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CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. **06.029.514**

Solicitud del examen de patentabilidad correspondiente a la Patente PCT Entrada en Fase Nacional, para:

"DERIVADOS DE IMINOACIDOS BICICLICOS COMO INHIBIDORES DE METALOPROTEINASAS DE MATRIZ"

Solicitante: **SANOFI-AVENTIS DEUTSCHLAND GMBH**

SOLICITUD EXAMEN DE PATENTABILIDAD

(CAPITULO I)

Yo, **LUIS PATIÑO LEYVA**, mayor de edad, identificado y domiciliado como aparece al pié de mi firma, obrando en mi calidad de apoderado de la sociedad solicitante, atentamente me permito solicitar a Ud. que se realice el examen de patentabilidad de la invención arriba citada, para lo cual anexo el comprobante de pago **No. 08-** 47.151 de **Junio** 12 **de 2008,** correspondiente a la tasa establecida para dicha solicitud.

En consecuencia, atentamente solicito a Ud. se anexe este memorial junto con el comprobante de pago al expediente correspondiente a esta solicitud de Patente PCT Entrada en Fase Nacional, y se continúe con su tramitación.

Señor Jefe,

Luis Patiño Leyva
C.C. No. **2.930.616** de Bogotá
T.P.A. No. **2.698** del C. S. J.
Calle 94 A No. 7 A-09 - Bogotá, D.C.
Teléfono (PBX): 610 7420

Bogotá, 13 JUN. 2008
LPL/gcb/P20206 (57946)

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 06-029514- -00005-0000

Fecha: 2008-06-13 15:53:23 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 538 PETICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 47,151
FECHA : JUNIO 12 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	341563	12/06/2008	5,445,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
			TOTAL : $	420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-29514

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **584** DE

FECHA **31 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **31 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___

US006207672B1

(12) **United States Patent**
Thorwart et al.

(10) **Patent No.: US 6,207,672 B1**
(45) **Date of Patent: Mar. 27, 2001**

(54) **CYCLIC AND HETEROCYCLIC N-SUBSTITUTED α-IMINOHYDROXAMIC AND CARBOXYCLIC ACIDS**

(75) Inventors: **Werner Thorwart**, Hochheim; **Wilfried Schwab**, Wiesbaden; **Manfred Schudok**, Hattersheim; **Burkhard Haase**, Maintal; **Eckart Bartnik**, Wiesbaden-Delkenheim; **Klaus-Ulrich Weithmann**, Hofheim, all of (DE)

(73) Assignee: **Aventis Pharma Deutschland GmbH**, Frankfurt am Main (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/068,497**

(22) PCT Filed: **Nov. 4, 1996**

(86) PCT No.: **PCT/EP96/04776**

§ 371 Date: **Mar. 9, 1999**

§ 102(e) Date: **Mar. 9, 1999**

(87) PCT Pub. No.: **WO97/18194**

PCT Pub. Date: **May 22, 1997**

(30) **Foreign Application Priority Data**

Nov. 13, 1995 (DE) 195 42 189
Mar. 28, 1996 (DE) 196 12 298

(51) **Int. Cl.**[7] **A61K 31/472**; A61K 31/403; C07D 455/02; C07D 453/02

(52) **U.S. Cl.** **514/279**; 514/312; 514/314; 514/423; 546/134; 546/136; 548/540

(58) **Field of Search** 514/210, 212, 514/312, 314, 423, 279; 546/134, 136; 548/540

(56) **References Cited**

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5,506,258 * 4/1996 Christophe et al. 514/423

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0 606 046 A1 7/1994 (EP) .
0 614 911 A1 9/1994 (EP) .

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R. Tripathi et al. "Synthesis and SAR studies in 2-substituted 1,2,3,4-tetrahydro-9H-pyrido-[3,4-b] indole-3-carboxylic acids—A new class of potent antiulcer agents", Indian Journal of Chemistry, 28B(4):333-337 (1989).

Abstract No. 76983z, XP002023924, Chemical Abstracts, 112(9), 1990.

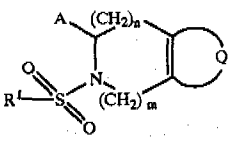
* cited by examiner

Primary Examiner—Alan L. Rotman
Assistant Examiner—Rita Desai
(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

(57) **ABSTRACT**

Compounds of the formula I

(I)



are suitable for preparing pharmaceuticals for the treatment of disorders in the course of which is involved an increased activity of matrix-degrading metalloproteinases.

