



Industria y Comercio
SUPERINTENDENCIA



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PETITORIO

SUPERINDUSTRIA Y COMERCIO

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: AKZO NOBEL N.V. sociedad constituida y existente bajo las leyes de Holanda. Dirección: Velperweg 76, 6824 BM Arnhem, Holanda Domicilio: Arnhem, Holanda	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número: _____	
3 REPRESENTANTE O APODERADO	Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax:: 217 92 11 E-mail: <u>clientes@camvp.com.</u> Domicilio: Bogotá, Colombia.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número: <u>438.019</u> T.P. <u>31.929</u>	
4 INVENTOR (ES) (72)	1- Johannes Bernardus Maria REWINKEL Bram van de Berghstraat 23, NL-5348 JT Oss. Holanda. 2- Cornelis Marius TIMMERS Laidael 14, NL-5351 SN Berghem, Holanda. 3- Paolo Giovanni Martino CONTI De Wisboom 35, NL-5384 HD Heesch, Holanda.		
5	PCT (86) Solicitud Internacional No. <u>PCT/EP01/07887</u> Fecha: <u>9 de julio de 2001</u> Publicación Internacional No. <u>WO 02/04423 A1</u> Fecha : <u>17 de enero de 2002</u>		
6	Título (54) <u>INHIBIDORES DE TROMBINA QUE COMPRENDEN UN GRUPO AMINOIS QUINOLINA</u>		
7	Clasificación Internacional (51) <u>C07D 217/22 , A61K 3 / 4725</u>		
8	Prioridad SI ☒ N ☐	(33) País de Origen <u>EP.</u>	(32) Fecha <u>12 de julio de 2000</u>
		(31) Número de Solicitud <u>00202491.7</u>	

9

Comprobante de pago No.: 03-106 Fecha: 2 de enero de 2003

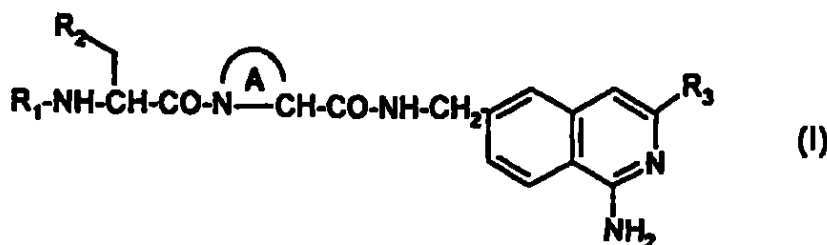
10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 4000.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11

FIGURA CARACTERISTICA:



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : 
C.C. 438.019 de Usaquén T.P. 31.929

 MRE/mrm-Id-198

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND
POWER OF ATTORNEY

I (we), the undersigned / Yo (nosotros), abajo firmado (s)

AKZO NOBEL N.V.

of/domiciliado (s) en Velperweg 76, 6824

CM Arnhem, THE NETHERLANDS

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primer o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, especially before administrative, administrative-contencioso-administrative, judicial, as well as before Arbitration Courts, in matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial emblems, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection of the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting or refusal, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this Day and Month in Year 6 AUG 1998

F.G.M. Hermans

in/en

Director Patents Pharma

Signature

AKZO NOBEL N.V.

E.H. Reerink

Deputy Director
Legal Affairs

CAVELIER ABOGADOS
WPPODERE-179 (MINUTA N° 12.1.12.5)

TRADUCCION No. 18.11/98
MARIA ELVIRA MARTÍNEZ
Traductora e Intérprete Oficial
Inglés - Español - Inglés
Res. No. 2679 Min. Justicia

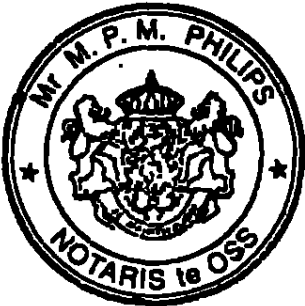
LEGALIZACION

El Señor Cónsul de Colombia debe expedir un certificado consular sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a consular certificate on (1) the legal existence of the company, (2) that it is in accordance with its company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).

Seen for legalization of the signatures of Mr. F.G.M. Hermans and Mr. E.H. Reerink by me, Mr. Martinus Petrus Maria Philips, notary public at Oss, the Netherlands, on this 26th day of August 1998.



[Signature]

TRADUCCION No.: 18.11/98

MARIA ELVIRA MARTEL
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

15499

CHAMBER OF COMMERCE AND INDUSTRY
FOR OOST-BRABANT (NETHERLAND)

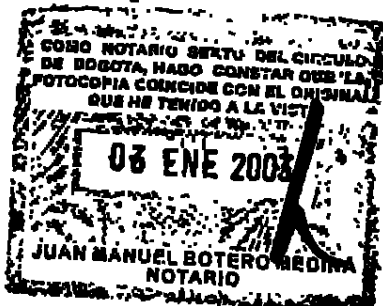
EXCLUSIVE FOR LEGALIZATION OF
THE SIGNATURE(S)



27 AUG 1998

KAMER VAN OOST-BRABANT
OOST-BRABANT
's-HERTOGENBOSCH

[Signature]
J. Schellekens



Gezien voor legalisatie van de handtekening
van: C. H. W. Schellekens

's-Gravenhage, 9 SEP 1998



De Minister van
Buitenlandse Zaken
voor deze,

Leges f 20,- H.H. van POORTEN

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.



CONSULADO DE COLOMBIA

2020 11 03 - 001-001-0

El suscrito Cónsul de Colombia en La Haya, Holanda,
vistos los documentos presentados por los interesados,

CERTIFICA:

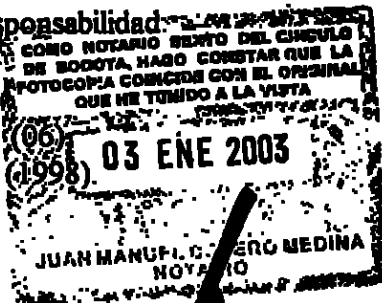
Que el Señor Martinus Petrus Maria PHILIPS, quien como Notario Público de Oss, Países Bajos, autenticó las firmas de los signatarios del poder precedente, ejercía en la fecha las funciones indicadas, y su firma corresponde a la registrada en este Consulado.

Que la Compañía AKZO NOBEL N.V. es una Sociedad constituida de acuerdo con las leyes de los Países Bajos, cumple su objeto conforme a las mismas y se halla registrada en la Cámara de Comercio y Fábricas de Centraal Gelderland, Arnhem, bajo el número 09007809;

Que los Señores Franciscus Guilielmus Maria HERMANS y Engbert Harmen REERINK, signatarios del presente documento, quienes en su carácter de Apoderados de la Empresa AKZO NOBEL N.V., conjuntamente tienen facultad para ello, y cuyas firmas fueron autenticadas ante el Notario Público de Oss, Señor Martinus Petrus Maria PHILIPS, son los representantes legales de la citada Empresa en este País.

El Cónsul de Colombia en La Haya, Países Bajos, no asume responsabilidad alguna por el contenido del documento.

Esta certificación se expide en La Haya, Países Bajos, a los seis
días del mes de Noviembre de mil novecientos noventa y ocho



Impuesto de Timbre	US\$	6.00.
Derechos Consulares	US\$.	100.00
Costo Total Pagado	US\$.	106.00

Certificación No. 206

JOSE IGNACIO VILLEGAS CORTES
CONSUL DE COLOMBIA
LA HAYA

TRADUCCION No.: 18.11/98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

MINISTERIO DE RELACIONES
EXTERIORES

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RECIBO Y CONTROL DEL TEXTO

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LA FIRMA APARECE EN EL
DECUENTO DESEMPENA
LAS FUNCIONES INDICADAS

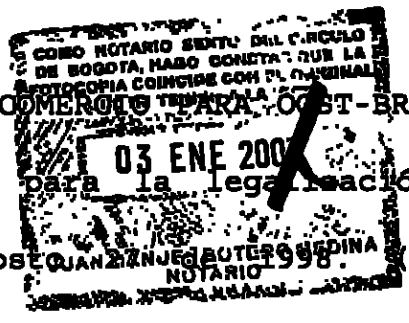
JEFE DE LEGALIZACIONES
BOGOTA D.C.
COMO NOTARIO SEXTO DEL CIRCULO
BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
03 ENE 2003
JUAN MANUEL LÓPEZ MEDINA
NOTARIO

TRADUCCIÓN OFICIAL No. 18.11/98 preparada por María Elvira Martelo, Traductora Oficial debidamente aprobada por el Ministerio de Justicia de Colombia por Resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

(A continuación se traducen los sellos y legalizaciones de un documento escrito en inglés y español, por el cual AKZO NOBEL N.V. otorga poder a EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA DE PAEZ Y GERMAN CAVELIER). Dado y firmado el 6 de agosto de 1998. (Firma ilegible) F.G.M. Hermans, Director de Patentes Farmacéuticas. (Firma ilegible) E.H. Reerink, Subdirector de Asuntos Jurídicos. (Sello Corporativo) AKZO NOBEL N.V.

(Al dorso) Visto por mí, Sr. Martinus Petrus Maria Philips, notario público en Oss, Países Bajos, hoy 26 de agosto de 1998, para legalización de las firmas de F.G.M. Hermans y E.H. Reerink. (Firma ilegible).

(Legalización) CAMARA DE INDUSTRIA Y COMERCIO PARA OOST-BRABANT (PAÍSES BAJOS). Visto exclusivamente para la legalización de la(s) firma(s) que antecede(n). Agosto 26 de 1998. (Firma ilegible) J. Schellenkens.



(Sello en holandés).

(En español) Certificación de las firmas que anteceden y de la existencia legal de AKZO NOBEL N.V. expedida por el Consulado de Colombia en La Haya el día 6 de noviembre de 1998, bajo el No.

206. Firmado JOSE IGNACIO VILLEGAS CORTES, Cónsul de Colombia, La Haya. Pagado impuesto de timbre.

(Al dorso) Legalización de la firma que antecede expedida por el MINISTERIO DE RELACIONES EXTERIORES bajo el No. 300803 del 19 de NOVIEMBRE de 1998, firmado por el Jefe de Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

COLO 11214-801-001-3

Id. 6

Nov. 20/98

Maria E. Martelo
TRADUCCION No. 18.11.98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEJO DEL CIRCULO DE SANTAFE DE BOGOTA. HAYO CONSTAN CUESTAS ANTERIORES) FIR-
MAS) FLESTAS) POR *[Signature]*
[Signature]
IDENTIFICADOS CON C.C. No.(s)
ES(SON) AUTENTICA(S)
SANTAFE DE BOGOTA. 23 NOV. 1998

COMO NOTARIO SEJO DEL CIRCULO DE BOGOTA. HAYO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
03 ENE 2000
JUAN MANUEL NOTERO MEDINA
NOTARIO

MINISTERIO DE RELACIONES EXTERIORES
198457
[Signature]
CUNA FOMA APARECE EN EL DOCUMENTO DESEMPERA LAS FUNCIONES INDICADAS

BOGOTA D.C. COLOMBIA
Circulo de Santafe de Bogota

NO SE ASUME RESPONSABILIDAD DEL TEXTO
98 NOV 24 PM 12: 06
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

**(19) World Intellectual Property Organization
International Bureau**

[illegible]

(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/04423 A1

- (51) International Patent Classification⁷: C07D 217/22, (74) Agent: HOGENBIRK, M.; P.O. Box 20, NL-5340 BH Oss (NL).
401/12, C07K 5/06, A61K 31/4725
- (21) International Application Number: PCT/EP01/07887 (81) Designated States (*national*): AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CH, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.
- (22) International Filing Date: 9 July 2001 (09.07.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 00202491.7 12 July 2000 (12.07.2000) EP
- (71) Applicant (*for all designated States except US*): AKZO NOVEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).
- (72) Inventors: and
- (75) Inventors/Applicants (*for US only*): REWINKEL, Johannes, Bernardus, Maria [NL/NL]; Bram van de Berghstraat 23, NL-5348 JT Oss (NL). TIMMERS, Cornelis, Marius [NL/NL]; Leidse 14, NL-5351 SN Berghem (NL). CONTI, Paolo, Giovanni, Martino [IT/NL]; De Wisboom 35, NL-5384 HD Heesch (NL).
- (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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

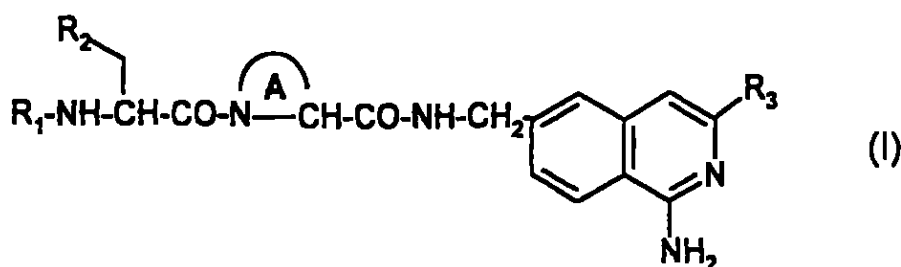
Published:

- with international search report

- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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

(54) Title: THROMBIN INHIBITORS COMPRISING AN AMINOISOUQUINOLINE GROUP



(57) Abstract: The invention relates to a compound having the formula (I) wherein R₁ is cyclopentyl, cyclohexyl or branched (3-4C) alkyl; R₂ is cyclohexyl or phenyl; R₃ is H or methyl; and A is an unsubstituted saturated 4, 5 or 6-membered ring; or a pharmaceutically acceptable salt thereof. The compounds of the invention have anticoagulant activity and can be used in treating or preventing thrombin-mediated and thrombin-associated diseases.

