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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señora

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo Industria y Turismo

E. S. D.

Ref.: Expediente No. 09.022.192

Solicitud de Patente de Invención Fase Nacional para: **DERIVADOS DE TARTRATO
PARA USO COMO INHIBIDORES DEL FACTOR DE COAGULACION IXA**

Solicitante: **SANOFI-AVENTIS**

RESPUESTA A EXAMEN DE FORMA

LUIS PATIÑO LEYVA, mayor de edad, identificado y domiciliado como aparece al pie de mi firma, en atención a su oficio No. 8136 notificado el 17 de julio de 2009, atentamente me permito dar respuesta al mismo de la siguiente manera:

Establece el funcionario examinador lo siguiente:

"...el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional del tratado PCT."

Con el objeto de atender a las anteriores observaciones, presento copia del Reporte Preliminar Internacional sobre Patentabilidad Capítulo II en inglés y la traducción a español de los anexos.

Cumplido así con lo dispuesto, atentamente solicito a Ud. se continúe con el trámite correspondiente a esta solicitud de Patente de Invención.

De la Señora Jefe,

Luis Patiño Leyva

C.C. No. 2.930.616 de Bogotá

T.P.A. No. 2698 del C. Sup. de la Judicatura

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10 SET. 2009

Bogotá, D.C.,

Patentes/P20235/MEMORIAL FORMA

(PCT Article 36 and Rule 70)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/EP2007/007612

Box No. I

Basis of the report

1. With regard to the language, this report is based on:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rule 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):

- ☐ the international application as originally filed/furnished
- ☒ the description:
- pages 1-34 as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☒ the claims:
- nos. _____ as originally filed/furnished
- nos.* _____ as amended (together with any statement) under Article 19
- nos.* 1-8 received by this Authority on 10.06.2008 with letter of
- nos.* _____ received by this Authority on 06.06.2008
- ☐ the drawings:
- sheets _____ as originally filed/furnished
- sheets* _____ received by this Authority on _____
- sheets* _____ received by this Authority on _____
- ☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (specify): _____
- ☐ any table(s) related to sequence listing (specify): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (specify): _____
- ☐ any table(s) related to sequence listing (specify): _____

5. ☐ This report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 70.2(e)).

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/EP2007/007612

Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement		
1. Statement			
Novelty (N)	Claims	1-8	YES
	Claims		NO
Inventive step (IS)	Claims	1-8	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO
2. Citations and explanations (Rule 70.7)			
D1: EP-A-0 308 364 (SCHERING AG [DE]) 22 March 1989 (1989-03-22)			
D2: DE 101 04 598 A1 (BOEHRINGER INGELHEIM PHARMA [DE]) 8 August 2002 (2002-08-08)			
D3: WO 94/22885 A (UNIV KINGSTON [CA]) 13 October 1994 (1994-10-13)			
1. D1 discloses, in example 11, compounds a) and b), which represent 2,3-acetoxy succinic acid derivatives and have phenyl rings substituted with a carbamoyl group. The compounds in present claim 1 differ from the compounds disclosed in D1 by the restricted definitions of "T" and "Z". The claimed compounds differ significantly in structure from the factor IX inhibitors known from D2 and D3, and more particularly, the presently claimed tartrate backbone cannot be found in either D2 or D3. Therefore, the present application meets the requirements of PCT Article 33(1), because the subject matter of claims 1 to 4 (compounds), 5 (production), and 6-8 (use) is novel within the meaning of			

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/EP2007/007612

Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

PCT Article 33(2).

2. The claimed compounds differ significantly in their structure from the factor IX inhibitors known from D2 and D3.

The problem to be solved in view of the closest prior art as disclosed in D1 or D2 is therefore that of providing further, alternative factor IX inhibitors.

The claimed compounds are a solution to the above-mentioned problem based on the examples presented, which can be acknowledged as being representative of the restricted set of claims.

This solution is also regarded as inventive because of the clear structural differences between the claimed compounds and the compounds known from D1 and D2.

Therefore, the subject matter of claims 1 to 8 involves an inventive step within the meaning of PCT Article 33(3).

3. Industrial applicability is established for all of the claims 1 to 8 (PCT Article 33(4)).

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

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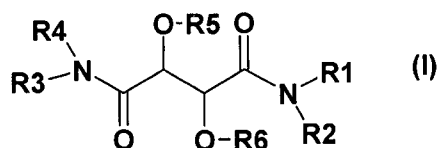
Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

1. The description has not been brought into line with present claims 1 to 8, since it goes beyond the scope of protection of the present claims (PCT Article 6).
2. The terminology in examples 1-3 is not identical to that of the compounds indicated in claim 4 (PCT Article 6).
3. Contrary to the requirements of PCT Rule 5.1(a)(ii), the description neither cites documents D2 and D3 nor indicates the relevant prior art disclosed therein.

