl). Representative examples include, but are not limited to, 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine, and the like.

"Heterocycle" or "Heterocyclo" means a saturated cyclic radical of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a

carbonyl group. The heterocyclo ring may be optionally substituted independently with one, two, or three substituents selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halo, cyano, acylamino, amino, monosubstituted amino, disubstituted amino, —OR (where R is hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl), —C(O)R (where R is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, haloalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl), —S(O)_nR [where n is an integer from 0 to 2 and R is hydrogen (provided that n is 0), alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, amino, monosubstituted amino, disubstituted amino, aryl, heteroaryl, aralkyl, or heteroaralkyl], —COOH, —(alkylene)—COOH, —COOR^a, —(alkylene)—COOR^a (where R^a is alkyl, heteroalkyl, aralkyl, or heteroaralkyl), —CONR^aR^b, —(alkylene)—CONR^aR^b (where R^a and R^b are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl) or an amino protecting group. More specifically the term heterocyclo includes, but is not limited to, tetrahydropyran-2-yl, piperidin-2-yl, piperazin-2-yl, morpholin-2-yl, thiomorpholin-2-yl, 1,1-dioxolane-2-yl, and the derivatives thereof.

"Heteroalkyl" means an alkyl, cycloalkyl, or cycloalkylalkyl radical as defined above, carrying a substituent selected from —NR^aR^b, —OR^c, —S(O)_nR^d, —P(O)(OR^e)₂ (OR^e), —P(O)(OR^e)R^f, or —P(O)(NR^aR^b)₂, wherein n is an integer from 0 to 2, R^a is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, heteroaralkenyl, or acyl; R^b is hydrogen, alkyl, aryl, aralkyl, acyl, —SO₂R (where R is alkyl, haloalkyl, amino, monosubstituted amino or disubstituted amino), —COOR (where R is hydrogen, alkyl, aralkyl, or heteroaralkyl), —CONR^aR^b, —(alkylene)CONR^aR^b (where R^a and R^b are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl), —P(O)(OR)₂ (where each R is independently alkyl, aryl or aralkyl), —P(O)(NR^aR^b)₂ (where R^a and R^b are independently selected from alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl), or —P(O)(OR)R^c (where R is alkyl, aryl, or aralkyl and R^c is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl); R^c is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, heteroaralkenyl, acyl, —CONR^aR^b (where R^a and R^b are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl), —P(O)(OR)₂ (where each R is independently alkyl, aryl or aralkyl), —P(O)(NR^aR^b)₂ (where R^a and R^b are independently selected from alkyl, alkenyl, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl), or —P(O)(OR)R^c (where R is alkyl, aryl, or aralkyl and R^c is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl); R^d is hydrogen (provided that n is 0), alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, amino, monosubstituted amino, or disubstituted amino; R^e and R^f are independently selected from alkyl or aryl; R^f is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; R^a and R^b are independently selected from alkyl, alkenyl, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl. Representative examples include, but are not limited to 2-methoxyethyl, benzyloxymethyl, thiophen-2-ylthiomethyl, and the like;

"Cycloalkylalkyl" means a radical —R^aR^b where R^a is an alkylene group and R^b is a cycloalkyl group as defined above e.g., cyclopropylmethyl, cyclohexylpropyl, 3-cyclohexyl-2-methylpropyl, and the like.

"Aralkyl" means a radical —R^aR^b where R^a is an alkylene group and R^b is an aryl group as defined above e.g., benzyl, phenylethyl, 3-(3-chlorophenyl)-2-methylpentyl, and the like.

"Aralkenyl" means a radical —R^aR^b where R^a is an alkenyl group and R^b is an aryl group as defined above e.g., 3-phenyl-2-propenyl, and the like.

"Heteroaralkyl" means a radical —R^aR^b where R^a is an alkylene group and R^b is a heteroaryl group as defined above e.g., pyridin-3-ylmethyl, 3-(benzofuran-2-yl)propyl, and the like.

"Heteroaralkenyl" means a radical —R^aR^b where R^a is an alkenyl group and R^b is a heteroaryl group as defined above e.g., 3-pyridin-3-ylpropen-2-yl, and the like.

