

OK



Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

PCT

06-96303

21 EXPEDIENTE No

54 TÍTULO Clorhidrato de [4-(5-aminometil-2-fluorofenil)-piperidin-1-il]-(4-bromo-3-metil-5-propoxitiofen-2-il)-metanona como un inhibidor de la triptasa de mastocitos

AGIK

AGIK 31/4/31

51 CLASIFICACIÓN INTERNACIONAL C07D 401.00 AGIP 11/06

71 SOLICITANTE Aventis Pharmaceuticals Inc.

DOMICILIO Bridgewater, New Jersey, Estado Unidos

74 APODERADO Luis Patiño Leyra

22 BOGOTÁ, D C, 25 de Septiembre de 2006

70 26/11/2006

70/11/2006

SS

FORMULARIO ÚNICO 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 AVENTIS PHARMACEUTICALS INC

Dirección 300 Somerset Corporate Boulevard
Bridgewater NJ 08807 2854 Estados Unidos

Nacionalidad o Domicilio Bridgewater New Jersey
Estados Unidos

Lugar de Constitución Estados Unidos

Teléfono

Fax

IDENTIFICACION

CC



NIT



CE



Otro



Cual

Número

REPRESENTANTE
O APODERADO

Nombre LUIS PATIÑO LEYVA

Dirección Cra 11ª No 94-76 - Of 308

Teléfono 6161948

Fax 6163976

E-mail

IDENTIFICACION

CC



NIT



CE



Otro



Cual

Número 2.930.616 TP 2698

④

INVENTOR (ES)
(72)

Nombre GAO Zhongli

Dirección 26 Running Brook Circle

Nacionalidad o Domicilio Flemington NJ 08822, Estados Unidos

⑤ PCT (86)

Solicitud Internacional No PCT/US2005/009899

Fecha Marzo 24 de 2005

Publicación Internacional No WO 2005/097780 A1

Fecha Octubre 20 de 2005

⑥ Título (54) [HIDROCLORURO DE [4-(5-AMINOMETIL-2-FLUORO-FENIL)-PIPERIDIN-1-IL]-4-BROMO-3-METIL-5-PROPOXI-TIOFEN-2-IL]-METANONA COMO UN INHIBIDOR DE LA TRIPTASA DE MASTOCITOS

⑦

Clasificación Internacional (51) C07D 409/06

⑧

PRIORIDAD

SI



NO



(33) País de Origen

Estados Unidos

(32) Fecha

Marzo 26 de 2004

(31) Número de Solicitud

60/556,927

⑨

Comprobante de pago 06-73,658

Fecha

Septiembre 22/2006

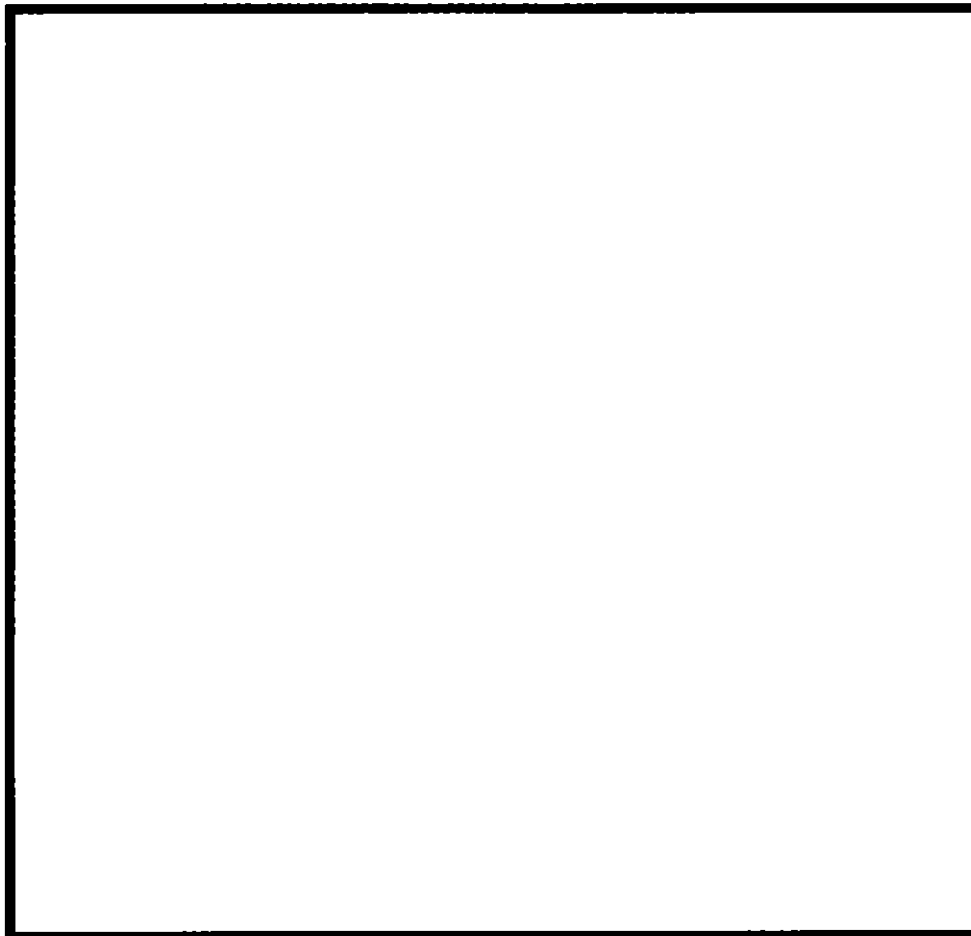
Instrucciones para el diligenciamiento del presente formulario ver reverso de esta página

①

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite 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 internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- ☒ Traducción del examen preliminar internacional 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
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional
- ☒ Otros Reporte de Búsqueda Internacional

(11) FIGURA CARACTERISTICA



(12) Solicito la concesión de la patente,

NOMBRE LUIS PATIÑO LEYVA

FIRMA.

C.C. 2.930.616 Bogotá T.P. 2698

Instrucciones para el diligenciamiento del presente formulario ver reverso de esta página.

Continuación nombre, dirección y domicilio de inventores

<u>Nombre</u>	<u>Dirección</u>	<u>Domicilio</u>
DAVIS Larry	7 Bird Lane	Sergeantsville, NJ 08557 Estados Unidos
LEVELL Julian	8 Woodland Road	Benardsville, NJ 07924 Estados Unidos
CZEKAJ Mark	3897 Charter Club Drive	Doylestown PA 18901, Estados Unidos
SLEDESKI Adam, W	24 Fisher Farm Road,	Belle Mead, NJ 08502 Estados Unidos
HADDAD El-Bdaoui	49 Battalion Drive,	Basking Ridge, NJ 07920 Estados Unidos

Otros anexos que se acompañan a la solicitud

Copia del formato PCT/RO/101 correspondiente a la solicitud internacional

Copia del formato PCT/IB/304 correspondiente a la notificación relativa al envío o transmisión del documento de prioridad

Copia formato PCT/IB/306 correspondientes a la notificación de un cambio

Copia formato PCT/IB/308 correspondiente a una noticia informando al solicitante de la comunicación de la solicitud internacional

Copia formato PCT/ISA/210 Reporte de Búsqueda Internacional

Copia formato PCT/ISA/237 referente a opinión escrita de la autoridad encargada de la búsqueda internacional

Copia formato PCT/IPEA/402 correspondiente a la notificación de recibo por la autoridad competente de la solicitud de Examen Preliminar Internacional

Comunicación relativa al artículo 34 y respuesta a la opinión escrita de la autoridad de búsqueda internacional

Respuesta a la opinión escrita de la autoridad de búsqueda internacional dirigida a la Oficina Europea de Patentes y su traducción al español

Comunicación relativa al artículo 34 y respuesta a la opinión escrita de la autoridad de búsqueda internacional y su traducción al español

Copia formato PCT/IB/332 información concerniente a las oficinas elegidas notificadas de su elección

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 06-086303-00000-0000
Fee 2006-09-25 16:58:39 Dep 2020 NUECREACIONES
Tra 11 PATENTEYII
Eve 379 FASENACIONALI
Act 411 PRESENTACION Folios: 115

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT 800176089-2

RECIBO DE C AL DE CAJA 06 73,638
FECHA SEPTIEMBRE 22 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Ar PAGO
DAVID HOLLMANN S	CONSIGNACION	BANCO POPULAR	950-00110 6	5.372990	21/09/2006	1,8 2,000 00

***** CONCEPTO *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50000-01-0	SOL CITIJDES	1 TRAMITES DE SOL DE PATENTE DE IN	463,000 00
		TOTAL	463,000

SOM CUATROCIENTOS SESENTA Y TRES MIL PESOS

Ref 58843

RESPONSABLE



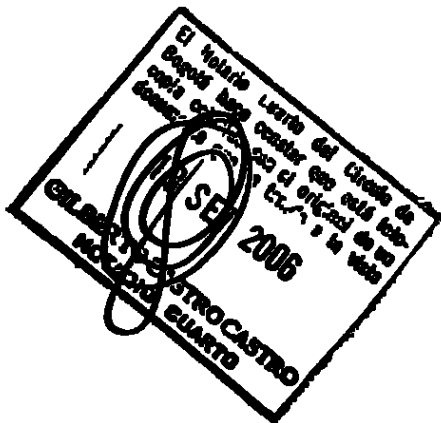
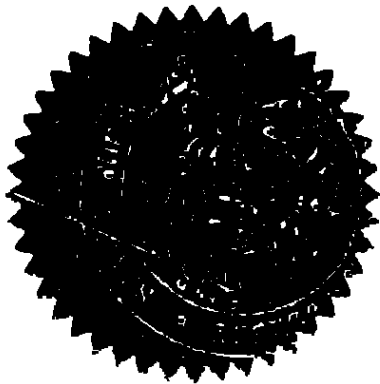
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

- 1 COUNTRY UNITED STATES OF AMERICA
- 2 THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY
R PETER WIDIN
- 3 ACTING IN THE CAPACITY OF
COUNTY CLERK
- 4 BEARS THE SEAL/STAMP OF
COUNTY OF SOMERSET

CERTIFIED

- 5 AT TRENTON NEW JERSEY
- 6 THE 9TH DAY OF APRIL 2002
- 7 BY John E McCormac CPA NEW JERSEY TREASURER
- 8 NO A149012
- 9 SEAL/STAMP
- 10 SIGNATURE



G HOLLMANN RESTREPO
ABOGADOS LTDAG. HOLLMANN RESTREPO
ABOGADOS LTDA

The undersigned acting on behalf of and representing of AVENTIS PHARMACEUTICALS INC domiciled in 300 Somerset Corporate Boulevard, Bridgewater New Jersey, USA, hereby appoint(s) GUSTAVO HOLLMANN RESTREPO and/or LUIS PATIÑO LEYVA, domiciled in Bogotá D.C. Republic of Colombia as our true and legal attorney with the necessary powers

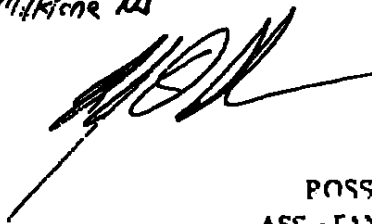
1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents utility models industrial designs and models commercial emblems and names trademarks slogans health licenses copyrights and domain names as well as their assignments extensions, renewals and changes of name, 2) To prepare apply for obtain, execute and register contracts licenses, authorizations and registrations of any kind, 3) To intervene as plaintiff or defendant, in any instance or appeal before any judge court, tribunal, corporation, public officer or authority in any judicial administrative or police action, such as action dealing with commercial emblems and names oppositions against trademark registrations caducity and nullity actions recovery actions, actions arising from obtainment and working of license agreements actions dealing with unfair competition, criminal actions actions claiming indemnity for damages complaints or remarks on all sort of industrial property matters the performance of precautionary measures and in any other similar action measure or appeal related to intellectual property matters

To this effect I (we) hereby authorize him to file applications make descriptions protests amendments declarations oppositions cancellations appeals and claims to pay taxes quotas and liens as provided by Law to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities to issue the respective releases and, in general, to take before said authorities pertinent steps to the above mentioned purposes and take all measures they may deem advisable to protect my (our) interests with all other necessary legal faculties and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit

This power comprises the authority to ratify or confirm on my (our) behalf any action, as well as the faculty of receiving, drafting, transacting, compromising, substituting and revoking substitutions taking notifications and appointing judicial or extra-judicial attorneys

Signed in on this 1st day of March of 2002

Est. M. K. H. N. T.