Patent claims

1. A compound of the formula I



- 5 and/or all stereoisomeric forms of the compound of the formula I and/or mixtures of these forms in any ratio, and/or a physiologically tolerable salt of the compound of the formula I, where

- 10 R1 is 1) $-(\text{C}_6\text{-C}_{14})\text{-aryl-Z}$, in which Z is a basic nitrogen-containing group, where the conjugated acid of this group has a pKa of 5 to 15 and in which aryl is unsubstituted or mono-, di- or trisubstituted by T, 2) a four- to fifteen-membered Het-Z, in which Z is a basic nitrogen-containing group, where the conjugated acid of this group has a pKa of 5 to 15 and in which Het is unsubstituted or additionally mono-, di- or trisubstituted by T,

- 15 R2 and R4 are identical and are each a hydrogen atom,

- R3 is 1) $-(\text{C}_0\text{-C}_4)\text{-alkylene-(C}_6\text{-C}_{14})\text{-aryl}$, in which aryl is unsubstituted or mono-, di- or trisubstituted by T, 2) $-(\text{C}_0\text{-C}_4)\text{-alkylene-(C}_6\text{-C}_{14})\text{-aryl-Q-(C}_6\text{-C}_{14})\text{-aryl}$, in which the two aryls in each case independently of one another are unsubstituted or mono-, di- or trisubstituted by T or, 20 3) $-(\text{C}_0\text{-C}_4)\text{-alkylene-(C}_6\text{-C}_{14})\text{-aryl-Q-Het}$, in which aryl and Het in each case independently of one another are unsubstituted or mono-, di- or trisubstituted by T,

- 25 Q is a covalent bond, $-(\text{C}_1\text{-C}_4)\text{-alkylene}$, $-\text{NH-}$, $-\text{N}((\text{C}_1\text{-C}_4)\text{-alkyl})\text{-}$, $-\text{O-}$, $-\text{SO}_2\text{-}$ or $-\text{S-}$,

- T is 1) halogen, 2) $-(\text{C}_1\text{-C}_6)\text{-alkyl}$, in which alkyl are unsubstituted or independently mono-, di- or trisubstituted by $-(\text{C}_1\text{-C}_3)\text{-fluoroalkyl}$, $-\text{N-C(O)-OH}$ or $-\text{N-C(O)-(C}_1\text{-C}_4)\text{-alkyl}$, 30

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3) $-(C_3-C_8)$ -cycloalkyl, or

4) $-NO_2$,

R5 and R6 are identical and are in each case a hydrogen atom.

5 2. A compound of the formula I as claimed in claim 1, where

R1 is 1) $-(C_6-C_{14})$ -aryl-Z, where aryl is selected from the group

consisting of phenyl and naphthyl, and in which aryl is unsubstituted or mono-, di- or trisubstituted by T and Z is amino, aminomethylene, amidino, guanidino, azetidiny, pyrrolidinyl, piperidinyl, pyridinyl or aminopyridinyl, or

10 2) a four- to fifteen-membered Het-Z, where Het is selected from the group consisting of acridinyl, azepinyl, azetidiny, benzimidazoliny, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzotetrazolyl, 15 benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, beta-carbolinyl, quinazolinyl, quinolinyl, quinoliziny, 4H-quinoliziny, quinoxalinyl, quinuclidiny, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dibenzofuranyl, dibenzothiophenyl, dihydrofuran[2,3-b]-tetrahydrofuranyl, dihydrofuranyl, dioxolyl, dioxanyl, dioxolenyl, 2H, 20 6H-1,5,2-dithiaziny, furanyl, furazanyl, imidazolidiny, imidazoliny, imidazolyl, 1H-indazolyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isoquinolinyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isothiazolidiny, 2-isothiazolinyl, isothiazolyl, isoxazolyl, isoxazolidiny, 2-isoxazolinyl, morpholinyl, naphthyridiny, 25 octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, oxothiolanyl, phenanthridiny, phenanthrenyl, phenanthroliny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperaziny, piperidinyl, pteridinyl, puriny, 30 pyranly, pyraziny, pyrazolidiny, pyrazolinyl, pyrazolyl, pyridaziny, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridothiophenyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrroliny, 2H-pyrrolyl, pyrrolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl,