"Heterocycloalkyl" means a radical —R^aR^b where R^a is an alkylene group and R^b is a heterocyclo group as defined above e.g., tetrahydropyran-2-ylmethyl, 4-methylpiperazin-1-ylethyl, and the like.

"Alkoxy", "aryloxy", "heteroaryloxy", "aralkyloxy", or "heteroaralkyloxy" means a radical —OR where R is an alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl respectively, as defined above e.g., methoxy, phenoxy, pyridin-2-yloxy, benzyloxy, and the like.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocyclo group optionally mono- or di-substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocyclo group is mono- or disubstituted with an alkyl group and situations where the heterocyclo group is not substituted with the alkyl group.

"Amino protecting group" refers to those organic groups intended to protect nitrogen atoms against undesirable reactions during synthetic procedures e.g., benzyl, benzyloxy-carbonyl (CBZ), tert-butoxycarbonyl (Boc), trifluoroacetyl, 2-trimethylsilylthanesulfonyl (SES), and the like.

Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (–)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. For example, if the R¹ and R² substituents in a compound of formula (I) are different, then the carbon

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to which they are attached is an asymmetric center and therefore the compound of formula (I) can exist as an (R)- or (S)-stereoisomer. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

"Pro-drugs" means any compound which releases an active parent drug according to formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound of formula (I) in such a way that the modifications may be cleaved in vivo to release the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group in compound (I) is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of formula (I), and the like.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

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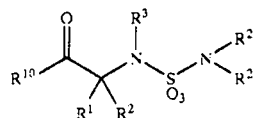
(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or
(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

Nomenclature

The naming and numbering of the compounds of this invention is illustrated below.

(I)



The nomenclature used in this application is generally based on the IUPAC recommendations, e.g., a compound of formula (I):

where R^{10} is —NHOH , R^1 is 2-propyl, R^2 is hydrogen, R^3 is benzyl, the stereochemistry at the carbon to which R^1 and R^2 are attached is (RS), and R^{20} and R^{21} together with the nitrogen atom to which they are attached form a piperidino ring substituted at the 4-position with phenoxy, is named N-hydroxy-2-(RS)-[[benzyl-4-(phenoxy)piperidino-1-sulfonyl]amino]-3-methylbutyramide

where R^{10} is —OH , R^1 is Me, R^2 and R^3 are hydrogen, the stereochemistry at the carbon to which R^1 and R^2 are attached is (RS), and R^{20} and R^{21} together with the nitrogen atom to which they are attached form a piperazino ring substituted at the 4-position with 4-chlorophenyl, is named 2-(RS)-[[4-(4-chlorophenyl)piperazine-1-sulfonyl]amino]propionic acid;

where R^{10} is —NHOH , R^1 and R^2 form a cyclopentane ring, R^3 is hydrogen, the stereochemistry at the carbon to which R^1 and R^2 are attached is (RS), and R^{20} and R^{21} together with the nitrogen atom to which they are attached form a piperazino ring substituted at the 4-position with 4-chlorophenyl, is named N-hydroxy-1-[[4-(4-chlorophenyl)piperazine-1-sulfonyl]amino]cyclopentane-1-(RS)-carboxamide;

where R^{10} is —NHOH , R^1 and R^3 form a piperidine ring, R^2 is hydrogen, the stereochemistry at the carbon to which R^1 and R^2 are attached is (R), and R^{20} and R^{21} together with the nitrogen atom to which they are attached form a piperazino ring substituted at the 4-position with phenoxy, is named N-hydroxy-1-[4-(phenoxy)piperazine-1-sulfonyl]piperidine-2-(R)-carboxamide. and

where R^{10} is —NHOH , R^2 is hydrogen, R^1 and R^3 together with the nitrogen atom to which they are attached form a piperazino ring substituted at the 4-position with N,N-dimethylaminocarbonyl and R^{20} and R^{21} together with the nitrogen atom to which they are attached form a 1,2,3,6-tetrahydropyridine substituted at the 4-position with 4-fluorophenyl, is named N-hydroxy-4-(N,N-dimethylaminocarbonyl)-1-[4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-1-sulfonyl]piperazine-2-(R)-carboxamide.

