

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINDUSTRIA Y COMERCIO
Radicacion : 83187408 00000003 Folios: 2
Fecha (AMD): 2005-12-14 17:44:31
Tramite : 011 PCT-PATENT 379 FASE NACI 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref: Expediente No. 03.107.408

Solicitud de patente de invención titulada:

"DERIVADOS DE PIRROLIDINA COMO INHIBIDORES DEL FACTOR XA".

Solicitante: GLAXO GROUP LIMITED

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTICULO 44 DE LA DECISION 486, GACETA No. 554

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$186.000 pesos para cubrir la tasa correspondiente, según la Resolución 31980 del año 2004.

Atentamente,



CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$186.000 pesos

JAB/P2003/000166 050810

155 

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03107400 00000003 Folios: 2
Fecha (AND): 2005-12-14 17:44:31
Tramite : 011 PCT-PATENT 379 FASE NACI 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 94,857
FECHA : DICIEMBRE 14 DE 2005

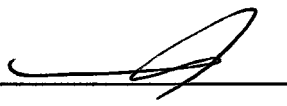
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	36765276	13/12/2005	3,967,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	186,000.00
		TOTAL :	\$ 186,000.00

SON: CIENTO OCHENTA Y SEIS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 03- 107408

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION -
PCT, FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 554,
DE FECHA 29 DE JULIO DE 2005, EL TERMINO HABIL SEÑALADO POR LA
LEY EXPIRA EL 25 DE OCTUBRE DE 2005.**

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 ☒ ☐

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



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22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19795 A1

(51) International Patent Classification⁷: **C07D 211/76**,
409/14, 401/12, 207/26, A61K 31/445, 31/40

Newtown Square, PA 19073 (US). **HALL, Jonathan, P.**
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(21) International Application Number: **PCT/US00/25006**

(74) Agents: **COVERT, John, M. et al.**; Sterne, Kessler, Gold-
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Washington, DC 20005-3934 (US).

(22) International Filing Date:
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(30) Priority Data:
60/153,236 13 September 1999 (13.09.1999) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

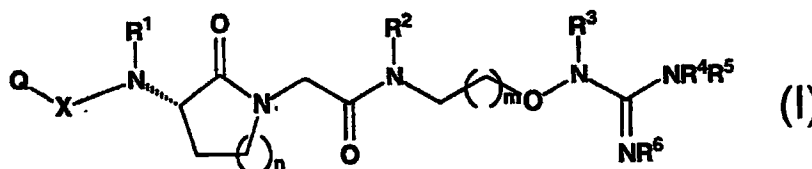
(75) Inventors/Applicants (*for US only*): **MILLER, Scott,**
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HASLOW, Kristin, D. [US/US]; 14 Ridgeview Road,

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: **AZACYCLOALKANONE SERINE PROTEASE INHIBITORS**



(57) Abstract: The present invention is directed to non-peptidic factor Xa inhibitors which are useful for the treatment of arterial and venous thrombotic occlusive disorders, inflammation, cancer, and neurodegenerative diseases. The factor Xa inhibitors provide compounds having Formula (I) or pharmaceutically acceptable salts thereof; wherein Q is phenyl, benzyl, pyridyl, thienyl, indolyl, quinolinyl, benzothienyl, biphenyl, or imidazolyl; any of which can include one or more optional substituents independently selected from halo, trifluoromethyl, hydroxy, amino, nitro, cyano, C₁₋₃ alkoxy, C₁₋₃ alkyl, methylenedioxy, carboxamido, acetamido, or amidino; X is methylene, carbonyl, or sulfonyl; Z is methylene, ethylene, or propylene; M is methylene or ethylene; and R¹, R², and R³ are independently hydrogen or C₁₋₃ alkyl.

WO 01/19795 A1

Azacycloalkanone Serine Protease Inhibitors

Background of the Invention

Field of the Invention

5 The present invention relates to novel compounds that function as proteolytic enzyme inhibitors, and particularly to a new class of inhibitors of thrombin production via factor Xa inhibition, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof.