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tetrahydropyridinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazinyl, thiazolyl, thienyl, thienoimidazolyl, thienooxazolyl, thienopyridinyl, thienopyrrolyl, thienothiazolyl, thienothiophenyl, thiomorpholinyl, thiopyranyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl or xanthenyl and in which Het is unsubstituted or mono-, di- or trisubstituted by T and in which Z is as defined above,

R2 and R4 are identical and are each a hydrogen atom,

R3 is 1) $-(C_0-C_4)\text{-alkylene-(}C_6-C_{14}\text{)-aryl}$, in which aryl is as defined

above and is unsubstituted or mono-, di- or trisubstituted by T,

2) $-(C_0-C_4)\text{-alkylene-(}C_6-C_{14}\text{)-aryl-Q-(}C_6-C_{14}\text{)-aryl}$, in which the two aryls in each case independently of one another are as defined above and in each case independently of one another are unsubstituted or mono-, di- or trisubstituted by T, or

3) $-(C_0-C_4)\text{-alkylene-(}C_6-C_{14}\text{)-aryl-Q-Het}$, in which aryl and Het are as defined above and in each case independently of one another are unsubstituted or mono-, di- or trisubstituted by T,

Q is a covalent bond, $-(C_1-C_4)\text{-alkylene}$, $-\text{NH-}$, $-\text{N}((C_1-C_4)\text{-alkyl})\text{-}$ or $-\text{O-}$,

T is 1) halogen,

2) $-(C_1-C_6)\text{-alkyl}$, in which alkyl is unsubstituted or independently mono-, di- or trisubstituted by $-(C_1-C_3)\text{-fluoroalkyl}$, $-\text{N-C(O)-OH}$ or $-\text{N-C(O)-(}C_1-C_4\text{)-alkyl}$,

3) $-(C_3-C_6)\text{-cycloalkyl}$, or

4) $-\text{NO}_2$,

R5 and R6 are identical and are each a hydrogen atom, $-\text{C(O)-R}_{12}$, $-\text{C(O)-O-R}_{12}$, $-\text{C(O)-NH-R}_{12}$ or $-(C_1-C_4)\text{-alkyl}$, where

R12 is $-(C_1-C_6)\text{-alkyl}$, $-(C_3-C_8)\text{-cycloalkyl}$, $-(C_6-C_{14})\text{-aryl}$ or Het, and in which aryl and Het are as defined above.

3. A compound of the formula I as claimed in claim 1, where

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R1 is carbamimidoylphenyl, aminomethylphenyl or Het-Z, where Het is selected from the group consisting of benzimidazolyl and isoquinolinyl, and in which Z is amino or amidino,

R2 and R4 are in each case a hydrogen atom,

- 5 R3 is 1) phenyl, in which phenyl is unsubstituted or mono- or disubstituted by T,
 2) -phenyl-Q-phenyl, in which the two phenyl radicals in each case independently of one another are unsubstituted or mono- or disubstituted by T or
 10 3) phenyl-Q-Het-2, in which Het-2 is selected from the group consisting of quinolinyl, quinoxalinyl, furanyl, indolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxadiazolyl, piperidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, thienopyrrolyl or thienothiophenyl, and in which phenyl and Het-2 in
 15 each case independently of one another are unsubstituted or mono- or disubstituted by T,

Q is a covalent bond, -CH₂-, -N(CH₃)- or -O-,

- T is 1) F, Cl or Br,
 2) -(C₁-C₄)-alkyl, in which alkyl are unsubstituted or independently
 20 mono- or disubstituted by -CF₃ or -N-C(O)-CH₃, or
 3) -NO₂, and

R5 and R6 are in each case a hydrogen atom.

4. 25 A compound of the formula I as claimed in one or more of claims 1 to 3, which is the compound
 (2R, 3R)-N-(1-aminoisoquinolin-6-yl)-2,3-dihydroxy-N'-p-tolylsuccinamide,
 (2R, 3R)-N-(2-amino-3H-benzimidazol-5-yl)-2,3-dihydroxy-N'-p-tolylsuccinamide,
 (2R, 3R)-N-(2-amino-3H-benzimidazol-5-yl)-N'-(4-cyclohexylphenyl)-2,3-
 30 dihydroxysuccinamide,
 (2R,3R)-N-(4-aminomethylphenyl)-2,3-dihydroxy-N'-p-tolylsuccinamide,
 (2R,3R)-N-(4-carbamimidoylphenyl)-2,3-dihydroxy-N'-p-tolylsuccinamide,