12 Claims, No Drawings

CYCLIC AND HETEROCYCLIC N-SUBSTITUTED α-IMINOHYDROXAMIC AND CARBOXYCLIC ACIDS

This application is filed under 35 U.S.C. § 371 from Application No. PCT/EP96/04776, filed Nov. 4, 1996.

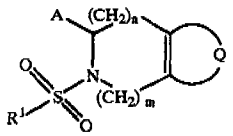
The invention relates to cyclic and heterocyclic N-substituted α-imino-hydroxamic and -carboxylic acids, to processes for their preparation and to their use as pharmaceuticals.

EP 0 606 046 discloses some arylsulfonamidohydroxamic acid derivatives and their action as matrix metalloproteinase inhibitors.

In the effort to find further efficacious compounds for the treatment of connective tissue disorders, it has now been found that the imino-hydroxamic acid derivatives according to the invention are inhibitors of metalloproteinases.

The invention relates to a compound of the formula I

(I)



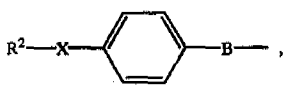
and/or an optionally stereoisomeric form of the compound of the formula I and/or a physiologically tolerable salt of the compound of the formula I,

where in the case i)

R^1 is

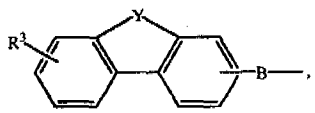
a) a radical of the formula II

(II)



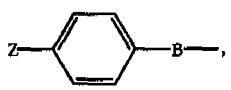
b) a radical of the formula III

(III)



c) a radical of the formula IV

(IV)



where Z is a radical of a heterocycle or a substituted heterocycle such as

1) pyrrole,
2) thiazole,
3) pyrazole,
4) pyridine,
5) imidazole,
6) pyrrolidine,
7) piperidine,

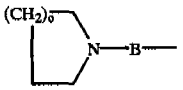
8) thiophene,
9) oxazole,
10) isoxazole,
11) morpholine or
12) piperazine,

d) naphthyl,

e) naphthyl, mono- or trisubstituted by R^2, or

f) a radical of the formula V

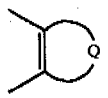
(V)



where o is the number 1 or 2 and one of the carbon atoms in the ring may be replaced by —O— or —S—, and

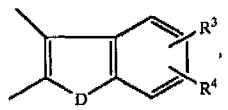
Q as part of the structural formula I

(I)



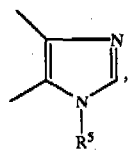
1) is the structural moiety VI

(VI)



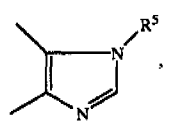
2) the structural moiety VII

(VII)



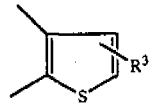
3) is the structural moiety VIII

(VIII)



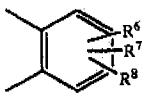
4) the structural moiety IX

(IX)



5) is the structural moiety X

(X)



R^2 is
1) phenyl or
2) phenyl which is mono- to trisubstituted by
2.1 hydroxyl,
2.2 —O—R^{10}, where R^{10}
1) is (C_1–C_6)-alkyl,
2) is (C_3–C_6)-cycloalkyl,
3) is benzyl or
4) is phenyl,
2.3 —COOH,
2.4 (C_1–C_6)-alkyl,
2.5 (C_3–C_6)-cycloalkyl-O-(C_1–C_4)-alkyl,
2.6 halogen,
2.7 —CN,
2.8 —NO_2,
2.9 —CF_3,
2.10 —O—C(O)—R^{10} and R^{10} is as defined above,
2.11 —O—C(O)-phenyl, mono- or disubstituted by R^3,
2.12 —C(O)—O—R^{10} and R^{10} is as defined above,
2.13 methylenedioxo,
2.14 —C(O)—$NR^{11}R^{12}$, where
R^{11} and R^{12} may be identical or different and each is
1) a hydrogen atom,
2) (C_1–C_4)-alkyl or
3) benzyl or
4) R^{11} and R^{12} together with the linking nitrogen atom form a pyrrolidine, piperidine, morpholine or piperazine radical, or
2.15 —$NR^{13}R^{14}$, where
R^{13} is a hydrogen atom or (C_1–C_4)-alkyl and R^{14}
1) is a hydrogen atom,
2) is (C_1–C_4)-alkyl,
3) is benzyl,
4) is —C(O)—R^{10} or
5) is —C(O)—O—R^{10},