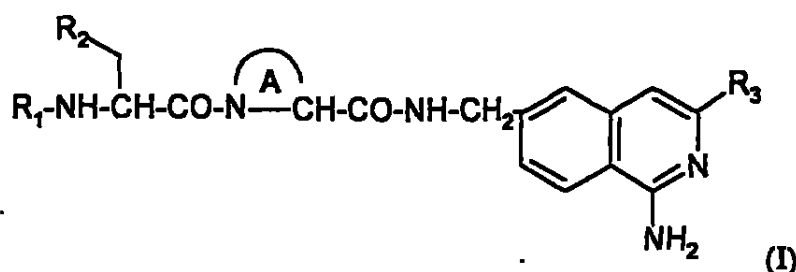
WO 02/0423 A1

THROMBIN INHIBITORS COMPRISING AN AMINOISOQUINOLINE GROUP

The invention relates to a thrombin inhibitor comprising an aminoisoquinoline group, a pharmaceutical composition containing the same, as well as the use of said inhibitor for the manufacture of a medicament for treating and preventing thrombin-related diseases.

In literature a large number of peptide-like thrombin inhibitors is disclosed. Most of those thrombin inhibitors contain basic groups at the so-called P₁-position, like the basic amino acids arginine and lysine, but also benzamidine and the like. Such a basic moiety is considered essential for antithrombin activity. On the other hand, the basicity of the compounds may impair the uptake of the compounds in the intestines when delivered via the oral route. In WO 98/47876 a class of thrombin inhibitors is disclosed having an aminoisoquinoline moiety as basic group, which show improved transepithelial transport properties. Within this latter class of compounds a new selection of compounds has now been identified having further improved pharmacological properties.

It has now been found that compounds of the formula (I)



wherein

R_1 is cyclopentyl, cyclohexyl or a branched (3-4C)alkyl;

R_2 is cyclohexyl or phenyl;

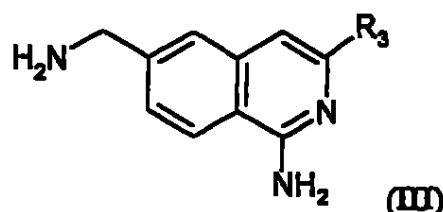
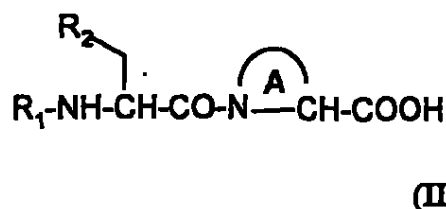
R_3 is H or methyl; and

A is an unsubstituted saturated 4, 5 or 6-membered ring;

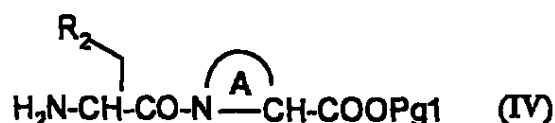
or a pharmaceutically acceptable salt thereof,

are potent thrombin inhibitors having a significantly increased plasma half-life. Most of the clinical situations in which anti-thrombotic drugs are needed require in general a prolonged half-life (see Sixma, J.J. et al., Thromb. Res. 67; 305-311 (esp. 307), 1992). The compounds of this invention thus are an important improvement in the art.

compounds of formula (III) may optionally carry a protective group such as benzoyl which can be removed after the coupling reaction.

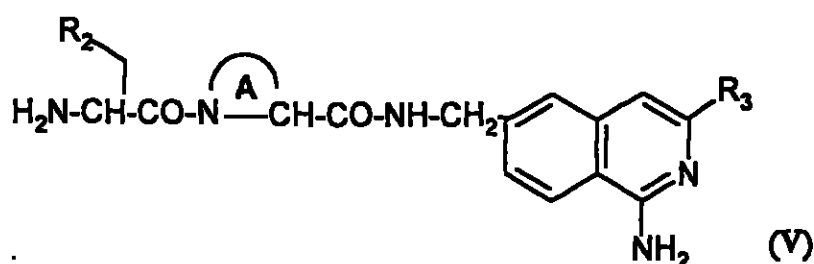


Compounds of formula (II) can be prepared from compounds of formula (IV), wherein Pg1 is a carboxylate protecting group like the benzyl ester, by treatment of compounds of formula (IV) with a appropriate ketone like cyclohexanone or acetone and a reductive agent like sodium triacetoxyborohydride under acidic conditions and thereafter removal of the carboxylate protecting group.



The compound of formula (III) wherein $\text{R}_3=\text{H}$ (1-amino-6-(aminomethyl)isoquinoline) is described in WO 98/47876. The compound of formula (III) wherein $\text{R}_3=\text{Me}$ (1-amino-6-(aminomethyl)-3-methylisoquinoline) can be prepared from 1-amino-6-methoxy-3-methylisoquinoline using the procedures described in WO 98/47876 for the transformation of 1-amino-6-methoxyisoquinoline into 1-amino-7-(aminomethyl)isoquinoline. 1-Amino-6-methoxy-3-methylisoquinoline can be prepared from 3-methoxyphenylacetone using the method described by W. Zielinski and M. Mazik in *Heterocycles* 38, 375 (1994).

Alternatively, compounds of formula (I) can be prepared from compounds of formula (V), by treatment of compounds of formula (V) with a appropriate ketone like cyclohexanone or acetone and a reductive agent like sodium triacetoxyborohydride under acidic conditions. In this reaction the aryl amine group of compounds of formula (V) may optionally be protected by a group such as benzoyl which can be removed after the reductive amination.



Compounds of formula (V) can be prepared by a peptide coupling of a dipeptide protected at the N-terminus with a protecting group like the Boc group and compounds of formula (III) using the coupling reagents described before.

Protection of the α -amino functions generally takes place by urethane functions such as the acid-labile tert-butyloxycarbonyl group (Boc), benzyloxycarbonyl (Cbz) group and substituted analogs, the base-labile 9-fluorenylmethyloxycarbonyl (Fmoc) group or the phthaloyl (Phth) group. Other suitable amino protective groups include Nps, Bpoc, Msc, etc. Removal of the protecting groups can take place in different ways, depending on the nature of those protecting groups. Usually deprotection takes place under acidic conditions and in the presence of scavengers. The Cbz group can also be removed by catalytic hydrogenation. An overview of amino protecting groups and methods for their removal is given in *The Peptides, Analysis, Synthesis, Biology*, Vol. 3 E. Gross and J. Meienhofer, Eds., (Academic Press, New York, 1981).

Protection of carboxyl groups can take place by ester formation e.g. base-labile esters like methyl- or ethylesters, acid labile esters like tert-butylesters, or hydrogenolytically-labile esters like benzylesters.

The compounds of the invention, which may be in the form of a free base, may be isolated from the reaction mixture in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts may also be obtained by treating the free base of the formula (I) with an organic or inorganic acid such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, maleic acid, malonic acid, methanesulphonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, and ascorbic acid.

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The compounds of this invention possess one or more chiral carbon atoms, and may therefore be obtained as a pure enantiomer, as a pure diastereomer, as a mixture of enantiomers, or as a mixture containing diastereomers. Methods for obtaining the pure enantiomers are well known in the art, e.g. crystallization of salts which are obtained from optically active acids and the racemic mixture, or chromatography using chiral columns. For diastereomers straight phase or reversed phase columns may be used.

The compounds of the invention may be administered enterally or parenterally, and for humans preferably in a daily dosage of 0.001-100 mg per kg body weight, preferably 0.01-10 mg per kg body weight. Mixed with pharmaceutically suitable auxiliaries, e.g. as described in the standard reference, Germaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture) the compounds may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied in the form of a solution, suspension, emulsion, e.g. for use as an injection preparation, or as a spray, e.g. for use as a nasal spray.

For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts.

The elimination half-life and percentage bioavailability of the compounds of the invention may suitably be tested according to the following test in dogs.

The residence time and percentage bioavailability of direct thrombin inhibitors in female Beagle dogs may be measured by determination of the anti-IIa activity in plasma after intravenous or oral administration. In view of the selectivity of the protease inhibitors of the invention, inhibition of thrombin linearly relates with the concentration of the measured protease inhibitor. After intravenous or oral administration of the serine protease inhibitor, blood is collected from the jugular vein at different time-points during the day. After centrifugation of the blood, plasma anti-IIa activities are determined of the plasma samples in a microtiter plate

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chromogenic assay using a calibration curve of the tested compound itself. The obtained data are analysed from the plasma vs time curve e.g. by means of a computerised iterative procedure, based on the Simplex method. Subsequently, the elimination half-lives are calculated using the model of relative error independent of the concentration, and the area under the curve (AUC) is determined with the trapezium rule. Assuming linear kinetics, the percentage bioavailability is calculated by dividing the AUC obtained after p.o. administration by the mean expected normalised AUC after i.v. administration of that dose (X100%).

The invention is further illustrated by the following examples.

EXAMPLES

The ¹H NMR measurements were performed on a BRUKER DRX 400 spectrophotometer operating at a ¹H frequency of 400 MHz. Mass spectra (MS) were recorded with a PE-sciex API-165.

Example 1.

N-cyclohexyl-3-cyclohexyl-D-alanyl-N-[(1-amino-6-isoquinoliny)methyl]-L-prolinamide hydrochloride (N-cyclohexyl-D-Cha-Pro-6Aig . HCl)

After stirring 0.91 g of 3-cyclohexyl-N-[(1,1-dimethylethoxy)carbonyl]-D-alanyl-L-proline phenylmethyl ester (Boc-D-Cha-Pro-OBzl) in 2.5 mL of dichloromethane and 2.5 mL of trifluoroacetic acid at room temperature for two hours the reaction mixture was concentrated in vacuo to yield 0.94 g of an oil. This oil was dissolved in 10 mL of N,N-dimethylformamide containing 1% (v/v) acetic acid and 0.26 mL of cyclohexanone and 0.64 g of sodium triacetoxyborohydride were added. After stirring at room temperature for 16 hours 5 mL of water was added to the reaction mixture and extracted with dichloromethane. The organic extract was dried over magnesium sulfate and concentrated to give 0.90 g of an oil (TLC; silica gel, dichloromethane / methanol = 95 / 5 (v/v) R_f = 0.8). This oil was dissolved in 50 mL of ethyl acetate, the pH of the solution was adjusted to five using acetic acid, 0.10 g of palladium on carbon (10%) was added and the suspension was hydrogenated at atmospheric pressure at

room temperature for one hour. The palladium catalyst was removed by filtration and the solvent was removed by evaporation at reduced pressure. The residue was dissolved in toluene and the toluene was evaporated under reduced pressure yielding 0.56 g of N-cyclohexyl-D-Cha-Pro-OH. This acid (0.35 g) was dissolved in 10 mL of N,N-dimethylformamide and 0.19 mg of 1-amino-6-aminomethylisoquinoline (WO 9847876) and 0.4 g of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate (TBTU) were added. The pH of the reaction mixture was adjusted to 8 using N,N-diisopropylethylamine (DIPEA). After stirring for 24 hours at room temperature an additional 0.1 g TBTU was added and the reaction mixture was stirred at room temperature for an additional 18 hours. Thereafter the reaction mixture was concentrated in vacuo. The residue was dissolved in 50 mL of dichloromethane and washed twice with aqueous sodium hydrogencarbonate, dried over magnesium sulfate and concentrated. The residue was dissolved in water and directly charged onto a preparative HPLC DeltaPak RP-C₁₈ using a gradient elution system of 20 % A / 80 % B to 20 % A / 30 % B / 50 % C over 60 min at a flow rate of 40 mL/min (A: 0.5M phosphate buffer pH 2.1, B: water, C: acetonitril/water = 6/4 (v/v)). Yield: 0.25 g of the title compound.

