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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO
Radicación : 00048529 00010000 Folios: 6
Fecha (ARD): 2004-08-31 18:15:06
Trámite : 002 PATENTES D 332 PRESENTAC 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-ASTRAZENECA AB.-Expediente número
00-048.529.-

1. Me refiero al asunto de la referencia.
2. Por medio del presente, atentamente me permito manifestar a ese Despacho, que hubo un **cambio** de Representante Legal para todos los asuntos de la Propiedad Industrial en Bogotá de **ASTRAZENECA AB**, una sociedad organizada y existente de conformidad con las leyes de Suecia, domiciliada en Sodertalje, Suecia.
3. En consecuencia, atentamente solicito a ese Despacho reconocerme personería, en este asunto, de conformidad con el documento de Representación Legal para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **ASTRAZENECA AB**, otorgado a favor de la **SUSCRITA (ALICIA LLOREDA)** y/o al doctor GUSTAVO TAMAYO y/o al doctor IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ de acuerdo con la copia debidamente autenticada ante Notario Público que adjunto al presente expediente (Artículos 26 y 39 de la Decisión 486 de la Comunidad Andina de Naciones).
4. Anexo al presente acompaño fotocopia, debidamente autenticada por Notario Público, de:
 - (a) Documento que acredita a la SUSCRITA y/o al doctor GUSTAVO TAMAYO y/o al doctor IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ en los términos del párrafo 1º. del Artículo 543 del Decreto-Ley 410 de 1971, como Representantes Legales en Bogotá para todos los asuntos relacionados con la propiedad industrial de la sociedad **ASTRAZENECA AB**, una sociedad organizada y existente de

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conformidad con las leyes de Suecia, domiciliada en Sodertalje, Suecia.

- (b) Certificación Notarial expedida el 26 de Julio de 2004; y
- © Traducción Oficial No. 2004-08-09-397 correspondiente a las partes pertinentes del documento anterior, también debidamente legalizada hasta por el Ministerio de Relaciones Exteriores bajo el número 250168 de 10 de Agosto de 2004.

5. Ruego a usted tomar atenta nota de lo anterior y continuar con el trámite correspondiente.

Señor Superintendente,


ALICIA LLOREDA RICAURTE
T.P. 53.215
Código 231

Los abajo firmados, AstraZeneca AB, una sociedad organizada y existente de conformidad con las leyes de Suecia,

con domicilio en

SE-15185 Sodertalje, Suecia,

nombramos por el presente a ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, domiciliados en Bogotá, Colombia, con oficinas en dicha ciudad, Calle 72 No. 5-83, piso 6o., nuestros representantes legales y verdaderos en Bogotá, con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales, con el fin de dar cumplimiento al parágrafo 1o. del artículo 543 del decreto 410 de 1971.

Los doctores ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, o los apoderados que cualquiera de ellos designe, quedan especialmente facultados para presentarnos ante las autoridades colombianas, administrativas, judiciales o de policía, en todos los trámites relativos a la propiedad industrial, a cuyo efecto les facultamos para dar ante dichas autoridades todos los pasos necesarios al objeto indicado; elevar solicitudes, declaraciones, reclamos, recursos y presentar desistimientos; formular descripciones, enmiendas, limitar el alcance de las solicitudes y los registros, presentar oposiciones y apelaciones; instaurar cancelaciones, renunciar total o parcialmente a los registros, abonar todos los impuestos y cuotas y efectuar todo otro pago determinado por la ley; recibir todos los documentos y valores, dando el descargo respectivo; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeran conducentes al resguardo de nuestros intereses; y adicionalmente quedan facultados para tomar intervención como demandantes o demandados ante los jueces que sean competentes, pudiendo transar, someter a arbitraje, desistir, percibir, conciliar y apelar, con todas las demás facultades que resulten necesarias, y por el presente declaramos desde ahora válido y bueno cuanto dichos representantes y/o los apoderados que cualquiera de ellos nombre hicieren en nuestro beneficio.

Asimismo, facultamos a los doctores ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, para solicitar en la Oficina de Propiedad Industrial la protocolización de este documento y de cualquier poder que cualquiera de ellos otorgue a nombre nuestro.

Dado y firmado el 22 de Julio de 2004 en Macclesfield, Inglaterra

The undersigned, AstraZeneca AB, a corporation organized and existing under the laws of Sweden,

domiciled at

SE-15185 Sodertalje
Sweden

hereby appoint, ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, of Bogota, Colombia, with offices in said town, Calle 72 No. 5-83, Sixth Floor, our true and legal representatives in Bogotá, with power to receive notifications and to appoint judicial or extrajudicial agents, so as to comply with paragraph 1o. of article 543 of decree 410 of 1971.

Doctors ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, or the agents by any one of them appointed, are especially empowered to represent us before the administrative, judicial or police authorities of Colombia, in all proceedings pertaining to industrial property, for which purpose we authorize them to take before the said authorities all the necessary steps for the said end; to file petitions, declarations, claims, recourses and withdrawals, to draw up specifications; to file amendments, to limit the scope of applications and registrations, file oppositions; file cancellations total or partially waive registrations, to pay all installments and effect all other payments prescribed by law; to receive proper receipts, to comply with all other requirements and, in short, to take all those measures which they may deem fit for the protection of our interests; and additionally we authorize said agents to act on our behalf, as complainants as well as defendants, before the competent judges, with full powers to make arrangements, to submit to arbitrators, to desist, to collect, to conciliate, to appeal and, in short, with all such further powers as may be required, and we hereby declare from now on as valid and good all that said representatives and/or the agents by any one of them appointed may do for our benefit.

We also authorize doctors ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, to apply for protocolization of this document and of any power of attorney by any one of them conferred in our name, before the Office of Industrial Property.

Given and signed this 22nd day of July 2004 at Macclesfield, England

SIMON RICHARD REEVES
Duly Authorised Signatory

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE VISTO A LA VISTA

12 AGR 2004

JUAN MANUEL VOTERO MERINA

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

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Hoy 26 de Julio de 2004, compareció
Simon Richard Reeves, a quien conozco y
de quien me consta que firmó el anterior documento,
y quien debidamente juramentado declaró y dijo que
él es firmante autorizado

de, AstraZeneca AB,
la compañía nombrada en el documento que
antecede, una sociedad debidamente organizada y
existente conforme a las leyes de Suecia
, domiciliada en la
ciudad de Vastra Malarehamnen 9, SE-151
85 Sodertalje, Suecia,
legalmente constituida para un período de duración
que aún no ha terminado, que ejerce su objeto social
conforme a las leyes de Suecia

que el declarante está autorizado por dicha
Compañía para conferir este poder; que el sello
empadado por él al pie de tal poder, en nombre y en
representación de la expresada Compañía, es el
sello oficial de ella; y que el objeto para el cual se
confiere este instrumento está comprendido dentro
de la sociedad.