POSSIBLE
ASS. SECRETARY

Yo (nosotros)

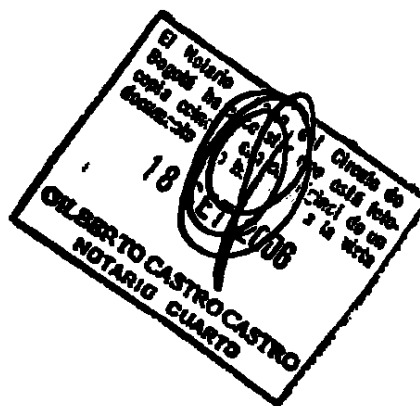
obrando en nombre propio y representación de AVENTIS PHARMACEUTICALS INC, con domicilio en 300 Somerset Corporate Boulevard, Bridgewater New Jersey Estados Unidos de América, nombro(amos) a GUSTAVO HOLLMANN RESTREPO y/o LUIS PATIÑO LEYVA, con domicilio en Bogotá D.C. República de Colombia Ora 11ª No 94 76 Oficina 308 apoderado verdadero y legal, con poder especial, amplio y suficiente

1) Para recibir de las oficinas y autoridades colombianas administrativas judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención modelos de utilidad dibujos y modelos industriales registro de marcas registro de lemas comerciales depósito de nombres y enseñanzas comerciales registros sanitarios derechos de autor y nombres de dominio así como sus traspaños prórrogas renovaciones y cambios de nombre 2) Elaborar tramitar solicitar, obtener realizar ejecutar y registrar contratos licencias autorizaciones y registros de cualesquiera clases 3) Intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales administrativas y de policía tales como acciones derivadas de nombre o enseña comerciales acciones reivindicatorias acciones derivadas de la obtención o explotación de licencias acciones de competencia desleal, demandas penales y civiles acciones de indemnización de perjuicios reclamos u observaciones a cualquier asunto sobre propiedad intelectual, al ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad intelectual

A este efecto, lo facultamos para elevar solicitudes formular descripciones enmiendas protestas declaraciones oposiciones cancelaciones apelaciones y reclamos pagar impuestos cuotas y gravámenes prescintos por la Ley renunciar o desistir a derechos concedidos o en curso de concesión, recibir toda clase de documentos y valores dando al descargo respectivo, y en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses con todas las facultades necesarias y por este documento desde ahora declaro(amos) válido y bueno todo cuanto los apoderados hicieren en mi (nuestro) beneficio

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado, así como la facultad de recibir desistir transigir comprometer sustituir y revocar sustituciones recibir notificaciones y nombrar apoderados judiciales o extrajudiciales

Firmado en el de de



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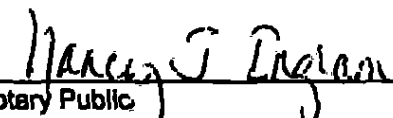
NOTARIAL CERTIFICATE (Corporation)

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss
COUNTY OF SOMERSET)

On this 1st day of March 2002 personally appeared before me Ross J Oehler Assistant Secretary known or identified to me to be the individual described in and who executed the foregoing document Power of Attorney, and acknowledged the same as a free act and deed for uses and purposes therein expressed by authority of the said Corporation incorporated under the laws of the State of Delaware United States of America

I further certify that said authority dated November 29 2000 is based on a Resolution of the Board of Directors of said Corporation which I have seen appointing the said individual Attorney in fact with full power to sign the foregoing document on behalf of the said Corporation and that the purposes for which said document is granted are within the scope of the objects or activities of said Corporation

SEAL

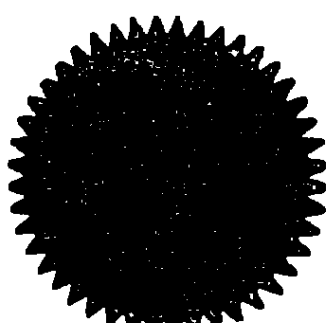


Notary Public
Nancy J. Ingram
Notary Public, State of New Jersey
My Commission Expires August 2 2004

Notary Signature
Print or Type Name
of Notary Public

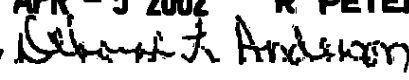
STATE OF NEW JERSEY }
COUNTY OF SOMERSET } ss.

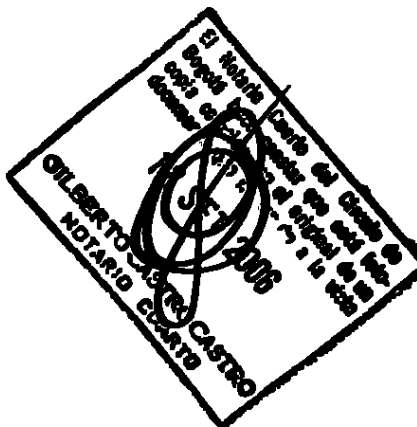
I PETER R. WIDIN Clerk of the County of Somerset and also Deputy Clerk of the Superior Court in and for said County the same being a Court of Record Do Hereby Certify that


Nancy J. Ingram
whose name is subscribed to the certificate of acknowledgement proof or affidavit of the annexed instrument was at the time of taking such acknowledgement proof or affidavit a NOTARY PUBLIC OF NEW JERSEY

in and for said State duly appointed qualified commissioned and sworn and authorized by law to take affidavits acknowledgements or proofs of deeds or conveyances for lands tenements or hereditaments and other instruments in writing in said State of New Jersey And I further Certify that I am well acquainted with the handwriting of said official and verily believe the signature to the said certificate of acknowledgement proof or affidavit is genuine

In Testimony Whereof I have hereunto set my hand and affixed the seal of said County on

APR - 5 2002 R. PETER WIDIN Clerk
by  Special Deputy Clerk



7
8

TRADUCCION OFICIAL DEL INGLES de las certificaciones y la
Apostilla adjuntas al poder que la compañía AVENTIS PHARMACEU-
TICALS INC domiciliada en Bridgewater, New Jersey, E U A ,
otorga a Gustavo Hollmann Restrepo y/o Luis Patiño Leyva

CERTIFICADO NOTARIAL (Sociedad)

ESTADOS UNIDOS DE AMERICA

ESTADO DE NEW JERSEY

CONDADO DE SOMERSET

El día 1° de Marzo del año 2002 ante la suscrita Notaria com-
pareció personalmente Ross J Oehler, Secretario Suplente,
quien yo sé o quien comprobó ante mí que es la persona mencio-
nada en el adjunto poder y quien lo ejecutó, y él reconoció
haber ejecutado dicho instrumento como un acto libre y volun-
tario destinado para los usos y propósitos allí expresados en
virtud a la autoridad que le concede la mencionada sociedad,
la cual está incorporada de conformidad con las leyes del Es-
tado de Delaware, Estados Unidos de América

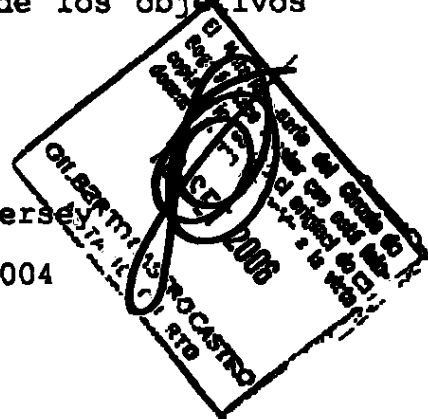
Certifico además que dicha autoridad, fechada el 29 de Noviem-
bre del 2000, se basa en una resolución de la Junta de Direc-
tores de la mencionada sociedad, documento que yo he tenido a
la vista, nombrando a la mencionada persona apoderado con todo
poder para firmar el instrumento adjunto en nombre de dicha
sociedad, y que los propósitos para los cuales se otorga dicho
instrumento se encuentran dentro del alcance de los objetivos
o actividades de la mencionada corporación

Nancy J Ingram

Notaria Pública del Estado de New Jersey

Mi comisión expira Agosto 2 del 2004

(Firma y Sello Oficial)



ESTADO DE NEW JERSEY, CONDADO DE SOMERSET

Yo, Peter S Widin, Secretario del Condado de Somerset y Secretario Suplente de la Corte Superior de dicho Condado, la cual es una Corte de Registro, certifico que Nancy J Ingram, cuyo nombre aparece suscrito al certificado de reconocimiento, prueba o declaración del instrumento adjunto, era en el momento de tomar tal reconocimiento, prueba o declaración Notaria Pública en y para el Estado de New Jersey, debidamente nombrada, calificada, comisionada y juramentada y autorizada por la ley para tomar declaraciones, reconocimientos o pruebas de escrituras o traspasos de tierras, tenencias o herencias y otros instrumentos escritos en el mencionado Estado. Y certifico además que conozco bien la firma de dicha funcionaria y estoy convencido de que la firma que aparece en el mencionado certificado de reconocimiento, prueba o declaración es genuina.

En testimonio de lo cual coloco mi firma y el sello del Condado el día de hoy 5 de Abril del 2002

R Peter Widin, Secretario

Deborah L Anderson, Secretaria Especial Suplente

(Firma y Sello Oficial)

APOSTILLA

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

- 1 País Estados Unidos de América
- Este documento público
- 2 Ha sido firmado por R Peter Widin
- 3 En su calidad de Secretario del Condado
- 4 Y lleva el sello del Condado de Somerset

Confirmado

- 5 En Trenton, New Jersey
- 6 El día Abril 9/2002
- 7 Por John E McCormac, CPA, Tesorero de New Jersey
- 8 Bajo el No A149012
- 9 Sello Secretaría de Estado de New Jersey
- 10 Firma (ilegible)



M Méndez S

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

(19) World Intellectual Property
Organization
International Bureau



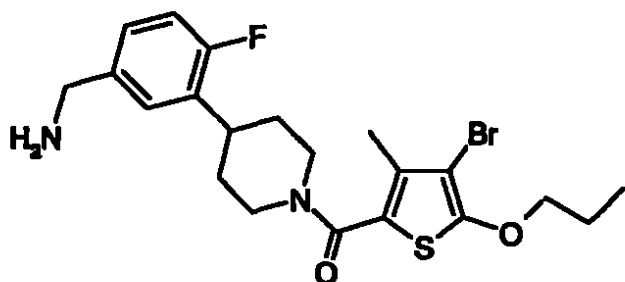
(43) International Publication Date
20 October 2005 (20.10.2005)

PCT

(10) International Publication Number
WO 2005/097780 A1

- (51) International Patent Classification⁷ C07D 409/06, A61K 31/4535 A61P 11/06 (74) Agents: KNICHT Julie, Anne et al. Aventis Pharmaceuticals Inc. Route 202 2061P O Box 6800 Bridgewater NJ 08807-0800 (US)
- (21) International Application Number⁷ PCT/US2005/009899 (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
- (22) International Filing Date 24 March 2005 (24.03.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/556,927 26 March 2004 (26.03.2004) US (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW); Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM); European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR); OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- (71) Applicant (for all designated States except US): AVENTIS PHARMACEUTICALS INC. [US/US] 300 Somerset Corporate Boulevard Bridgewater NJ 08807 2854 (US).
- (72) Inventors and (75) Inventors/Applicants (for US only): GAO, Zhongli [US/US] 26 Running Brook Circle, Flemington NJ 08822 (US); DAVIS, Larry [US/US] 7 Bird Lane, Sergeantville, NJ 08557 (US); LEVELL, Julian [GB/US] 8 Woodland Road, Bernardsville NJ 07924 (US); CZEKAJ, Mark [US/US] 3897 Charter Club Drive, Doylestown, PA 18901 (US); SLEDZSKI, Adam, W [PL/US] 24 Fisher Farm Road, Belk Mead NJ 08502 (US); HADDAD, El-Badoui [FR/US] 49 Battalion Drive, Basking Ridge, NJ 07920 (US).
- Declarations under Rule 4.17
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations of inventorship (Rule 4.17(iv)) for US only
- Published
— with international search report
- 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: [4-(5-AMINOMETHYL-2-FLUORO-PHENYL)-PIPERIDIN-1-YL]-[4-BROMO-3-METHYL-5-PROPOXY THIO-PHEN-2-YL]-METHANONE HYDROCHLORIDE AS AN INHIBITOR OF MAST CELL TRYPTASE



(I)

(57) Abstract. The present invention extends to the compound of formula I or a prodrug, pharmaceutically acceptable salt, or solvate of said compound. Furthermore, the present invention is directed to a pharmaceutical composition comprising a pharmaceutically effective amount of the compound of formula I and a pharmaceutically acceptable carrier. Furthermore, the present invention is directed to the use of a compound of

formula I as an inhibitor of tryptase, comprising introducing the compound into a composition comprising tryptase. In addition, the present invention is directed to the use of a compound of formula I for treating a patient suffering from, or subject to, a physiological condition in need of amelioration of an inhibitor of tryptase comprising administering to the patient a therapeutically effective amount of the compound of Claim 1. The present invention is directed also to the preparation of a compound of formula I.