¹H-NMR 400MHz (CD₃OD) δ: 0.84 - 2.41 (27H, m), 2.91 - 3.01 (1H, m), 3.57 - 3.65 (1H, m), 3.81 - 3.88 (1H, m), 4.30 (1H, t, J = 7Hz), 4.49 - 4.77 (3H, m), 7.26 (1H, d, J = 7Hz), 7.57 (1H, d, J = 7Hz), 7.73 (1H, dd, J = 2Hz and J = 9Hz), 7.92 (1H, d, J = 2Hz), 8.38 (1H, d, J = 9Hz).

Example 2.

N-cyclohexyl-3-cyclohexyl-D-alanyl-N-[(1-amino-3-methyl-6-isoquinolinyl)methyl]-L-prolinamide hydrochloride (N-cyclohexyl-D-Cha-Pro-6(3Me)Aig.HCl)

2a. 1-Amino-6-methoxy-3-methyl-isoquinoline

A solution of 2.12 g of 3-methoxyphenylacetone and 1.26 mL of phosphoryl chloride in 45 mL of anhydrous toluene was heated under reflux. After 30 minutes the mixture was cooled to 0 °C and a solution of 0.57 g of cyanamide in 23 mL of anhydrous ether was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for one hour. Then the stirred mixture was cooled to 0 °C and 1.5 mL of titanium tetrachloride was added dropwise. The reaction mixture was heated under reflux for 2.5 hours, cooled, 34 mL of

water added, the mixture filtered and the sediment was washed with ethyl acetate. The filtrate was made basic using 2N aqueous sodium hydroxide and extracted with ethyl acetate. The organic extracts were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by silica chromatography (dichloromethane / methanol = 95 / 5) yielding 0.42 g of the title compound. ¹H-NMR 400MHz (CDCl₃) δ: 2.45 (3H, s), 3.91 (3H, s), 5.0 (2H, br. s), 6.81 (1H, s), 6.90 (1H, d, J = 3Hz), 7.02 (1H, dd, J = 3Hz and J = 9Hz); 7.65 (1H, d, J = 9Hz).

2b. 1-Amino-6-hydroxy-3-methyl-isoquinoline

Boron tribromide (4 mL) in 6 mL of dichloromethane was added dropwise to a stirred solution of 1-amino-6-methoxy-3-methylisoquinoline (2 g) in 10 mL of dichloromethane at 0°C. After stirring for 16 hours at ambient temperature the reaction mixture was poured on ice, the organic layer removed and the pH of the aqueous layer adjusted to pH 9 by adding concentrated aqueous ammonia. The precipitated material was collected by filtration and dried in vacuo to give 1.6 g of the title compound. ESI-MS: 175 (MH⁺).

2c. Trifluoro-methanesulfonic acid 1-amino-3-methylisoquinolin-6-yl ester

A mixture of 1.4 g of 1-amino-6-hydroxy-3-methyl-isoquinoline and 4.3 g of N-phenyl-bis(trifluoromethanesulfonimid) in 19.5 mL of dichloromethane and 19.5 mL of dioxane was cooled in an ice bath and 2.8 mL of N,N-diisopropylethylamine added dropwise. The resulting mixture was heated for 24 h at 70°C, after which the volatiles were removed in vacuo. The remaining residue was dissolved in ethyl acetate, washed with successive portions of 2N aqueous sodium hydroxide, water and brine and dried (sodium sulfate). Filtration and concentration afforded a colourless oil, which was triturated in toluene to give 1.3 g of a solid. The toluene solution was purified by silica chromatography (toluene/ethanol = 95/5) yielding an additional 0.6 g of the title compound. Total yield 1.9 g. ESI-MS: 307 (MH⁺).

2d. 1-Amino-6-cyano-3-methylisoquinoline

Palladium acetate (0.28 g) was added to a heated mixture of trifluoro-methanesulfonic acid 1-amino-3-methylisoquinolin-6-yl ester (1.9 g), zinc cyanide (0.74 g) and triphenylphosphine (0.33 g) in 24 mL of N-methyl-pyrrolidone at 190°C (exothermic!). Stirring was continued at

190°C for 2 h. After cooling to room temperature, ethyl acetate was added and the organic mixture washed with 2N aqueous ammonia, water and brine and dried (magnesium sulfate). Filtration and concentration afforded a brownish oil, which was purified by silica chromatography (dichloromethane / methanol = 98/2) to give 0.68 g of the title compound. ESI-MS: 184 (MH⁺).

2e. 1-Amino-6-(aminomethyl)-3-methylisoquinoline

To a stirred solution of 1-amino-6-cyano-3-methylisoquinoline (0.68 g) in 15 mL of tetrahydrofuran at room temperature under a nitrogen atmosphere was added 8.4 mL of 2M borane-methylsulfide complex in tetrahydrofuran and thereafter heated at 60 °C for 50 minutes. The reaction mixture was cooled in an ice bath and 7.5 mL of methanol was added slowly. After 15 minutes 18.8 mL of 1M hydrogen chloride in ether was added. The reaction mixture was allowed to warm to room temperature and stirred for an additional 16 hours. The solid was isolated to afford 0.34 g of 1-amino-6-(aminomethyl)-3-methylisoquinoline hydrogenschloride. The filtrate was purified using column chromatography (silica gel; methanol / ammonia = 98/2) to yield an additional 0.15 g of 1-amino-6-(aminomethyl)-3-methylisoquinoline. ESI-MS: 188 (MH⁺).

2f. N-cyclohexyl-3-cyclohexyl-D-alanyl-N-[(1-amino-3-methyl-6-isoquinolinyl)methyl]-L-prolinamide hydrogenschloride (N-cyclohexyl-D-Cha-Pro-6(3Me)Aiq.HCl)

To a stirred mixture of 0.17 g of 1-amino-6-(aminomethyl)-3-methylisoquinoline hydrogenschloride, 0.30 g of N-cyclohexyl-D-Cha-Pro-OH, 0.5 mL of acetonitrile and 0.37 mL of N,N-diisopropylethylamine in 3 mL of N,N-dimethylformamide at room temperature was added in one hour a solution of 0.35 g of bromotripyrrolidionophosphonium hexafluorophosphate (PyBroP) in 1.3 mL of N,N-dimethylformamide. After stirring for 24 hours at room temperature the reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with aqueous sodium hydrogencarbonate and brine, dried over magnesium sulfate and concentrated. The residue was purified by silica chromatography (dichloromethane/methanol = 9/1) and lyophilisation from t-butanol/hydrochloric acid yielded 0.13 g of the title compound. ¹H-NMR 400MHz (CD₃OD) δ: 0.85 - 2.40 (27H, m), 2.50 (0.3H, s), 2.51 (2.7H, s), 2.92 - 3.00 (1H, m), 3.54 - 3.68 (1H, m), 3.81 - 3.88 (1H, m), 4.30 (1H, t, J

= 7Hz), 4.46 - 4.74 (3H, m), 7.02 (1H, s), 7.64 (1H, dd, J = 2Hz and J = 9Hz), 7.80 (1H, d, J = 2Hz), 8.32 (1H, d, J = 9Hz).

Example 3.

5 N-cyclohexyl-D-phenylalanyl-N-[(1-amino-6-isoquinolinyl)methyl]-L-prolinamide
hydrogenchloride (N-cyclohexyl-D-Phe-Pro-6Aiq . HCl)

Starting with 0.85 g of N-[(1,1-dimethylethoxy)carbonyl]-D-phenylalanyl-L-proline phenylmethyl ester (Boc-D-Phe-Pro-OBzl) gave 0.82 g of N-cyclohexyl-D-phenylalanyl-L-proline (N-cyclohexyl-D-Phe-Pro-OH) using the procedures described in example 1 for N-cyclohexyl-D-Cha-Pro-OH. N-cyclohexyl-D-Phe-Pro-OH (0.82 g) was dissolved in 10 mL of N,N-dimethylformamide and 0.33 mg of 1-amino-6-aminomethylisoquinoline and 1.1 g of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) were added and the pH was adjusted to 8 using N,N-diisopropylethylamine (DIPEA). After stirring for 16 hours at room temperature the reaction mixture was concentrated in vacuo. The residue was dissolved in 50 mL of dichloromethane and washed twice with water and brine, dried over magnesium sulfate and concentrated. The residue was purified by silica chromatography (dichloromethane / methanol (containing 2% ammonia) = 9 / 1) and lyophilisation from t-butanol/hydrochloric acid yielded 0.19 g of the title compound. ¹H-NMR 400MHz (CD₃OD) δ: 0.87 - 2.13 (14H, m), 2.38 - 2.45 (1H, m), 2.94 - 3.03 (1H, m), 3.06 - 3.13 (1H, m), 3.25 - 3.38 (2H, m), 4.33 - 4.73 (4H, m); 7.25 - 7.40 (6H, m), 7.58 (1H, d, J = 7Hz), 7.71 (1H, dd, J = 2Hz and J = 9Hz), 7.92 (1H, d, J = 2Hz), 8.35 (1H, d, J = 9Hz).

Example 4.

25 N-cyclopentyl-3-cyclohexyl-D-alanyl-N-[(1-amino-6-isoquinolinyl)methyl]-L-prolinamide
hydrogenchloride (N-cyclopentyl-D-Cha-Pro-6Aiq . HCl)

Using the procedures described in example 1 starting with 0.30 g of Boc-D-Cha-Pro-OBzl using cyclopentanone instead of cyclohexanone gave crude N-cyclopentyl-D-Cha-Pro-6Aiq which was purified using column chromatography (silica gel; dichloromethane / methanol = 10 / 1 gradient to 5 / 1). Lyophilisation from t-butanol/hydrochloric acid yielded 0.16 g of the title compound. ¹H-NMR 400MHz (CD₃OD) δ: 0.85 - 2.41 (25H, m), 3.43 - 3.52 (1H, m), 3.59 - 3.65 (1H, m), 3.80 - 3.86 (1H, m), 4.20 (1H, t, J = 7Hz), 4.51 - 4.73 (3H, m), 7.25 (1H, d, J =

7Hz), 7.57 (1H, d, J = 7Hz), 7.73 (1H, dd, J = 2Hz and J = 9Hz), 7.90 (1H, d, J = 2Hz), 8.38 (1H, d, J = 9Hz).

Example 5.

5 N-(1-methylethyl)-3-cyclohexyl-D-alanyl-N-[(1-amino-6-isoquinolinyl)methyl]-L-prolinamide hydrochloride (N-(1-methylethyl)-D-Cha-Pro-6Aiq . HCl)

Using the procedures described in example 1 starting with 0.92 g of Boc-D-Cha-Pro-OBzl using acetone instead of cyclohexanone gave 0.04 g of N-(1-methylethyl)-D-Cha-Pro-6Aiq .HCl. ¹H-NMR 400MHz (CD₃OD) δ: 0.85 - 2.41 (23H, m), 3.27 - 3.35 (1H, m), 3.59 - 3.65 (1H, m), 3.82 - 3.89 (1H, m), 4.27 (1H, t, J = 7Hz), 4.51 - 4.74 (3H, m), 7.26 (1H, d, J = 7Hz), 7.57 (1H, d, J = 7Hz), 7.72 (1H, dd, J = 2Hz and J = 9Hz), 7.91 (1H, d, J = 2Hz), 8.38 (1H, d, J = 9Hz).

Anti-thrombin assay

15 The anti-thrombin activity of compounds of the present invention was assessed by measuring spectrophotometrically the rate of hydrolysis of the chromogenic substrate s-2238 exterted by thrombin. This assay for anti-thrombin activity in a buffer system was used to assess the IC₅₀-value of a test compound.

20 Test medium: Tromethamine-NaCl-polyethylene glycol 6000 (TNP) buffer

Reference compound: I2581 (Kabi)

Vehicle: TNP buffer. Solubilisation can be assisted with dimethylsulphoxide, methanol, ethanol, acetonitrile or tert.-butyl alcohol which are without adverse effects in concentrations up to 2.5% in the final reaction mixture.

25 Technique

Reagents* 1. Tromethamine-NaCl (TN) buffer [Composition of the buffer: Tromethamine (Tris) 6.057 g (50 mmol), NaCl 5.844 g (100 mmol), Water to 1 l. The pH of the solution is adjusted to 7.4 at 37 °C with HCl (10 mmol.l⁻¹)]; 2. TNP buffer (Polyethylene glycol 6000 is dissolved in TN buffer to give a concentration of 3 g.l⁻¹); 3. S-2238 solution [One vial S-2238 (25 mg; Kabi Diagnostica, Sweden) is dissolved in 20 ml TN buffer to give a concentration of 1.25 mg.ml⁻¹ (2 mmol.l⁻¹)]; 4. Thrombin solution [Human thrombin (16 000 nKat.vial⁻¹;

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Centraal Laboratorium voor Bloedtransfusie, Amsterdam, The Netherlands) is dissolved in TNP buffer to give a stock solution of 835 nKat·ml⁻¹. Immediately before use this solution is diluted with TNP buffer to give a concentration of 3.34 nKat·ml⁻¹.]