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(2R, 3R)-N-(2-amino-3H-benzimidazol-5-yl)-N'-(4-fluorophenyl)-2,3-dihydroxy-succinamide,

(2R, 3R)-N-(2-amino-3H-benzimidazol-5-yl)-N'-(4-chlorophenyl)-2,3-dihydroxysuccinamide,

5 (2R, 3R)-N-(2-amino-3H-benzimidazol-5-yl)-2,3-dihydroxy-N'-phenyl-succinamide,

(2R, 3R)-N-(2-amino-3H-benzimidazol-5-yl)-2,3-dihydroxy-N'-(4-nitrophenyl)-succinamide,

10 (2R, 3R)-N-(2-amino-3H-benzimidazol-5-yl)-2,3-dihydroxy-N'-(4-isopropyl-phenyl)succinamide,

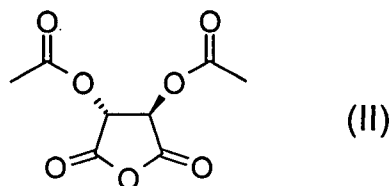
(2R, 3R)-N-(2-amino-3H-benzimidazol-5-yl)-2,3-dihydroxy-N'-(4-piperidin-1-yl-phenyl)succinamide or

(2R, 3R)-N-(2-amino-3H-benzimidazol-5-yl)-2,3-dihydroxy-N'-(4-phenoxy-phenyl)succinamide.

15

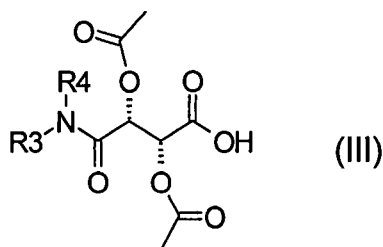
5. A process for the preparation of the compound of the formula I as claimed in one or more of claims 1 to 4, which comprises

a) reacting a compound of the formula II



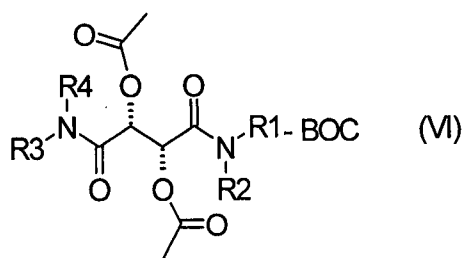
20

with a compound NH(R3)(R4) to give a compound of the formula III,



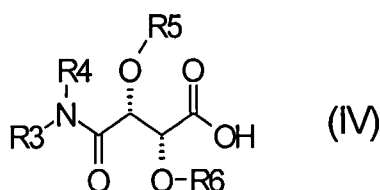
where the radicals R3 and R4 are as defined in formula I, and reacting the compound of the formula III with a compound NH(R2)(R1)-Boc to give a compound of the formula VI,

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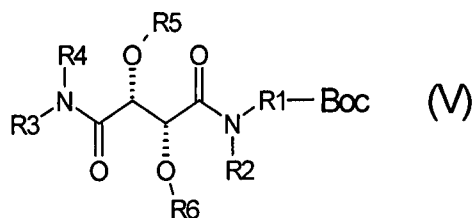


where the radicals R1, R2, R3 and R4 are as defined in formula I and Boc is the protective group butoxycarbonyl, and subsequently reacting to give a compound of the formula I, or

- 5 b) reacting a compound of the formula IV



where the radicals R3, R4, R5 and R6 are as defined in formula I, with a compound NH(R2)(R1)-Boc to give a compound of the formula V,



- 10 where the radicals R1, R2, R3, R4, R5 and R6 are as defined in formula I and Boc is the protective group butoxycarbonyl, and subsequently reacting to give a compound of the formula I, or

- 15 c) either isolating the compound of the formula I prepared according to process a) or b) in free form or releasing it from physiologically intolerable salts or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salts, or
- 20 d) separating a compound of the formula I prepared according to process a) or b), or a suitable precursor of the formula I which on account of its chemical structure occurs in enantiomeric or diastereomeric forms, into the pure enantiomers or diastereomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as

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amino acids, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups.