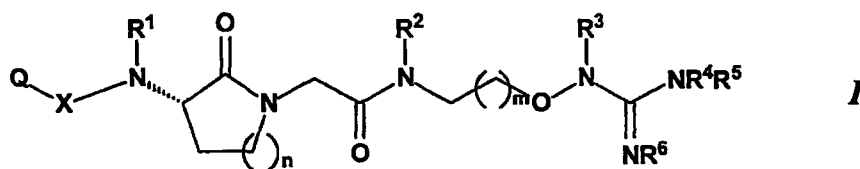
Related Art

10 Proteases are enzymes that cleave proteins at single, specific peptide bonds. Proteases can be classified into four generic classes: serine, thiol or cysteinyl, acid or aspartyl, and metalloproteases (Cuypers *et al.*, *J. Biol. Chem.* 257:7086 (1982)). Proteases are essential to a variety of biological activities, such as digestion, formation and dissolution of blood clots, reproduction and the immune reaction to foreign cells and organisms. Aberrant proteolysis is
15 associated with a number of disease states in man and other mammals. The human neutrophil proteases, elastase and cathepsin G, have been implicated as contributing to disease states marked by tissue destruction. These disease states include emphysema, rheumatoid arthritis, corneal ulcers and glomerular nephritis. (Barret, in *Enzyme Inhibitors as Drugs*, Sandler, ed., University Park Press, Baltimore, (1980)).
20 Additional proteases such as plasmin, C-1 esterase, C-3 convertase, urokinase, plasminogen activator, acrosin, and kallikreins play key roles in normal biological functions of mammals. In many instances, it is beneficial to disrupt the function of one or more proteolytic enzymes in the course of therapeutically treating a mammal.

25 Serine proteases include such enzymes as elastase (human leukocyte), cathepsin G, plasmin, C-1 esterase, C-3 convertase, urokinase, plasminogen activator, acrosin, chymotrypsin, trypsin, thrombin, factor Xa and kallikreins.

What Is Claimed Is:

1. A compound having Formula I:



or pharmaceutically acceptable salts thereof; wherein

Q is C₆₋₁₄ aryl, C₆₋₁₄ ar(C₁₋₄)alkyl, C₆₋₁₄ ar(C₂₋₄)alkenyl, pyridyl, thienyl, indolyl, quinoliny, benzothienyl, or imidazolyl; any of which can include one or more optional substituents independently selected from halo, trifluoromethyl, hydroxy, amino, nitro, cyano, C₁₋₃ alkoxy, C₁₋₃ alkyl, methylenedioxy, carboxy-amino, C₁₋₄ alkoxy-carbonylamino, C₆₋₁₀ aryloxy-carbonylamino, C₇₋₁₁ aralkoxy-carbonylamino, aminocarbonyl, mono- or di-(C₁₋₄)alkylaminocarbonyl, acetamido, amidino, pyridyl, naphthyl, pyrimidinyl, alkenyl, mono- or di-(C₁₋₄)alkylamino, or combinations thereof;

X is methylene, carbonyl, or sulfonyl;

R¹ is hydrogen or C₁₋₃ alkyl;

n is 1, 2 or 3;

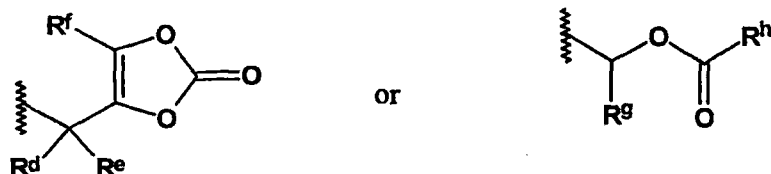
m is 1-4, preferably 1 or 2;

R² is hydrogen or C₁₋₃ alkyl;

R³ is hydrogen or C₁₋₃ alkyl; and

R⁴, R⁵ and R⁶ are independently hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, cyano or -CO₂R^w, where R^w, in each instance, is preferably one of C₁₋₄alkyl, C₄₋₇cycloalkyl, benzyl, or R^w is one of

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where R^d , R^e and R^g are each hydrogen, R^f is methyl, and R^h is benzyl or *tert*-butyl.