R^3 and R^4 are identical or different and each is
1) a hydrogen atom,
2) (C_1–C_5)-alkyl,
3) (C_1–C_5)-alkoxy,
4) halogen,
5) hydroxyl,
6) —O—C(O)—R^{10} and R^{10} is as defined above, or
7) R^3 and R^4 together form the radical —O—CH_2—O—,

R^5 is
a) a hydrogen atom,
b) (C_1–C_5)-alkyl or
c) benzyl, and

R^6, R^7 and R^8 are identical or different and each is
a) a hydrogen atom, or
b) has, in the case of i), the meaning of R^2 under items 2.1 to 2.14, and

n is zero, 1 or 2,

m is zero, 1 or 2, the sum of n and m being 1, 2 or 3, or

where in the case ii)

R^1 is
1) phenyl or
2) phenyl, mono- to trisubstituted by R^2 where R^2 is as defined for the case i) under items 2.1 to 2.15,

Q is the structural moiety X and

R^6, R^7 and R^8 are identical or different and each is defined as above,

n is 1 and

m is 1, or

where in the case iii)

R^1, Q, R^6, R^7 and R^8 are identical or different and each has the meaning mentioned for the case ii),

m and n are zero, 1 or 2 and where the meanings of n and m are not identical, and

X is
a) a covalent bond,
b) —O—,
c) —S—,
d) —S(O)—,
e) —$S(O)_2$—,
f) —C(O)— or
g) —C(OH)—, and

Y is
a) —O— or
b) —S—, and

A is HO—NH— C(O)— or HO—C(O)— and

B is
a) —$(CH_2)_q$—, where q is zero, 1, 2, 3 or 4, or
b) is —CH=CH—.

Preference is given to a compound of the formula I and/or a physiologically tolerable salt of the compound of the formula I and/or an optionally stereoisomeric form of the compound of the formula I, where

R^1 in the case i) is a radical of the formula II or III and Q is the structural moiety VI, VII, VIII or X,

R^1 in the case ii) is phenyl or phenyl, mono- to trisubstituted by methoxy, and Q is the structural moiety X, or

R^1 in the case iii) is phenyl, Q is the structural moiety X, n is zero and m is 2, and

A is HO—NH—C(O)— or HO—C(O)—,

B is a covalent bond,

X is an oxygen atom or a covalent bond, and

R^2 is phenyl or phenyl substituted by
a) hydroxyl,
b) —O—R^{10}, where R^{10} is (C_1–C_3)-alkyl or benzyl,
c) (C_1–C_2)-alkyl,
d) fluorine or chlorine,
e) —CN,
f) —CF_3 or
g) $NR^{13}R^{14}$, where R^{13} and R^{14} are each (C_1–C_3)-alkyl,

R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each is
a) a hydrogen atom,
b) methoxy,
c) methylenedioxo,
d) amino or
e) hydroxyl.

Particular preference is given to the compounds

R-2-(biphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3-hydroxamic acid,

R-2-(4-chlorobiphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3-hydroxamic acid,

R-2-(4-chlorobiphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

R-2-(4-phenoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3-hydroxamic acid,

R-2-(4-phenoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

R-2-(4-(4-dimethylaminophenoxy)benzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3-hydroxamic acid,

R-2-(4-dimethylaminobiphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

R-2-(4-benzoylphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3-hydroxamic acid,

R-2-(4-methoxybenzenesulfonyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-hydroxamic acid,

R-2-(4-methoxybenzenesulfonyl)-7-nitro-1,2,3,4-tetrahydroisoquinoline-3-hydroxamic acid,

2-(4-methoxybenzenesulfonyl)-6,7-propylene-1,2,3,4-tetrahydroisoquinoline-1-hydroxamic acid,

R-5-(4-methoxybenzenesulfonyl)4,5,6,7-tetrahydro-1H-imidazo-(4,5-c)-pyridine-6-hydroxamic acid,

R-2-(4-methoxybenzenesulfonyl)-1,2,3,4-tetrahydro-9H-pyrido-(3,4-c)-indole-3-hydroxamic acid,

R-2-(4-phenoxybenzenesulfonyl)-1,2,3,4-tetrahydro-9H-pyrido-(3,4-c)-indole-3-hydroxamic acid.