WO 2005/097780 A1

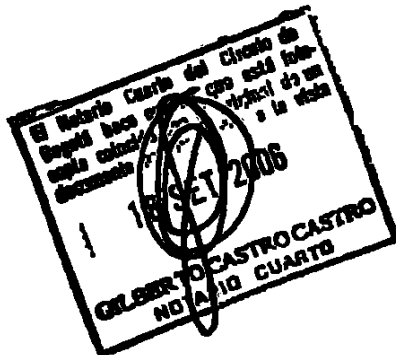
MINISTERIO DE RELACIONES
EXTERIORES

223893
JH Tiendes
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES

NO SE Asume
RESPONSABILIDAD DEL TEXTO

2002 APR 22 P 12 19

JEFE DE DELEGACIONES
SANTAFE DE BOGOTA D.C.



14-(5-AMINOMETHYL-2-FLUORO PHENYL)-PIPERIDIN
1-YL-1-(4-BROMO-3-METHYL-5-PROPOXY-THIOPHEN 2-YL)-METHANONE
HYDROCHLORIDE AS AN INHIBITOR OF MAST CELL TRYPTASE

FIELD OF THE INVENTION

This invention is directed to a substituted arylmethylamine compound, its preparation, a pharmaceutical composition comprising the compound, its use, and intermediates thereof

BACKGROUND OF THE INVENTION

Mast cell mediated inflammatory conditions, in particular asthma, are a growing public health concern. Asthma is frequently characterized by progressive development of hyper-responsiveness of the trachea and bronchi to both immunospecific allergens and generalized chemical or physical stimuli which lead to the onset of chronic inflammation. Leukocytes containing IgE receptors, notably mast cells and basophils, are present in the epithelium and underlying smooth muscle tissues of bronchi. These leukocytes initially become activated by the binding of specific inhaled antigens to the IgE receptors and then release a number of chemical mediators. For example, degranulation of mast cells leads to the release of proteoglycans, peroxidase, arylsulfatase B, chymase, and tryptase, which results in bronchiole constriction.

Tryptase is stored in the mast cell secretory granules and is the major secretory protease of human mast cells. Tryptase has been implicated in a variety of biological processes, including degradation of vasodilating and bronchorelaxing neuropeptides (Caughey et al. J Pharmacol Exp Ther 1988 244 pages 133-137; Franconi et al. J Pharmacol Exp Ther 1988 248 pages 947-951; and Tam, et al. Am. J Respir Cell Mol Biol 1990 3 pages 27-32) and modulation of bronchial responsiveness to histamine (Sekizawa, et al. J Clin Invest. 1989 83 pages 175-179).

As a result, tryptase inhibitors may be useful as anti-inflammatory agents (K Rice, P.A. Sprengler, Current Opinion in Drug Discovery and Development, 1999 2(5), pages 463-474) particularly in the treatment of chronic asthma (M.Q. Zhang, H. Timmerman, Mediators Inflamm. 1997 112, pages 311-317) and may also be useful in treating or preventing allergic rhinitis (S. J. Wilson et al, Clin Exp Allergy 1998 28 pages 220-227), inflammatory bowel disease (S.C. Bischoff)

et al, Histopathology 1996 28, pages 1-13) psoriasis (A. Naukkarinen et al Arch. Dermatol. Res 1993 285 pages 341-346) conjunctivitis (A.A. Iranzadeh et al J Allergy Clin. Immunol 1990 86, pages 34-40) atopic dermatitis (A. Jarvikallio et al, Br J Dermatol. 1997 136 pages 871-877) rheumatoid arthritis (L.C Tetlow et al Ann Rheum. Dis 1998 54, pages 549-555) osteoarthritis (M.G. Buckley et al, J Pathol 1998 186 pages 67-74) gouty arthritis, rheumatoid spondylitis and diseases of joint cartilage destruction

In addition, tryptase has been shown to be a potent mitogen for fibroblasts suggesting its involvement in the pulmonary fibrosis in asthma and interstitial lung diseases (Ruoss et al J Clin. Invest. 1991 88 pages 493-499)

Therefore, tryptase inhibitors may be useful in treating or preventing fibrotic conditions (J.A. Cairns and A.F. Walls J Clin. Invest 1997 99 pages 1313-1321) for example, fibrosis, scleroderma, pulmonary fibrosis, liver cirrhosis, myocardial fibrosis, neurofibromas and hypertrophic scars

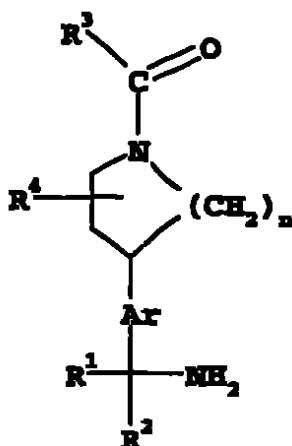
Additionally tryptase inhibitors may be useful in treating or preventing myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture (M. Jezionska et al, J Pathol 1997 182, pages 115-122)

Tryptase has also been discovered to activate prostromelysin that in turn activates collagenase, thereby initiating the destruction of cartilage and periodontal connective tissue, respectively

Therefore, tryptase inhibitors could be useful in the treatment or prevention of arthritis, periodontal disease, diabetic retinopathy and tumor growth (W.J. Beil et al, Exp. Hematol (1998) 26 pages 158-169) Also, tryptase inhibitors may be useful in the treatment of anaphylaxis (L.B. Schwarz et al, J Clin. Invest. 1995 96, pages 2702-2710) multiple sclerosis (M. Steinhoff et al Nat. Med. (N.Y.) 2000 6(2), pages 151-158), peptic ulcers and syncytial viral infections

Substituted arylmethanamines, represented as the compounds of formula (A), their preparation, pharmaceutical compositions containing these compounds, and their pharmaceutical use in the treatment of disease states capable of being modulated by the inhibition of tryptase are reported in pending US Application Serial No. 09/843 126. Encompassed within the generic disclosure of the compounds of formula (A) of US Application Serial No. 09/843 126 is the compound of the present invention, formula I. However, the compound of formula I is not specifically disclosed in US Application Serial No. 09/843 126.

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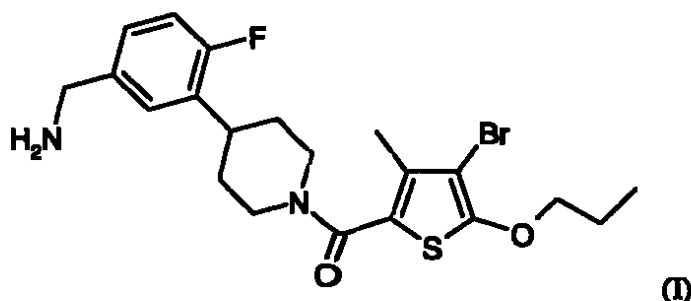


(A)

Accordingly what is needed is a novel and useful compound having particularly valuable pharmaceutical properties, in its ability to inhibit tryptase. Such a compound should readily have a utility in treating a patient suffering from conditions that can be ameliorated by the administration of an inhibitor of tryptase, e.g. mast cell mediated inflammatory conditions, inflammation and diseases or disorders related to the degradation of vasodilating and bronchorelaxing neuropeptides.

SUMMARY OF THE INVENTION

The present invention extends to the compound of formula I



(I)

or a prodrug, pharmaceutically acceptable salt, or solvate of said compound.

Furthermore, the present invention is directed to a pharmaceutical composition comprising a pharmaceutically effective amount of the compound of formula I and a pharmaceutically acceptable carrier.

Furthermore, the present invention is directed to the use of a compound of formula I as an inhibitor of tryptase comprising introducing the compound into a composition comprising tryptase. In addition, the present invention is directed to the use of a compound of formula I for treating a patient suffering from, or subject to, a physiological condition in need of amelioration of an inhibitor of tryptase comprising administering to the patient a therapeutically effective amount of the compound of

Claim 1

The present invention is directed also to the preparation of a compound of formula I.

Brief Description of the Drawings

Aspects, features and advantages of the present invention will be better understood from the following detailed descriptions taken in conjunction with the accompanying Figures, all of which are given by way of illustration only and are not limitative of the present invention, in which.

Figure I. Compound I levels in plasma, bronchoalveolar lavage (BAL) fluid and lung, measured 2 hour after dosing compound I at 1 mg/kg, p.o. Values are mean $\pm$ SE of 6-8 animals

Figure II. Plasma and lung compound I levels measured 24 hour post dosing. Values are mean $\pm$ SE of 3-4 animals.

DETAILED DESCRIPTION

Definitions

As used above, and throughout the instant specification and appending claims, the following terms, unless otherwise indicated, shall be understood to have the following meanings

As used herein, the term "compound of the present invention" and equivalent expressions are meant to embrace the compound of formula I, as hereinbefore described, which expression includes the prodrug, the pharmaceutically acceptable salt and the solvate, e.g. hydrate. Similarly reference to intermediates, whether or not they themselves are claimed, is meant to embrace the salts, and solvates where the context so permits. For the sake of clarity particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and they are not intended to exclude other instances when the context so permits

As used herein, the term "treatment" or "treating" includes prophylactic therapy as well as treatment of an established condition.

"Patient" means a human or other mammal

"Effective amount" is meant to describe an amount of a compound effective in producing the desired therapeutic effect.

"Prodrug" means a compound that is suitable for administration to a patient without undue toxicity irritation, allergic response, and the like, and is convertible in vivo by metabolic means (e.g. by hydrolysis) to the compound of the present invention. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series and in Edward B. Roche, ed. Bioresversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987 both of which are incorporated herein by reference.

Particular or Preferred Embodiments

In addition, the present invention is directed to the use of the compound of formula I for treating a patient suffering from a physiological condition that can be ameliorated by administering to the patient a therapeutically effective amount of the compound of formula I. Particular embodiments

12
13

of physiological conditions that can be treated with the compound of the present invention include, but certainly are not limited to inflammatory diseases, e.g. joint inflammation, arthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis, and other chronic inflammatory joint diseases. Other embodiments of physiological conditions that can be treated by the present invention include physiological conditions such as chronic obstructive pulmonary disease (COPD), COPD exacerbations, joint cartilage destruction, ocular conjunctivitis, vernal conjunctivitis, inflammatory bowel disease, asthma, allergic rhinitis, interstitial lung diseases, fibrosis, scleroderma, pulmonary fibrosis, liver cirrhosis, myocardial fibrosis, neurofibromas, hypertrophic scars, various dermatological conditions, for example atopic dermatitis and psoriasis, myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture, as well as periodontal disease, diabetic retinopathy, tumor growth, anaphylaxis, multiple sclerosis, peptic ulcers, and syncytial viral infections.

In a particular embodiment, the present invention is directed to the use of a compound of formula I for treating a patient suffering from asthma, comprising administering to the patient a physiologically effective amount of the compound.