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Human prostromelysin-1 was purified from the culture medium of synovial fibroblasts by affinity chromatography using an immobilized monoclonal antibody. The zymogen was activated by treatment with trypsin (1.5 μ g/ml) for 1 hour at 23° C. to give a mixture of 45 and 28 kD species. The catalytic domain of human stromelysin-1 was prepared by expression and purification of prostromelysin-1 from *E. Coli* and activated with 1 mM APMA for 1 hour at 37° C., followed by dialysis.

Rat prostromelysin-1 was expressed in Chinese Hamster Ovary cells and purified from the culture media. It was activated by 1 mM APMA for 1 hour at 37° C., followed by dialysis.

Human promatrilysin was expressed and purified from Chinese Hamster Ovary cells as described in Barnett, J. et al., *Prot. Express. Pur.*, 5, 27, (1994). The zymogen was activated by treatment with 1 mM APMA for 1 hour at 37° C., and then purified by zinc chelate chromatography.

Example 32

Inhibition of Matrix Metalloproteases in vitro

The matrix metalloprotease inhibitory activity of compounds of this invention in vitro was determined based on the hydrolysis of MCA-Pro-Leu-Gly-Leu-DPA-Ala-Arg-NH₂ (Bachem, Inc.) at 37° C. as described in Knight, C. G., et al., *FEBS Lett.*, 296, 263-266 (1992).

The matrix metalloprotease enzyme was diluted with assay buffer (50 mM Tricine pH 7.5, 200 mM NaCl, 10 mM CaCl₂, and 0.005% Brij-35) containing 10 μ mole of above substrate dissolved in DMSO. Compounds of the invention dissolved in DMSO or only DMSO (control samples) were added such that the final DMSO concentration in all assays was 2.5%. The fluorescence changes were monitored with a Perkin-Elmer LS-50B fluorimeter using an excitation wavelength of 328 nm and an emission wavelength of 393 nm.

Compounds of this invention were active in this assay.

MMP inhibitory activities (expressed as IC₅₀, the inhibitor concentration causing 50% inhibition of the activity in the control) of some compounds of the invention were:

CPD #	Collagenase-I IC ₅₀ , nM	Collagenase-III IC ₅₀ , nM	CPD #	Collagenase-I IC ₅₀ , nM	Collagenase-III IC ₅₀ , nM
1	550	660	262	88	0.13
16	22000	21	286	29	0.063
50	220	1.3	294	>50000	340
51	490	2.6	298	130	0.2
59	110	0.18	299	>50000	410
74	7600	0.73	309	>50000	500
102	338	0.92	315	NA	0.1
105	129	0.59	342	170	2.1
106	223	0.52	345	530	6.6
133	20000	18	355	650	56
177	9300	1.6	401	250	0.19
179	23	0.073	413	9300	260
242	67	0.063	414	>50000	3400
254	>50000	181	430	2200	890
255	120	0.19	431	>50000	6500
256	26000	33			

Example 33

Degradation of Cartilage Plug in vitro

The ability of the compounds of this invention to inhibit the degradation of the collagen matrix (as judged by release of hydroxyproline) was determined by the cartilage plug degradation assay in vitro by following a slight modification of the method described in Spirito, S., Dougherty, E., et al., "Metalloproteinase inhibitors halt collagen breakdown in IL-1 induced bovine nasal cartilage cultures" *Inflamm. Res.*, 44, Supp. 2: S131-S132, (1995).

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Cartilage explants prepared from freshly sacrificed bovine knee joints were added to the culture medium (Dubelco's modified eagle medium, Gibco # 21063-001, Gibco BRL Products, Gaithersburg, Md.), without phenol red, but with HEPES, and L-glutamine and fungizone 2.5 μ g/ml, gentamicin 50 μ g/ml, penicillin 100 μ g/ml, and streptomycin 100 μ g/ml. The cultures were stimulated with IL-1- α at a final concentration of 20 ng/ml. Compounds of Formula (I), were added at concentrations between 10 and 300 nM in DMSO. The control samples contained only IL-1- α . The cultures were incubated at 37° C. in an atmosphere of air with 6% CO₂ for 21 days during which time the medium was changed twice/week. The cartilage plugs were removed, hydrolyzed and the hydroxyproline content was determined. The MMP inhibitory activity of test materials is the measure of the hydroxyproline content in the test group relative to the vehicle treated group (control group).