Furthermore, particular emphasis is given to those compounds of the formula I where the central carbon atom between amino and acid group is present as R enantiomer.

The term halogen is understood as meaning fluorine, chlorine, bromine or iodine. The term alkyl or alkoxy is understood as meaning radicals whose carbon chain may be straight-chain, branched or cyclic. Cyclic alkyl radicals are, for example, 3- to 6-membered monocycles such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

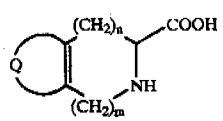
The "heterocycles of the formula V" include, for example, thiomorpholine, piperidine, morpholine or piperazine.

Suitable physiologically tolerable salts of the compound of the formula I are, for example, alkali metal, alkaline earth metal and ammonium salts including those of organic ammonium bases or basic amino acids.

The invention also provides a process for preparing the compound of the formula I and/or a physiologically tolerable salt of the compound of the formula I and/or an optionally stereoisomeric form of the compound of the formula I which comprises

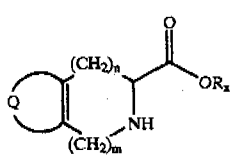
a) reacting an imino acid of the formula XI

(XI)



where the radical Q and n and m are as defined in the formula I with a (C_1–C_4)-alcohol or a benzyl alcohol to give the compound of the formula XII

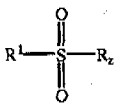
(XII)



where R_x is (C_1–C_4)-alkyl or benzyl, or

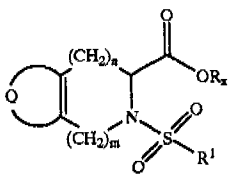
b) reacting a compound of the formula XII prepared according to process a) with the compound of the formula XIII

(XIII)



where R^1 is as defined in formula I and R_Z is a chlorine atom, imidazolyl or —OH, in the presence of a base or, if appropriate, a dehydrating agent to give a compound of the formula XIV

(XIV)

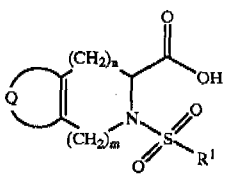


where Q, R^1, n and m are as defined in formula I and R_x is as defined in formula XII, or

c) reacting a compound of the formula XII prepared according to process a) with a base and subsequently with a compound of the formula XIII to give a compound of the formula XIV, or

d) reacting a compound of the formula XI with a compound of the formula XIII to give a compound of the formula XV

(XV)



where Q, R^1, n and m are as defined in formula I, or

e) reacting a compound of the formula XIV to give a compound of the formula XV, or

f) reacting a compound of the formula XIV prepared according to process b) or c) with the hydroxylamine of the formula XVI

H_2N—OR_y (XVI)

where R_y is a hydrogen atom or a protective group for oxygen, to give the compound of the formula I and, if appropriate, removing the protective group for oxygen, or

g) reacting a compound of the formula XV prepared according to process d) or e) with the hydroxylamine of the formula XVI to give the compound of the formula I, or

h) separating into the pure enantiomers a compound of the formula I prepared according to process f) or g) which, owing to its chemical structure, exists in enantiomeric forms, by forming salts with enantiomerically pure

acids or bases, chromatography using chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the resulting diastereomers, and removal of the chiral auxiliary, or

i) isolating the compound of the formula I prepared according to processes f), g) or h) either in free form or, if acidic or basic groups are present, converting it, if appropriate, into physiologically tolerable salts.

In the case of the (C_1–C_4)-alcohols, the reaction according to process step a) is carried out under customary reaction conditions in the presence of HCl gas or thionyl chloride. The preparation of the corresponding benzyl esters of the formula XII is carried out in benzene or toluene using the appropriate alcohol and an acid such as p-toluenesulfonic acid. Tert-butyl esters can be prepared, for example, by known processes using isobutene and sulfuric acid.

The reaction according to process step b) is carried out in the presence of a basic compound such as N-methylmorpholine (NMM), N-ethylmorpholine (NEM), triethylamine (TEA), diisopropylethylamine (DIPEA), pyridine, collidine, imidazole or sodium carbonate in solvents such as tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide, dioxane, acetonitrile, toluene, chloroform or methylene chloride, or even in the presence of water. Preference is given to using the sulfonyl chlorides of the formula XIII in the presence of NMM in THF.