El suscrito Notario ha visto los Estatutos de
incorporación firmados en Stockholm
, con fecha Oct. 31/1913
y certifica que de conformidad con la legislación de
dicho Estado la anterior declaración juramentada es
prueba suficiente de que los hechos sobre que ella
versa son ciertos o verdaderos, de lo cual da fe.

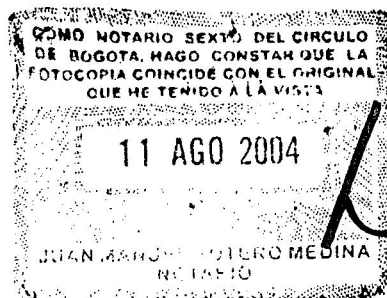
Notary Public (Notario Público).

On this 26th day of July, 2004,
personally Simon Richard Reeves
came
to me known, and known to me to be the person who
signed the foregoing instrument, who being by me
duly sworn did depose and say that he is the
duly authorised signatory of, AstraZeneca AB,
the company named within, a Corporation organized
and existing under the laws of Sweden
, domiciled at
Vastra-Malarehamnen 9, SE-151 85 Sodertalje,
Sweden
legally constituted for a period of tenure not yet
expired, which exercises its corporate purposes
according to the laws of Sweden

that the deponent is authorized by said Company to
confer this power of attorney; that the seal affixed
hereunto by the deponent in the name and on behalf
of said Corporation is the corporate seal thereof; and
that the purpose for which this instrument is granted
is included within the corporate purposes of the
Company.

The undersigned Notary Public has seen the articles
of Incorporation of said Corporation executed at
STOCKHOLM
under date of 31 October 1913
and hereby certifies that under the laws of said State
the foregoing acknowledgment is sufficient proof that
the facts therein contained are true, which he attests.

J. H. Huse
Notary Public
Wilkes-Barre
Schuylkill
Pennsylvania



COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

12 AGO 2004

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by **Joan Haig Ekserdjian**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres

6. the/le **02 August 2004**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No

G479981

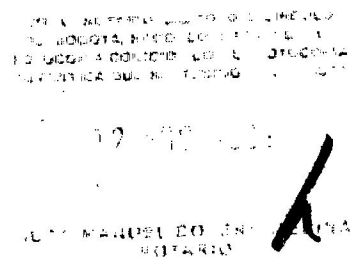
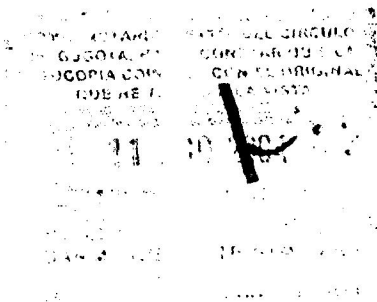
9. Stamp:
timbre:

10. Signature: **E. M. Fitzgerald**



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.



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TRADUCCION OFICIAL No. 2004-08-09-397 de un documento escrito en Inglés, la cual para efectos del presente lleva el sello personal de **Martha Lucia Arciniegas M.**, Traductora e Intérprete Oficial en virtud de la Res 1523 /88 del Ministerio de Justicia.

Legalización de un Poder de Representación Legal conferido a: ALICIA LLOREDA, y/o GUSTAVO TAMAYO, y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ otorgado por **AstraZeneca AB**

Firmado por:

SIMON RICHARD REEVES

Certificación Notarial

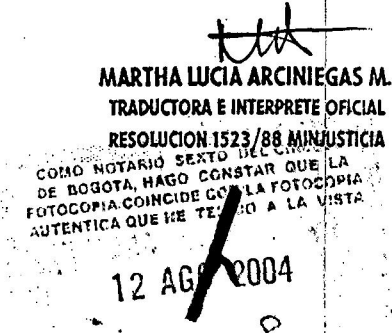
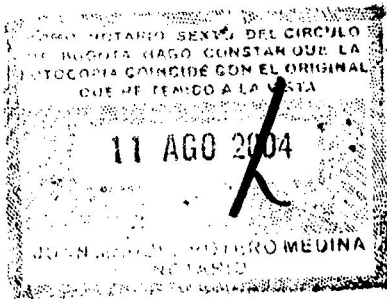
Certificación de la firma precedente, debidamente legalizada por Notario Público,

John Haig Ekserdjian

[Sello Lacrado de Notario Público]

JOHN HAIG EKSERDJIAN

Notario Público de Wilmslow, Cheshire, Inglaterra



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APOSTILLA

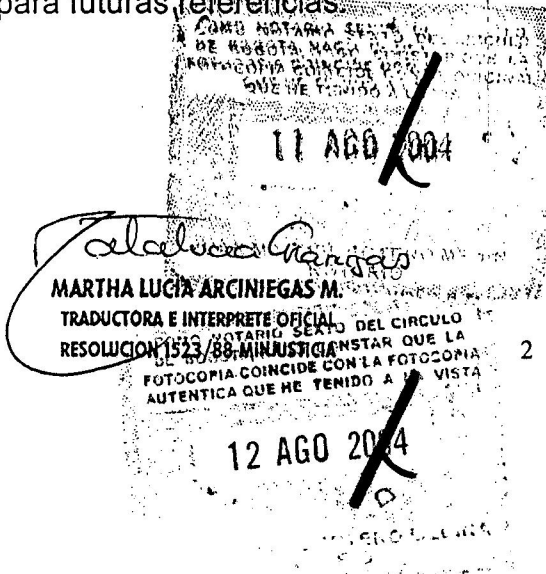
(Convención de La Haya del 5 de Octubre de 1961)

- 1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento público
- 2. ha sido firmado por **John Haig Erkserdjian**
- 3. actuando como **Notario Público**
- 4. y lleva el sello/estampilla **del Mencionado Notario Público**

Certificado

- 5. en Londres
- 6. el 2 de agosto del 2004
- 7. Por el Secretario Principal de Su Majestad para Asuntos Exteriores y del Commonwealth
- 8. No. G479981
- 9. Timbre/Sello
- 10. Firma
- Aparece el Sello de la Oficina **E.M. Fitzgerald**
- de Asuntos Exteriores y del Commonwealth

Según mi leal saber y entender, ésta en una traducción fiel y completa de su original en inglés, de la cual se deja copia para futuras referencias.