2. The compound of claim 1, wherein Q is aryl, aralkyl or thienyl, any of which can include one or more optional substituents independently selected from the group consisting of halo, trifluoromethyl, hydroxy, amino, nitro, cyano, C_{1-3} alkoxy, C_{1-3} alkyl, methylenedioxy, carboxyamino, C_{1-4} alkoxycarbonylamino, C_{6-10} aryloxycarbonylamino, C_{7-11} aralkoxycarbonylamino, aminocarbonyl, mono- or di- (C_{1-4})alkylaminocarbonyl, acetamido, amidino, pyridyl, naphthyl, pyrimidinyl, alkenyl, mono- or di- (C_{1-4})alkylamino, and combinations thereof.

3. The compound of claim 2, wherein Q is phenyl or biphenyl, any of which can include one or more optional substituents independently selected from the group consisting of halo, trifluoromethyl, hydroxy, amino, nitro, cyano, C_{1-3} alkoxy, C_{1-3} alkyl, methylenedioxy, carboxyamino, C_{1-4} alkoxycarbonylamino, C_{6-10} aryloxycarbonylamino, C_{7-11} aralkoxycarbonylamino, aminocarbonyl, mono- or di- (C_{1-4})alkylaminocarbonyl, acetamido, amidino, pyridyl, naphthyl, pyrimidinyl, alkenyl, mono- or di- (C_{1-4})alkylamino, and combinations thereof.

4. The compound of claim 2, wherein Q is naphth-1-yl, naphth-2-yl, 5-dimethylaminonaphth-1-yl, 6-chloronaphth-2-yl, 6-bromonaphth-2-yl, benzyl, 2-nitrobenzyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-(n-propyl)phenyl, 4-(t-butyl)phenyl, 4-(t-amyl)phenyl, 4-methoxyphenyl, 4-iodophenyl, 4-fluorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-nitrophenyl,



US005489583A

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United States Patent [19]

Mack et al.

[11] **Patent Number:** **5,489,583**[45] **Date of Patent:** **Feb. 6, 1996**

[54] **2-SUBSTITUTED
3-(4-AMIDINOPHENYL)PROPIONIC ACID
DERIVATIVES**

[75] **Inventors:** **Helmut Mack, Meckenheim; Thomas
Pfeiffer, Limburgerhof; Hans W.
Hoeffken, Ludwigshafen;
Hans-Joachim Boehm, Limburgerhof;
Wilfried Hornberger, Ludwigshafen,
all of Germany**

[73] **Assignee:** **BASF Aktiengesellschaft,
Ludwigshafen, Germany**

[21] **Appl. No.:** **170,357**

[22] **PCT Filed:** **Jun. 23, 1992**

[86] **PCT No.:** **PCT/EP92/01411**

§ 371 Date: **Dec. 28, 1993**

§ 102(e) Date: **Dec. 28, 1993**

[87] **PCT Pub. No.:** **WO93/01208**

PCT Pub. Date: Jan. 21, 1993

[30] **Foreign Application Priority Data**

Jul. 3, 1991 [DE] Germany 41 20 947.3

[51] **Int. Cl.⁶** **A61K 31/395; C07D 403/12**

[52] **U.S. Cl.** **514/183; 540/362; 540/463;
540/527; 546/216; 546/164; 546/146; 548/546;
514/210; 514/211; 514/212; 514/228.8;**

514/235.2; 514/307; 514/311; 514/327;
514/408; 514/235.5

[58] **Field of Search** **540/362, 463,
540/527; 546/216, 164, 146; 548/546; 514/183,
210, 211, 212, 228.8, 307, 311, 327, 408**

[56] **References Cited****FOREIGN PATENT DOCUMENTS**

0236163 9/1987 European Pat. Off. 514/183

OTHER PUBLICATIONS

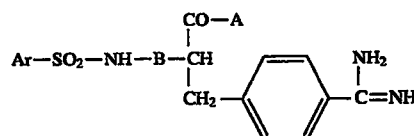
Voigt et al. "Pharmazie" vol. 41 (1986) pp. 233-235.