The MMP inhibitory activities of some compounds of this invention in this assay were:

CPD#	% protection	CPD#	% protection
50	71	60	89
51	35	100	68
59	54	242	27

Example 34

Cartilage Plug Degradation in vivo

The activity of compounds of this invention in inhibiting the destruction of the collagen matrix was determined by the cartilage plug implant assay, in rats, using a minor modification of the method described in Bishop, J., et al., *J. Pharm. Tox. Methods*, 30, 19, (1993).

In this assay, bovine nasal cartilage plugs weighing approximately 20 mg were embedded in polyvinyl sponges impregnated with Mycobacterium tuberculosis and implanted subcutaneously in female Lewis rats. After a week, test materials, dissolved in DMSO (using a volume required for 5% final volume), were administered to female rats prepared as solutions or suspensions in an aqueous vehicle containing 0.9% sodium chloride, 0.5% sodium carboxymethyl-cellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol (CMC vehicle). Control rats received vehicle alone. The experiment was terminated after 8 or 9 days. The plugs were removed, weighed, hydrolyzed, and the hydroxyproline content was measured. The MMP inhibitory activity of test materials is the measure of the hydroxyproline content in the test group relative to the vehicle treated group (control group).

The MMP inhibitory activities of some compounds of this invention in this assay were:

CPD#	% protection	CPD#	% protection
50	70	74	46
51	45	100	40
59	58	179	63

Example 35

Inhibition of TNF release in vitro Assay

The activity of compounds of this invention in inhibiting the TNF release was determined, using the a minor modification of the method described in Pradines-Figueres, A. and Raetz, C. R. H., *J. Biol. Chem.*, 267 (32), 23261, (1992).

Human Monomac 6 cells (Ziegler-Heitbrock, H. W. L., et al., *Int. J. Cancer*, 41, 456, (1988)) were cultured at 37° C.

in RPMI 1640 medium containing 10% fetal calf serum to a density of 1×10^5 cells/ml. 0.23 ml of these cells were placed in each well of a tissue culture plate and the cells were incubated for 15 min. The test compounds were dissolved in above mentioned medium and added and the incubation was continued for an additional 15 min. 10 μ l of an lipopolysaccharide/phorbol-12-myristate-13-acetate (LPS/PMA) mixture was added such that the final concentration of lipopolysaccharide was 10 ng/ml and the final concentration of phorbol-12-myristate-13-acetate was 30 ng/ml. The cells were incubated for 2 h after which the plate was centrifuged and the medium was removed and analyzed for TNF content. The analysis was performed using a TNF Quantikine® Immunoassay (R & D Systems, Minneapolis, Minn. 55413) by following the manufacturer's protocol.

Compounds of this invention were active in this assay.

The TNF- α inhibitory activity of test materials, i.e., the measure of the TNF- α content in the test group relative to the vehicle treated group (control group) was:

CPD #	Conc. μ M	% inhibition	CPD #	Conc. μ M	% inhibition
1	10	<15	298	2	70
16	10	<15	299	2	90
50	10	<15	309	2	94
74	10	17	313	2	73
102	10	56	314	2	72
105	10	20	315	2	86
106	10	41	319	2	81
133	10	32	321	2	93
177	10	<15	355	10	<15
179	10	<15	375	2	85
242	10	85	381	2	10
254	10	94	384	10	96
255	10	97	401	10	97
256	10	79	402	10	93
262	2	90	409	10	86
294	2	97			

Example 36

inhibition of LPS induced TNF- α Production in Mice in vivo Assay

The activity of compounds of this invention in inhibiting the TNF- α release was determined, using minor modification of the methods described in Zanetti, G.; Heumann, D., et. al., "Cytokine production after intravenous or peritoneal Gram-negative bacterial challenge in mice" *J. Immunol.*, 148, 1890, (1992) and Sekut, L., Menius, J. A., et. al., "Evaluation if the significance of elevated levels of systemic and localized tumor necrosis factor in different animal models of inflammation" *J. Lab. Clin. Med.*, 124, 813, (1994).