MINISTERIO DE

250169

Martha Acamiegas

COPIA FIDELITAR: REVEREND
DOCUMENTO ORIGINAL
LAS FUNCIONES INDICADAS

SECRETARÍA DE
GOBIERNO

2006

SECRETARÍA DE
GOBIERNO

NOTA: NO SE PUEDE EL CÍRCULO
SE DEBE HACER CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE SE TIENE A LA VISTA
11 AGO 2004

COPIA FIDELITAR

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

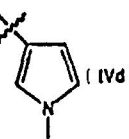
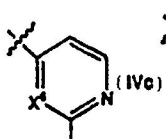
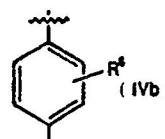
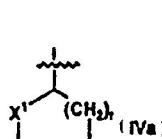
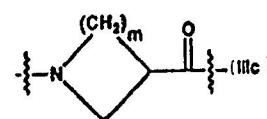
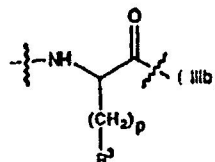
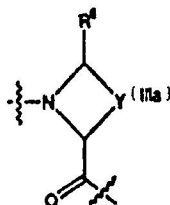
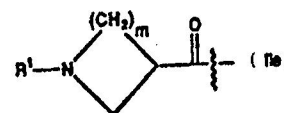
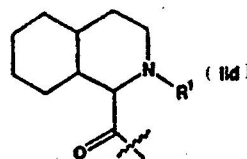
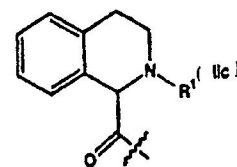
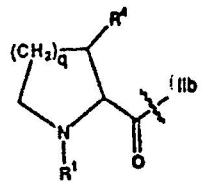
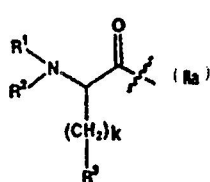
(51) International Patent Classification ⁵ : C07K 5/06, 5/02, A61K 38/55, C07C 257/18, 257/16, C07D 239/14, 211/26, 205/04, 207/09		A1	(11) International Publication Number: WO 94/29336 (43) International Publication Date: 22 December 1994 (22.12.94)
(21) International Application Number: PCT/SE94/00535 (22) International Filing Date: 2 June 1994 (02.06.94) (30) Priority Data: 9301916-4 3 June 1993 (03.06.93) SE		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): ANTONSSON, Karl, Thomas [SE/SE]; Torkels väg, Pl 3503, S-437 34 Lindome (SE). BYLUND, Ruth, Elvy [SE/SE]; Forellgatan 60, S- 426 58 Västra Frölunda (SE). GUSTAFSSON, Nils, David [SE/SE]; Änghagavägen, Pl 3758, S-430 41 Kullavik (SE). NILSSON, Nils, Olov, Ingemar [SE/SE]; Rågvägen 50, S- 430 33 Fjärås (SE). (74) Agent: SAMUELSSON, Britta; Astra Aktiebolag, Patent Dept., S-151 85 Södertälje (SE).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	

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(54) Title: NEW PEPTIDE DERIVATIVES

(57) Abstract

The invention relates to new competitive inhibitors of trypsin-like serine proteases, their synthesis, pharmaceutical compositions containing the compounds as active ingredients, and the use of the compounds as thrombin inhibitors, anticoagulants and anti-inflammatory inhibitors for prophylaxis and treatment of related diseases, according to the formulas (I): A¹-A²-NH-(CH₂)_n-B and (V): A¹-A²-NH-(CH₂)_n-B-D wherein A¹ represents a structural fragment of formulas (IIa), (IIb), (IIc), (IId), (IIe), A² represents a structural fragment of formulas (IIIa), (IIIb), (IIIc), B represents a structural fragment of formulas (IVa), (IVb), (IVc), (IVd). Further described are novel compounds, the new use of compounds and especially new structural fragment in synthesis of pharmaceutical compounds.



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and n is 1 or 2, or

More particularly preferred are compounds wherein B
represents a structural fragment fo formula IVb
5 wherein:

X^5 represents $C(NH)-NH_2$, R^6 is H, and $n = 1$

Preferred compounds of the invention are:

10

$HOOC-CH_2-(R)Cgl-Aze-Pab$

$HOOC-CH_2-CH_2-(R)Cgl-Aze-Pab$

$HOOC-CH_2-(R)Cgl-Pro-Pab$

$HOOC-CH_2-CH_2-(R)Cgl-Pro-Pab$

15

$(HOOC-CH_2)_2-(R)Cgl-Pro-Pab$

$H-(R)Cgl-Pic-Pab$

$HOOC-CH_2-(R,S)CH(COOH)-(R)Cgl-Pic-Pab$

$H-(R)Cha-Aze-Pab$

$HOOC-CH_2-(R)Cha-Aze-Pab$

20

$HOOC-CH_2-(R,S)CH(COOH)-(R)Cha-Aze-Pab$

$HOOC-CH_2-(RorS)CH(COOH)-(R)Cha-Aze-Pab/a$

$HOOC-CH_2-(RorS)CH(COOH)-(R)Cha-Aze-Pab/b$

$HOOC-CH_2-CH_2-(R)Cha-Aze-Pab$

$HOOC-CH_2-NH-CO-CH_2-(R)Cha-Aze-Pab$

25

$H-(R)Cha-Pro-Pab$

$HOOC-CH_2-(R)Cha-Pro-Pab$

$HOOC-CH_2-(Me)(R)Cha-Pro-Pab$

$HOOC-CH_2-CH_2-(R)Cha-Pro-Pab$

$HOOC-CH_2-CH_2-(Me)(R)Cha-Pro-Pab$

30

$HOOC-CH_2-(RorS)CH(COOH)-(R)Cha-Pro-Pab/a$

$HOOC-CH_2-(RorS)CH(COOH)-(R)Cha-Pro-Pab/b$

$HOOC-CH_2-NH-CO-CH_2-(R)Cha-Pro-Pab$

$EtOOC-CH_2-CH_2-CH_2-(R)Cha-Pro-Pab$

$Ph(4-COOH)-SO_2-(R)Cha-Pro-Pab$

35

$H-(R)Cha-Pic-Pab$

$HOOC-CH_2-(R)Cha-Pic-Pab$

$HOOC-CH_2-(RorS)CH(COOH)-(R)Cha-Pic-Pab/a$

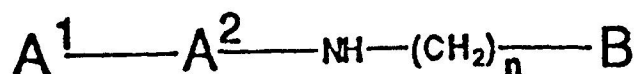
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carbon atom noted "RorS". The stereoisomer can be identified for each compound with reference to the experimental part herein. "R,S" refers to a mixture of stereoisomers.