* - All ingredients used are of analytical grade

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- For aqueous solutions ultrapure water (Milli-Q quality) is used.

Preparation of test and reference compound solutions

The test and reference compounds are dissolved in Milli-Q water to give stock concentrations of 10⁻³ mol·l⁻¹. Each concentration is stepwise diluted with the vehicle to give concentrations of 10⁻³, 10⁻⁴ and 10⁻⁵ mol·l⁻¹. The dilutions, including the stock solution, are used in the assay (final concentrations in the reaction mixture: 3·10⁻³; 10⁻³; 3·10⁻⁴; 10⁻⁴; 3·10⁻⁵; 10⁻⁵; 3·10⁻⁶ and 10⁻⁶ mol·l⁻¹, respectively).

10

Procedure

At room temperature 0.075 ml and 0.025 ml test compound or reference compound solutions or vehicle are alternately pipetted into the wells of a microtiter plate and these solutions are diluted with 0.115 ml and 0.0165 ml TNP buffer, respectively. An aliquot of 0.030 ml S-2238 solution is added to each well and the plate is pre-heated and pre-incubated with shaking in an incubator (Amersham) for 10 min. at 37 °C. Following pre-incubation the hydrolysis of S-2238 is started by addition of 0.030 ml thrombin solution to each well. The plate is incubated (with shaking for 30 s) at 37 °C. Starting after 1 min of incubation, the absorbance of each sample at 405 nm is measured every 2 min. for a period of 90 min. using a kinetic microtiter plate reader (Twinstar plus, Flow Laboratories).

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All data are collected in an IBM personal computer using LOTUS-MEASURE. For each compound concentration (expressed in mol·l⁻¹ reaction mixture) and for the blank the absorbance is plotted versus the reaction time in min.

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Evaluation of responses: For each final concentration the maximum absorbance was calculated from the assay plot. The IC₅₀-value (final concentration, expressed in μmol·l⁻¹, causing 50% inhibition of the maximum absorbance of the blank) was calculated using the logit transformation analysis according to Hafner et al. (Arzueim.-Forsch./Drug Res. 1977; 27(II): 1871-3).

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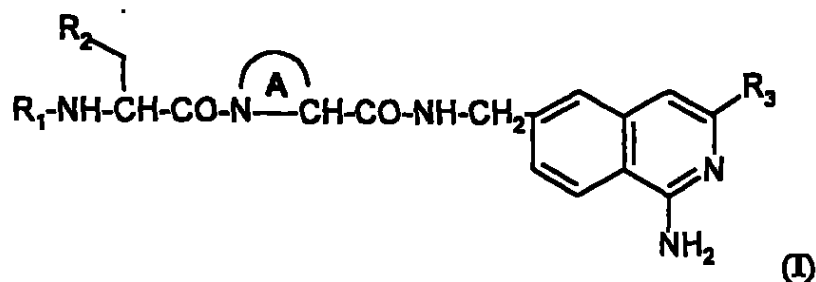
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Antithrombin activity:

Example	IC ₅₀ (mol·l ⁻¹)
1	0.03
2	0.14
3	0.13
4	0.12
5	0.29

CLAIMS

1. A compound having the formula (I)



wherein

R_1 is cyclopentyl, cyclohexyl or a branched (3-4C)alkyl;

R_2 is cyclohexyl or phenyl;

R_3 is H or methyl; and

10 A is an unsubstituted saturated 4, 5 or 6-membered ring;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein A is a five-membered ring.

15 3. The compound of claim 1, wherein R_2 is cyclohexyl

4. The compound of claim 1, wherein R_3 is H.

5. The compound of claim 1, wherein R_1 is cyclohexyl.

20 6. The compound of claim 5, wherein R_1 is cyclohexyl, R_2 is cyclohexyl, R_3 is H and A is a five-membered ring.

7. A pharmaceutical composition comprising the compound of any one of claims 1 to 6 and
25 pharmaceutically suitable auxiliaries.

8. The compound of any one of claims 1 to 6 for use in therapy.

9. Use of the compound of any one of claims 1 to 6 for the manufacture of a medicament for treating or preventing thrombin-related diseases.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

2000.565 WO

Box No. I TITLE OF INVENTION

"THROMBIN INHIBITORS COMPRISING AN AMINOISOQUINOLINE GROUP"

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

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of America only☐the States indicated in
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This person is:

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applicant only

☒

applicant and inventor

☐inventor only (If this check-box is
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for the purposes of:☐all designated
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Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the
applicant(s) before the competent International Authorities as:☒

agent

☐

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

M. Hogenbirk**P.O. Box 20****5340 BH OSS****The Netherlands**

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Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below) TIMMERS, Cornelis, Marius Leidsel 14 5351 SN BERGHEM The Netherlands	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality: NL	State (i.e. country) of residence: NL
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below) CONTI, Paolo, Giovanni, Martino De Wisboom 35 5384 HD HEESCH The Netherlands	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality: IT	State (i.e. country) of residence: NL
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of residence:
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of residence:
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATION OF STATES Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

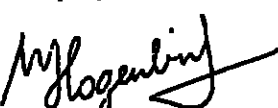
National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|--|--|---|
| ☒ AE United Arab Emirates | ☐ GH Ghana | ☒ MX Mexico |
| ☒ AG Antigua and Barbuda | ☐ GM Gambia | ☒ MZ Mozambique |
| ☒ AL Albania | ☒ HR Croatia | ☒ NO Norway |
| ☐ AM Armenia | ☒ HU Hungary | ☒ NZ New Zealand |
| ☐ AT Austria | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AU Australia | ☒ IL Israel | ☐ PT Portugal |
| ☐ AZ Azerbaijan | ☒ IN India | ☒ RO Romania |
| ☒ BA Bosnia and Herzegovina | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BB Barbados | ☒ JP Japan | |
| ☒ BG Bulgaria | ☐ KE Kenya | ☐ SD Sudan |
| ☒ BR Brazil | ☐ KG Kyrgyzstan | ☐ SE Sweden |
| ☐ BY Belarus | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BZ Belize | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ CA Canada | ☐ KZ Kazakhstan | ☒ SK Slovakia |
| ☐ CH & LI Switzerland and Liechtenstein | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CN China | ☒ LK Sri Lanka | ☐ TJ Tajikistan |
| ☒ CO Colombia | ☒ LR Liberia | ☐ TM Turkmenistan |
| ☒ CR Costa Rica | ☐ LS Lesotho | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☐ LU Luxembourg | ☐ TZ United Republic of Tanzania |
| ☐ DE Germany | ☒ LV Latvia | ☒ UA Ukraine |
| ☐ DK Denmark | ☒ MA Morocco | ☐ UG Uganda |
| ☒ DM Dominica | ☐ MD Republic of Moldova | ☒ US United States of America |
| ☒ DZ Algeria | | |
| ☒ EC Ecuador | ☒ MG Madagascar | ☒ UZ Uzbekistan |
| ☒ EE Estonia | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VN Viet Nam |
| ☐ ES Spain | ☒ MN Mongolia | ☒ YU Yugoslavia |
| ☐ FI Finland | ☐ MW Malawi | ☒ ZA South Africa |
| ☐ GB United Kingdom | | ☐ ZW Zimbabwe |
| ☒ GD Grenada | | |
| ☒ GE Georgia | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box ☐	
The priority of the following earlier application(s) is hereby claimed:			
Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) NL	12-07-2000	00202491.7	EPO
item (2)			
item (3)			
<i>Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):</i>			
☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : 1			
Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA /EPO			
Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request			
Country (or regional Office): EP		Date (day/month/year) 12-07-2000	Number: 00202491.7
Box No. VIII CHECK LIST			
This international application contains the following number of sheets:		This international application is accompanied by the item(s) marked below:	
1. request: 4 sheets		1. ☐ separate signed power of attorney	5. ☒ fee calculation sheet
2. description: 13 sheets		2. ☒ copy of general power of attorney	6. ☐ separate indications concerning deposited microorganisms
3. claims: 2 sheets		3. ☐ statement explaining lack of signature	7. ☐ nucleotide and/or amino acid sequence listing (diskette)
4. abstract: 1 sheets		4. ☐ priority document(s) identified in Box No VI	8. ☒ other (specify): Request refund Letter / Copy European Search Report.
5. drawings: sheets		as item(s):	
6. sequence listing: sheets			
Total : 20 sheets			
Figure No. of the drawings (if any) should accompany the abstract when it is published.			
Box No. IX SIGNATURE OF APPLICANT OR AGENT			
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading request)			
 M. Hogenbirk			

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

PCT

FEE CALCULATION SHEET

For receiving Office use only

Annex to the Request

International application No.

Applicant's or agent's
file reference

2000.565 WO

Date stamp of the receiving Office

Applicant
Akzo Nobel N.V.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE EUR 102,= T

2. SEARCH FEE EUR 945,= S

International search to be carried out by EPO
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 20 sheets.
first 30 sheets

EUR 409,= b₁

EUR 9,= EUR b₂

remaining sheets additional amount

Add amounts entered at b₁ and b₂ and enter total at B EUR 409,= B

Designation Fees

The international application contains 62 designations

number of designation fees payable (maximum 6) amount of designation fee EUR 528,= D

Add amounts entered at B and D and enter total at I EUR 937,= I
(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT EUR 30,= P

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P,
and enter total in the TOTAL box EUR 2014,=

TOTAL

☐ The designation fee is not paid at this time.

MODE OF PAYMENT

☒ authorization to charge deposit account (see below) ☐ bank draft ☐ coupons
☐ cheque ☐ cash ☐ other (specify):
☐ postal money order ☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ EPO

☒

is hereby authorized to charge the total fees indicated above to my deposit account.

☒

is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐

is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

2809 0012

06/07/2001

Deposit Account Number

Date (day/month/year)

Signature M. Hogenbirk

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Bitte übermitteln die 3 Blätter 1004.1-3 dem EPA in München, Direktion 5.1.1, und beachten Sie Blatt 1004.4, insbesondere Nr.3 b.
Please forward the 3 sheets 1004.1-3 to the EPO at Munich, Directorate 5.1.1 and pay attention to sheet 1004.4, especially point 3 b.
Prière de faire parvenir les 3 feuilles 1004.1-3 à l'OEB à Munich, Direction 5.1.1 et de tenir compte de la feuille 1004.5, notamment du point 3 b.

**ALLGEMEINE VOLLMACHT
GENERAL AUTHORISATION
POUVOIR GENERAL**

Nur für amtlichen Gebrauch / For official use only
Cadre réservé à l'administration
Nr. der allgemeinen Vollmacht / General Authorisation No.
N° du pouvoir général

59 (rev.)

Ich (Wir) / I (We) / Je (Nous)



Akzo Nobel N.V.
Intellectual Property Department (Dept. AIP)
P.O. Box 9300
6800 SB Arnhem
the Netherlands



bevollmächtige(n) hiermit / do hereby authorise / autorise (autorisons) par la présente

Schalkwijk, Pieter Cornelis
Fett, Günter
Van Deursen, Petrus Hubertus
Quelle-Fontijn, Monique
Verbart, Jeannette J.M.
Helmann, Anette
Beetz, Tom
Hesslink, Dinah E.
Aalbers, Arnt Reiner
De Vries, Adriaan Jacobus
Zonneveld, Hendrik Jan
Alferink, Petrus Johannes Theodorus

Address of place of business:
Akzo Nobel N.V.
Intellectual Property Department (Dept. AIP)
P.O. Box 9300
6800 SB Arnhem
the Netherlands

mich (uns) in den durch das Europäische Patentübereinkommen geschaffenen Verfahren in allen meinen (unseren) Patentangelegenheiten zu vertreten, alle Handlungen für mich (Uns) vorzunehmen und Zahlungen für mich (Uns) in Empfang zu nehmen.

to represent me (us) in all proceedings established by the European Patent Convention and to act for me (us) in all patent transactions and to receive payments on my (our) behalf.

à me (nous) représenter pour ce qui concerne toutes mes (nos) affaires de brevet dans toute procédure instituée par la Convention sur le brevet européen et, à ce titre, à agir en mon (notre) nom et à recevoir des paiements pour mon (notre) compte.



Die Vollmacht gilt auch für Verfahren nach dem Vertrag über die Internationale Zusammenarbeit auf dem Gebiet des Patentwesens.
This authorisation shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.
Ce pouvoir s'applique également à toute procédure instituée par le Traité de coopération en matière de brevets.