In another particular embodiment, the present invention is directed to the use of a compound of formula I for treating a patient suffering from COPD, comprising administering to the patient a physiologically effective amount of the compound.

In another particular embodiment, the present invention is directed to the use of a compound of formula I for treating a patient suffering from COPD exacerbations, comprising administering to the patient a physiologically effective amount of the compound.

In another particular embodiment, the present invention is directed to the use of a compound of formula I for treating a patient suffering from allergic rhinitis, comprising administering to the patient a physiologically effective amount of the compound.

In another particular embodiment, the present invention is directed to the use of a compound of formula I for treating a patient suffering from joint inflammation, comprising administering to the patient a physiologically effective amount of the compound.

In another particular embodiment, the present invention is directed to the use of a compound of formula I for treating a patient suffering from inflammatory bowel disease, comprising administering to the patient a physiologically effective amount of the compound.

In addition, the present invention extends to a pharmaceutical composition comprising the compound of formula I, a second compound selected from the group consisting of a beta adrenergic agonist, an anticholinergic, an anti-inflammatory corticosteroid, and an anti-inflammatory agent, and a pharmaceutically acceptable carrier thereof. In such a composition the compound of formula I and the second compound are present in amounts such that provide a therapeutically efficacious activity, i.e.

additive or synergistic effect. Particular inflammatory diseases or disorders that can be treated with such a pharmaceutical composition include, but is not limited to, asthma.

Moreover the present invention is directed to a method for treating a patient suffering from an inflammatory disorder comprising administering to the patient the compound of formula I and a second compound selected from the group consisting of a beta andrenergic agonist, an anticholinergic, an anti-inflammatory corticosteroid and an anti-inflammatory agent. In such a method, the compound of formula I and the second compound are present in amounts such that provide a therapeutically efficacious activity i.e. additive or synergistic effect. In such a method of the present invention, the compound of the present invention can be administered to the patient before a second compound, a second compound can be administered to the patient before a compound of the present invention, or a compound of the present invention and a second compound can be administered concurrently. Particular examples of andrenergic agonists, anticholinergics anti inflammatory corticosteroids and anti-inflammatory agents having application according to the method are described *infra*.

Pharmaceutical Compositions

As explained above, the compound of the present invention exhibits useful pharmacological activity and accordingly may be incorporated into a pharmaceutical composition and used in the treatment of patients suffering from certain medical disorders. The present invention thus provides according to a further aspect, pharmaceutical compositions comprising the compound of the invention, and a pharmaceutically acceptable carrier thereof. As used herein, the term "pharmaceutically acceptable" preferably means approved by a regulatory agency of a government in particular the Federal government or a state government, or listed in the U.S. Pharmacopoeia or another generally recognized pharmacopoeia for use in animals, and more particularly in humans. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

Pharmaceutical compositions according to the present invention can be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, fillers, binders, disintegrants, glidants, lubricants, surfactants, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, capsules, pills, sustained release formulations, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings or stabilizers in order to obtain pharmaceutically acceptable preparations. The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the active compound, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, microcrystalline cellulose, pregelatinized starch, unmodified starch, silicified microcrystalline cellulose, mannitol, sorbitol, xylitol, dextrates, fructose, sodium citrate, calcium carbonate, dicalcium phosphate dihydrate

anhydrous dicalcium phosphate, calcium sulfate, along with binders such as polyvinylpyrrolidone, hydroxypropylmethyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methyl cellulose, sodium carboxymethyl cellulose, pregelatinized starch, starch, polyethylene glycols, polyethylene oxide, polycarbophils, gelatin and acacia and disintegrating agents such as sodium croscarmellose, sodium starch glycolate, crospovidone, starch, microcrystalline cellulose, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil, mineral oil, polyethylene glycols, glyceryl esters of fatty acids, sodium lauryl sulfate and glidants such as silicon dioxide, talc, starch, along with some suitable wetting agent such as sodium lauryl sulfate, sorbitan esters, polyoxyethylene fatty acid esters, poloxamer, polyoxyethylene ether, sodium docusate, polyethoxylated castor oil, and benzalkonium chloride may be used for preparing tablets. To prepare a capsule, it is advantageous to use fillers such as lactose, microcrystalline cellulose, pregelatinized starch, unmodified starch, silicified microcrystalline cellulose alone or a mixture of two or more fillers with and without binders as described above along with suitable wetting agent(s), disintegrants, glidants, lubricants, etc. as listed above. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used. Such pharmaceutically acceptable carriers can also be sterile water and oils including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include mannitol, human serum albumin (HSA), starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium carbonate, magnesium stearate, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol and the like. These compositions can take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained-release formulations and the like.

Naturally, a pharmaceutical composition of the present invention will contain a therapeutically effective amount of the active compound together with a suitable amount of carrier so as to provide the form for proper administration to the patient. While intravenous injection is a very effective form of administration, other modes can be employed, such as by injection or by oral, nasal or parenteral administration, which are discussed *infra*.

Methods of Treatment

The compound of formula I possesses tryptase inhibition activity according to tests described in the literature and described hereinafter and which test results are believed to correlate to pharmacological activity in humans and other mammals. Thus, in a further embodiment, the present invention is directed to the use of formula I or a composition comprising it for treating a patient.

suffering from, or subject to, a condition that can be ameliorated by the administration of an inhibitor of tryptase. For example, the compound of formula I is useful for treating an inflammatory disease, for example, joint inflammation, including arthritis rheumatoid arthritis and other arthritic condition such as rheumatoid spondylitis, gouty arthritis traumatic arthritis, rubella arthritis psoriatic arthritis osteoarthritis or other chronic inflammatory joint disease, or diseases of joint cartilage destruction, Ocular conjunctivitis, vernal conjunctivitis inflammatory bowel disease, asthma, allergic rhinitis, interstitial lung diseases, fibrosis, scleroderma, pulmonary fibrosis, liver cirrhosis, myocardial fibrosis, neurofibromas hypertrophic scars, various dermatological conditions for example, atopic dermatitis and psoriasis myocardial infarction, stroke, angina or other consequences of atherosclerotic plaque rupture, as well as periodontal disease, diabetic retinopathy tumor growth, anaphylaxis multiple sclerosis, peptic ulcers or a syncytial viral infection

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of tryptase, for example conditions as heretofore described, which comprises the administration to the patient of an effective amount of compound of the invention or a composition containing a compound of the invention.

Combination Therapy

As explained above, other pharmaceutically active agents can be employed in combination with the compound of formula I depending upon the disease being treated. For example, in the treatment of asthma, beta-adrenergic agonists such as albuterol terbutaline, formoterol, fenoterol or prenaline can be included, as can anticholinergics such as ipratropium bromide, anti-inflammatory corticosteroids such as beclomethasone dipropionate, triamcinolone acetamide, flunisolide or dexamethasone, and anti-inflammatory agents such as sodium cromoglycate and nedocromil sodium. Thus, the present invention extends to a pharmaceutical composition comprising the compound of formula I and a second compound selected from the group consisting of a beta adrenergic agonist, an anticholinergic, an anti-inflammatory corticosteroid, and an anti-inflammatory agent; and a pharmaceutically acceptable carrier thereof. Particular pharmaceutical carriers having applications in this pharmaceutical composition are described herein.

Furthermore, the present invention extends to a method for treating a patient suffering from asthma, comprising administering the patient the compound of the present invention, and a second compound selected from the group consisting of a beta adrenergic agonist, an anticholinergic, an anti-inflammatory corticosteroid, and an anti-inflammatory agent. In such a combination method the compound of the present invention can be administered prior to the administration of the second compound, the compound of the present invention can be administered after administration of the second compound, or the compound of the present invention and the second compound can be administered concurrently.

Modes of Delivery

According to the invention, the compound of formula I, or a pharmaceutical composition comprising the compound, may be introduced parenterally transmucosally *e.g.* orally nasally pulmonarily or rectally or transdermally to a patient.

Oral Delivery

Contemplated for use herein are oral solid dosage forms which are described generally in Remington's Pharmaceutical Sciences, 18th Ed 1990 (Mack Publishing Co. Easton PA 18042) at Chapter 89 which is herein incorporated by reference. Solid dosage forms include tablets, capsules, pills, troches or lozenges, cachets or pellets. Also, liposomal or proteinoid encapsulation may be used to formulate the present compositions (as, for example, proteinoid microspheres reported in U.S. Patent No. 4,925,673). Liposomal encapsulation may be used and the liposomes may be derivatized with various polymers (*e.g.* U.S. Patent No. 5,013,556). A description of possible solid dosage forms for a therapeutic is given by Marshall, K. In *Modern Pharmaceutics* Edited by G.S. Banker and C.T. Rhodes Chapter 10, 1979 herein incorporated by reference. In general, the formulation will include a compound of the present invention and inert ingredients that allow for protection against the stomach environment, and release of the biologically active material, i.e. a compound of the present invention in the intestine.

Also specifically contemplated are oral dosage forms of the compound of the present invention. Such a compound may be chemically modified so that oral delivery is more efficacious. Generally the chemical modification contemplated is the attachment of at least one moiety to the component molecule itself where said moiety permits (a) inhibition of proteolysis and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the compound of the present invention, and increase in circulation time in the body. Examples of such moieties include: polyethylene glycol, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. Abuchowski and Davis, 1981 'Soluble Polymer-Enzyme Adducts' In: *Enzymes as Drugs* Hosenberg and Roberts, eds. Wiley Interscience, New York, NY pp 367-383. Newmark, et al. 1982 J Appl Biochem. 4:185-189. Other polymers that could be used are poly 1,3-dioxolane and poly-1,3,6-tioxocane. Preferred for pharmaceutical usage, as indicated above, are polyethylene glycol moieties.

For the compound of the present invention, the location of release may be the stomach, the small intestine (the duodenum, the jejunum, or the ileum) or the large intestine. One skilled in the art has available formulations that will not dissolve in the stomach, yet will release the material in the duodenum or elsewhere in the intestine. Preferably the release will avoid the deleterious effects of the stomach environment, either by protection of the compound of the present invention, or by release of the compound beyond the stomach environment, such as in the intestine.

To ensure full gastric resistance a coating impermeable to at least pH 5.0 is essential.

Examples of the more common inert ingredients that are used as enteric coatings are cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP) HPMCP 50, HPMCP 55 polyvinyl acetate phthalate (PVAP), Eudragit L30D Aquateric, cellulose acetate phthalate (CAP) Eudragit L, Eudragit S and shellac. These coatings may be used as mixed films.

A coating or mixture of coatings can also be used on tablets which are not intended for protection against the stomach. This can include sugar coatings, or coatings that make the tablet easier to swallow. Capsules may consist of a hard shell (such as gelatin) for delivery of dry therapeutic i.e. powder for liquid forms, a soft gelatin shell may be used. The shell material of cachets could be thick starch or other edible paper. For pills, lozenges, molded tablets or tablet triturates, moist massing techniques can be used.

The therapeutic can be included in the formulation as fine multi-particulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the compound of the present invention may be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the therapeutic with an inert material. These diluents could include carbohydrates especially mannitol, α lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may be also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrates include, but are not limited to starch, including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylcopectin, sodium alginate, gelatin, orange peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginate acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone

(PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic

An anti frictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE) liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the therapeutic into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or benzethonium chloride. The list of potential non-ionic detergents that could be included in the formulation as surfactants are laurmacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of a compound of the present invention either alone or as a mixture in different ratios.

Additives that potentially enhance uptake of the compound of the present invention are, for instance, the fatty acids oleic acid, linoleic acid and linolenic acid. Controlled release oral formulation may be desirable. The drug could be incorporated into an inert matrix that permits release by either diffusion or leaching mechanisms, e.g. gums. Slowly degrading matrices may also be incorporated into the formulation. Some enteric coatings also have a delayed release effect.

Another form of a controlled release of this therapeutic is by a method based on the Oros therapeutic system (Alza Corp.), i.e. the drug is enclosed in a semipermeable membrane which allows water to enter and push drug out through a single small opening due to osmotic effects.