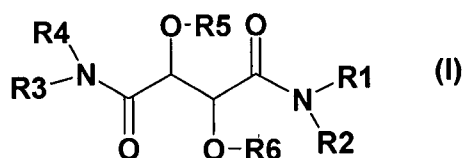
6. A medicament which comprises an efficacious amount of at least one
5 compound of the formula I as claimed in one or more of claims 1 to 4 together with a pharmaceutically suitable and physiologically tolerable vehicle, additive and/or other active substances and auxiliaries.
7. The use of the compound of the formula I as claimed in one or more of claims
10 1 to 4 for the production of a medicament for the prophylaxis, secondary prevention and therapy of all those diseases which accompany thromboses, embolisms, hypercoagulability or fibrotic changes.
8. The use as claimed in claim 7, wherein the disease is a myocardial infarct,
15 angina pectoris and other forms of acute coronary syndrome, stroke, peripheral vascular diseases, deep vein thrombosis, pulmonary embolism, embolic or thrombotic events caused by cardiac arrhythmias, cardiovascular events such as restenosis after revascularization and angioplasty and similar interventions such as stent implantations and bypass operations, or the
20 reduction of the risk of thrombosis after surgical interventions such as in knee and hip joint operations, or disseminated intravascular coagulation, sepsis and other intravascular events which accompany inflammation, atherosclerosis, diabetes and the metabolic syndrome and their sequelae, tumor growth and tumor metastasis, inflammatory and degenerative joint diseases such as
25 rheumatoid arthritis and arthrosis, disorders of the hemostatic system such as fibrin deposits, fibrotic changes of the lungs such as chronic obstructive pulmonary disease, adult respiratory distress syndrome or fibrin deposits in the eye after eye operations or prevention and/or treatment of scar formation.

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REIVINDICACIONES MODIFICADAS BAJO EL**ARTICULO 34 DEL PCT**

1.- Un compuesto de la fórmula I

5



y/o todas las formas estereoisómeras del compuesto de la fórmula I y/o las mezclas de estas formas en cualquier relación, y/o una sal fisiológicamente

10 tolerable del compuesto de la fórmula I, en la que

R1 es 1) -aril (C₆-C₁₄)-Z, donde Z es un grupo que contiene nitrógeno básico,

donde el ácido conjugado de este grupo tiene un pKa de 5 a 15 y

donde el arilo no está sustituido o está mono-, di- o trisustituido

15

con T,

2) un Het-Z de cuatro a quince miembros, donde Z es un grupo que contiene nitrógeno básico donde el ácido conjugado de este grupo tiene un pKa de 5 a 15 y donde Het no está sustituido o está adicionalmente mono-, di- o trisustituido con T,

20 R2 y R4 son idénticos o diferentes y cada uno es un átomo de hidrógeno,

R3 es 1) -alquilen (C₀-C₄)-arilo (C₆-C₁₄), donde el arilo no está sustituido o está

mono-, di- o trisustituido con T,

- 2) -alquilen (C₀-C₄)-aril (C₆-C₁₄)-Q-arilo (C₆-C₁₄), donde los dos arilos, en cada caso independientemente uno del otro, no están sustituidos o están mono-, di- o trisustituidos con T,
- 3) -alquilen (C₀-C₄)-aril (C₆-C₁₄)-Q-Het, donde arilo y Het, donde arilo y Het, en cada caso independientemente uno del otro, no están sustituidos o están mono-, di- o trisustituidos con T,

5 Q es un enlace covalente, -alquileo (C₁-C₄), -NH-, -N(alquilo (C₁-C₄))- , -O-,

-SO₂- o -S-,

- 10 T es 1) halógeno,
- 2) -alquilo (C₁-C₆), donde el alquilo no está sustituido o está mono-, di- o trisustituido con -fluoroalquilo (C₁-C₃), -N-C(O)-OH o -N-C(O)-alquilo (C₁-C₄),
- 3) -cicloalquilo (C₃-C₈), o
- 15 4) -NO₂,

R₅ y R₆ son idénticos y en cada caso son un átomo de hidrógeno.

2.- Un compuesto de la fórmula I según la reivindicación 1, en el que

- R₁ es 1) -aril (C₆-C₁₄)-Z, donde el arilo se selecciona del grupo que consiste en
- 20 fenilo y naftilo, y donde el arilo no está sustituido o está mono-, di- o trisustituido con T, y Z es amino, aminometileno, amidino,