The reaction according to process step c) is carried out in the presence of a base such as KOH, LiOH or NaOH.

The reaction according to process step d) is carried out in an aqueous organic solvent system, preferably in THF and water in the presence of a base such as sodium carbonate and the compound of the formula XIII. Furthermore, the reaction can be carried out in the absence of solvent with or without base under reduced pressure, as obtained by use of an oil pump.

The hydrolysis of the compound of the formula XIV to give the compound of the formula XV (process step e) is carried out, for example, basic, preferably acidic or, in the case of the benzyl derivatives, by hydrogenolysis. In the case of basic hydrolysis, it is necessary to free the carboxylic acid from the carboxylic acid salt by treatment with another acid, for example dilute hydrochloric acid.

The reaction according to process step f) is carried out under the conditions which are customary for the formation of carboxamides, in a suitable solvent, for example an alcohol or dimethylformamide.

For the reaction according to process step g), the carboxylic acids of the formula XV are activated. Activated carboxylic acids are, for example, acyl halides, acyl azides, mixed anhydrides and carbonates. Preference is given to acyl chlorides or fluorides, mixed anhydrides and carbonates of pivaloyl chloride, ethyl, isopropyl or isobutyl chloroformate; active esters such as cyanoethyl, o- or p-nitrophenyl, succinimido or phthalimido, and to the activated carboxylic acids which are obtainable using coupling reagents such as diisopropylcarbodiimide (DIC), carbonyldiimidazole (CDI), dicyclohexylcarbodimide (DCC) or benzotriazolyltetramethyluronium tetrafluoroborate (TBTU), if appropriate with addition of hydroxybenzotriazole (HObt) or oxohydroxybenzotriazine (HOObt), preferred solvents being aprotic solvents.

The starting materials and reagents employed can either be prepared by known processes, or they are commercially available.

Suitable imino acids of the formula XI where n and m are 1 its, for example, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,2,3,4-tetrahydro-9H-pyrido(3,4-b)-indole-3-carboxylic acid or optionally 1- or 3-substituted 4,5,6,7-tetrahydro-1H-imidazo-(4,5-c)-pyridine-6-carboxylic acids. They are preferably prepared by cyclizing the corresponding amino acids with formaldehyde in the presence of an acid such as hydrochloric acid or sulfuric acid using the method of Pictet-Spengler (see W. M. Whaley, Organic Reactions 6 (1951) 151.

In the case that in the imino acid of the formula XI n is zero and m is 2, it is possible to use, for example, 1,2,3,4-tetrahydro-9H-pyrido(3,4-b)indol-1-carboxylic acid and 6,7-propylene-1,2,3,4-tetraisoquinoline-1-carboxylic acid as starting material. To prepare the latter compound, indane is Friedel-Crafts alkylated with phenylsulfonylarziridine. The cyclization of the resulting 4-(2-benzenesulfonamidoethyl) indane is carried out using glyoxylic acid in HBr/glacial acetic acid; the subsequent cleavage of the benzenesulfonyl radical is carried out using iodine/red phosphorus in HBr/glacial acetic acid.

An example of the case where in the compound XI n is 1 and m is zero is indoline-2-carboxylic acid. It is prepared, for example, by catalytic hydrogenation of indol-2-carboxylic acid. Furthermore, mention may be made of the cyclization of 2-chlorophenylalanine or 2-hydroxy-3-(2-chlorophenyl)-propionic acid to give imino acids of the formula XI.