5

According to the invention it has been found that compounds of the general Formula Ib, either as such or in the form of physiologically acceptable salts, and including stereoisomers, are potent inhibitors of kininogenases:

10



Ib

15 wherein:

A¹ represents a structural fragment of formula IIa, IIb or IIe, preferably IIa or IIb;
wherein:

20

k is an integer 0, 1, 2, 3 or 4, preferably 0, 1;

q is an integer 0, 1, 2, or 3, preferably 1;

25 R¹ represents H, an alkyl group having 1 to 4 carbon atoms, or R¹¹OOC-alkyl-, where the alkyl group has 1 to 4 carbon atoms and is possibly substituted in the position which is alpha to the carbonyl group, and the alpha substituent is a group R¹⁷-(CH₂)_p-, wherein p is
30 0, 1 or 2 and R¹⁷ is methyl, phenyl, OH, COOR¹², CONHR¹², where R¹² is H or an alkyl group having 1 to 4 carbon atoms, and R¹¹ is H or an alkyl group having 1 to 6 carbon atoms, or

35 R¹ represents Ph(4-COOR¹²)-CH₂-, where R¹² is H or an alkyl group having 1 to 4 carbon atoms, or

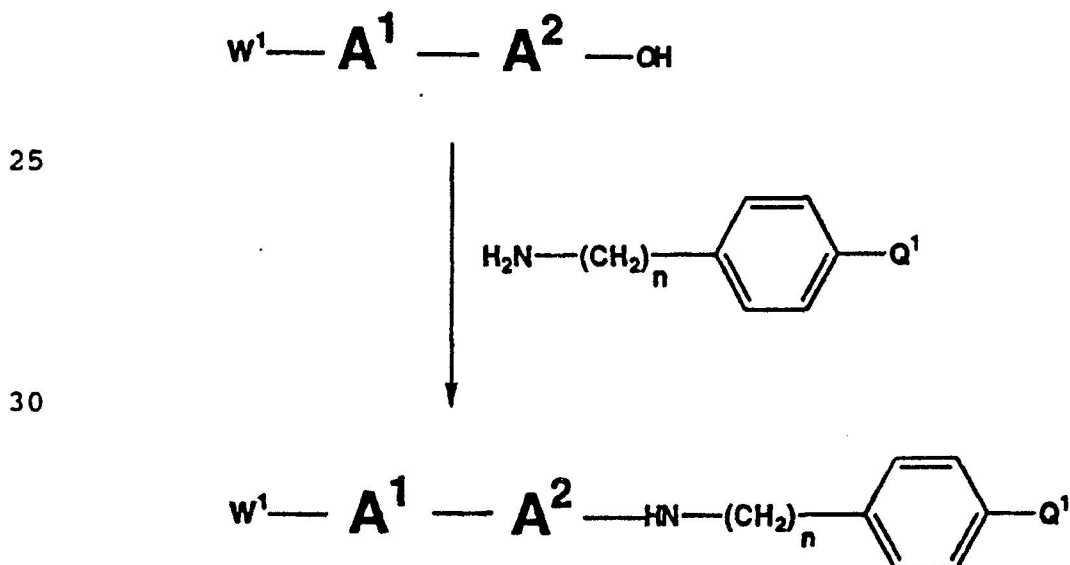
14. A compound selected from

- HOOC-CH₂-(R) Cgl-Aze-Pab
HOOC-CH₂-CH₂-(R) Cgl-Aze-Pab
5 HOOC-CH₂-(R) Cgl-Pro-Pab
HOOC-CH₂-CH₂-(R) Cgl-Pro-Pab
(HOOC-CH₂)₂-(R) Cgl-Pro-Pab
H-(R) Cgl-Pic-Pab
HOOC-CH₂-(R, S) CH(COOH)-(R) Cgl-Pic-Pab
10 H-(R) Cha-Aze-Pab
HOOC-CH₂-(R) Cha-Aze-Pab
HOOC-CH₂-(R, S) CH(COOH)-(R) Cha-Aze-Pab
HOOC-CH₂-(RorS) CH(COOH)-(R) Cha-Aze-Pab/a
HOOC-CH₂-(RorS) CH(COOH)-(R) Cha-Aze-Pab/b
15 HOOC-CH₂-CH₂-(R) Cha-Aze-Pab
HOOC-CH₂-NH-CO-CH₂-(R) Cha-Aze-Pab
H-(R) Cha-Pro-Pab
HOOC-CH₂-(R) Cha-Pro-Pab
HOOC-CH₂-(Me) (R) Cha-Pro-Pab
20 HOOC-CH₂-CH₂-(R) Cha-Pro-Pab
HOOC-CH₂-CH₂-(Me) (R) Cha-Pro-Pab
HOOC-CH₂-(RorS) CH(COOH)-(R) Cha-Pro-Pab/a
HOOC-CH₂-(RorS) CH(COOH)-(R) Cha-Pro-Pab/b
HOOC-CH₂-NH-CO-CH₂-(R) Cha-Pro-Pab
25 EtOOC-CH₂-CH₂-CH₂-(R) Cha-Pro-Pab
Ph(4-COOH)-SO₂-(R) Cha-Pro-Pab
H-(R) Cha-Pic-Pab
HOOC-CH₂-(R) Cha-Pic-Pab
HOOC-CH₂-(RorS) CH(COOH)-(R) Cha-Pic-Pab/a
30 HOOC-CH₂-(RorS) CH(COOH)-(R) Cha-Pic-Pab/b
HOOC-CH₂-CH₂-(R) Cha-Pic-Pab
HOOC-CO-(R) Cha-Pic-Pab
HOOC-CH₂-CO-(R) Cha-Pic-Pab
Me-OOC-CH₂-CO-(R) Cha-Pic-Pab
35 H₂N-CO-CH₂-(R) Cha-Pic-Pab
Boc-(R) Cha-Pic-Pab

protecting group such as a benzyloxy carbonyl- or
tertbutyloxy carbonyl- or p-toluenesulphonyl group or X
is a group transferable into B followed by removal of
the protecting group(s) or deprotection of the N-
5 terminal nitrogen followed by alkylation of the N-
terminal nitrogen and if desired deprotection by known
methods and if desired forming a physiologically
acceptable salt, and in those cases where the reaction
results in a mixture of stereoisomers, these are
10 optionally separated by standard chromatographic or
re-crystallisation techniques, and if desired a single
stereoisomer is isolated.

21. A process according to claim 20 for preparing a
15 compound according to any of claims 1-19, which
process comprises:

a) (Method Ia) Coupling of an N-terminally protected
dipeptide, selected from A¹ and A² in Formulas I or V by
20 using standard peptide coupling, shown in the formula



35 wherein n is as defined in Formula I, w¹ is an N-
terminal amino protecting group such as tert-butyloxy

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245

18. A compound selected from

H-(R)Pro-Phe-Pab

HOOC-CH₂-(R)Pro-Phe-Pab

5 H-(R)Phe-Phe-Pab

HOOC-CH₂-(R)Phe-Phe-Pab

HOOC-CO-(R)Phe-Phe-Pab

10 either as such or stereoisomer thereof or in the form
of a physiologically acceptable salt.