guanidino, azetidino, pirrolidino, piperidino, piridino o aminopiridino, o

- 2) Het-Z de cuatro a quince miembros, donde Het se selecciona del grupo que consiste en acridino, azepino, azetidino, bencimidazolino, bencimidazolilo, benzofurano, benzotiofurano, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, bencisoxazolilo, bencisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolino, beta-carbolino, quinazolino, quinolino, quinolizino, 4H-quinolizino, quinoxalino, quinuclidino, cromanilo, cromenilo, cinolino, deca-hidroquinolino, dibenzofurano, dibenzotiofenilo, dihidrofuran[2,3-b]-tetrahidrofuranilo, dihidrofuranilo, dioxolilo, dioxanilo, dioxolenilo, 2H, 6H-1,5,2-ditiazino, furano, furazano, imidazolidino, imidazolino, imidazolilo, 1H-indazolilo, indolino, indolizino, indolilo, 3H-indolilo, isobenzofurano, isoquinolino, isocromanilo, isoindazolilo, isoindolino, isoindolilo, isotiazolidino, 2-isotiazolino, isotiazolilo, isoxazolilo, isoxazolidino, 2-isoxazolino, morfolino, naftiridino, octahidroisoquinolino, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidino, oxazolilo, oxazolidino, oxotolanilo, fenantridino, fenantreno, fenantrolino, fenazino, fenotiazino, fenoxatino, fenoxazino, ftalazino, piperazino, piperidino, pteridino, purino, pirano, pirazino, pirazolidino, pirazolino, pirazolilo, piridazino, piridoxazolilo, piridoimidazolilo, piridotiazolilo, piridotiofenilo, piridilo, piri-

- midinilo, pirrolidinilo, pirrolinilo, 2H-pirrolilo, pirrolilo, tetrahydrofurani-
lo, tetrahydroisoquinolinilo, tetrahydroquinolinilo, tetrahidropiridinilo, 6H-
1,2,5-tiadazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazoli-
lo, 1,3,4-tiadiazolilo, tiantrenilo, tiazinilo, tiazolilo, tienilo, tienoimida-
zolilo, tienooxazolilo, tienopiridinilo, tienopirrolilo, tienotiazolilo, tieno-
tiofenilo, tiomorfolinilo, tiopiranilo, triazinilo, 1,2,3-triazolilo, 1,2,4-
triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo o xantenilo y donde Het no
está sustituido o está mono-, di- o trisustituido con T y donde Z es tal
como se definió anteriormente,
- 10 R2 y R4 son idénticos y cada uno es un átomo de hidrógeno,
R3 es 1) -alquilen (C₀-C₄)-arilo (C₆-C₁₄), donde el arilo es tal como se de-
finió
anteriormente y no está sustituido o está mono-, di- o trisustituido
con T,
- 15 2) -alquilen (C₀-C₄)-aril (C₆-C₁₄)-Q-arilo (C₆-C₁₄), donde los dos
arilo, en cada caso independientemente uno del otro, son tal
como se definió anteriormente y, en cada caso independiente-
mente uno del otro, no están sustituidos o están mono-, di- o tri-
sustituidos con T, o
- 20 3) -alquilen (C₀-C₄)-aril (C₆-C₁₄)-Q-Het, donde arilo y Het son como
se definió anteriormente y, en cada caso independientemente
uno del otro, no están sustituidos o están mono-, di- o trisustitui-
dos con T,

- Q es un enlace covalente, -alquileo (C₁-C₄), -NH-, -N(alquilo (C₁-C₄))- o -O-,
- T es 1) halógeno,
- 2) -alquilo (C₁-C₆), donde el alquilo no está sustituido o está mono-
- 5 , di- o
- trisustituido con -fluoroalquilo (C₁-C₃), -N-C(O)-OH o -N-C(O)-alquilo (C₁-C₄),
- 3) -cicloalquilo (C₃-C₆), o
- 4) -NO₂,
- 10 R5 y R6 son idénticos y cada uno es un átomo de hidrógeno, -C(O)-R12, -C(O)-O-R12, -C(O)-NH-R12 o -alquilo (C₁-C₄), donde
- R12 es -alquilo (C₁-C₆), -cicloalquilo (C₃-C₈), -arilo (C₆-C₁₄) o Het, y donde arilo y Het son como se definió anteriormente.
- 15 3.- Un compuesto de la fórmula I según la reivindicación 1, en el que
- R1 es carbamimidoilfenilo, aminometilfenilo o Het-Z, donde Het se selecciona del grupo que consiste en bencimidazolilo e isoquinolinilo, y donde Z es amino o amidino,
- R2 y R4 en cada caso son un átomo de hidrógeno,
- 20 R3 es 1) fenilo, donde el fenilo no está sustituido o está mono- o disustituido con
- T,