Other coatings may be used for the formulation. These include a variety of sugars that could be applied in a coating pan. The therapeutic agent could also be given in a film-coated tablet and the materials used in this instance are divided into 2 groups. The first are the non-enteric materials and include methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methylhydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, providone and the polyethylene glycols. The second group consists of the enteric materials that are commonly esters of phthalic acid.

A mix of materials might be used to provide the optimum film coating. Film coating may be carried out in a pan-coater or in a fluidized bed or by compression coating.

Pulmonary Delivery

Also contemplated herein is pulmonary delivery of the compound of the present invention, either alone or in a pharmaceutical composition. The compound is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. Other reports of this include Adjei et al 1990 *Pharmaceutical Research*, 7 565-569 Adjei et al. 1990 *International Journal of Pharmaceutics* 63 135-144 (leuprolide acetate) Braquet et al. 1989 *Journal of Cardiovascular Pharmacology* 13(suppl. 5):143-146 (endothelin-1) Hubbard et al. 1989 *Annals of Internal Medicine*, Vol. III, pp 206-212 (a1- antitrypsin), Smith et al 1989 *J Clin. Invest.* 84:1145-1146 (a1-proteinase) Oswein et al 1990 "Aerosolization of Proteins" *Proceedings of Symposium on Respiratory Drug Delivery II*, Keystone, Colorado, March, (recombinant human growth hormone) Debs et al. 1988 *J Immunol* 140:3482-3488 (interferon- γ and tumor necrosis factor alpha) and Platz et al U.S. Patent No. 5,284,656 (granulocyte colony stimulating factor) A method and composition for pulmonary delivery of drugs for systemic effect is described in U.S. Patent No. 5,451,569 issued September 19 1995 to Wong et al

Contemplated for use in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers and powder inhalers all of which are familiar to those skilled in the art.

Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer manufactured by Mallinckrodt, Inc. St. Louis, Missouri the Acorn II nebulizer manufactured by Marquest Medical Products Englewood, Colorado; the Ventolin metered dose inhaler manufactured by Glaxo Inc. Research Triangle Park, North Carolina, and the Spinhaler powder inhaler manufactured by Fisons Corp., Bedford, Massachusetts, to name only a few. All such devices require the use of formulations suitable for the dispensing of the compound of the present invention. Typically each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, adjuvants and/or carriers useful in therapy. Also, the use of liposomes, microcapsules or microspheres inclusion complexes, or other types of carriers is contemplated. A chemically modified compound of the present invention may also be prepared in different formulations depending on the type of chemical modification or the type of device employed.

Formulations suitable for use with a nebulizer either jet or ultrasonic, will typically comprise the compound of the present invention dissolved in water at a concentration of about 0.1 to 25 mg of compound per mL of solution. The formulation may also include a buffer and a simple sugar (e.g. for stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a

surfactant, to reduce or prevent surface induced aggregation of the compound caused by atomization of the solution in forming the aerosol

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the compound of the invention suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, hydrochlorofluorocarbon, hydrofluorocarbon, or hydrocarbon including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing the compound of the invention, and may also include a bulking agent, such as lactose, sorbitol, sucrose, or mannitol in amounts which facilitate dispersal of the powder from the device, e.g. 50 to 90% by weight of the formulation. The compound of the present invention should most advantageously be prepared in particulate form with an average particle size of less than 10 mm (or microns) most preferably 0.5 to 5 mm, for most effective delivery to the distal lung.

Nasal Delivery

Nasal delivery of the compound of the present invention is also contemplated. Nasal delivery allows the passage of the compound to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran.

Transdermal Delivery

Various and numerous methods are known in the art for transdermal administration of a drug, e.g. via a transdermal patch have applications in the present invention. Transdermal patches are described in for example, U.S. Patent No. 5,407,713 issued April 18, 1995 to Rolando et al. U.S. Patent No. 5,352,456 issued October 4, 1994 to Fallon et al. U.S. Patent No. 5,332,213 issued August 9, 1994 to D'Angelo et al. U.S. Patent No. 5,336,168 issued August 9, 1994 to Sibalis. U.S. Patent No. 5,290,561 issued March 1, 1994 to Farhadieh et al. U.S. Patent No. 5,254,346, issued October 19, 1993 to Tucker et al. U.S. Patent No. 5,164,189 issued November 17, 1992 to Berger et al. U.S. Patent No. 5,163,899 issued November 17, 1992 to Sibalis. U.S. Patent Nos. 5,088,977 and 5,087,240 both issued February 18, 1992 to Sibalis. U.S. Patent No. 5,008,110, issued April 16, 1991 to Benecke et al. and U.S. Patent No. 4,921,475 issued May 1, 1990 to Sibalis; the disclosure of each of which is incorporated herein by reference in its entirety.

It can be readily appreciated that a transdermal route of administration may be enhanced by use of a dermal penetration enhancer e.g. such as enhancers described in U.S. Patent No. 5,164,189 (*supra*), U.S. Patent No. 5,008,110 (*supra*) and U.S. Patent No. 4,879,119 issued November 7, 1989 to Aruga et al. the disclosure of each of which is incorporated herein by reference in its entirety.

Topical Administration

For topical administration, gels (water or alcohol based), creams or ointments containing compounds of the invention may be used. Compounds of the invention may also be incorporated in a gel or matrix base for application in a patch, which would allow a controlled release of compound through the transdermal barrier

Rectal Administration

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing the compound of the invention.

Dosages

The percentage of active ingredient in the composition of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.001 to about 50, preferably about 0.001 to about 5 mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10 mg/kg body weight per day by oral administration, and from about 0.001 to about 10 preferably 0.01 to 1 mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

Furthermore, the compound according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day in accordance with the physiological requirements of each particular patient. Generally the active product may be administered orally 1 to 4 times per day. Of course, for some patients it will be necessary to prescribe not more than one or two doses per day.

Naturally a patient in whom administration of the compound of the present invention is an effective therapeutic regimen is preferably a human, but can be any animal. Thus, as can be readily appreciated by one of ordinary skill in the art, the methods and pharmaceutical compositions of the present invention are particularly suited to administration to any animal particularly a mammal, and including, but by no means limited to, domestic animals, such as feline or canine subjects, farm animals, such as but not limited to bovine, equine, caprine, ovine and porcine subjects, wild animals (whether in the wild or in a zoological garden), research animals, such as mice, rats, rabbits, goats,

sheep pigs dogs, cats etc avian species, such as chickens, turkeys songbirds, etc i.e. for veterinary medical use.

Preparatory Details

The compound of formula I may be prepared by the application or adaptation of known methods by which is meant methods used heretofore or described in the literature, for example those described by R.C.Larock in *Comprehensive Organic Transformations* VCH publishers, 1989 or as described herein.

In the reactions described hereinafter it may be necessary to protect reactive functional groups for example, amino groups to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T W Greene and P G.M Wuts in *Protective Groups in Organic Chemistry* John Wiley and Sons, 1991. In particular the compound of formula I may be prepared as shown through Schemes I-III.

For example, the compound of the present invention is an achiral compound whose preparation is comprised of a convergent synthesis. Scheme I below shows the procedures that culminate in the preparation of amine 10. Scheme II below shows the procedures that culminate in the preparation of acid 16. Scheme III below shows the procedures that culminate in the preparation of the compound of formula I, to yield the compound of formula I in a two-step sequence. The preparation of 10, 16 and the compound of formula I of the present invention are discussed in turn below.

Compound 2 is converted to compound 3 by protecting the amino group with an amino protecting agent, such as 1,2-bis(chlorodimethylsilyl)ethane, in the presence of a tertiary amine, such as triethylamine, in a suitable inert solvent, such as dichloromethane, to yield protected compound 3.

Compound 3 is converted to compound 5 by alkylating compound 4 using compound 3 under alkylating conditions comprising a strong base, such as n-butyllithium, in a suitable aprotic solvent, such as tetrahydrofuran to yield the hydroxyl derivative compound 5.

Compound 5 is converted to compound 6 by deprotecting the amino group thereof with a deprotecting agent, such as a strong inorganic acid, such as phosphoric acid, in the presence of an inert solvent, such as heptane, to yield deprotected compound 6.

Compound 6 is converted to compound 7 by dehydrating, using an strong inorganic acid, such as phosphoric acid, and subsequent neutralizing the product using a strong inorganic base, such as aqueous sodium hydroxide to yield the dehydrated compound 7.

Compound 7 is converted to compound 8 by protecting the amino group with an amino protecting agent, such as boc anhydride, in a mixed aqueous/organic solvent system, wherein the organic solvent is a polar organic solvent such as methanol using a strong inorganic base, such as aqueous sodium hydroxide to yield boc-protected compound 8.

Compound 8 is converted to compound 9 by hydrogenating using a reducing agent, such as palladium hydroxide on carbon (20%) in a mixed solvent system, such as methanolic acetic acid to yield the deprotected piperidine salt, compound 9

Compound 9 is converted to its free base form, compound 10 by neutralizing using a strong inorganic base, such as aqueous sodium hydroxide, to yield final compound 10

Carbon disulfide is converted to compound 11 by acylating using the acylating agent ~~propyl~~ chloroformate in the presence of a strong inorganic base, such as potassium hydroxide, in ~~n-propanol~~ to yield compound 11

Compound 11 is converted to compound 12 by alkylating acetone with compound 11 in the presence of a strong base such as sodium hydride to yield alkylated compound 12.

Compound 12 is converted to compound 13 by alkylating compound 12 with α -bromo methyl acetate in the presence of a tertiary amine such as triethylamine to yield the alkylated compound 13

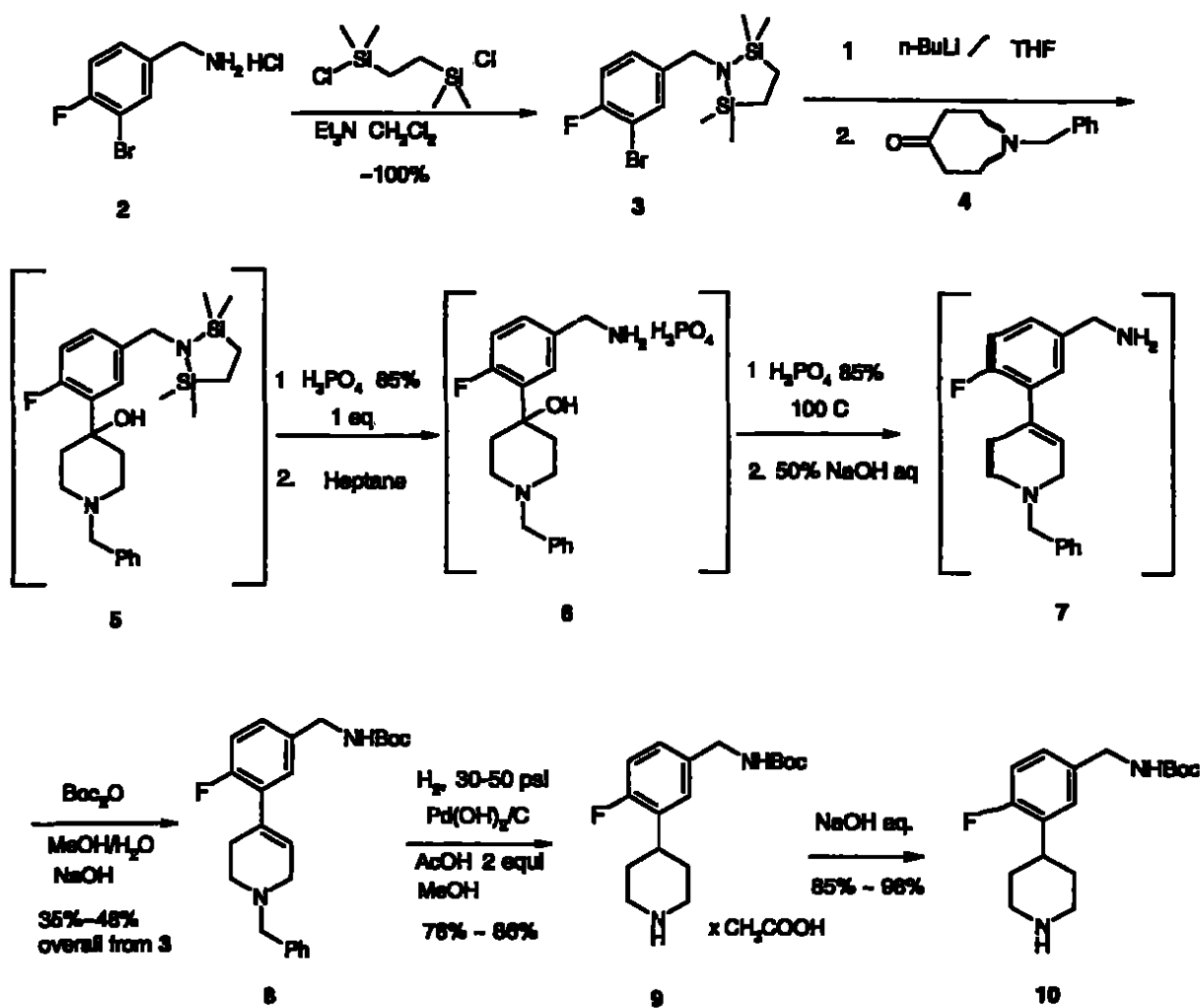
Compound 13 is converted to compound 14 by cyclizing under strong base conditions, such as sodium methoxide, in the presence of a protic organic solvent such as methanol to yield the cyclized compound 14.