Weitere Vertreter sind auf einem gesonderten Blatt angegeben. / Additional representatives indicated on supplementary sheet.
Les autres mandataires sont mentionnés sur une feuille supplémentaire.



Untervollmacht kann erteilt werden. / Sub-authorisation may be given. / Le pouvoir pourra être délégué.

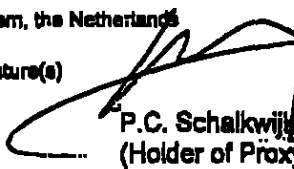


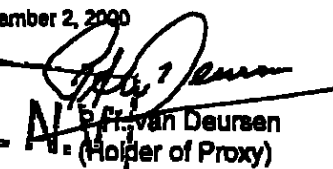
Bitte die gelbe Kopie, ergänzt um die Nr. der allgemeinen Vollmacht, an den Vollmachtgeber zurücksenden.
Please return the yellow copy, supplemented by the General Authorisation No., to the authoriser.
Prière de renvoyer la copie jaune au mandant, munie du n° du pouvoir général.

Ort/Place/Lieu Arnhem, the Netherlands

Datum / Date November 2, 2000

Unterschrift(en) / Signature(s)


P.C. Schalkwijk
(Holder of Proxy)


P.H. van Deursen
(Holder of Proxy)

AKZO NOBEL

Das Formblatt muß vom (von den) Vollmachtgeber(n) (bei juristischen Personen vom Unterschriftsberechtigten) eigenhändig unterschrieben sein. Nach der Unterschrift bitte den (die) Namen des (der) Unterzeichneten mit Schreibmaschine wiederholen (bei juristischen Personen die Stellung des Unterschriftsberechtigten innerhalb der Gesellschaft angeben).

The form must bear the personal signature(s) of the authoriser(s). (In the case of legal persons, that of the officer empowered to sign). After the signature, please type the name(s) of the signatory(ies) adding, in the case of legal persons, his (their) position within the company.

Le formulaire doit être signé de la propre main du (des) mandant(s) (dans le cas de personnes morales, de la personne ayant qualité pour signer). Veuillez ajouter à la machine, après la signature, le (les) nom(s) du (des) signataire(s) en mentionnant, dans le cas de personnes morales, ses (leurs) fonctions au sein de la société.

European Patent Office
Patentlaan 2
2280 HV RIJSWIJK (ZH)

Your ref. :

Our ref:

2000.565 WO

Direct Line

tel.: +31.412.666.379

fax: +31.412.650.592

Oss,

06 July 2001

Re: Request for refund search fee

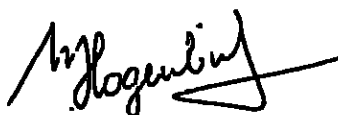
Dear Sir(s),

The undersigned hereby request for a refund (by remittance in favour of our deposit account no. 2809 0012) of the search fee paid with respect to the New International Patent Application (PCT), claiming priority of the European patent application No. 00202491.7, filed 12-07-2000.

The reason for the request for refund is that the ISA/EPO has established the European search report.

A copy of the European search report is enclosed herewith.

The agent



M. Hogenbirk

Encl.: European Search Reports



Patent Department
N.V. Organon
P.O. Box 20
Weth. van Eschstraat 1
5340 BH Oss
The Netherlands
Tel. 0412 666380
Telefax 0412 650592
E-mail patent@organon.
oss.akzonobel.nl

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**Power of Attorney
(Concerning a Given International Application)**

**PATENT CO-OPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE**

POWER OF ATTORNEY

The undersigned applicant(s):

REWINKEL
Johannes, Bernardus, Maria
Bram van de Berghstraat 23
5348 JT OSS
The Netherlands

TIMMERS
Cornelis Marius
Leidsel 14
5351 SN BERGHEM
The Netherlands

CONTI
Paolo, Giovanni, Martino
De Wisboom 35
5384 HD HEESCH
The Netherlands

hereby appoints (appoint) Mr. (Ms., Miss, Mrs.) (Name, address):

H. Kraak

P.G.W. de Weerd

F.G.M. Hermans

M. Hogenbirk

P.M.G.F. van Wezenbeek

J.J.L. Mestrom

J.A.R. Keus

M. van Gent

*All residing at:
Postbus 20
5340 BH Oss
The Netherlands*

☒ as agent

☐ as common representative

to act on his (her, their) behalf before the competent International Authorities in connection with the international application on [title of the invention, applicant's or agent's file reference, if any has been indicated in the request, international application number, if already available]:

Our ref.: 2000.565 WO

Title: " THROMBIN INHIBITORS COMPRISING AN AMINOISOQUINOLINE GROUP"

filed with the (name of the Office): *EPO*
as receiving Office and to make or receive payments on his (her, their) behalf.

Place: Date:

Signature of the applicant (where there are several applicants, each of them must sign):

Oss, 25 June 2001

J.B.M. Rewinkel

Oss, 25 June 2001

C.M. Timmers

Oss, 9 Juli 2001

P.G.M. Conti

[Type the name under the (each) signature and add, in case of legal persons, an indication of the capacity in which the person signs]

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2000.565 WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 01/07887	International filing date (day/month/year) 09/07/2001	(Earliest) Priority Date (day/month/year) 12/07/2000
Applicant AKZO NOBEL N.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the International search was carried out on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.

☐ the International search was carried out on the basis of a translation of the International application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the International application, the International search was carried out on the basis of the sequence listing:

☐ contained in the International application in written form.

☐ filed together with the International application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/07887

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D217/22 C07D401/12 C07K5/06 A61K31/4725

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 47876 A (AKZO NOBEL NV; BOECKEL CONSTANT ADRIAAN ANTON (NL); GALEN PHILIPPU) 29 October 1998 (1998-10-29) cited in the application claims 1-3,8,27-29; examples 76,77 page 179, tables Id, Ie, If; page 181, tables Ik, Il; page 185, table "Antithrombin activity."	1-9

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

29 October 2001

Date of mailing of the international search report

06/11/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/07887

33

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9847876	A	29-10-1998	AU	7648698 A		13-11-1998
			WO	9847876 A1		29-10-1998
			EP	0975600 A1		02-02-2000
			US	6194409 B1		27-02-2001
			ZA	9803176 A		21-10-1998

PATENT COOPERATION TREATY

09 JUL 2002

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

HOGENBIRK, M.
P.O. Box 20
NL-5340 BH Oss
PAYS-BAS

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)		08/07/2002
Applicant's or agent's file reference 2000.565 WO		IMPORTANT NOTIFICATION
International application No. PCT/EP 01/ 07887	International filing date (day/month/year) 09/07/2001	Priority date (day/month/year) 12/07/2000
Applicant AKZO NOBEL N.V.		

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER
The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).
Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.
For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.
For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27 (5), 33 (5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/



European Patent Office, Gitschiner Str. 103
D-10969 Berlin - Germany
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2000.565 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 01/ 07887	International filing date (day/month/year) 09/07/2001	Priority date (day/month/year) 12/07/2000
International Patent Classification (IPC) or national classification and IPC C07D217/22		
Applicant AKZO NOBEL N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 11/02/2002	Date of completion of this report 03/07/2002
Name and mailing address of the IPEA/  European Patent Office, Gitschiner Str. 103 D-10969 Berlin - Germany Tel.: (+49-30) 25901-0 Fax: (+49-30) 25901-840	Authorized officer DE BUNDEL E R J Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) (July 1998)



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/ EP 01/ 07887

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

37

IPEA/

PCT

CHAPTER II

These documents represent
confirmation of an application filed by
facsimile

DEMAND

Date of facsimile: 11-01-01

under Article 31 of the Patent Cooperation Treaty:
I request that the international application specified below be the subject of
international preliminary examination according to the Patent Cooperation Treaty.

Name of authority with which facsimile
was filed: E.P.O.

or International Preliminary Examining Authority use only

IDENTIFICATION OF THE

Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 2000.565 WO	
International application No. PCT/EP01/07887	International filing date (day/month/year) 09-07-2001	(Earliest) Priority date (day/month/year) 12-07-2000	
Title of invention "THROMBIN INHIBITORS COMPRISING AN AMINOISOQUINOLINE GROUP"			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Akzo Nobel N.V. Velperweg 76 6824 RM ARNHEM The Netherlands		Telephone No.: 0412-666360	
		Facsimile No.: 0412-650392	
		Teleprinter No.:	
State (i.e. country) of nationality: NL		State (i.e. country) of residence: NL	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) REWINKEL, Johannes, Bernardus, Maria am van de Berghstraat 23 3348 JT OSS The Netherlands			
State (i.e. country) of nationality: NL		State (i.e. country) of residence: NL	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) TIMMERS, Cornelis, Marius Leidsel 14 5351 SN BERGHEM The Netherlands			
State (i.e. country) of nationality: NL		State (i.e. country) of residence: NL	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. 11 APPLICANT(s)

If none of the following sub-boxes is used, this sheet is not to be included in the demand

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

CONTI, Paolo, Giovanni, Martino
De Wisboom 35
5384 HD HEESCH
The Netherlands

State (i.e. country) of nationality:

IT

State (i.e. country) of residence:

NL

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

☐

Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> M. Hogenbirk P.O. Box 20 5340 BH Oss The Netherlands	Telephone No.: 0412-666360
	Facsimile No.: 0412-650592
	Teleprinter No.:

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority*

(i) ☒ to start the international preliminary examination on the basis of the international application as originally filed.

(ii) ☐ to take into account the amendments under Article 34 of

- ☐ the description (amendments attached).
- ☐ the claims (amendments attached).
- ☐ the drawings (amendments attached).

☐ to take into account any amendment of the claims under Article 19 filed with the International Bureau (a copy is attached).

(iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.

(v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as amended.

Box No. V ELECTION OF STATES

☒ The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except.....
.....
.....
(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

1. amendments under Article 34

description	:	sheets
claims	:	sheets
drawings	:	sheets

2. letter accompanying amendments under Article 34

: sheets

3. copy of amendments under Article 19

: sheets

4. copy of statement under Article 19

: sheets

5. other (specify):

: sheets

For International Preliminary
Examining Authority use only

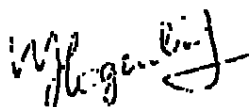
received	not received
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney4. ☒ fee calculation sheet2. ☐ copy of general power of attorney5. ☐ other (specify):3. ☐ statement explaining lack of signature

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



M. Hogenbirk

For International Preliminary Examining Authority use

1. Date of actual receipt of DEMAND:

Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5 below, does not apply.☐ The applicant has been informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/EP01/07887	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 2000.565 1 'O	Date stamp of the IPEA
Applicant Akzo Nobel N.V.	
Calculation of prescribed fees	
Preliminary examination fee.....	Euro 1533,= P
2 Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are, so entitled, the amount to be entered at H is 25% of the handling fee.).....	Euro 147,= H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	Euro 1680,= TOTAL
Mode of Payment	
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash
☐ cheque	☐ revenue stamps
☐ postal money order	☐ coupons
☐ bank draft	☐ other (specify):
Deposit Account Authorization (this mode of payment may not be available at all IPEAs)	
The IPEA / EPO ☒ is hereby authorized to charge the total fees indicated above to my deposit account.	
☒ (this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.	
2800 0012	11 February 2002
Deposit Account Number	Date (day month/year)
Form PCT/IPEA/401 (Annex) (January 1996)	Signature <i>M. Hogenbirk</i>

See Notes to the fee calculation sheet

INHIBIDORES DE TROMBINA QUE COMPRENDEN UN GRUPO

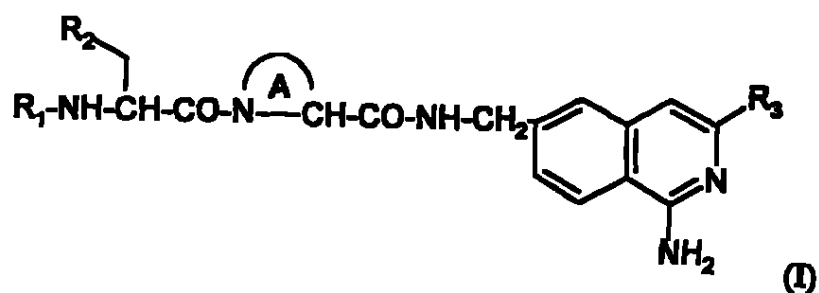
AMINOISOQUINOLINA

La invención se relaciona con un inhibidor de trombina que comprende un grupo aminoisoquinolina, una composición farmacéutica que contiene el mismo, lo mismo que el uso de dicho inhibidor para la elaboración de un medicamento para el tratamiento y prevención de enfermedades relacionadas con trombina.