19. A compound selected from

Boc-(R)Pro-Phe-Pab(Z)

15 BnOOC-CH₂-(R)Pro-Phe-Pab(Z)

Boc-(R)Phe-Phe-Pab(Z)

MeOOC-CO-(R)Phe-Phe-Pab(Z)

BnOOC-CH₂-(R)Phe-Phe-Pab(Z)

20 either as such or stereoisomer thereof or in the forms
of a physiologically acceptable salt.

20. A process for preparing a compound according to any
of claims 1-19, which process comprises coupling of an
25 N-terminally protected amino acid or dipeptide or amino
acid, when an N-terminally amino acid is used a second
aminoacid is added afterwards using standard methods
to a compound

30



wherein n is an integer 0, 1, 2, 3 or 4, X is B or B-D,
35 where B is as defined in formula I and D is as defined
in formula V as such or having the guanidino or amidino

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PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 5/00, A61K 38/55	A1	(11) International Publication Number: WO 97/23499 (43) International Publication Date: 3 July 1997 (03.07.97)
(21) International Application Number: PCT/SE96/01680 (22) International Filing Date: 17 December 1996 (17.12.96) (30) Priority Data: 9526273.9 21 December 1995 (21.12.95) GB (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): ANTONSSON, Thomas [SE/SE]; Torkels Väg, PL 3503, S-437 34 Lindome (SE). GUSTAFSSON, David [SE/SE]; Änghagavägen, PL 3758, S-429 32 Kullavik (SE). HOFFMANN, Kurt- Jürgen [DE/SE]; Korshamnsvägen 11, S-429 31 Kullavik (SE). NYSTRÖM, Jan-Erik [SE/SE]; Flintstensvägen 36, S-437 32 Lindome (SE). SÖRENSEN, Henrik [DK/SE]; Videvägen 37, S-435 38 Mölnlycke (SE). SELLÉN, Mikael [SE/SE]; Pontus Wiknersgatan 3, S-411 32 Göteborg (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: PRODRUGS OF THROMBIN INHIBITORS (57) Abstract There is provided compounds of formula (I): R¹O(O)C-CH₂-(R)Cgl-Aze-Pab-R², wherein R¹ and R² have meanings given in the description, which are useful as prodrugs of inhibitors of trypsin-like proteases, such as thrombin, and in particular in the treatment of conditions where inhibition of thrombin is required (e.g. thrombosis) or as anticoagulants.		

Prodrugs of Thrombin Inhibitors**Field of the Invention**

5 This invention relates to pharmaceutically useful prodrugs of pharmaceutically active compounds, which active compounds are, in particular, competitive inhibitors of trypsin-like serine proteases, especially thrombin, the use of the prodrugs as medicaments, pharmaceutical compositions containing them and synthetic routes to their
10 production.

Background

Blood coagulation is the key process involved in both haemostasis (ie the
15 prevention of blood loss from a damaged vessel) and thrombosis (ie the formation of a blood clot in a blood vessel, sometimes leading to vessel obstruction).

Coagulation is the result of a complex series of enzymatic reactions. One
20 of the ultimate steps in this series of reactions is the conversion of the proenzyme prothrombin to the active enzyme thrombin.

Thrombin is known to play a central role in coagulation. It activates platelets, leading to platelet aggregation, converts fibrinogen into fibrin
25 monomers, which polymerise spontaneously into fibrin polymers, and activates factor XIII, which in turn crosslinks the polymers to form insoluble fibrin. Furthermore, thrombin activates factor V and factor VIII leading to a "positive feedback" generation of thrombin from prothrombin.

30 By inhibiting the aggregation of platelets and the formation and

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crosslinking of fibrin, effective inhibitors of thrombin would therefore be expected to exhibit antithrombotic activity. In addition, antithrombotic activity would be expected to be enhanced by effective inhibition of the positive feedback mechanism.

5

Prior Art

The development of low molecular weight inhibitors of thrombin has been described by Claesson in Blood Coagul. Fibrin. (1994) 5, 411.

10

Blombäck *et al* (in J. Clin. Lab. Invest. 24, suppl. 107, 59, (1969)) reported thrombin inhibitors based on the amino acid sequence situated around the cleavage site for the fibrinogen A α chain. Of the amino acid sequences discussed, these authors suggested the tripeptide sequence Phe-
15 Val-Arg would be the most effective inhibitor.

Low molecular weight peptide-based thrombin inhibitors have subsequently been disclosed in, for example, US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 94/29336, WO
20 93/18060 and WO 95/01168; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642 and 601 459.

More recently, thrombin inhibitors based on peptide derivatives have been
25 disclosed in European Patent Application 0 669 317 and International Patent Applications WO 95/23609, WO 95/35309, WO 96/25426 and WO 94/29336.

In particular, the latter application discloses the peptide derivatives
30 R^aOOC-CH₂-(R)Cgl-Aze-Pab-H, wherein R^a represents H, benzyl or C₁₋₆

alkyl.

Although these active compounds are known to exhibit significant antithrombin activity, it would be beneficial to improve their pharmacokinetic properties both after oral and parenteral administration. Examples of pharmacokinetic properties which it is desirable to improve include:

- (a) providing an improved absorption from the gastro-intestinal tract, with a view to reducing intra- and/or inter-individual variability in relation to the bioavailability of the active compounds;
- (b) flattening the plasma concentration time profile (ie reducing the peak/trough ratio in the plasma concentration over the dosing interval), with a view to reducing the risk of falling outside the therapeutic interval and the side effects caused by a concentration peak which is too high (eg bleeding), and those caused by one which is too low (eg thrombus formation); and
- (c) increasing the duration of action of the active compounds.

Moreover, oral and parenteral administration of active thrombin inhibitors may lead to undesirable local bleeding (eg in the intestinal lumen or subcutaneously) as a result of a high local concentration,

Finally, orally administered active thrombin inhibitors which also inhibit trypsin and other serine proteases in the gastrointestinal tract may exhibit additional side effects, including indigestion (eg if trypsin is inhibited in the intestinal lumen).

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Although certain N-benzyloxycarbonyl derivatives of the aforementioned active compounds are also disclosed as thrombin inhibitors in International Patent Application WO 94/29336, that these derivatives may be useful as prodrugs is not mentioned. In fact, WO 94/29336 makes no mention of
5 suitable prodrugs of the active compounds.

We have found that the above problems may be solved by administering compounds according to the present invention which, whilst inactive *per se*, upon oral and/or parenteral administration are metabolised in the body
10 to form active thrombin inhibitors, including those mentioned above.