Female Balb/c mice were anesthetized and injected subcutaneously with the test compounds dissolved in CMC vehicle or hydroxypropylmethyl cellulose based vehicle. Control animals received only the vehicle. After 1 h, LPS (50 μ g/mouse, Sigma #13129, Sigma Chemical Co., St. Louis, Mo.) was injected intraperitoneally. After 1.5 h, blood was collected from the retro-orbital plexus region of the animals in a microtainer serum separator tube (Becton Dickinson, Cat. No. #5960, Becton Dickinson & Co., Franklin Lakes, N.J.). The sera was separated and the amount of TNF- α was determined using the EM-TNFA® kit (Endogen, Woburn, Mass.) by following the manufacturer's protocol.

The TNF inhibitory activities of some compounds of the invention were:

CPD #	% inhibition	CPD #	% inhibition
134	42	294	90
216	41	299	52
232	73	309	46
233	46	319	50
234	46	321	50
262	50		

Example 37

TNF Receptor Shedding Immunoassay

Human Monomac 6 cells are cultured to a density of 1×10^6 cells/mL at 37° C. in RPMI 1640 medium supplemented with 10% fetal calf serum. All subsequent incubations are performed at 37° C. 230 μ l of these cells are placed in each well of a 96-well tissue culture plate and the cells are incubated for 15 minutes. 10 μ l of desired concentration of compounds of formula (I) in the above mentioned medium are added to the appropriate wells and incubated for an additional 15 minutes. To each well is added 10 μ l of PMA at a final concentration of 30 ng/mL. The cells are then incubated for 16 hours after which the plate is centrifuged and the medium is removed and analyzed for TNF receptor content. The analysis is performed using an R & D Systems TNF receptor Quantikine® Immunoassay (Endogen, Woburn, Mass.) following the manufacturer's protocol. Measurements of each TNF receptor (receptor I and receptor II) are performed in this way. The IC₅₀ is calculated from the percent inhibition of TNF released into the medium.

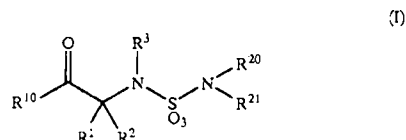
The compounds of Formula (I), when tested in this assay, exhibited the ability to selectively inhibit TNF production.

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

What is claimed:

1. A compound selected from the group of compounds represented by formula (I):



wherein:

R¹ and R² are independently selected from hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclo, heterocycloalkyl, heteroalkyl, or -(alkylene)-C(O)-X where X is alkyl, haloalkyl, alkoxy, haloalkyloxy, amino, monosubstituted amino, disubsti-

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

2020
Bogotá, D.C.

Abogado
CARLOS R. OLARTE
Apoderado

ASUNTO	Radicación	04122695-A
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	No 5 9 4 3
	Folios	002

Como resultado del examen de búsqueda de anterioridades y con fundamento en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina 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 excederán de 3 meses, uno o más de los siguientes documentos relativos a una o más de las 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 invención, se determinó que existen en el estado de la técnica los siguientes documentos, que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- SANCHEZ J P ET AL : « QUINOLONE ANTIBACTERIAL AGENTS. SYNTHESIS AND STRUCTURE- ACTIVITY RELATIONSHIPS OF A SERIES OF AMINO ACID PRODRUGS OF RACEMIC AND CHIRAL 7-(3-AMINO – 1-PYRROLIDINYLQUINOLONES, HIGHLY SOLUBLE QUINOLONE PRODRUGS WITH IN VIVO PSEUDOMONAS ACTIVITY » JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 10, 15 May 1992, pages 1764-1773, XP001026653. ISSN : 0022.2623.