- 2) -fenil-Q-fenilo, donde los dos radicales fenilo, en cada caso independientemente uno del otro, no están sustituidos o están mono- o disustituidos con T,
- 3) fenil-Q-Het-2, donde Het-2 se selecciona del grupo que consiste en quinolinilo, quinoxalinilo, furanilo, indolilo, isoquinolinilo, isotiazolilo, isoxazolilo, oxadiazolilo, piperidinilo, pirazolilo, piridazino, piridilo, pirimidinilo, pirrolilo, tiadiazolilo, tiazolilo, tienilo, tienopirrolilo o tienotiofenilo y donde fenilo y Het-2, en cada caso independientemente uno del otro, no están sustituidos o están mono- o disustituidos con T,
- Q es un enlace covalente, -CH₂-, -N(CH₃)- o -O-,
- T es 1) F, Cl o Br,
- 2) -alquilo (C₁-C₄), donde el alquilo no está sustituido o está mono- o disustituido independientemente con -CF₃ o -N-C(O)-CH₃, o
- 3) -NO₂, y

R5 y R6 en cada caso son un átomo de hidrógeno.

4.- Un compuesto de fórmula I según una o más de las reivindicaciones 1 a 3, que es el compuesto

- 20 (2R, 3R)-N-(1-aminoisoquinolin-6-il)-2,3-dihidroxi-N'-p-tolil-tartaramida,
 (2R, 3R)-N-(2-amino-3H-bencimidazol-5-il)-2,3-dihidroxi-N'-p-toliltartaramida,
 (2R,3R)-N-(2-amino-3H-bencimidazol-5-il)-N'-(4-ciclohexilfenil)-2,3-dihidroxi-tartaramida,

(2R,3R)-N-(4-aminometilfenil)-2,3-dihidroxi-N'-p-tolilsuccinamida;

(2R,3R)-N-(4-carbamimidoilfenil)-2,3-dihidroxi-N'-p-tolilsuccinamida,

(2R,3R)-N-(2-amino-3H-bencimidazol-5-il)-N'-(4-fluorofenil)-2,3-dihidroxi-tartaramida,

5 (2R, 3R)-N-(2-amino-3H-bencimidazol-5-il)-N'-(4-clorofenil)-2,3-dihidroxi-tartaramida,

(2R, 3R)-N-(2-amino-3H-bencimidazol-5-il)-2,3-dihidroxi-N'-feniltartaramida,

(2R, 3R)-N-(2-amino-3H-bencimidazol-5-il)-2,3-dihidroxi-N'-(4-nitrofenil)-tartaramida,

10 (2R,3R)-N-(2-amino-3H-bencimidazol-5-il)-2,3-dihidroxi-N'-(4-isopropilfenil)-tartaramida,

(2R,3R)-N-(2-amino-3H-bencimidazol-5-il)-2,3-dihidroxi-N'-(4-piperidin-1-il-fenil)tartaramida o

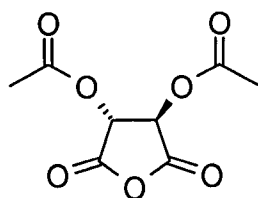
(2R, 3R)-N-(2-amino-3H-bencimidazol-5-il)-2,3-dihidroxi-N'-(4-fenoxifenil)-tar-

15 taramida.

5.- Un procedimiento para la preparación del compuesto de la fórmula I, según una o más de las reivindicaciones 1 a 4, que comprende

a) hacer reaccionar un compuesto de la fórmula II

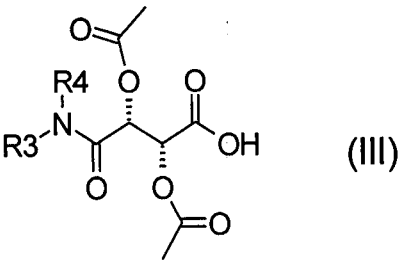
20



(II)

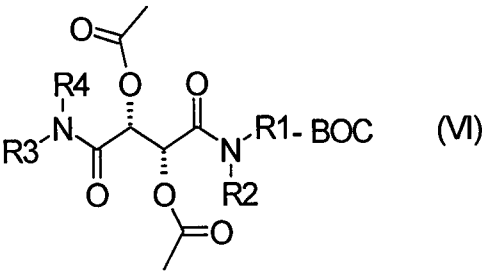
con un compuesto NH(R3)(R4) para dar un compuesto de la fórmula III,

5



donde los radicales R3 y R4 son tal como se definió en la fórmula I, y
hacer reaccionar el compuesto de la fórmula III con un compuesto
NH(R2)(R1)-Boc para dar un compuesto de la fórmula VI,