Primary Examiner—Robert T. Bond

Attorney, Agent, or Firm—Keil & Weinkauff

[57] **ABSTRACT**

2-Substituted 3-(4-amidinophenyl)propionic acid deriva-
tives of the formula



in which A, Ar and B have the meanings stated in the
description, and the preparation thereof are described. The
compounds are suitable for controlling diseases.

4 Claims, No Drawings

5,489,583

1

2-SUBSTITUTED 3-(4-AMIDINOPHENYL)PROPIONIC ACID DERIVATIVES

The present invention relates to novel 2-substituted 3-(4-amidinophenyl)propionic acid derivatives, the preparation thereof and the use thereof for controlling diseases.

Thrombin belongs to the group of serine proteases and plays a central part in the blood coagulation cascade as terminal enzyme. Both the intrinsic and the extrinsic coagulation cascade lead via several intensification states to the production of thrombin from prothrombin. The thrombin-catalyzed cleavage of fibrinogen then initiates blood coagulation and thus also possible thrombus formation. Thrombin additionally stimulates the aggregation of platelets which in turn, owing to the formation of platelet factor 3 and coagulation factor XIII as well as a whole series of highly active mediators, intensify thrombin formation.

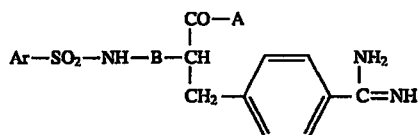
The formation and action of thrombin are central events in the development both of white, arterial and of red, venous thrombi, and therefore potentially effective sites of attack of drugs. Thrombin inhibitors are, in contrast to heparin, able completely to inhibit, independently of cofactors, simultaneously the actions of thrombin both in the coagulation cascade and on platelets. They are able in the acute phase to prevent thromboembolic events after percutaneous transluminal coronary angioplasty (PCTA) and lysis and to act as anticoagulants in extracorporeal circulation (heart-lung machine, hemodialysis). They can also be used generally for thrombosis prophylaxis, for example after surgical interventions.

Two classes of compounds have to date been described as low molecular weight thrombin inhibitors, namely

a) substances of the benzamidine type (DD 155,954, FR 2,593,812, FR 2,593,813, EP 236,164 and C.A. 113, (1990) 6182j) and

b) substances of the arginine type (U.S. Pat. No. 4,258, 192, DE 2,801,478, EP 293,881, EP 185,390).

We have now found that 2-substituted 3-(4-amidinophenyl)propionic acid derivatives of the formula



where
A is

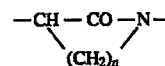


or $-\text{OR}^3$ in which R^1 and R^2 , which can be identical or different, are each hydrogen, saturated or unsaturated alkyl with up to 6 carbons or aralkyl or aryl, or R^1 and R^2 together with the nitrogen to which they are bonded are a 5- to 7-membered saturated ring which is unsubstituted or substituted by alkyl radicals with up to 4 carbons and can contain an oxygen atom, where the nitrogen and oxygen atoms are in the 1,2 or 1,4 positions,

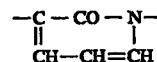
and where R^3 is hydrogen, saturated or unsaturated alkyl with up to 6 carbons, cycloalkyl or aralkyl,

B is

2



(where n is 1, 2, 3, 4 or 5) or



Ar is phenyl or α - or β -naphthyl which is unsubstituted or substituted by one or more halogen atoms, nitro groups, amino groups, C_{1-4} -mono- or bisalkylamino groups, hydroxyl groups, C_{1-4} -alkyl radicals, C_{1-4} -alkoxy groups, a methylenedioxy or ethylenedioxy radical, or Ar is pyridyl, quinolyl or isoquinolyl which is unsubstituted or substituted by one or more C_{1-4} -alkyl groups or C_{1-4} -alkoxy groups,

and the salts thereof with physiologically tolerated acids have an improved action.