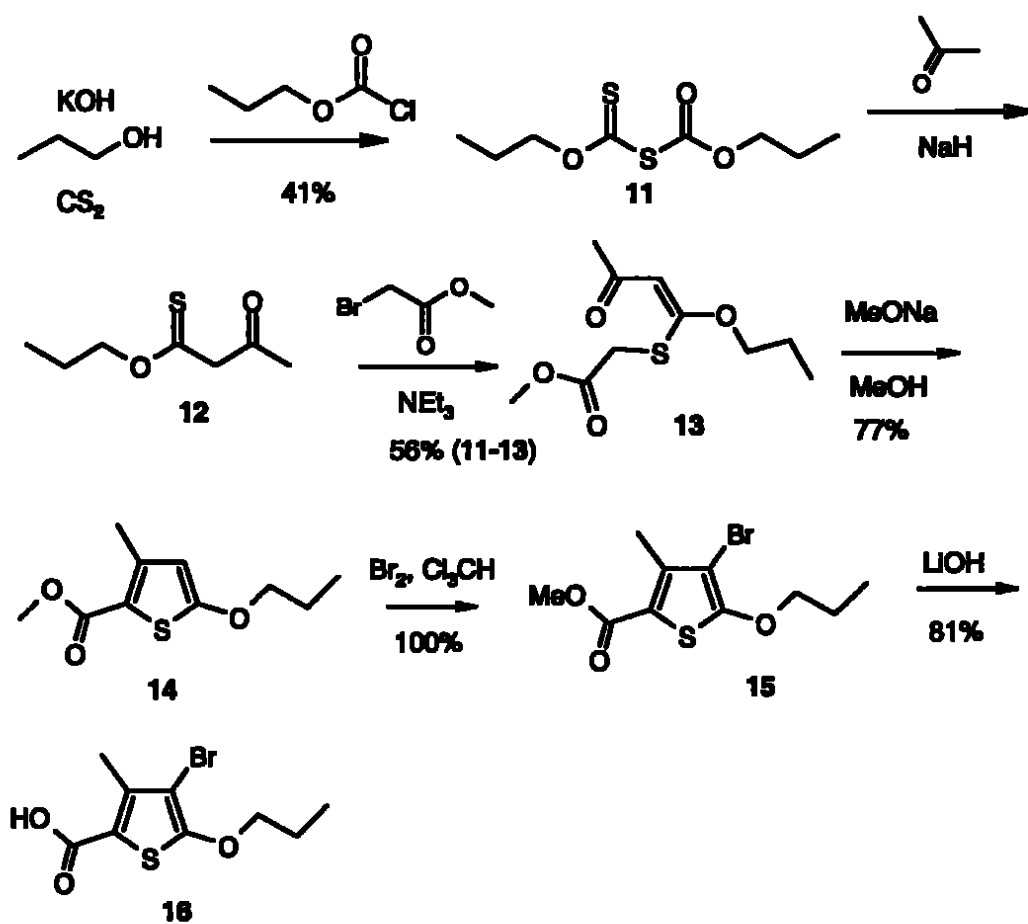
Compound 14 is converted to compound 15 by brominating in an inert organic solvent, such as trichloromethane or a TBME/heptane mixture, to yield the brominated compound 15

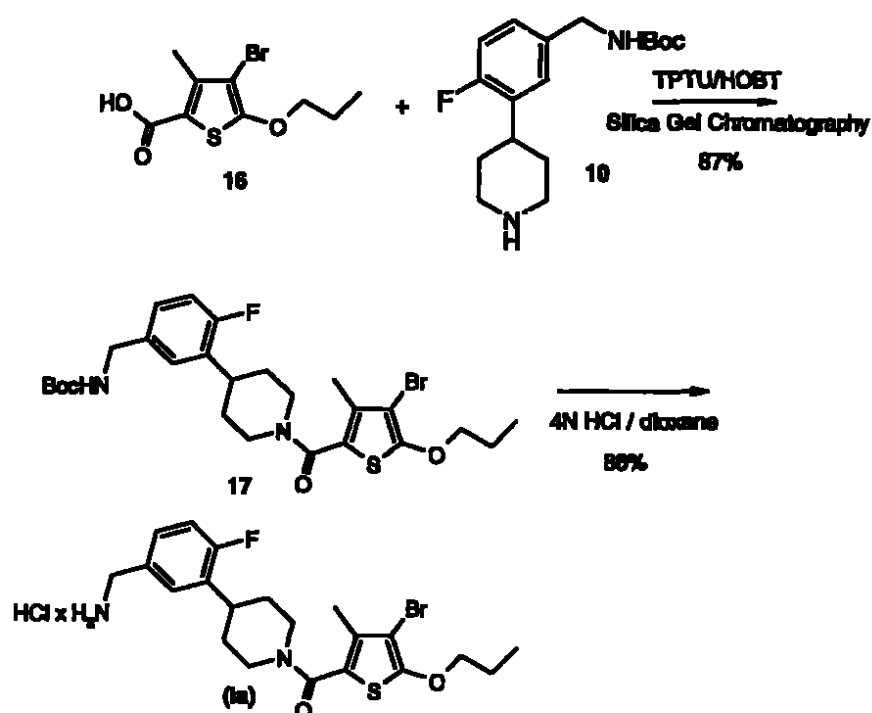
Compound 15 is converted to compound 16 by hydrolyzing using a strong inorganic base such as lithium hydroxide.

Compound 16 is converted to compound 17 by coupling with compound 10 using a coupling agent, such as TPTU/HOBT or EDC, in the presence of an inert solvent, such as dichloromethane and a tertiary amine such as diisopropyl ethylamine under anhydrous conditions to yield the coupled compound 17

Compound 17 is converted to compound I by deprotecting under strong acid conditions such as hydrochloric acid in the presence of a polar organic solvent, such as dioxane, to yield the deprotected compound I.

Scheme I

Scheme 2

Scheme 3

The compound of the present invention is basic and such compound is useful in the form of the free base or in the form of a pharmaceutically acceptable acid addition salt thereof.

Acid addition salts may be a more convenient form for use and in practice use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is salts whose anions are non toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compound is preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as for example, when the salt is formed only for purposes of purification and identification or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention include those derived from mineral acids and organic acids and include hydrohalides e.g. hydrochloride and hydrobromide, sulfates, phosphates, nitrates, sulfamates, acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b- hydroxynaphthoates, benzoates, tosylates, gentisates, isethionates, di-p-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates and quinate. A more particular salt is salt of the compound of formula I is the hydrochloride salt.

As well as being useful in itself as an active compound, salts of the compound of the invention are useful for the purposes of purification of the compound for example by exploitation of the

solubility differences between the salts and the parent compound, side products and/or starting materials by techniques well known to those skilled in the art.

According to a further feature of the invention, the acid addition salt of the compound of this invention may be prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compound of this invention may be prepared either by dissolving the free base in water or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compound of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, the parent compound of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

The starting materials and intermediates may be prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

The present invention is also directed to some intermediates in the above schemes and, as such, the processes described herein for their preparation constitute further features of the present invention.

Examples

The present invention may be better understood by reference to the following non-limiting Examples, which are provided as exemplary of the invention. The following examples are presented in order to more fully illustrate particular embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

In the nuclear magnetic resonance spectra (NMR) reported *infra*, the chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significances: br = broad, dd = double doublet, s = singlet, m = multiplet.

EXAMPLE 1

Step 1 Preparation of 1-(3-Bromo-4-fluoro-benzyl)-2,2,5,5-tetramethyl-[1,2,5] azadisilolidine (Compound 3)

110 g (0.46 mol) of 3-bromo-4-fluoro-benzylamine hydrochloride (2) is suspended in 900 mL of methylene chloride in a 2-L, three-neck, round-bottom flask equipped with N₂ blanket, Teflon-coated thermocouple temperature sensor and mechanical stirring and cooled to -5°C in an ice bath. A total of 144 g (1.42 mol, 3.1 equiv d=0.7) is added resulting in a thick suspension. A solution of 1,2-bis (chlorodimethylsilyl) ethane (100 g, 0.46 mol) in 250 mL of methylene chloride is then added

drop-wise over 1.5 hours while maintaining the temperature of the reaction mixture between 5 and 8°C. The mixture is stirred for 30 min and then warmed up to room temperature. The triethylamine hydrochloride suspension is filtered off. The filtrate is concentrated in vacuo (40°C, <50 mbar). 1 L of pentane is added and additional Et₃N x HCl precipitate that formed is filtered off. The procedure is repeated with another 1 L of pentane. The filtrate is concentrated in vacuo (40°C, <5 mbar) to a colorless liquid that solidifies upon cooling to give 159 g (~100%) of compound 3 as a white crystalline solid.

Completion of the reaction should be monitored using ¹H NMR to insure that any remaining starting material 2 and triethylamine hydrochloride is essentially absent as they consume n butyl lithium in the subsequent step thereby resulting in a lower reaction yield.

Step 2. Preparation of 1-Benzyl-4-[2-fluoro-5-(2,2,5,5 tetramethyl [1,2,5]-azadisilolidin-1 ylmethyl) phenyl] piperidin-4-ol (Compound 5)

A solution of compound 3 (159 g, 0.4574 mol) in 1.5 L of anhydrous THF is placed in a 5 L, three-neck, round-bottom flask equipped with N₂ blanket, Teflon-coated thermocouple temperature sensor and mechanical stirring and is cooled to -75°C. To this stirred solution is added drop-wise a 2.5 M solution of n butyl lithium (192 ml, 0.48 mol, 1.05 equiv) over about 1 hour while maintaining the reaction mixture temperature between -72°C to -75°C. After 30 min, a solution of 1-benzyl-4-piperidone (Compound 4, 88.2 g, 0.47 mol, 1.02 equiv) in anhydrous THF (350 mL + 50 mL rinse) is added drop-wise over 1 h while maintaining the reaction temperature below -70°C. After stirring for 20 min at -70°C to -75°C, 200 mL of methanol is added to the reaction mixture (color changes from orange to yellow) then the mixture is allowed to warm to room temperature. The reaction solution is concentrated in vacuo (50°C) to give 295 g of brown oil, compound 5.

Step 3. Preparation of 4-(5-Aminomethyl-2-fluorophenyl) 1-benzylpiperidin-4-ol (phosphate salt) (Compound 6)

The crude compound 5 (~295 g) is diluted with 1 L of methylene chloride and transferred to a 3 L, three-neck, round-bottom flask equipped with Teflon-coated thermocouple temperature sensor and mechanical stirring. To this solution is slowly added 53 g of 85% H₃PO₄ (1 equiv) while stirring (exothermic) and the mixture is concentrated in vacuo (40°C). 1 L of methylene chloride is added and the mixture is concentrated in vacuo (40°C, 1 mbar) to yellow foam, which is then slurried in 1 L of heptane. The solid is formed and isolated by filtration. The tan solid is dried to give 190 g of the compound 6. MS m/z 315 (M+H) found.