If compounds of the formula I permit diastereomeric or enantiomeric forms and are obtained as mixtures thereof in the synthesis chosen, separation into the pure stereoisomers is possible either by chromatography over an optionally chiral carrier material or, if the racemic compound of the formula I or a compound of the formula XI is capable of forming salts, by fractional crystallization of the diastereomeric salts formed with an optically active base or acid as auxiliary. Suitable chiral stationary phases for thin-layer- or column-chromatographic separation of enantiomers are, for example, modified silica carriers (Pirkle phases) and high-molecular-weight carbohydrates such as triacetylcellulose. For analytical purposes, gas-chromatographic methods using chiral stationary phases may also be used, after appropriate derivatization known to the person skilled in the art. The enantiomers of racemic carboxylic acids are separated using an optically active, usually commercially available base such as (−)-nicotine, (+)- and (−)-phenylethylamine, quinine bases, L-lysine or L- and D-arginine to form the diastereomeric salts, which differ in solubility. The less soluble component is isolated as a solid, the more soluble diastereomer is recovered from the mother liquor, and the pure enantiomers are obtained from the resulting diastereomeric salts. In basically the same manner, the racemic compounds of the formula I which contain a basic group such as an amino group can be converted into the pure enantiomers using optically active acids such as (+)-camphor-10-sulfonic acid, D- and L-tartaric acid, D- and L-lactic acid and (+) and (−)-mandelic acid. It is also possible to convert chiral compounds containing alcohol or amine functions into the corresponding esters or amides using appropriately activated or optionally n-protected enantiomerically pure amino acids, or, conversely, to convert chiral carboxylic acids into the amides using carboxyl-protected enantiomerically pure amino acids, or into the corresponding chiral esters using enantiomerically pure hydroxycarboxylic acids such as lactic acid. The chirality of the enantiomerically pure amino acid or alcohol radical can then be employed to separate the isomers by resolving the diastereomers that are now present using crystallization or chromatography over suitable stationary phases and then

166

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
LUIS PATIÑO LEYVA
(Apoderado)

ASUNTO	Radicación	06029514
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	№ 08204
	Folios	010

Patente de Invención [X] Patente de Modelo de Utilidad [ ]

Vía Nacional [ ]

Vía PCT (fase nacional) [X] Cap.I [X] Cap. II [ ]

No. Sol. Internacional PCT/EP2004/010248
Fecha de Presentación Internacional 14-09-2004

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:

1.1. Descripción: (Folios: 52 a 105) como se radicó inicialmente.

1.2. Reivindicaciones: 1 a 9 (Folios: 106 a 129) como se radicó inicialmente.

1.3. Prioridad: 27/09/2003, DE 10344936.1.

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. **Objeto de la invención:**

La presente solicitud se titula: "Derivados de iminoácidos bicíclicos como inhibidores de metaloproteinasas de matriz".

El objeto de la presente solicitud se refiere a derivados de iminoácidos bicíclicos saturados, en particular, ácido decahidroisoquinolino-1-carboxílico, a métodos para prepararlos y a su uso como productos farmacéuticos.

Según la descripción, en enfermedades como la osteoartritis y el reumatismo, tiene lugar la destrucción de las articulaciones, y esta destrucción está provocada por la descomposición proteolítica del colágeno debido a las colagenasas; éstas pertenecen a la superfamilia de las metaloproteinasas (MP) o metaloproteinasas de matriz (MMP). Las MMP forman un grupo de enzimas dependientes de Zn que están involucradas en al descomposición biológica de la matriz extracelular.

La actividad de las MMP es esencial además para muchos procedimientos que desempeñan una función en la formación de la placa aterosclerótica, como la infiltración de células inflamatorias y la migración de células de músculos lisos, así como en la proliferación y angiogénesis.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 6 (folios: 106 a 127): Un compuesto de fórmula I y/o todas las formas estereoisómeras del compuesto de fórmula I y/o mezclas de estas formas en cualquier relación y/o una sal fisiológicamente tolerada del compuesto de fórmula I.

Reivindicación 7 (folios: 127 a 129): Un procedimiento para preparar el compuesto de la fórmula I.

Reivindicación 8 (folio: 129): Un producto farmacéutico que comprende un contenido eficaz de al menos un compuesto de fórmula I junto con una sustancia portadora farmacéuticamente adecuada y fisiológicamente tolerada, un aditivo y/o otros compuestos activos y sustancias auxiliares.

Reivindicación 9 (folio: 129): El uso de un compuesto de fórmula I.

El problema planteado en esta solicitud es la necesidad de compuestos inhibidores de MMP con mayor especificidad.

La solución propuesta por la presente solicitud consiste en compuestos derivados de iminoácidos bicíclicos de fórmula I, que son inhibidores de MMP-2, MMP-3, MMP-8, MMP-9 y MMP-13.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 495/04, 217/24, 217/26.

4. **De la solicitud de Patente**

4.1. Descripción *(artículo 28 D. 486)*

De acuerdo con lo revelado en la descripción, el título de la solicitud debe hacer alusión a los compuestos específicos que se están reclamando y no a la actividad que éstos puedan tener.