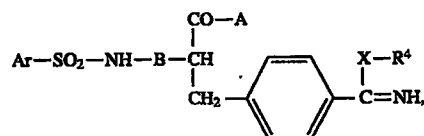
Preferred compounds are those where B is a pyrrolidinone, a piperidinone or a piperidone group, A is $-\text{NR}^1\text{R}^2$ where R^1 and R^2 together with the nitrogen atom are a 5- to 7-membered ring which may be substituted by C_{1-4} -alkyl radicals, and Ar is β -naphthyl which is substituted by one or more C_{1-4} -alkoxy radicals.

Particularly preferred compounds are those where A and B have the abovementioned meanings and Ar is β -naphthyl which is substituted by 1 or 2 methoxy groups in position 4, 5, 6, 7 and/or 8 or by a methylenedioxy or ethylenedioxy group in these positions.

The novel compounds have one or two asymmetric centers. They may be in the form either of the racemates or of the antipodes with respect to the two asymmetric centers. Compounds which have the R configuration and the phenylalanine moiety are preferred.

The novel compounds can, if required, be in the form of their salts with physiologically tolerated acids. Examples of suitable physiologically tolerated acids are: hydrochloric acid, hydroiodic acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, malonic acid, salicylic acid, maleic acid, fumaric acid, succinic acid, ascorbic acid, malic acid, methanesulfonic acid, lactic acid, gluconic acid, glucuronic acid, sulfamic acid, benzoic acid and tartaric acid.

The novel compounds are prepared by reacting a compound of the formula II



where R^4 is C_{1-3} -alkyl or benzyl and X is oxygen or sulfur, with ammonia or an ammonium salt, and converting the resulting compounds where appropriate into their salts with physiologically tolerated acids.

The reaction of II is normally carried out at 40° to 80° C. in a polar organic solvent such as tetrahydrofuran, acetone, dioxane, methanol or dimethylformamide. It is usually complete after 1 to 10 hours.

The starting materials required for the preparation of the novel compounds have not previously been described. They can be obtained as follows:

I Synthesis of the p-cyanophenylalanine moiety

a) The preparation of p-cyanophenylalanine is described in DD-C 155 954. After alkylation of acetaminomalononic ester with p-cyanobenzyl halides, the resulting

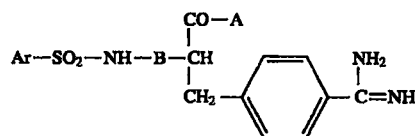
5,489,583

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- 63) 3-(6,7-Methylenedioxy-naphthalene-2-sulfonylamino)-1-[2-(4-amidinophenyl)-1-ethoxycarbonylethyl]-2-piperidinone
- 64) 3-(6,7-Methylenedioxy-naphthalene-2-sulfonylamino)-1-[2-(4-amidinophenyl)-1-carboxyethyl]-2-piperidinone
- 65) 3-(6,7-Methylenedioxy-naphthalene-2-sulfonylamino)-1-[2-(4-amidinophenyl)-1-piperidinocarbonylethyl]-2-pyrrolidinone
- 66) 3-(6,7-Methylenedioxy-naphthalene-2-sulfonylamino)-1-[2-(4-amidinophenyl)-1-ethoxycarbonylethyl]-2-pyrrolidinone
- 67) 3-(6,7-Methylenedioxy-naphthalene-2-sulfonylamino)-1-[2-(4-amidinophenyl)-1-carboxyethyl]-2-pyrrolidinone
- 68) 3-(6,7-Ethylenedioxy-naphthalene-2-sulfonylamino)-1-[2-(4-amidinophenyl)-1-piperidinocarbonylethyl]-2-piperidinone
- 69) 3-(6,7-Ethylenedioxy-naphthalene-2-sulfonylamino)-1-[2-(4-amidinophenyl)-1-piperidinocarbonylethyl]-2-pyrrolidinone

We claim:

1. A 2-substituted 3-(4-amidinophenyl) propionic acid of the formula



where

A is

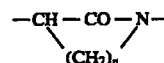


or ---OR^3 in which R^1 and R^2 , which can be identical or

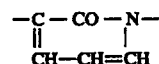
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different, are each hydrogen, alkyl or alkenyl with up to 6 carbons, or R^1 and R^2 together with the nitrogen to which they are bonded are a 5-to 7-membered saturated ring which is unsubstituted or substituted by alkyl radicals with up to 4 carbons and can contain an oxygen atom, where the nitrogen and oxygen atoms are in the 1,2 or 1,4 positions, and where R^3 is hydrogen, alkyl or alkenyl with up to 6 carbons,

B is



(where n is 1, 2, 3, 4 or 5) or



Ar is phenyl or α - or β -naphthyl which is unsubstituted or substituted by one or more halogen atoms, nitro groups, amino groups, C_{1-4} -mono- or bisalkylamino groups, hydroxyl groups, C_{1-4} -alkoxy groups, a methylenedioxy or ethylenedioxy radical, or Ar is pyridyl, quinolyl or isoquinolyl which is unsubstituted or substituted by one or more C_{1-4} -alkyl groups or C_{1-4} -alkoxy groups,

and the salts thereof with physiologically tolerated acids.

2. The 2-substituted 3-(4-amidinophenyl)propionic acid of claim 1, wherein

A is



where R^1 and R^2 together with the nitrogen atom are a 5-to 7-membered ring which may be substituted by $\text{C}_1\text{---C}_4$ -alkyl radicals;

B is a pyrrolidone, a piperidinone or a piperidone group; and

Ar is β -naphthyl which is substituted by one or more $\text{C}_1\text{---C}_4$ -alkoxy radicals.

3. The 2-substituted 3-(4-amidinophenyl)propionic acid of claim 2, wherein

Ar is β -naphthyl which is substituted by one or two methoxy groups in position 4, 5, 6, 7 and/or 8 by a methylene dioxy or ethylenedioxy radical.

4. A method of treating thromboembolic disorders in a patient in need thereof which comprises administering to the patient an effective amount of a 2-substituted 3-(4-amidinophenyl)propionic acid as defined in claim 1.

* * * * *

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

2020

Bogotá, D.C., Julio 06 de 2007

Dr.
CARLOS OLARTE
Apoderado
GLAXO GROUP LIMITED

ASUNTO	Radicación	03-107408
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	8927
	Folios	004

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

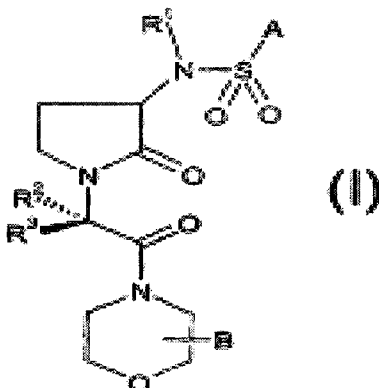
- 1.1. Descripción: Folios: 50 a 122 como se radicó inicialmente
- 1.2. Reivindicaciones: Folios 123 a 130 como se radicó inicialmente
- 1.3. Prioridad: Se reivindica prioridad de número 0114005.2 presentada en el Reino Unido de fecha 08/06/2001 en el petitorio (folio 1) y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

2. Objeto de la invención

Título de la solicitud: DERIVADOS DE PIRROLIDINA COMO INHIBIDORES DEL FACTOR Xa.

Objeto de la invención:

La invención se refiere a compuestos inhibidores del factor Xa de fórmula general (I), a sus derivados farmacéuticamente aceptables y a procesos para su preparación:



Reivindicaciones 1 a 10: Compuestos de la fórmula (I) y sus derivados farmacéuticamente aceptables.

Reivindicación 11: Una composición farmacéutica que comprende compuestos de la fórmula (I) o sales de los mismos, junto con un vehículo farmacéutico.

Reivindicación 12: Uso de compuestos de la fórmula (I) para la fabricación de un medicamento para el tratamiento de un paciente que sufre una enfermedad susceptible de mejorar por medio de un inhibidor del factor Xa.

Reivindicación 13: Un método para tratar a un paciente que sufre una enfermedad susceptible de mejorar por medio de un inhibidor del factor Xa, que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de fórmula (I).