10

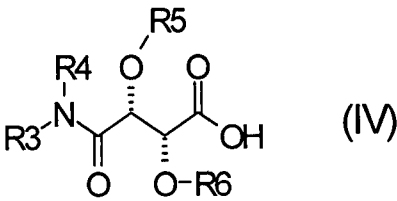


15

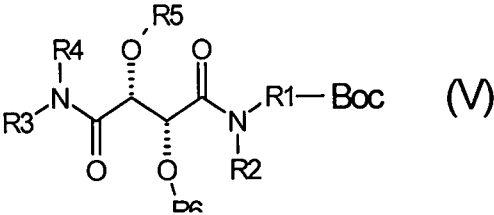
donde los radicales R1, R2, R3 y R4 son tal como se definió en la fór-
mula I y Boc es el grupo protector butoxycarbonilo, y posteriormente
hacer reaccionar para dar un compuesto de la fórmula I, o

b) hacer reaccionar un compuesto de fórmula IV

20



donde los radicales R3, R4, R5 y R6 son tal como se definió en la fór-
mula I, con un compuesto NH(R2)(R1)-Boc para dar un compuesto de
la fórmula V,



5 donde los radicales R1, R2, R3, R4, R5 y R6 son tal como se definió en la fórmula I y Boc es el grupo protector butoxicarbonilo, y posteriormente hacer reaccionar para dar un compuesto de la fórmula I, o

c) bien aislar el compuesto de la fórmula I preparado según el procedimiento a) o b) en forma libre o liberarlo a partir de sales fisiológicamente intolerables o, en el caso de presencia de grupos ácidos o básicos, 10 convertirlo en sales fisiológicamente tolerables, o

d) separar un compuesto de la fórmula I preparado según el procedimiento a) o b), o un precursor adecuado de la fórmula I, que a causa de su estructura química se da en formas enantiómeras o diastereómeras, por formación de sal con ácidos o bases enantioméricamente puros, 15 cromatografía sobre fases estacionarias quirales o derivatización por medio de compuestos quirales enantioméricamente puros tales como aminoácidos, separación de los diastereómeros así obtenidos, y eliminación de los grupos quirales auxiliares en los enantiómeros o diastereómeros puros.

20

6.- Un medicamento que comprende una cantidad eficaz de por lo menos un compuesto de la fórmula I según una o más de las reivindicaciones 1 a 4

junto con un vehículo farmacéuticamente adecuado y fisiológicamente tolerable, aditivo y/u otras sustancias activas y auxiliares.

7.- El uso del compuesto de la fórmula I según una o más de las reivindicaciones 1 a 4, para la producción de un medicamento para la profilaxis, prevención secundaria y terapia de todas las enfermedades acompañadas de trombosis, embolias, hipercoagulabilidad o cambios fibróticos.

8.- El uso según la reivindicación 7, donde la enfermedad es un infarto de miocardio, angina de pecho y otros tipos de síndrome coronario agudo, accidentes cerebrovasculares, enfermedades vasculares periféricas, trombosis de venas profundas, embolia pulmonar, acontecimientos embólicos o trombóticos provocados por arritmias cardíacas, acontecimientos cardiovasculares como reestenosis después de una revascularización, y angioplastia y procedimientos similares como implantes de endoprótesis vasculares y operaciones de derivación vascular, o la reducción del riesgo de trombosis después de procedimientos quirúrgicos como en operaciones de articulaciones de rodilla y cadera, o coagulación intravascular diseminada, septicemia y otros acontecimientos intravasculares que acompañan una inflamación, aterosclerosis, diabetes y el síndrome metabólico y sus secuelas, crecimiento de tumores y metástasis tumoral, enfermedades de las articulaciones degenerativas e inflamatorias como artritis reumatoide y artrosis, trastornos del sistema hemostático como depósitos de fibrina, cambios fibróticos del pulmón como enfer-

medad pulmonar obstructiva crónica, síndrome de insuficiencia respiratoria de adultos o depósitos de fibrina en el ojo después de operaciones oculares, o la prevención y/o tratamiento de la formación de cicatrices.



2020
Bogotá D.C.,

Doctor(a)
PATIÑO LEYVA LUIS
Apoderado(a) y/o Representante de
SANOFI AVENTIS

REFERENCIA	Radicación No.	9 22192
	Solicitud internacional	PCT/EP2007/007612
	Fecha inicio fase nacional	13/04/2009
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	11134
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

13 SET. 2010

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

jfernand