Disclosure of the Invention

According to the invention there is provided a compound of formula I,
15
$$R^1O(O)C-CH_2-(R)Cgl-Aze-Pab-R^2 \quad I$$

wherein

R^1 represents $-R^3$ or $-A^1C(O)N(R^4)R^5$ or $-A^1C(O)OR^4$;

A^1 represents C_{1-5} alkylene;

R^2 (which replaces one of the hydrogen atoms in the amidino unit of
20 Pab-H) represents OH, $OC(O)R^6$, $C(O)OR^7$ or $C(O)OCH(R^8)OC(O)R^9$;
 R^3 represents H, C_{1-10} alkyl, or C_{1-3} alkylphenyl (which latter group is optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or halogen);

R^4 and R^5 independently represent H, C_{1-6} alkyl, phenyl, 2-naphthyl or, when R^1 represents $-A^1C(O)N(R^4)R^5$, together with the nitrogen atom to
25 which they are attached represent pyrrolidinyl or piperidinyl;

R^6 represents C_{1-17} alkyl, phenyl or 2-naphthyl (all of which are optionally substituted by C_{1-6} alkyl or halogen);

R^7 represents 2-naphthyl, phenyl, C_{1-3} alkylphenyl (which latter three groups are optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or
30 halogen), or C_{1-12} alkyl (which latter group is optionally substituted by C_{1-6}

Claims

1. A compound of formula I,



5 wherein

R^1 represents $-R^3$ or $-A^1C(O)N(R^4)R^5$ or $-A^1C(O)OR^4$;

A^1 represents C_{1-5} alkylene;

R^2 (which replaces one of the hydrogen atoms in the amidino unit of Pab-H) represents OH, $OC(O)R^6$, $C(O)OR^7$ or $C(O)OCH(R^8)OC(O)R^9$;

10 R^3 represents H, C_{1-10} alkyl, or C_{1-3} alkylphenyl (which latter group is optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or halogen);

R^4 and R^5 independently represent H, C_{1-6} alkyl, phenyl, 2-naphthyl or, when R^1 represents $-A^1C(O)N(R^4)R^5$, together with the nitrogen atom to which they are attached represent pyrrolidinyl or piperidinyl;

15 R^6 represents C_{1-17} alkyl, phenyl or 2-naphthyl (all of which are optionally substituted by C_{1-6} alkyl or halogen);

R^7 represents 2-naphthyl, phenyl, C_{1-3} alkylphenyl (which latter three groups are optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, nitro or halogen), or C_{1-12} alkyl (which latter group is optionally substituted by C_{1-6}

20 alkoxy, C_{1-6} acyloxy or halogen);

R^8 represents H or C_{1-4} alkyl; and

R^9 represents 2-naphthyl, phenyl, C_{1-6} alkoxy or C_{1-8} alkyl (which latter group is optionally substituted by halogen, C_{1-6} alkoxy or C_{1-6} acyloxy);

provided that when R^1 represents R^3 , R^3 represents benzyl, methyl, ethyl, 25 *n*-butyl or *n*-hexyl and R^2 represents $C(O)OR^7$, then R^7 does not represent benzyl;

or a pharmaceutically-acceptable salt thereof.

2. A compound of formula I, as defined in Claim 1, wherein A^1 represents

30 C_{1-3} alkylene when R^1 represents $-A^1C(O)N(R^4)R^5$.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 47/34, 9/00, 38/55		A1	(11) International Publication Number: WO 98/16252
			(43) International Publication Date: 23 April 1998 (23.04.98)
(21) International Application Number: PCT/SE97/01652 (22) International Filing Date: 1 October 1997 (01.10.97) (30) Priority Data: 9603724-7 11 October 1996 (11.10.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): LUNDGREN, Anna [SE/SE]; Topeliusgatan 4, S-412 68 Göteborg (SE). SKANTZE, Urban [SE/SE]; Östersnäs vägen 30, S-431 36 Mölnådal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: NEW PHARMACEUTICAL PARENTERAL FORMULATION OF A THROMBIN INHIBITOR			
(57) Abstract A pharmaceutical formulation of a thrombin inhibitor for parenteral use having an extended release effect, as well as a process for its preparation and the use of the formulation in arterial and/or venous thromboembolism, the extended release formulation comprising a thrombin inhibitor selected from the group consisting of melagatran, inogatran and their physiologically acceptable water soluble salts, and one or more block copolymer having the general formula: $HO[C_2H_4O]_a[C_3H_6O]_b[C_2H_4O]_cH$, wherein each a independently is an integer 1 - 250 and b is an integer 1 - 250 and wherein the formulation has a solution-gelation transition temperature below 37 °C.			

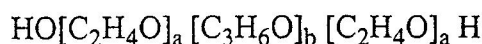
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pH regulating agents are of major importance. The effect on viscosity parameters and the solution-gelation transition temperature due to interaction between a particular compound, and the formulation components is not predictable and thus not the in vivo extended release effect.

5

It has now surprisingly been found that a formulation comprising a water solution of a low molecular weight, water soluble thrombin inhibitor with a short half life selected from the group consisting of melagatran, inogatran and their physiologically acceptable water soluble salts and an additive selected from the group consisting of a block copolymer

10 having the general formula



wherein a is an integer 1-250 and b is an integer 1-250, and wherein the additive(s) together with the trombin inhibitor in the formulation have a solution-gelation transition temperature below 37°C, provides an extended release effect in vivo after subcutaneous

15 administration.

Melagatran is the compound $\text{HOOC-CH}_2\text{-(R)-Cgl-Aze-Pab}$ (disclosed in EP 701 568) and inogatran is the compound $\text{HOOC-CH}_2\text{-(R)-Cha-Pic-Nag}$ (disclosed in EP 618 926),

wherein

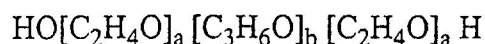
- 20 Aze is (S)-azetidine-2-carboxylic acid
Cgl is (S)-cyclohexylglycine
Cha is (S)-β-cyclohexyl alanine
Nag is noragmatine
Pab is 1-amidino-4-aminomethyl benzene
- 25 Pic is (S)-pipecolic acid.

Physiologically acceptable salts may be any of the following salts of inorganic and organic acids, namely hydrobromide, hydrochloride, sulphate, nitrate, salts from sulphonic acids, e.g. methane sulphonate, ethane sulphonate, benzene sulphonate, toluene sulphonate,

30 'naphthalene-2-sulphonate, salts from carboxylic acids, e.g. maleate, benzoate, salicylate,

acetate, malate, succinate, gluconate, glycollate, lactate, tartrate, citrate, ascorbate, hexanoate, octanoate, decanoate, undecylenate, dodecylsulphate, oleate, stearate.

As additives are used poloxamers, which are block copolymers having the general
5 formula



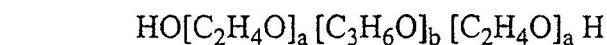
wherein a is an integer 1-250 and b is an integer 1-250.

The additive(s) could be a single poloxamer or a mixture of two or more poloxamers.
10

The preferred poloxamers have the general formula defined above wherein a is an integer 5 -150 and b is an integer 15-75.

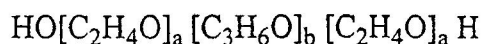
The most preferred poloxamers have the general formula defined above wherein a is an
15 integer 70-105 and b is an integer 25-70.