Reivindicación 14: Procedimientos para la preparación de compuestos de fórmula (I).

El problema técnico planteado es la necesidad de proveer nuevos compuestos y formulaciones de los mismos para que funcionen como inhibidores del factor Xa y sean útiles en terapia para el tratamiento de enfermedades vasculares agudas, en el tratamiento de metástasis tumoral y de enfermedades neurovegetativas

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos derivados de pirrolidina, sus procesos de preparación y composiciones farmacéuticas que contienen estos compuestos.

De acuerdo a las características de los compuestos, se catalogó según la Clasificación Internacional de Patentes (IPC) en las categorías C07D 207/267, A61K 31/40 y A61P 7/02.

3. Excepción a la patentabilidad (artículo 20 D486 literal d)

La reivindicación 13 se refiere a un método de tratamiento y estos no son patentables de acuerdo a lo contenido en este artículo.

4. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D486)

Las reivindicaciones 10 y 12 indican el uso de los compuestos de la fórmula (I), lo cual no se considera como invención y por lo tanto no es patentable.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 08/06/2001, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta:

Nº	Documento	Título	Fecha de publicación
D1	WO 01/19795	AZACYCLOALKANONE SERINE PROTEASE INHIBITORS	22/03/2001
D2	US 5489583	2-SUBSTITUTED 3-(4- AMIDINOPHENYL) PROPIONIC ACID DERIVATIVES	06/02/1996

6. Análisis de patentabilidad (según requisito) (artículo 14 D486)

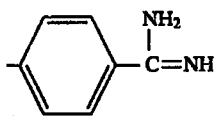
Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

6.1. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: Compuestos de fórmula (I) (ver folio 123).

En el documento D1 (folios 157 a 160) se describen compuestos inhibidores del factor Xa así como sus formulaciones y procesos de elaboración. Dichos compuestos, al igual que los de la presente solicitud, tienen un núcleo básico de pirrolidin-2-ona sustituido en la posición 3 del anillo con una sulfonamida y funcionan como potentes inhibidores del factor Xa, la diferencia en la estructura química con respecto a los de la presente solicitud, se encuentra en los sustituyentes de la carboxamida unida al nitrógeno del anillo de pirrolidina.

El documento D2 (folios 161 a 163) menciona compuestos inhibidores de la trombina, que solo se diferencian de los compuestos reivindicados, en que, asumiendo que R2 es Hidrógeno, el radical R3, representa Hidrógeno, Alquilo C1 a C3 o CF3, mientras que en D2 este radical corresponde al siguiente grupo:



Por lo tanto, los compuestos reivindicados en esta solicitud se pueden considerar como compuestos semejantes a los de D2 ya que además de su similitud estructural, también son útiles para el tratamiento de enfermedades vasculares.

Teniendo en cuenta el problema técnico que soluciona la presente solicitud, el cual es proveer nuevos compuestos inhibidores del factor Xa, vemos que la información de cualquiera de las dos anterioridades citadas le sugieren al experto en la materia, de acuerdo a sus conocimientos generales, a realizar procesos de síntesis para obtener compuestos como los reivindicados en la presente solicitud de patente con las mismas propiedades farmacológicas como inhibidores del factor Xa y funcionar en el tratamiento de enfermedades vasculares.

De acuerdo a lo anterior, los compuestos reivindicados no brindan un efecto técnico inesperado ya que debido a su estructura y a su actividad farmacológica, siguen siendo útiles para el tratamiento de enfermedades en las cuales está indicado un inhibidor del factor Xa, y por lo tanto son considerados compuestos alternativos a los ya conocidos.

Así mismo, esta solicitud no menciona una característica de los compuestos reivindicados, que conceda un efecto diferente o especial que pueda considerarse como un aporte a la técnica, así que resultan obvios para una persona versada en la materia, y por lo tanto el objeto reivindicado no tiene 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 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
27 JUL 2007

CONCEPTO TECNICO No. 1021	EXAMINADOR TECNICO Código No. 202077
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