En la literatura se describen un gran número de inhibidores de trombina similares a péptidos. La mayoría de aquellos inhibidores de trombina contienen grupos básicos en la así llamada posición P_1 , como los aminoácidos básicos arginina y lisina, pero también benzamidina y similares. Tal porción básica se considera esencial para la actividad de antitrombina. De otra parte, la basicidad de los compuestos puede afectar la toma de los compuestos en los intestinos cuando se suministra por vía de ruta oral. En la WO 98/47876 una clase de inhibidores de trombina se describe que tiene una parte de aminoisoquinolina como grupo básico que muestra unas propiedades de transporte transepitelial

mejoradas. Dentro de esta última clase de compuestos una nueva selección de compuestos ha sido ahora identificada que tiene propiedades farmacológicas aún más mejoradas.

Se ha encontrado que los compuestos de fórmula (I)



En donde

R_1 es ciclopentil, ciclohexil o un alquilo con 3 a 4 átomos de carbono ramificado;

R_2 es ciclohexilo o fenilo;

R_3 es H o metilo; y

A es un anillo con 4, 5 o 6 miembros no sustituidos saturado;

O una sal farmacéuticamente aceptable de ellos,

Son inhibidores de trombina potentes que tienen una vida media del plasma significativamente incrementada. La mayoría de las situaciones clínicas en la cual las drogas antitrombóticas se requieren necesitan en general una vida media prolongada (ver Sixma, J.J. et al., Thromb. Res. 67; 305-311 (esp. 307), 1992). Los compuestos de esta invención así son una importante mejora en la técnica.

Los compuestos de la presente invención son útiles para tratar y prevenir las enfermedades mediadas con trombina o asociada con la trombina. Esto incluye un número de estados tromboticos y protromboticos en los cuales la cascada de coagulación es activada lo cual incluye, pero no está limitada a, trombosis de venas profundas, embolismo pulmonar, tromboflebitis, oclusión arterial de trombosis o embolismo, reoclusión arterial durante o después de una angioplastia o trombolisis, restenosis seguida por daño arterial y procedimientos cardiológicos invasivos, trombosis o embolismo venoso postoperatorio, arteroesclerosis crónica o aguda, ataque, infarto del miocardio, cáncer y metástasis, y

enfermedades neurodegenerativas. Los compuestos de la invención también pueden ser usados como anticoagulantes en circuitos de sangre extracorpóreos, necesarios en la diálisis y cirugía. Los compuestos de la invención también pueden ser usados como anticoagulantes in vitro.

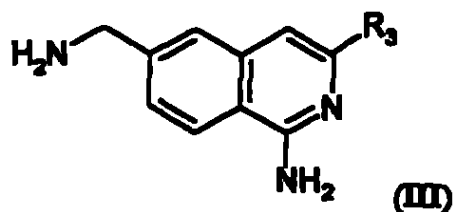
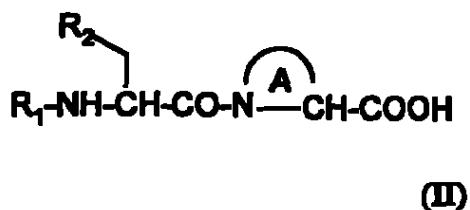
Los inhibidores de trombina preferidos de acuerdo con la invención son compuestos en donde A es un anillo de cinco miembros, preferiblemente, R_2 es ciclohexilo. Otros compuestos preferidos son aquellos, donde R_3 es H. más preferido son los compuestos en donde R_1 es ciclohexilo. Los más preferidos como inhibidores de trombina de acuerdo con la invención es el compuesto en donde R_1 es ciclohexilo, R_2 es ciclohexilo, R_3 es H y A es un anillo de cinco miembros.

El término alquilo de 3 a 4 carbonos ramificado significa un grupo alquilo ramificado que tiene 3 a 4 átomos de carbono, por ejemplo isopropilo.

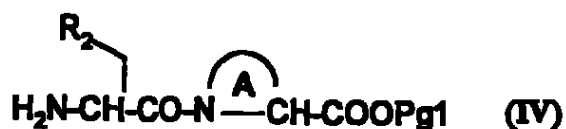
La invención incluye adicionalmente un proceso para la preparación de inhibidores de trombina, que incluye el acoplamiento de aminoácidos protegidos adecuados y

derivados de aminoisoquinolina, seguido por la remoción de los grupos protectores.

Los compuestos de acuerdo con la fórmula (I) pueden ser preparados de una manera convencional para tales compuestos. Ellos pueden ser preparados por un acoplamiento péptido de los compuestos de fórmula (II) con compuestos de fórmula (III) usando como reactivo de acoplamiento, por ejemplo N,N-diciclohexilcarbodiimida (DCCI) y 1-hidroxibenzotriazol (HOBT) o 2-(1H-benzotriazol-111-il)-1,1,3,3-tetrametiluronio tetrafluoborato (TBTU), en donde R_1 , R_2 , R_3 y A tienen los significados definidos anteriormente. El terminal N de los compuestos de fórmula (II) puede opcionalmente llevar un grupo protector tal como un grupo t-butoxicarbonilo (Boc). El grupo aril amina de los compuestos de fórmula (III) pueden opcionalmente portar un grupo protector tal como el benziolo que puede ser removido después de la reacción de acoplamiento.



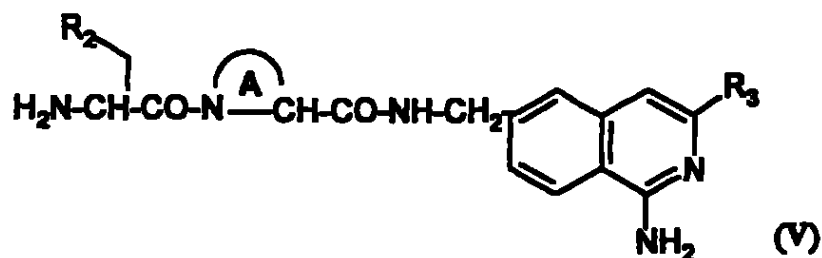
Los compuestos de fórmula (II) pueden ser preparados a partir de compuestos de fórmula (IV), en donde Pgl es un grupo protector de carboxilato similar al benzoéster, por tratamiento de los compuestos de fórmula (IV) con la acetona apropiada como la ciclohexanona o la acetona y un agente reductor tal como el triacetoxiborohidruro de sodio bajo condiciones ácidas y de ahí en adelante la remoción del grupo protector carboxilato.



El compuesto de fórmula (III) en donde $R_3=H$ (1-amino-6-(aminometil)isoquinolina) se describe en la WO 98/47876. El compuesto de fórmula (III) en donde $R_3=Me$ (1-amino-6-(aminometil)-3-metilisoquinolina) puede ser preparado a partir de 1-amino-6-metoxi-3-metilisoquinolina usando los procedimientos descritos en la WO 98/47876 para la transformación de 1-amino-6-metoxiisoquinolina en 1-amino-7-(aminometil)isoquinolina.

1-amino-6-metoxi-3-metilisoquinolina puede ser preparado de 3-metoxifenilacetona usando el método descrito por W. Zielinski y M. Mazik en heterociclos 38, 375 (1994).

Alternativamente, los compuestos de fórmula (I) pueden ser preparados a partir de compuestos de fórmula (V), por el tratamiento de los compuestos de fórmula (V) con una acetona apropiada como ciclohexanona o acetona y un agente reductor como el triacetoxiborohidruro de sodio bajo condiciones ácidas. En esta reacción el grupo aril amino de los compuestos de fórmula (V) puede estar opcionalmente protegido por un grupo tal como benzoilo que puede ser removido después de la aminación reductiva.



Los compuestos de la fórmula (V) pueden ser preparados por un acoplamiento péptido o un dipéptido protegido en el terminal N con un grupo protector similar al grupo BOC y los compuestos de fórmula (III) usan los reactivos de acoplamiento descritos anteriormente.

La protección de las funciones a-amino generalmente tiene lugar por funciones uretano tales como el grupo acil labil terc-butiloxicarbonil (Boc), benziloxicarbonil (Cbz) y análogos sustituidos, la base-labil 9-fluorenilmetiloxicarbonil (Fmoc) o el grupo ftaloilo (Phth). Otros grupos protectores amino incluyen el Nps, Bpoc, Msc, etc. La remoción de los grupos protectores puede tener lugar de diferentes maneras, dependiendo de la naturaleza de aquellos grupo protectores. Usualmente la desprotección tiene lugar bajo condiciones acídicas y en la presencia de secuestrantes. El grupo Cbz puede también ser removido por hidrogenación catalítica. Una visión general de los grupos protectores amino y los métodos para su remoción se da en *The peptides, Analysis, Syntesis, Biology*, Vol. 3 E. Gross y J. Meienhofer, Ed., (Academic Press, New York, 1981).

La protección de los grupos carboxilo puede tener lugar por formación de éster por ejemplo ésteres de base labil similares a metil- o etilésteres, ésteres de ácido labil como el terc-butilésteres, o ésteres hidrogenolíticamente labiles como benzilésteres.

Los compuestos de la invención, puede pueden estar en la forma de una base libre, pueden ser aislados a partir de la mezcla de reacción en la forma de una sal farmacéuticamente aceptable. Las sales farmacéuticamente aceptables también pueden ser obtenidas tratando la base libre de la fórmula (I) con un ácido orgánico o inorgánico tal como el cloruro de hidrógeno, bromuro de hidrógeno, yoduro de hidrógeno, ácido sulfúrico, ácido fosfórico ácido acético, ácido propiónico, ácido glicólico, ácido maleico, ácido malónico, ácido metanosulfónico, ácido fumárico, ácido succínico, ácido tartárico, ácido cítrico, ácido benzoico, y ácido ascórbico.

Los compuestos de esta invención poseen uno o más átomos de carbono quiral, y pueden por lo tanto ser obtenidos como enantiómeros puros, como diastereómeros puros, o una mezcla de enantiómeros, o como un mezcla que contiene diastereómeros. Los métodos para obtener los enantiómeros puros son bien conocidos en la técnica, por ejemplo cristalización de sales que son obtenidas a partir de ácido activos ópticamente y la mezcla racémica, o la cromatografía usando columnas quirales. Para la fase

recta de diastereómeros o las columnas de fase inversa pueden ser usados.

Los compuestos de la invención pueden ser administrados enteralmente o parenteralmente, y para humanos preferiblemente en una dosificación diaria de 0,001-100 mg x kg de peso del cuerpo, preferiblemente 0,01-10 mg por kg de peso del cuerpo. Mezclados con auxiliares farmacéuticamente adecuados, por ejemplo, como se describió en la referencia estándar, Genaro et al., Remington's Pharmaceutical Sciences, (18th ed., Marck Publishing Company, 1990, ver especialmente parte 8: Preparaciones farmacéuticas y su fabricación) los compuestos pueden ser comprimidos en unidades de dosificación sólida tales como píldoras, tabletas o pueden ser procesados en cápsulas o supositorios. Por medio de líquidos farmacéuticamente adecuados los compuestos también pueden ser aplicados en la forma de una solución, suspensión, emulsión, por ejemplo para uso como una preparación de inyección, como un rociado, por ejemplo, para uso como un rociado nasal.

Para hacer unidades de dosificación, por ejemplo tabletas, el uso de aditivos convencionales tales como

cargas, colorantes, aglomerantes poliméricos, y similares es contemplado. En general cualesquier aditivo farmacéuticamente aceptable que no interfiera con la función de los compuestos activos pueden ser usados. Los portadores adecuados para los cuales las composiciones pueden ser administradas incluyen la lactosa, el almidón, los derivados de celulosa y similares, o mezclas de los mismos, usados en cantidades adecuadas.

La eliminación de la vida media y el porcentaje de biodisponibilidad de los compuestos de la invención puede ser ensayado de acuerdo con los siguientes ensayos en perros.

El tiempo de residencia y el porcentaje de biodisponibilidad de los inhibidores de trombina en perros beagle hembra puede ser medido por la determinación de la actividad anti-IIa en el plasma después de administración intravenosa u oral. En vista de la selectividad de los inhibidores de proteasa de la invención la invención de la trombina se relaciona linealmente con la concentración del inhibidor de proteasa medido. Después de administración intravenosa u oral del inhibidor de proteasa de serína, la sangre es

recolectada de la vena yugular en diferentes puntos en el tiempo durante el día. Después de centrifugación de la sangre, las actividades de plasma anti-IIa son determinadas de las muestras de plasma en un ensayo cromogénico de placa de microtítulo usando una curva de calibración del compuesto ensayado en sí mismo. Los datos obtenidos son analizados a partir del plasma contra la curva de tiempo, por ejemplo, por medio de un procedimiento iterativo computarizado, con base en el método Simplex. Subsecuentemente, la eliminación de las vidas medias son calculadas usando el modelo de rol relativo independiente de la concentración, y el área bajo la curva (AUC) es determinada con la regla del trapecio, asumiendo cinéticas lineales, el porcentaje de biodisponibilidad es calculado dividiendo la AUC obtenida después de la administración por el medio esperado normalizado AUC después de administración intravenosa de aquella dosis ($\times 100\%$).