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO equivalente a esta solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione las publicaciones completas, 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 quinto (5), del título primero de la circular única N° 10 de 2001.


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

El anterior requerimiento fue notificado por fijación en lista, de fecha _____, **22 MAYO 2009**

CONCEPTO TÉCNICO Nº: 1022	EXAMINADOR TÉCNICO Código N°: 202087	EXAMINADOR JURÍDICO Código N°:
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE
Apoderado

ASUNTO	Radicación	04122695-A
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	Nº 5 9 4 2
	Folios	421

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒
No. Sol. Internacional	PCT/US03/15405		
Fecha de Presentación Internal.	6/06/2003		

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

1. Documentos estudiados

Descripción: Folios 178 a 375 solicitud de divisional no aceptada inicialmente

Reivindicaciones: Folios 376 a 384 solicitud de divisional no aceptada inicialmente por lo cual se encuentra en la divisional original
Folios 385 a 390 reivindicaciones de la solicitud de divisional modificadas como respuesta del solicitante al artículo 45 de la divisional original.
Folios 401 a 405 reivindicaciones modificadas de la solicitud de divisional como respuesta del solicitante al primer examen de fondo de la divisional.

Prioridad: Fecha: 11/06/2002 y 3/10/2002
País: EP y US
Número: 02380120.2
02380121.0
60/415.936
60/415.937

Respuesta del solicitante: Folios: 397 a 405

2. Objeto de la invención

- Título de la solicitud: Profármacos de aminoácidos excitadores. número de folio: 2.

El problema planteado en esta solicitud es la necesidad de compuestos útiles para trastornos neurológicos y psiquiátricos que mejoren la potencia in vivo del compuesto precursor respectivo y produzcan mayor exposición oral del precursor con mayor biodisponibilidad oral.

Para solucionar este problema técnico la solicitud en estudio proporciona profármacos de aminoácidos sintéticos para el tratamiento de trastornos neurológicos y trastornos psiquiátricos.

Clasificación Internacional de Patentes (IPC.): A61K38/05

3. Determinación del Estado de la Técnica

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

Fecha de presentación de la solicitud prioritaria 11/06/2002

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

Nº	Documento	Título	Fecha de publicación*
D ₁	US5688826	EXCITATORY AMINO ACID DERIVATIVES	18/11/1997
D ₂	US 5998412	SULFAMIDE – METALLPROTEASE INHIBITORS	1999/12/7

4. Análisis de patentabilidad (artículo 14 D486)

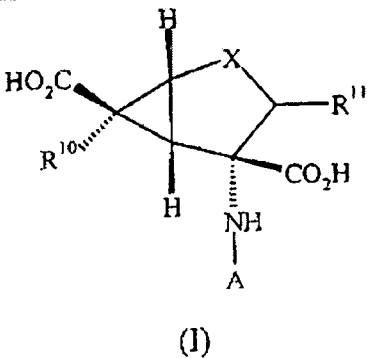
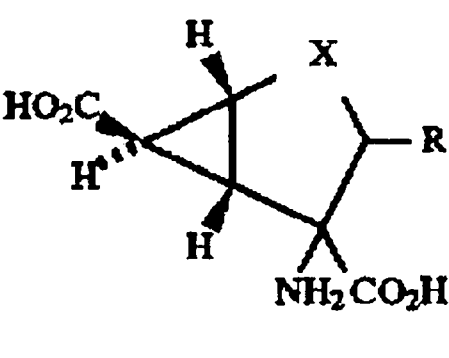
La presente Solicitud de Patente reivindica (de 1 – 12) un compuesto de fórmula general (I) y (13) una formulación que comprende dicho compuesto más un vehículo, diluyente o excipiente:

Dicho compuesto se ve afectado por los siguientes documentos del Estado de la Técnica:

D₁ que enseña según tabla 1-A (ver folio 391, abstract) compuestos útiles como moduladores del receptor de glutamato metabotrópico.

D₂ que enseña que la modificación de un compuesto activo conocido con aminoácidos es una práctica normal para incrementar la solubilidad en agua y la biodisponibilidad del compuesto de origen (ver folios 407-408).