Step 4. Preparation of 3-(1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-fluoro-benzylamine

(Compound 7)

A total of 190 g of the dried compound 6 is transferred to 2-L, three-neck, round-bottom flask equipped with Teflon-coated thermocouple temperature sensor and mechanical stirring. A total of 600 mL of 85% H_3PO_4 is added. The resulting suspension is gradually heated to 100°C while stirring. The reaction is monitored by HPLC for the reaction completion (typically 2 to 3 hours). Once the reaction completed, the reaction solution is cooled to room temperature, and diluted with 800 mL of water. The aqueous layer is washed with ether (2 x 200 mL). The aqueous layer is then neutralized with 50% aq. NaOH to pH > 9 while maintaining temperature below 30 °C. This aqueous solution is a very concentrated buffer system in which the pH remains unchanged at around 7-8 till the neutralization point is reached. Confirmation for complete neutralization is effected by adding a few drops of base to a small sample of the supernatant liquid to insure that no additional precipitation is observed. A large amount of salt precipitated out. The mixture is filtered and the solid is rinsed with DCM (methylene dichloride) (approximate 3 L) and 2 L of water. The organic layer (bottom) is separated and washed with water (2 x 1 L). The organic solution is concentrated in vacuo (40°C) to give 107 g of brown oil, compound 7. MS m/z 297 (M+H) found.

Step 5 Preparation of [3-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)-4-fluoro-benzyl] carbamic acid tert-butyl ester (Compound 8)

To a 2-L, three-neck, round bottom flask equipped with Teflon-coated thermocouple temperature sensor and mechanical stirring is added 50 g of compound 7 and a solution of methanol (800 mL) and water (400 mL). 36.8 g of BOC anhydride and 2 mL of 50% NaOH are added and the mixture is stirred at room temperature. The product is precipitated out of the solution after 2 hours stirring. If the Boc product doesn't precipitate, decant the top aqueous layer and add n-heptane to the oil to solidify the product. The mixture is stirred overnight at room temperature. The solid is isolated by filtration and slurried in 1.05 L of MeOH/water (2:1 by volume) for 4 hours, then isolated by filtration and dried for 4 days to give 40 g (overall yield is about 35% to 48% from compound 3) of compound 8 as a light yellow solid. Purity 96.3% by HPLC. MS m/z 397 (M+H), 398 (M+2H).

Step 6: Preparation of 6-(4-Fluoro-3-piperidin-4-yl-benzyl) carbamic acid tert-butyl ester acetate salt (Compound 9)

64 g (0.16 mol) of compound 8, 6.4 g of palladium hydroxide/C 20%, 19.5 g (2 equiv.) of glacial acetic acid and 250 mL of methanol are charged to a 1-L hydrogenation vessel. The reaction mixture vessel is purged (N_2 /vacuum, 3 times), then filled H_2 to 40 psi and shook overnight at room temperature. The catalyst is filtered off and the filtrate is concentrated in vacuo (40°C) to yield an oil. 200 mL of isopropyl ether is added and stirred overnight. A white solid, which precipitates out, is filtered, rinsed with isopropyl ether and dried to give 53.5 g of white solid with 95.4 % purity by

HPLC. The solid is slurried in 500 mL of MTBE for 5 hours, then isolated by filtration, and slurried again in 500 mL of MTBE overnight. The solid is isolated by filtration and dried to afford 51.3 g (86.3%) white solid of the acetate salt of compound 9. Elemental analysis. Calculated for $C_{17}H_{25}FN_2O_2$: C, 61.94; H, 7.93; N, 7.6. Found: C, 62.0; H, 8.17; N, 7.49. KF 0.34% water. HPLC: R_t 9.14 min, purity 97% by AUC. MS: m/z 309 (M+H), 310 (M+2H).

Step 7 Preparation of (4-Fluoro-3-piperidin-4-yl-benzyl) carbamic acid tert-butyl ester (Compound 10)

The acetate salt of compound 9 (51 g) is dissolved in 400 mL of water and the pH is adjusted to 5 with 2N HCl. The aqueous solution is washed with ether (2 x 200 mL). The aqueous layer is neutralized to pH > 12 with 50% aq. NaOH and extracted with ether (2 x 300 mL). The organic layer is washed with water and dried over Na_2SO_4 and then concentrated to oil. To the oil is added 200 mL of n-pentane and stirred for 3 hours. The product solid is isolated by filtration, washed with n-pentane, and dried at room temperature under house vacuum for 24 h to afford 42 g of compound 10 (98%) as a white solid. MS (ESI) m/z 309 (M + H). Elemental analysis. Calculated for $C_{17}H_{25}FN_2O_2$: C, 66.21; H, 8.17; N, 9.08. Found without correction for water: C, 64.30; H, 8.64; N, 8.77. KF 2.57% water. HPLC: R_t 9.16 min, purity 98.1% by AUC.

Note If the purity of the acetate salt compound 9 is less than 95% by HPLC, a solution of n-pentane and ether (up to 1:1 by volume) can be used to solidify the product (free base) from oil instead of only n-pentane. The product is very soluble in ether so if more ether is used, then more product will be lost, thereby resulting in a lower yield.

EXAMPLE 2

Step 1 Preparation of bis(propoxythiocarbonyl) sulfide (compound 11)

84.2 g power potassium hydroxide (1.27 mol) is added to 530 mL n-propanol placed in a three-necked round bottom flask equipped with a mechanical stirrer and a cooling bath at room temperature. 80 mL carbon disulfide (1.33 mol) is then added to the solution via a pressure-equalized additional funnel dropwise over 1 hour. The stirring is continued for 3 hours. 200 mL water is added. 73.5 g (0.6 mol) of propyl chloroformate is added in neat form dropwise via a pressure-equalized additional funnel. The mixture is stirred at room temperature overnight. The mixture is then diluted with 400 mL heptane. The aqueous layer is extracted with 100 mL heptane twice. The combined organic layer is washed with 100 mL water, 100 mL brine, then dried over potassium carbonate and evaporated. The residual propanol is further removed by high vacuum distillation to obtain a clear yellow liquid. 10 g of the clear yellow liquid is dissolved in 10 g of heptane and purified by silica gel chromatography eluting with heptane to obtain 8.35 g of compound 11 (41% yield).

Step 2. Preparation of 3-oxo-thiobutyric acid O-propyl ester (Compound 12)

1.82 g (45 mmol) sodium hydride is suspended in 40 mL toluene. To this suspension is added a solution of 1.74 g (30 mmol) acetone and 4.76 g (20 mmol) compound 11 in 10 mL toluene at 40°C with stirring. The reaction is initiated by introducing small amount of potassium hydride. When doing so, bubbles evolve and the color of the reaction mixture changes from yellow to orange. The reaction mixture is stirred at 40°C for one hour and then cooled to 0°C in an ice-water bath. The reaction mixture is then poured into a beaker containing 11 mL 4N HCl, ice and 150 mL ether. The organic layer is separated and concentrated. The crude product is purified by silica gel chromatography eluting with 5% ethyl acetate in heptane to obtain 3-oxo-thiobutyric acid O-propyl ester (compound 12).

Step 3. Preparation of (3-oxo-1-propoxy-but-1-enylsulfanyl)-acetic acid methyl ester (Compound 13)

Compound 12 is then dissolved in 40 mL DMF and cooled to 0°C. To this solution is added 4.6 g α -bromo methyl acetate in 5 mL DMF and 5.2 mL of triethylamine. A white precipitate is formed instantly. This suspension is stirred at 0°C for 2 hours and then is poured into ether/ice-water. The organic layer is separated and concentrated. The crude product is purified by silica gel chromatography and then is eluted with 3 % methanol in DCM to obtain 2.61 g of compound 13 (56% yield for two steps).

Step 4. Preparation of 3-methyl 5 propoxy-thiophene-2-carboxylic acid methyl ester (compound 14)

A mixture of 2.61 g (11.24) compound 13 and 2 mL 0.5M sodium methoxide/methanol in 40 mL methanol is heated at 70-73°C for 40 min. The mixture is then poured into ether/ice-water. The organic layer is separated and concentrated. The crude product is purified by silica gel chromatography eluting with DCM to obtain 1.85 g (76.8 yield) of compound 14.

Step 5. Preparation of 4-bromo-3-methyl-5 propoxy-thiophene-2-carboxylic acid methyl ester (compound 15)

To a solution of 1.22 g (5.7 mmol) compound 14 in 20 mL trichloromethane is added 11 mL 0.55M bromine/trichloromethane at 0°C and stirred for 10 min. The mixture is quenched with sodium sulfite aqueous solution, and extracted with DCM. The organic layer is separated and concentrated. The crude product is purified by potassium carbonate-silica gel pad and rinsed with DCM to obtain 1.67 g (100% yield) of compound 15.

Step 6: Preparation of 4-bromo-3-methyl-5-propoxy-thiophene-2-carboxylic acid (compound 16)

To a solution of 1.67 g of compound 15 (5.70 mmol) in 27 mL dioxane is added 10 mL of 2M LiOH/water and 9 mL water. The mixture is stirred at room temperature for 4 hours. The mixture is

then diluted with 10 mL water and extracted with 10 mL ether twice. The aqueous solution is cooled in an ice-water bath and acidified with 4M HCl. The white solid is collected by suction filtration to provide 1.28 g (80.5% yield) of compound 16.

EXAMPLE 3

Step 1. Preparation of {3-[1-(4-bromo-3-methyl-5-propoxy-thiophene-2-carbonyl)-piperidin-4-yl]-4-fluoro-benzyl}-carbamate tert-butyl ester (compound 17)

To a solution of 170 mg compound 16 (0.61 mmol) in 25 mL DCM under N₂ is added 170 mg TPTU (0.61 mmol) and 80 mg 1-hydroxy-1H-benzotriazole (HOBt) (0.61 mmol). The mixture is stirred for 3 minutes. To the mixture is then added a solution of 200 mg (0.65 mmol) of compound 10 in 5 mL DCM and 0.3 mL diisopropyl ethylamine (1.2 mmol). The mixture is stirred at room temperature for 24 hours. The mixture is then washed with 20 mL water, dried over anhydrous sodium sulfate and concentrated. The oil crude is purified by silica gel chromatography, eluting with 3% methanol in DCM to obtain 0.3 g (86.5% yield) of compound 17.

¹H NMR [CDCl₃] δ (TMS) 7.14-7.04 (m, 2H), 6.95 (dd, H), 4.82 (br s, H), 4.38 (br d, 2H), 4.23 (d, 2H), 4.05 (t, 2H), 3.17-2.95 (m, 3H), 2.21 (s, 3H), 1.92-1.59 (m, 6H), 1.44 (s, 9H), 1.05 (t, 3H).
MS(ESI+) 569 (M⁺+1)

Step 2. Preparation of [4-(5-aminomethyl-2-fluoro-phenyl) piperidin-1-yl]-(4-bromo-3-methyl-5-propoxy-thiophen-2-yl) methanone hydrochloride (compound I)

A solution of 0.25 g compound 17 (0.44 mmol) in 8 mL 4M HCl/dioxane under nitrogen is stirred at room temperature for 3 hours. The solution is diluted with 30 mL ether and stirred for 5 min. The liquid is decanted from the solid. The solid is washed with 30 mL ether and the liquid is decanted again. The solid is then dissolved in 3% methanol in DCM and purified by silica gel chromatography, eluting with 3% to 10% methanol in DCM. Compound I, 0.19 g (86.4% yield), is obtained as an amorphous solid by removing the solvent from combined pure fractions of the product by evaporation. The product is an amorphous glass.

¹H NMR [CDCl₃] δ (TMS) 8.62 (br s, 3H), 7.53-7.43 (m, H), 7.36-7.26 (m, H), 6.97 (dd, H), 4.22 (br d, 2H), 4.18-3.99 (m, 4H), 3.16-2.90 (m, 3H), 2.17 (s, 3H), 2.00-1.60 (m, 6H), 1.02 (t, 3H).
MS(ESI+) 469 (M⁺+1). 100% purity by LC/MS (UV 220 nm and total ion count).