4.2. Reivindicaciones *(artículo 30 D 486)*

De acuerdo con lo revelado en el capítulo reivindicatorio, es bastante amplio puesto que los significados de los sustituyentes son demasiados y resulta un número elevado de compuestos, lo cual le resta concisión a lo que se pretende proteger y dichos compuestos pueden no estar suficientemente sustentados en la descripción. Por ejemplo: "het de 4 a 15 miembros" resultan anillos muy distintos unos de otros, además, no se dice cuál o cuáles heteroátomos tiene, ni las posiciones en los que se encuentran ni puntos de unión al núcleo principal o grupo enlazante. Los significados para "G" son demasiados y resulta un alto número de compuestos, que pueden ser diferentes entre sí. Se deben revisar otros sustituyentes del compuesto que se está reclamando.

5. **Reivindicaciones relativas a un uso o a un uso distinto** *(artículos 14 y 21 D 486)*

La(s) reivindicación (es) 9 (folio: 129), que se refiere(n) a el uso de un compuesto de fórmula I, no se encuentra(n) dentro del campo de la patentabilidad (productos y procedimientos).

6. **Análisis de la(s) Oposición(es):** *(artículo 43 D. 486)*

No se presentaron oposiciones al objeto reivindicado en la presente solicitud de patente.

7. **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 27-09-2003.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

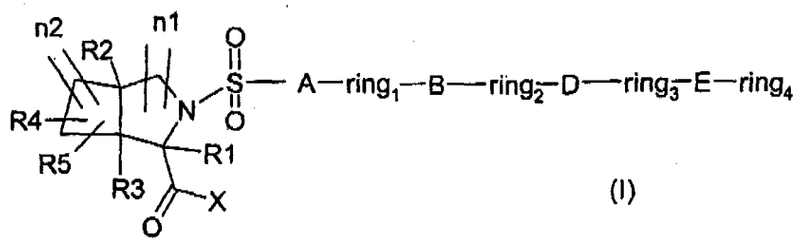
Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	US 6207672	Cyclic and heterocyclic N-substituted α-iminohydroxamic and carboxyclic acids	27 de marzo de 2001

8. Análisis de patentabilidad (artículo 14 D486)

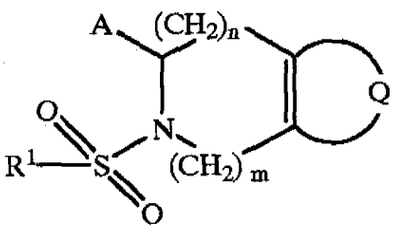
8.1. Nivel inventivo *(artículo18 D486)*

La presente Solicitud de Patente reivindica lo siguiente: Un compuesto de fórmula I



(I)

La anterioridad se relaciona con compuestos derivados de ácido α-iminohidroxámico y carboxíclico de fórmula I:



Estos compuestos de la anterioridad también son inhibidores de MMP tal como los compuestos de la presente solicitud. A lo largo de la solicitud en estudio no se encuentran las ventajas técnicas frente a la anterioridad US 6207672 y en donde se pueda observar que los compuestos de la presente solicitud tienen una mayor especificidad frente a MMP.

El problema técnico planteado en esta solicitud: la necesidad de compuestos inhibidores de MMP con mayor especificidad, se había resuelto previamente mediante compuestos iminoácidos bicíclicos ya conocidos(as). Por esta razón se considera que las sustituciones de los iminoácidos bicíclicos reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

Las reivindicaciones 1 a 8 de esta solicitud no mencionan una característica que conceda un efecto inesperado o especial a los compuestos, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1 divulgaba previamente compuestos iminoácidos bicíclicos inhibidores de MMP (folios: 161 a 165), una persona conocedora de la materia

motivada por tal sugerencia lograría el objeto de esta solicitud compuestos derivados de iminoácidos bicíclicos; de manera que para una persona medianamente versada en la materia sería obvio utilizar este documento. Por lo cual puede no haber Nivel Inventivo.

9. **Conclusión:**

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US 6207672	1 a 8	Nivel Inventivo

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

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

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

El anterior requerimiento fue notificado por fijación en lista, de fecha 17 JUL. 2009

CONCEPTO TÉCNICO No. 2335	**EXAMINADOR TÉCNICO** Código No. 202005