Poloxamer 188 is a block copolymer having the general formula



20 wherein a is approximately 79 and b is approximately 28, having a molecular weight in the range of 7689-9510 and with a mass fraction of polyoxyethylene of approximately 81%.

Poloxamer 407 is a block copolymer having the general formula
25



wherein a is approximately 98 and b is approximately 67, having a molecular weight in the range of 9840-14600 and with a mass fraction of polyoxyethylene of approximately 73%.

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The concentration of the thrombin inhibitor is preferably in the range 0.01-20% (w/w), and more preferably 0.1-10% (w/w) of the ready to use formulation.

- 5 The concentration of the poloxamer is preferably 15-40 % (w/w), and more preferably 20-35% (w/w) but most preferably 25-30% (w/w) of the ready to use formulation.

The solution-gelation transition temperature of the ready to use formulation is below 37°C, preferably in the range 15-37° C and most preferably in the range 25-35°C.

10

Due to physiological considerations a pH between 3-10 is preferred. If necessary the pH is adjusted with an acidifying agent, such as for instance acetic acid, ascorbic acid, citric acid, fumaric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, propionic acid, sulfuric acid or tartaric acid, or an alkalising agent, such as sodium hydroxide.

15

The formulation may contain further additional components, such as antioxidants, antimicrobial preservatives, tonicity modifiers and/or buffer components.

20

The formulation is prepared conveniently by dissolving the solid components in water, adjusting the pH and sterilizing the resulting solution. The order in which the components are dissolved and at which stage the pH adjustment or sterilization is performed is not critical and may be chosen according to what is most suitable.

25

Suitable daily parenteral doses for the thrombin inhibitor in the therapeutical treatment of humans are 0.001-50 mg/kg body weight, preferably 0.005-5 mg/kg.

The pharmaceutical formulation is intended for prophylaxis and/or treatment in arterial as well as venous thromboembolism.

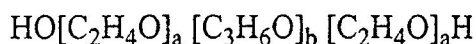
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The formulation is intended for parenteral use, including intracutaneous, subcutaneous, intra linomateus intra muscular and intraperitoneal administration

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Claims

1. An extended release formulation for parenteral administration of a water solution of a low molecular weight water soluble thrombin inhibitor with a short half life comprising a thrombin inhibitor selected from the group consisting of melagatran, inogatran and their physiologically acceptable water soluble salts, and one or more block copolymer having the general formula



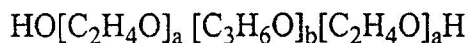
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wherein each a independently is an integer 1-250 and b is an integer 1-250 and wherein the formulation have a solution-gelation transition temperature below 37°C.

2. A formulation according to claim 1, having at least one additional component which is an acidifying or alkalising agent, antimicrobial preservative, tonicity modifier, antioxidant and/or buffer.

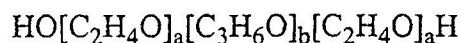
3. A formulation according to claim 1 or 2, wherein the block copolymer has the general formula

20



wherein each a independently is an integer 5-150 and b is an integer 15-75.

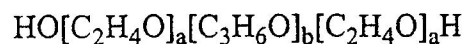
4. A formulation according to claims 1 or 2, wherein the additive is a block copolymer having the general formula



wherein each a independently is an integer 70-105 and b is an integer 25-70.

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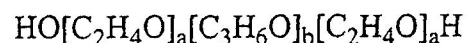
5. A formulation according to any one of claims 1 to 4, wherein the additive is a block copolymer having the general formula



5

wherein each a is approximately 79 and b is approximately 28, having a molecular weight in the range of 7689-9510 and with a mass fraction of polyoxyethylene of approximately 81%.

10 6. A formulation according to any one of claims 1 to 4, wherein the additive is a block copolymer having the general formula



15 wherein each a is approximately 98 and b is approximately 67, having a molecular weight in the range of 9840-14600 and with a mass fraction of polyoxyethylene of approximately 73%.

20 7. A formulation according to any of the preceding claims wherein the additive is a mixture of the block copolymers defined in claim 5 and claim 6.

8. A formulation according to any one of claims 1 to 7, wherein the additive(s) together with the thrombin inhibitor in the formulation have a solution-gelation transition temperature within the range 15-37°C.

25

9. A formulation according to claim 8, wherein the additive(s) together with the thrombin inhibitor in the formulation have a solution-gelation transition temperature within the range 25-35°C.

- 214 210
10. A formulation according to any one of claims 1 to 9 wherein the thrombin inhibitor is melagatran or a physiologically acceptable salt thereof.
11. A formulation according to any one of claims 1 to 10 wherein the concentration of the
5 thrombin inhibitor is in the range 0.01 - 20 % (w/w) of the ready to use formulation.
12. A formulation according to claim 11 wherein the concentration of the additive(s) is 15
- 40 % (w/w) of the ready to use formulation.
- 10 13. An extended release formulation as defined in any of claims 1-12 for use in the prophylaxis and/or treatment in arterial and/or venous thromboembolism in mammals including man.
14. A process for the preparation of a formulation according to any of the preceding claims
15 wherein the thrombin inhibitor and the additives are dissolved in water, the pH is adjusted and the resulting solution is sterilized, the separate steps being performed in any order.
15. A method for the prophylaxis and/or treatment of arterial and/or venous thromboembolism in mammals including man by administering to a host in need thereof of
20 a formulation as defined in any of claims 1-13.
16. Use of the components of the extended release formulation defined in any one of claims 1 to 13 for the manufacture of a medicament useful in the prophylaxis and /or treatment of arterial and /or venous thromboembolism.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

2020

Bogotá, D.C., Junio 21 de 2005

Doctora

ALICIA LLOREDA RICAURTE

ASUNTO	Radicación No.	00 048 529
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	
	Folios	0 05818

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 5 – 35 y 123 – 145 y el nuevo capítulo reivindicatorio de los folios 172 - 174 de la solicitud en estudio.

2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 – 8 se refieren a una forma cristalina de melagatrán (hemihidrato, anhidrato e isopropanolato/hidrato).

Las reivindicaciones 9 – 17 se refieren a un proceso para producir una forma cristalina de melagatrán que consiste en la cristalización en un sistema solvente (acetatos, alcoholes, hidrocarburos, éteres, cetonas, soluciones acuosas, alquilacetatos, alquilalcoholes, hidrocarburos aromáticos, dialquiléteres, como p. ej. acetato de etilo, etanol, isopropanol, isooctano, n-heptano, tolueno, diisopropil éter, metil isobutilcetona, acetonitrilo, agua ó mezcla de ellos) y un antisolvente (acetato de etilo, acetonitrilo).

La reivindicación 18 se refiere a una formulación farmacéutica que contiene un compuesto de las reivindicaciones 1 - 8 con un auxiliar ó vehículo farmacéuticamente aceptables.