La invención se ilustra adicionalmente por los siguientes ejemplos.

EJEMPLOS

Las mediciones ^1H RMN fueron llevadas a cabo usando un espectrofotómetro BRUKER DRX 400 que opera a una frecuencia ^1H de 400 MHz. El espectro de masa (MS) fue registrado con un PE-sciex API-165.

Ejemplo 1

N-ciclohexil-3-ciclohexil-D-alanil-N-[(1-amino-6-isoquinolinil)metil]-1-prolinamida hidrogencloruro (N-ciclohexil-D ha-Pro-6Aiq.HCl)

Después de agitar 0,91 g de éster de 3-ciclohexil-N-[(1,1-dimetiletoxi)carbonil]-D-alanil-1-prolina fenilmetilo (Boc-D-Cha-Pro-OBzl) en 2,5 ml de diclorometano y 2,5 ml de ácido trifluoroacético a temperatura ambiente durante 2 horas la mezcla de reacción fue concentrada en vacío para dar 0,94 g de un aceite. Este aceite fue disuelto en 10 ml de N,N-dimetilformamida que contenía 1% v/v) de ácido acético y 0,26 ml de ciclohexanona y 0,64 g de trioacetoxiborohidruro de sodio fueron agregados. Después de agitación a temperatura ambiente durante 16 horas se



agregaron 5 ml de agua a la mezcla de reacción y se extrajo con diclorometano. El extracto orgánico fue secado sobre sulfato de magnesio y concentrado para dar 0,90 g de un aceite (TLC; gel de sílice, diclorometano/metanol = 95/5 (v/v) $R_f \approx 0,8$). Este aceite fue disuelto en 50 ml de acetato de etilo, el pH de la solución fue ajustado a 5 usando ácido acético, se agregó 0,10 g de paladio sobre carbono (10%) y la suspensión fue hidrogenada a presión atmosférica a temperatura ambiente durante 1 hora. El catalizador de paladio fue removido por filtración y el disolvente fue removido por evaporación a presión reducida. el residuo fue disuelto en tolueno y el tolueno fue evaporado bajo presión reducida dando 0,56 g de N-ciclohexil-D-Cha-Pro-OH. Este ácido (0,35 g) fue disuelto en 10 ml de N,N-dimetilformamida y se agregaron 0,19 mg de 1-amino-6-aminometilisoquinolina (WO 9847876) y 0,4 g de tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluroinio (TBTU). El pH de la mezcla de reacción fue ajustado a 8 usando N,N-diisopropiletilamina (DIPEA). Después de agitación durante 24 horas a temperatura ambiente se agregó 0,1 g adicional de TBTU y la mezcla de reacción fue agitada a temperatura ambiente durante 18 horas adicionales. De ahí en adelante la mezcla de

reacción fue concentrada en vacío. El residuo fue disuelto en 50 ml de diclorometano y fue lavado dos veces con hidrogenocarbonato de sodio acuoso, secado sobre sulfato de magnesio y concentrado. El residuo fue disuelto en agua y cargado directamente en un preparativo de HPLC DeltaPack RP-C₁₈ usando un sistema de elusión de gradiente de 20% A / 80% B a 20% A / 30% B / 50% C durante 60 minutos a una velocidad de flujo de 40 ml/minuto (A: 0,5M de amortiguador de fosfato pH 2,1, B: agua, C: acetonitrilo/agua = 6/4 (v/v)). Producto: 0,25 g del compuesto titulado.

¹H-NMR 400MHz (CD₃OD) δ: 0.84 - 2.41 (27H, m), 2.91 - 3.01 (1H, m), 3.57 - 3.65 (1H, m), 3.81 - 3.88 (1H, m), 4.30 (1H, t, J = 7Hz), 4.49 - 4.77 (3H, m), 7.26 (1H, d, J = 7Hz), 7.57 (1H, d, J = 7Hz), 7.73 (1H, dd, J = 2Hz y J = 9Hz), 7.92 (1H, d, J = 2Hz), 8.38 (1H, d, J = 9Hz).

EJEMPLO 2

Hidrogencloruro de N-ciclohexil-3-ciclohexil-D-
alanil-N-[(1-amino-3-metil-6-isoquinolinil)metil]-L-
prolinamida (N-ciclohexil-D-Cha-Pro-6(3Me)Aiq.HCl)

2a. 1-amino-6-metoxi-3-metil-isoquinolina

Una solución de 2,12 g de 3-metoxifenilacetona y 1,26 ml de cloruro de fosforilo en 45 ml de tolueno anhidroso fueron calentados bajo reflujo. Después de 30 minutos la mezcla fue enfriada a 0° C y una solución de 0,57 de cianamida en 23 ml de éter anhidroso fue agregada gota a gota. La mezcla de reacción se le permitió calentarse a temperatura ambiente y se agitó a esta temperatura durante una hora. Entonces la mezcla de reacción fue enfriada a 0° C y se agregó gota a gota 1,5 ml de tetracloruro de titanio. La mezcla de reacción fue calentada bajo reflujo durante 2,5 horas, enfriada, se agregó 34 ml de agua, la mezcla fue filtrada y el sedimento fue lavado con acetato de etilo. El filtrado fue hecho básico usando hidróxido de sodio acuoso al 2N y extraída con acetato de etilo. Los extractos orgánicos fueron lavados con salmuera, secados sobre sulfato de magnesio y concentrados. El residuo fue purificado por cromatografía de sílice (diclorometano/metanol = 95/5) produciendo 0,42 g del compuesto titulado

¹H-NMR 400MHz (CDCl₃) δ: 2.45 (3H, s), 3.91 (3H, s), 5.0 (2H, br. s), 6.81 (1H, s), 6.90 (1H, d, J = 3Hz), 7.02 (1H, dd, J = 3Hz y J = 9Hz); 7.65 (1H, d, J = 9Hz).

2b. 1-amino-6-hidroxi-3-metil-isoquinolina

tribromuro de boro (4 ml) en 6 ml de diclorometano fueron agregados gota a gota a una solución agitada de 1-amino-6-metoxi-3-metilisoquinolina (2 g) en 10 ml de diclorometano a 0° C. Después de agitación durante 16 horas a temperatura ambiente la mezcla de reacción fue vertida sobre hielo, la capa orgánica fue removida y el pH de la capa acuosa fue ajustado a un pH 9 agregando amoniaco acuoso concentrado. El material precipitado fue recolectado por filtración y secado en vacío para dar 1,6 g del compuesto titulado ESI-MS: 175 (MH⁺).

2c. éster de trifluoro-ácido metanosulfónico 1-amino-3-metilisoquinonil-6-il

Una mezcla de 1,4 g de 1-amino-6-hidroxi-6-metil-isoquinolina y 4,3 g de N-fenil-bis(trifluorometanosulfonimida) en 19,5 ml de diclorometano y 19,5 ml de dioxano fueron enfriados en un baño de hielo y se agregó gota a gota 2,8 ml de N,N-diisopropiletilamina. La mezcla resultante fue calentada durante 24 horas a 70° C, después de lo cual los

volátiles fueron removidos en vacío. El residuo restante fue disuelto en acetato de etilo, lavado con porciones sucesivas de hidróxido de sodio acuoso al 2N, agua y salmuera y secado (sulfato de sodio). La filtración y la concentración dio un aceite sin color, el cual fue triturado en tolueno para dar 1,3 g de un sólido. La solución de tolueno fue purificada por cromatografía de sílice (tolueno/etanol = 95/5) produciendo 0,6 g adicionales del compuesto titulado. Producto total 1,9 g. ESI-MS: 307 (MH^+).

2d. 1-amino-6-ciano-3-metilisoquinolina

Se agregó acetato de paladio (0,28 g) a una mezcla caliente de éster de trifluoro-ácido metanosulfónico 1-amino-3-metilisoquinolin-6-il (1,9 g), cianuro de zinc (0,74 g) y trifenilfosfina (0,33 g) en 24 ml de N-metil-pirrolidona a 190° C (exotérmica). La agitación fue continuada a 190° C durante dos horas. Después de enfriar a temperatura ambiente, el acetato de etilo fue agregado y la mezcla orgánica fue lavada con amoníaco acuoso al 2N, agua y salmuera y secado (sulfato de magnesio). La filtración y concentración dio un aceite medio café, el cual fue purificado por cromatografía de sílice

(diclorometano/metanol = 98/2) para dar 0,68 g del compuesto titulado. ESI-MS:184 (MH^+).

2e. 1-amino-6-(aminometil)-3-metilisoquinolina

A una solución agitada de 1-amino-6-ciano-3-metilisoquinolina (0,68 g) en 15 ml de tetrahidrofurano a temperatura ambiente bajo atmósfera de nitrógeno se agregó 8,4 ml de un complejo de borano-metilsulfuro al 2M en tetrahidrofuran y luego fue calentada a 60° C durante 50 minutos. La mezcla de reacción fue enfriada en un baño de hielo y se agregó lentamente 7,5 ml de metanol. Después de 15 minutos se agregó 18,8 ml de cloruro de hidrógeno al 1M en éter. La mezcla de reacción se le permitió calentarse a temperatura ambiente y se agitó durante 16 horas adicionales. El sólido fue aislado para dar 0,34 g de hidrogencloruro de 1-amino-6-(aminometil)-3-metilisoquinolina. El filtrado fue purificado usando cromatografía de columna (gel de sílice; metanol/amoniaco = 98/2) para dar 0,15 g adicionales de 1-amino-6-(aminometil)-3-metilisoquinolina. ESI-MS:188 (MH^+).

2f. Hidrogencloruro de N-ciclohexil-3-ciclohexil-D-alanil-N-[(1-amino-3-metil-6-isoquinolinil)metil]-L-prolinamida (N-ciclohexil-D Cha-Pro-6(3Me)Aiq.HCl)

A una mezcla agitada de 0,17 g de hidrogen cloruro de 1-amino-6-(aminometil)-3-metilisoquinolina, se agregó 0,30 g de N-ciclohexil-D-Cha-Pro-OH, 0,5 ml de acetonitrilo y 0,37 ml de N,N-diisopropiletilamina en 3 ml de N,N-dimetilformamida a temperatura ambiente en una hora una solución de 0,35 g de hexafluorofosfato de bromotripirrolidonofosfonio (PyBroP) en 1,3 ml de N,N-dimetilformamida. Después de agitación durante 24 horas a temperatura ambiente la mezcla de reacción fue concentrada en vacío. El residuo fue disuelto en acetato de etilo y lavado con hidrogencarbonato de sodio acuoso y salmuera, secado sobre sulfato de magnesio y concentrado. El residuo fue purificado por cromatografía de sílice (diclorometano/metanol = 9/1) y liofilización a partir de t-butanol/ácido clorhídrico lo que produjo 0,13 g del compuesto titulado.

¹H-NMR 400MHz (CD₃OD) δ: 0.85 - 2.41 (25H, m), 3.43 - 3.52 (1H, m), 3.59 - 3.65 (1H, m), 3.80 - 3.86 (1H, m), 4.20 (1H, t, J = 7Hz), 4.51 - 4.73 (3H, m), 7.25 (1H, d, J = 7Hz), 4.46 - 4.74 (3H, m), 7.02 (1H, s), 7.64 (1H, dd, J = 2Hz y J = 9Hz), 7.80 (1H, d, J = 2Hz), 8.32 (1H, d, J = 9Hz).

EJEMPLO 3

Hidrogen cloruro de N-ciclohexil-D-fenilalanil-N-[(1-amino-6-isoquinolinil)metil]-L-prolinamida (N-ciclohexil-D-Phe-Pro-6Aiq.HCl)

Agitando con 0,85 g éster de N-[(1,1-dimetiletoxi)carbonil]-D-fenilalanil-L-prolinafenilmetil (Boc-D-Phe-Pro-OBzl) dio 0,82 g de N-ciclohexil-D-fenilalanil-L-prolina (N-ciclohexil-D-Phe-Pro-OH) usando los procedimientos descritos en el ejemplo 1 para N-ciclohexil-D-Cha-Pro-OH. El N-ciclohexil-D-Phe-Pro-OH (0,82 g) fue disuelto en 10 ml de N,N-dimetilformamida y se agregó 0,33 mg de 1-amino-6-aminometilisoquinolina y 1,1 g de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfato (HATU) y el pH fue ajustado a 8 usando N,N-diisopropiletilamina (DIPEA). Después de agitación durante 16 horas a temperatura

ambiente la mezcla de reacción fue concentrada en vacío. El residuo fue disuelto en 50 ml de diclorometano y lavado doble vez con agua y salmuera, secado sobre sulfato de magnesio y concentrado. El residuo fue purificado por cromatografía de sílice (diclorometano/metanol (que contiene 2% de amoníaco) = 9/1) y liofilización a partir de t-butanol/ácido clorhídrico lo que produjo 0,19 g del compuesto titulado.