TABLA 1-A

SOLICITUD		ANTERIORIDAD (D ₁)		comparación
(I)		(I)		
R ₁₀	H		H	IGUAL
X	SO ₂	X	SO ₂	IGUAL
A	H-(Q) ₁₋₁₀ ⁻ Q se selecciona independientemente del grupo amino acilo derivado de un aminoácido natural o no natural		H	DIFERENTE grupo amino acilo o aminoácido adicional
R ₁₁	H	R	H	IGUAL

La única **diferencia con D₁** es que esta solicitud **agrega un aminoácido** como sustituyente adicional en “A” pero esta diferencia no parece conceder ningún efecto inesperado.

De esta forma el **efecto técnico logrado por esta diferencia** es mayor solubilidad y biodisponibilidad del compuesto original por ser convertido en profármaco de mismo.

Por lo tanto **el Problema Técnico Objetivo fundamental** de la Invención Reivindicada se define en: “Cómo conseguir profármacos de los compuestos aminoácidos excitadores para que se conviertan a la forma activa de agonistas mGluR2”, siendo tan solo una alternativa, sin algún efecto inesperado que los haga superior a lo previamente conocido.

Por consiguiente resultaría obvio el diseño de este tipo de compuestos y formulaciones para un experto en la materia que conozca el estado de la técnica ya que **D2 también sugería previamente** que la modificación de un compuesto activo conocido pegandole aminoácidos, es una práctica normal para incrementar la solubilidad en agua y la biodisponibilidad del compuesto de origen por lo tanto haría una combinación de éstos documentos llegando de tal manera a la propuesta de la presente solicitud, adicionalmente se considera obvio para un experto en la materia saber que la administración de una forma profármaco de un compuesto se convierta en el principio activo deseado en el organismo y su biodisponibilidad se vea incrementada por esta causa

En conclusión no se considera que la presente solicitud posea nivel inventivo.

5. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D ₁	US5688826	1-13	NIVEL INVENTIVO

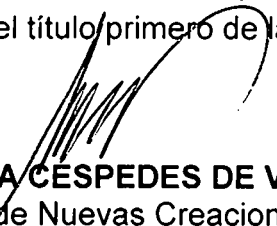
D ₂	US 5998412	1-13	NIVEL INVENTIVO
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6. Respuesta a los argumentos del solicitante:

- Se subsanan las objeciones presentadas al capítulo reivindicatorio mediante la eliminación de las reivindicaciones 5, 8 y 14 y las modificaciones a la reivindicación 1.
- Ante la solicitud esbozada en la respuesta del solicitante (folio 399, página 3) para que se muestren los apartes específicos en el estado de la técnica que hubieran conducido a una persona medianamente versada en la materia a incluir un grupo aminoácido en el núcleo farmacofórico de los compuestos divulgados, se ha añadido el documento D₂ y en aras de demostrar la misma situación se solicita adicionalmente, mediante artículo 46 el documento "QUINOLONE ANTIBACTERIAL AGENTS. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF A SERIES OF AMINO ACID PRODRUGS OF RACEMIC AND CHIRAL 7-(3-AMINO – 1- PYRROLIDINYLQUINOLONES, HIGHLY SOLUBLE QUINOLONE PRODRUGS WITH IN VIVO PSEUDOMONAS ACTIVITY " que enseña el pro fármaco alanil de la quinolona que muestra un incremento de 400 veces la solubilidad del compuesto activo el cual es rápidamente distribuido in vivo y que ha resultado además más activo que el compuesto original, solamente por pegar aminoácidos lo cual resultaba ser normal en la práctica para incrementar la solubilidad en agua y la biodisponibilidad del medicamento de origen.
- No se considera como argumento válido el hecho de que haya sido otorgada la patente en otro país ya que cada país es responsable de sus propios exámenes de patentabilidad.

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

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


ALIX CARMENZA CÉSPEDES DE VERGEL
 Jefe de División de Nuevas Creaciones

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

22 MAYO 2009

CONCEPTO TÉCNICO No. 1022	EXAMINADOR TÉCNICO Código No. 202087
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