El problema planteado en esta solicitud es la necesidad de proporcionar, posterior a la síntesis, una forma más pura y estable de melagatrán. }

Para resolver este problema técnico la solicitud en estudio proporciona una forma cristalina de melagatrán (hemihidrato, anhidrato e isopropanolato/hidrato) y la cristalización para obtenerla.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 38/55.

También se reivindica prioridad de la Solicitud de Patente de Suecia 9902550-4 julio 2 de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Claridad de las reivindicaciones

Con referencia la reivindicación 2 se observa que la expresión “una forma cristalina de melagatrán, la cual contiene por lo menos 0.5 mol de agua por mol de melagatrán” (que eventualmente correspondería a un hemihidrato), no tiene sustento en la descripción, en donde tan solo se menciona el monohidrato. Se debe hacer la aclaración necesaria.

Con referencia a las reivindicaciones 14 y 15 se observa que se mencionan el acetato de etilo y el acetonitrilo como solvente y como antisolvente; lo cual es contradictorio. Porque no pueden ser los dos simultáneamente. Se debe hacer la aclaración necesaria.

4. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *“El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40”.

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es julio 2 de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	WO 94 29336	Derivados de nuevos péptidos	Dic 22, 1994
D2	WO 97 23499	Prodrogas de inhibidores de trombina	Jul 3, 1997
D3	WO 98 16252	Nuevas formulaciones farmacéuticas parenterales de un inhibidor de trombina	Abr 23, 1998
D4	Libro (*)	Remington Farmacia	1995

(*) GENNARO, Alfonso. “Remington Farmacia”. Ed Panamericana. 19ª ed. Argentina, 1995.

5. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina

establece que "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de 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.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

Las reivindicaciones 1 – 8 se refieren a una forma cristalina de melagatrán (hemihidrato, anhidrato e isopropanolato/hidrato).

Las reivindicaciones 9 – 17 se refieren a un proceso para producir una forma cristalina de melagatrán que consiste en la cristalización en un sistema solvente (acetatos, alcoholes, hidrocarburos, éteres, cetonas, soluciones acuosas, alquilacetatos, alquilalcoholes, hidrocarburos aromáticos, dialquiléteres, como p. ej. acetato de etilo, etanol, isopropanol, isooctano, n-heptano, tolueno, diisopropil éter, metil isobutylcetona, acetonitrilo, agua ó mezcla de ellos) y un antisolvente (acetato de etilo, acetonitrilo).

La reivindicación 18 se refiere a una formulación farmacéutica que incluye un compuesto de las reivindicaciones 1 – 8 y un vehículo farmacéuticamente aceptable.

D1 enseña melagatrán (pág 19) y aclara que se puede separar por técnicas normales de re-cristalización (pág 246).

D2 enseña melagatrán y sus sales farmacéuticamente aceptables.

D3 enseña melagatrán, sus sales farmacéuticamente aceptables y formulaciones que las contienen.

D4 enseña "cuando la disolución de un compuesto en agua se sobrepasa, la solución se hace sobresaturada y el compuesto puede precipitar o cristalizar". "La velocidad de cristalización ó crecimiento de los núcleos es proporcional a la sobresaturación" (pág 371, folio 170). "El tamaño de las partículas cristalinas depende fuertemente de la concentración de la sustancia precipitante" (pág 372, folio 171). "Los solvatos de drogas sólidas, p. ej. los hidratos, tienen estructuras cristalinas diferentes y solubilidades o más altas o más bajas que las formas anhidras" (pág 373, folio 172). El proceso de cristalización depende de tres estados sucesivos: un estado de sobresaturación (superenfriamiento), formación de núcleos y crecimiento de cristales ó de partículas amorfas. La sobresaturación se puede lograr por evaporación de los solventes de una solución, por enfriamiento de la solución, si el soluto tiene un calor de disolución positivo, por producción de más soluto como consecuencia de una reacción química ó al modificar el medio solvente por adición de diversas sustancias secundarias solubles. Según las condiciones de cristalización es posible

controlar o modificar la índole de los cristales obtenidos. Cuando existe polimorfismo, suele ser necesario un control cuidadoso de la temperatura y realizar una siembra con la forma de cristal deseada. A menudo el hábito o la **forma de un cristal dado depende** en gran medida de las impurezas de la solución, del pH, de la velocidad de agitación, de la de enfriamiento **y del solvente**. (pág 374, folio 173).

En cuanto a las formas cristalinas de las reivindicaciones 1 a 8 se observa que si bien estas no están expresamente mencionadas en la anterioridad, se considera que no tienen nivel inventivo, porque la disposición de las moléculas para formar uno u otro cristal es una característica intrínseca del compuesto denominada polimorfismo.

Y el hecho de establecer cuáles son los polimorfos de un compuesto, su estabilidad, solubilidad, mejor forma de obtención de cada uno de ellos y su posterior integración con los demás componentes de la formulación, es un proceso rutinario y obligatorio, previo a la elaboración de una preparación con el fin de que esta tenga un comportamiento reproducible.

No se aprecia nivel inventivo porque el compuesto presenta las mismas propiedades anticoagulantes, inhibidoras de trombina y no presenta propiedades sorprendentes ó inesperadas que resuelvan algún problema en la técnica, cuando se compara con el compuesto del estado del arte. Puesto que no se observa una ventaja comparativa sorprendente con respecto al compuesto enseñado en la anterioridad, es claro que no hay nivel inventivo.

El proceso mencionado es una forma convencional para obtener una sal cristalizada, de modo que también carece de nivel inventivo.

Debido a que: (a) son conocidos el compuesto melagatrán y la cristalización en solventes, para una persona conocedora de la materia era evidente el obtener los cristales de esta solicitud de manera similar; (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a las formas cristalinas (hemihidrato, anhidrato e isopropanolato/hidrato) que pueda considerarse como un aporte a la técnica, así que estas son obvias para una persona versada en la materia y (c) el problema planteado en esta solicitud era la necesidad de proporcionar posterior a la síntesis, una forma más pura y estable de melagatrán y puesto que para resolver este problema técnico la solicitud proporciona una forma cristalina de melagatrán (hemihidrato, anhidrato e isopropanolato/hidrato) y la cristalización para obtenerla de manera similar a como se resolvía en las anterioridades D1 ó D4; entonces esta solicitud no tiene **nivel inventivo**.

6. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 94 29336	1 - 18	Nivel inventivo
D2	WO 97 23499	1 - 18	Nivel inventivo
D3	WO 98 16252	1 - 18	Nivel inventivo
D4	Libro (*)	1 - 18	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

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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 Unica No. 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL

Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha
14 JUL 2005.

CONCEPTO TÉCNICO No. 953	EXAMINADOR TÉCNICO Código 202007
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