¹H-NMR 400MHz (CD₃OD) δ:
0.87 - 2.13 (14H, m), 2.38 - 2.45 (1H, m), 2.94 - 3.03 (1H, m), 3.06 - 3.13 (1H, m), 3.25 - 3.38 (2H, m), 4.33 - 4.73 (4H, m), 7.25 - 7.40 (6H, m), 7.58 (1H, d, J = 7Hz), 7.71 (1H, dd, J = 2Hz y J = 9Hz), 7.92 (1H, d, J = 2Hz), 8.35 (1H, d, J = 9Hz).

Ejemplo 4.

Hidrogen cloruro de N-ciclopentil-3-ciclohexil-D-alanil-N-[(1-amino-6-isoquinolinil)metil]-L-prolinamida (N-ciclopentil-D-Cha-Pro-6Aiq.HCl

Usando los procedimientos descritos en el ejemplo 1 partiendo con 0,30 g de Boc-D-Cha-Pro-OBzl usando ciclopentanona en lugar de ciclohexanona dio un crudo de

N-ciclopentil-D-Cha-Pro-6Aiq el cual fue purificado usando cromatografía de columna (gel de sílice; diclorometano/metanol = 10/1 gradiente de 5/1). La liofilización a partir de t-butanol/ácido clorhídrico produjo 0,16 g del compuesto titulado.

¹H-NMR 400MHz (CD₃OD) δ: 0.85 - 2.41 (25H, m), 3.43 - 3.52 (1H, m), 3.59 - 3.65 (1H, m), 3.80 - 3.86 (1H, m), 4.20 (1H, t, J = 7Hz), 4.51 - 4.73 (3H, m), 7.25 (1H, d, J = 7Hz), 7.57 (1H, d, J = 7Hz), 7.73 (1H, dd, J = 2Hz y J = 9Hz), 7.90 (1H, d, J = 2Hz), 8.38 (1H, d, J = 9Hz).

EJEMPLO 5

Hidrogen cloruro de N-(1-metiletil)-3-ciclohexil-D-alanil-N-[(1-amino-6-isoquinolinil)metil]-L-prolinamida (N-(1-metiletil)-D-Cha-Pro-6Aiq.HCl

Usando los procedimientos descritos en el ejemplo 1 partiendo con 0,92 g de Boc-D-Cha-Pro-OBzl usando acetona en lugar de ciclohexanona dio 0,04 g de N-81-metiletil)-D-Cha-Pro-6Aiq.

$^1\text{H-NMR}$ 400MHz (CD_3OD) δ : 0.85 - 2.41 (23H, m), 3.27 - 3.35 (1H, m), 3.59 - 3.65 (1H, m), 3.82 - 3.89 (1H, m), 4.27 (1H, t, $J = 7\text{Hz}$), 4.51 - 4.74 (3H, m), 7.26 (1H, d, $J = 7\text{Hz}$), 7.57 (1H, d, $J = 7\text{Hz}$), 7.72 (1H, dd, $J = 2\text{Hz}$ y $J = 9\text{Hz}$), 7.91 (1H, d, $J = 2\text{Hz}$), 8.38 (1H, d, $J = 9\text{Hz}$).

Ensayo de Antitrombina

La actividad antitrombina de los compuestos de la presente invención fue lograda midiendo espectrofotométricamente la velocidad de la hidrólisis del sustrato cromogénico s-2238 extraído por trombina. Este ensayo para la actividad antitrombina en un sistema amortiguador fue utilizado para lograr calcular el valor de IC_{50} en un compuesto de ensayo.

Medio de ensayo: amortiguador Trometaina-NaClpolietilenglicol 6000 (TNP)

Compuesto de Referencia: I2581 (Kabi)

Vehículo: Amortiguador TNP. Solubilización puede ser asistida con dimetilsulfóxido, metanol, etanol, acetonitrilo o terc-butilalcohol los cuales no tienen

efectos adversos en concentraciones hasta 2,5% en la mezcla de reacción final.

Técnica:

Reactivos* 1. Amortiguador de Trometamina-NaCl (TN) [Composición del amortiguador: Trometamina (Tris) 6,057 g (50 mmoles), NaCl 5,844 g (100 mmoles), agua a 1 l. El pH de la solución es ajustado a 7,4 a 37° C con HCl (10 mmoles·l⁻¹)]; 2. Amortiguador TNP (polietilenglicol 6000 es disuelto en el amortiguador Tn para dar una concentración de 3 g·l⁻¹; 3. Solución de S-2238 [un frasco de S-2238 (25 mg; Kabi Diagnóstica, Suecia) es disuelto en 20 ml del amortiguador TN para dar una concentración de 1,25 mg · ml⁻¹ (2 mmoles · l⁻¹)]; 4. Solución de Trombina [Trombina humana (16000 nKat·vial⁻¹;

]Central Laboratorium Vorblodentransfusie, Amsterdam, holanda) es disuelto en un amortiguador de TNP para dar una solución base de 835 [nKat ml - iApos. Inmediatamente antes del uso de esta solución es diluida con un amortiguador de TNP para dar una concentración de 3,34 NKAT No. ml⁻¹.]]. Todos los ingredientes usados son

de grado analítico - para soluciones acuosas de agua ultra pura [(mili-q)calidad] se usa.

El ensayo y los compuestos de referencia son disueltos en mili-q agua para dar las concentraciones de partida de $[10^{-2}]$ $[\text{mol}\cdot\text{l}^{-1}]$ cada concentración se da en pasos diluidos con el vehículo para dar concentraciones de $[10^{-3}, 10^{-4}$ y 10^{-5} moles;] las diluciones, incluyen la solución base, y son usadas en el ensayo (concentraciones finales en la mezcla de reacción: $[3\cdot 10^{-10}; 10^{-3}; 3\cdot 10^{-4};]$ $10^{-4}; [3 \times 10^{-5}]; [3 \times 10^{-6}]$ y $[10^{-6}$ moles] respectivamente).

Procedimiento

A temperatura ambiente 0,075 ml y 0,025 ml del compuesto de ensayo o soluciones del compuesto de referencia o vehículo son pipeteados alternativamente en pozos de una placa microtítulo y estas soluciones son diluidas con 0,115 ml y 0,0165 ml del amortiguador TNP, respectivamente. Una alícuota de 0,030 ml de la solución S-2238 es agregada a cada pozo y la placa es precalentada y preincubada con agitación en un incubador (Amersham) durante 10 minutos a 37° C. luego de la preincubación la

hidrólisis de S-2238 se inicia agregando 0,030 ml de solución de trombina a cada pozo. La placa es incubada (con agitación durante 30 segundos) a 37° C. iniciando después de 1 minuto de incubación, la absorbancia de cada muestra A 405 nm es medida cada dos minutos. Durante un periodo de 90 minutos usando una un lector de placa de microtítulo cinético (Tween Readers plus, Flow Laboratories).

Todos los datos son recolectados en un computador personal IBM usando Lotus-measure. Para cada concentración de compuesto (expresada en moles $\times 1^{-1}$ la mezcla de reacción y para el blanco la absorbancia es graficada contra el tiempo de reacción en minutos.

Evaluación de las Respuestas:

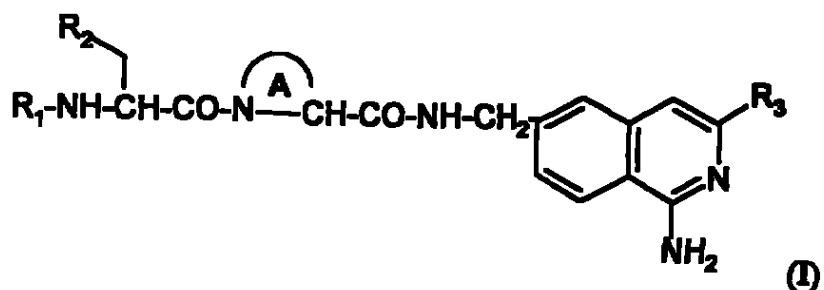
Para cada concentración final la absorbancia máxima fue calculada a partir del gráfico de ensayo. El valor ISO (concentración final, expresado en micromoles l^{-1} , que causa el 50% de la inhibición del máximo de absorbancia en el blanco) fue calculado usando el análisis de

transformación logit de acuerdo con Hafner et al.
Arsnime., Forch./drug res (1977; 27 it:1871-3).

Actividad antitrombina. Ejemplo IC_{50} (mol x l⁻¹)
10,03 20,14, 30,13, 40,12, 50,29.

REIVINDICACIONES

1. Un compuesto que tiene la fórmula (I)



En donde

R_1 es ciclopentil, ciclohexil o un alquilo con 3 a 4 átomos de carbono ramificado;

R_2 es ciclohexilo o fenilo;

R_3 es H o metilo; y

A es un anillo con 4, 5 o 6 miembros no sustituidos saturado;

O una sal farmacéuticamente aceptable de ellos.

2. El compuesto de la reivindicación 1, en donde A es un anillo de 5 miembros.
3. El compuesto de la reivindicación 1, en donde R_2 es ciclohexilo.
4. El compuesto de la reivindicación 1, en donde R_3 es H.
5. El compuesto de la reivindicación 1, en donde R_1 es ciclohexilo.
6. El compuesto de la reivindicación 5 en donde R_1 es ciclohexilo, R_2 es ciclohexilo, R_3 es H y A es un anillo de 5 miembros.
7. Una composición farmacéutica que comprende el compuesto de una cualquiera de las reivindicaciones 1 a 6 y auxiliares farmacéuticamente adecuados.
8. El compuesto de una cualquiera de las reivindicaciones 1 a 6 para uso en terapia.

9. El uso del compuesto de una cualquiera de las reivindicaciones 1 a 6 para la fabricación de un medicamento para el tratamiento o prevención de enfermedades relacionadas con la trombina.

RESUMEN

La invención se relaciona con un compuesto que tiene la fórmula (I) en donde R_1 es ciclopentilo, ciclohexilo, o un alquilo ramificado con 3 a 4 carbonos; R_2 es ciclohexilo o fenilo; R_3 es H o metilo; y A es un anillo con 4, 5 o 6 miembros no sustituidos y saturado; o una sal farmacéuticamente aceptable del mismo. Los compuestos de la invención tienen una actividad anticoagulante y pueden ser usados para el tratamiento y prevención de enfermedades mediadas y asociadas con trombina.

Expediente No		0300 10 19	No de Follo
Item		No de unidades	✓
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA	✓ 1	✓
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:

contiene Arde final

127 : 0017.007.0



75

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SUPERINDUSTRIA Y COMERCIO

Folios: 75

FCIO

CIA

RECIBO DE PAGAR : 07 - 001
FECHA : 0000 01 DE 2003

Radicacion : 03001019 00000000

Fecha (MM): 2003-01-09 17:11:33

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

888: 00000000000000000000

CONCEPTO	Tipo	Valor	Cuenta	No. PCT	Fecha	Valor
TRAMITE PRESENTACION	CONTRATACION	TRAMITE PRESENTACION	000 0110-6	2134924	02/31.2003	70,700,000.00

8888 C O N C E P T O 8888

CONCEPTO	CONCEPTO	TOTAL CONCEPTO
1 50000-01-21 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	70,700,000.00
	TOTAL :	70,700,000.00

SOL: CONTRATACION MIL PESOS

RESPONSABLE : *[Handwritten signature]*

RECIBO DE CASH APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
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Bogotá, D.C., Colombia

0000 11214-841-004-9

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCION	MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.		()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	()
- Descripción de la invención.		()	()
- Dibujos de ser estos pertinentes.		()	()
- Comprobante de Pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()	()	()
DISEÑO INDUSTRIAL ()			
- Indicación de que se solicita el registro de Diseño Industrial		()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.		()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.		()	()
- Comprobante de pago de las tasas establecidas		()	()
COMPLETA ()	INCOMPLETA	()	()
ESQUEMA DE TRAZADO ()			
- Indicación de que solicita el registro de un Esquema de trazado.		()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.		()	()
- Representación gráfica del esquema de trazado		()	()
- Comprobante de pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA	()	()

Firma Responsable:

ANDREA ROSE

Fecha:



2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado
Alzo Nobel N.V.

Oficio N° 08192

ASUNTO:	Radicación N°	03-1019
	Solicitud internacional	PCT/EP2001/07887
	Fecha Inicio fase nacional	12/02/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 28-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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

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

El anterior requerimiento fue notificado por fijación en lista de fecha 03 OCT. 2003.