BIOLOGICAL ACTIVITY

The properties of the compound of the present invention are demonstrated by 1) its β -Tryptase Inhibitory Potency (IC_{50} and K_i values), and 2) its activity as measured in the Guinea Pig Model of Airway Hyperreactivity (Oral ED_{50})

IN VITRO TEST PROCEDURE

As all the actions of tryptase, as described in the background section, are dependent on its catalytic activity then compounds that inhibit its catalytic activity will potentially inhibit the actions of tryptase. Inhibition of this catalytic activity may be measured by the in vitro enzyme assay and the cellular assay

Tryptase inhibition activity is confirmed using either isolated human lung tryptase or recombinant human β tryptase expressed in yeast cells. Essentially equivalent results are obtained using isolated native enzyme or the expressed enzyme. The assay procedure employs a 96 well microplate (Costar 3590) using L-pyroglutamyl-L-prolyl-L-arginine-*para*-nitroanilide (S2366 Quadrachem) as substrate (essentially as described by McEuen *et. al* Biochem Pharm, 1996, 52, pages 331-340). Assays are performed at room temperature using 0.5mM substrate ($2 \times K_m$) and the microplate is read on a microplate reader (Beckman Biomek Plate reader) at 405 nm wavelength.

Materials and Methods for Tryptase primary screen (Chromogenic assay)

Assay buffer

50 mM Tris (pH 8.2) 100 mM NaCl, 0.05% Tween 20, 50 μ g/mL heparin.

Substrate

S2366 (Stock solutions of 2.5 mM)

Enzyme

Purified recombinant beta Tryptase Stocks of 310 μ g/mL.

Protocol (Single point determination)

- Add 60 μ L of diluted substrate (final concentration of 500 μ M in assay buffer) to each well
- Add compound in duplicates final concentration of 20 μ M, volume 20 μ L
- Add enzyme at a final concentration of 50 ng/mL in a volume of 20 μ L
- Total volume for each well is 100 μ L
- Agitate briefly to mix and incubate at room temp in the dark for 30 minutes
- Read absorbencies at 405 nm

Each plate has the following controls

Totals 60 μ L of substrate, 20 μ L of buffer (with 0.2% final concentration of DMSO),
 20 μ L of enzyme

Non-specific 60 μ L of substrate, 40 μ L of buffer (with 0.2 DMSO)

Totals 60 μ L of substrate 20 μ L of buffer (No DMSO) 20 μ L of enzyme

Non-specific 60 μ L of substrate, 40 μ L of buffer (No DMSO)

Protocol (IC_{50} and K_i determination)

The protocol is essentially the same as above except that the compound is added in duplicates at the following final concentrations 0.01 0.03 0.1 0.3 1 3 10 μ M (All dilutions carried out manually) For every assay whether single point or IC_{50} determination, a standard compound is used to derive IC_{50} for comparison. From the IC_{50} value the K_i can be calculated using the following formula $K_i = IC_{50}/(1 + [Substrate]/K_m)$

The β -Tryptase inhibitory potency for the compound of formula I is IC_{50} and K_i values of 76 nM and 15 nM respectively

IN VIVO TEST PROCEDURE

Assay protocol

Sensitization and drug treatment. Male Hartley guinea pigs (225-250 g) are sensitized with ovalbumin (0.5 mL of 1% solution, i.p. and s.c.). On day 4, animals received a booster injection (i.p.) of 0.5 mL of 1% ovalbumin. On day 21, animals are orally dosed (2 mL/kg) with either vehicle (0.5% methylcellulose/0.2% Tween 80) or test compound 2 hours prior to antigen challenge. Thirty minutes before antigen challenge the animals are also injected with mepyramine (30 mg/kg i.p.) to prevent anaphylactic collapse. Animals are then exposed for 5 minutes to an aerosol of either saline (control animals) or 1% ovalbumin using a deVilbiss Ultraneb nebulizer.

AHR measurement. Eighteen to twenty-four hours after challenge, animals are anesthetized with a combination of ketamine (133 mg/kg) and xylazine (24 mg/kg) given intramuscularly. Surgically prepared and then mounted in a whole body plethysmograph for lung function measurement. Animals are connected to Ugo-Basile ventilators delivering a tidal volume of 1 mL/100g at a rate of 50 breaths/minute via a tracheal cannula. The jugular vein is also cannulated for histamine challenge. A water-filled esophageal cannula is placed such that transpulmonary pressure is recordable. Transpulmonary pressure is measured as the difference between the tracheal and esophageal cannulas using a differential pressure transducer. The volume, airflow, and transpulmonary pressure signals are monitored using a pulmonary analysis system (Buxco XA software) and used to calculate pulmonary resistance (cm H₂O/mL/s) and dynamic compliance (mL/cm H₂O). Airway resistance and dynamic compliance are computed on a breath-by-breath basis. Histamine is administered intravenously and reactivity to increasing concentrations (0.3-20 μ g/kg) assessed. ED_{50} s are estimated from the area under the curve (AUC) values derived from the individual histamine dose-response curves.

Plasma and lung drug levels

Plasma and lung compound levels are determined in satellite groups. Three to four guinea pigs from each of the experimental-drug treatment groups are used for the determination of drug levels. At

the indicated time point, (either 2-or 24 hours after dosing) animals are euthanized, and 1 mL blood samples are obtained by cardiac puncture and collected into heparin-coated syringes containing 20 μ L (per 1 mL of blood) of a 5 mM hydralazine solution. Plasma is separated from the cellular component of the blood by centrifugation, and stored at -20°C until assayed. Lung samples are dissected free of connective tissues, blotted dry weighed and stored in 20 mL vials containing 5 mL of a 5 mM hydralazine solution in saline. The frozen plasma samples are then transferred on dry ice to the Pilot PK group for compound levels determination.

Results.

Efficacy of compound I is profiled on Airway Hyperresponsiveness (AHR) to histamine in sensitized guinea pigs, via oral route. Compound I has no effect on basal airway resistance or basal dynamic lung compliance.

Sensitization and single challenge with ovalbumin results in an increase in bronchial reactivity to histamine as denoted by a leftward shift in the dose-response curve of the spasmogen and also by a significant increase in the area under the curve (AUC) for both airway resistance and lung compliance. Absolute values represent an increase in airway resistance and a decrease in lung compliance.

Upon oral dosing, 2 hours prior to ovalbumin challenge compound I significantly protects against antigen-stimulated AHR to histamine with an $\text{ED}_{50} = 0.1 \text{ mg/kg}$ as measured by airway resistance and dynamic lung compliance.

In separate animals, compound I levels are measured in bronchoalveolar lavage fluid (BAL), lung and plasma, 2 hours after compound dosing (1mg/kg, p.o.). There is an appreciable amount of compound I in target organs such lung and BAL (not taking into account dilution factor for BAL). Plasma compound levels are detected at a much lower level.

In satellite animals compound I levels in both lung and plasma, are also measured 24 hours after dosing. While no plasma could be detected, there is, however a dose-dependent appreciable amount of compound I detected in guinea pig lung 24 hours after dosing. Compound I is also shown to possess a long duration of action with an average ED_{50} of 0.4 mg/kg when dosed 24 hours prior to antigen challenge. This long duration of action is in agreement with its extended long exposure.

The oral data of the compound of the present invention in the guinea pig model of airway hyperresponsiveness clearly shows that the compound exhibits tryptase inhibition activity. Consequently the compound of the present invention readily has application as a pharmaceutical for treating a wide variety of tryptase related conditions, and naturally in methods for treating such conditions in a patient.

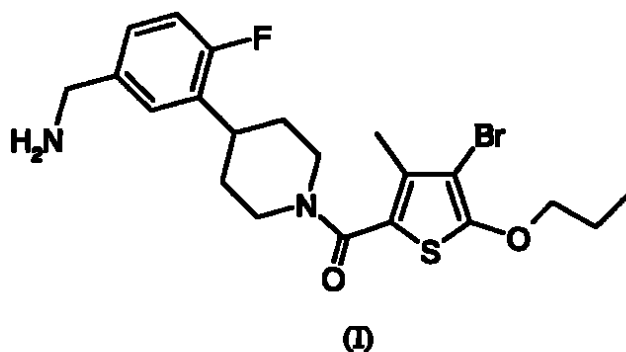
The present invention is not to be limited in scope by the specific embodiments describe herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

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Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

WHAT IS CLAIMED IS

- 1 A compound of formula I.



or a prodrug, pharmaceutically acceptable salt, or solvate thereof

- 2 The compound of Claim 1 as a pharmaceutically acceptable salt thereof
- 3 The compound of Claim 2 wherein the pharmaceutically acceptable salt is a hydrochloride.
- 4 A method for treating a patient suffering from, or subject to, a physiological condition in need of amelioration of an inhibitor of tryptase comprising administering to the patient a therapeutically effective amount of the compound of Claim 1
- 5 The method of Claim 4 wherein the physiological condition is selected from the group consisting of inflammatory disease, a disease of joint cartilage destruction, ocular conjunctivitis, vernal conjunctivitis, inflammatory bowel disease, asthma, allergic rhinitis, interstitial lung disease, fibrosis, scleroderma, pulmonary fibrosis, liver cirrhosis, myocardial fibrosis, neurofibroma, hypertrophic scar, dermatological condition, condition related to atherosclerotic plaque rupture, periodontal disease, diabetic retinopathy, tumor growth, anaphylaxis, multiple sclerosis, peptic ulcer, and syncytial viral infection.
- 6 The method of Claim 5 wherein the physiological condition is inflammatory disease.
- 7 The method of Claim 6 wherein the inflammatory disease is joint inflammation, arthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis, or osteoarthritis.
- 8 The method of Claim 5 wherein the physiological condition is COPD.
- 9 The method of Claim 5 wherein the physiological condition is COPD exacerbations.
- 10 The method of Claim 5 wherein the physiological condition is a dermatological condition.
- 11 The method of Claim 10 wherein the dermatological condition is atopic dermatitis or psoriasis.
- 12 The method of Claim 5 wherein the physiological condition is related to atherosclerotic plaque rupture.

- 13 The method of Claim 12, wherein the atherosclerotic plaque rupture is consequent to myocardial infarction, stroke, or angina.
- 14 A method for treating a patient suffering from asthma, comprising administering to the patient a combination of a therapeutically effective amount of a compound of Claim 1 and a second compound selected from the group consisting of a beta adrenergic agonist, anticholinergic anti-inflammatory corticosteroid, and anti-inflammatory agent.
- 15 The method of Claim 4 wherein the administering is such that the compound of Claim 1 is preferentially distributed to lung tissue versus plasma.
- 16 A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier thereof.
- 17 A pharmaceutical composition comprising a compound of Claim 1 and a therapeutically effective amount of a second compound selected from the group consisting of a beta adrenergic agonist, anticholinergic anti-inflammatory corticosteroid, and anti-inflammatory agent, and a pharmaceutically acceptable carrier.
- 18 The pharmaceutical composition of Claim 17 wherein the second compound is a beta adrenergic agonist.
- 19 The pharmaceutical composition of Claim 18, wherein the beta adrenergic agonist is selected from albuterol, terbutaline, formoterol, fenoterol, or prenaline.
- 20 The pharmaceutical composition of Claim 17 wherein the second compound is an anticholinergic.
- 21 The pharmaceutical composition of Claim 20 wherein the anticholinergic is ipratropium bromide.
- 22 The pharmaceutical composition of Claim 17 wherein the second compound is an anti-inflammatory corticosteroid.
- 23 The pharmaceutical composition of Claim 22, wherein the anti-inflammatory corticosteroid is selected from beclomethasone dipropionate, triamcinolone acetonide, flunisolide or dexamethasone.
- 24 The pharmaceutical composition of Claim 17 wherein the second compound is an anti-inflammatory agent.
- 25 The pharmaceutical composition of Claim 24, wherein the anti-inflammatory agent is sodium cromoglycate or nedocromil sodium.
- 26 The pharmaceutical composition of Claim 17 wherein the second compound is a pharmaceutically acceptable carrier thereof.

Figure I

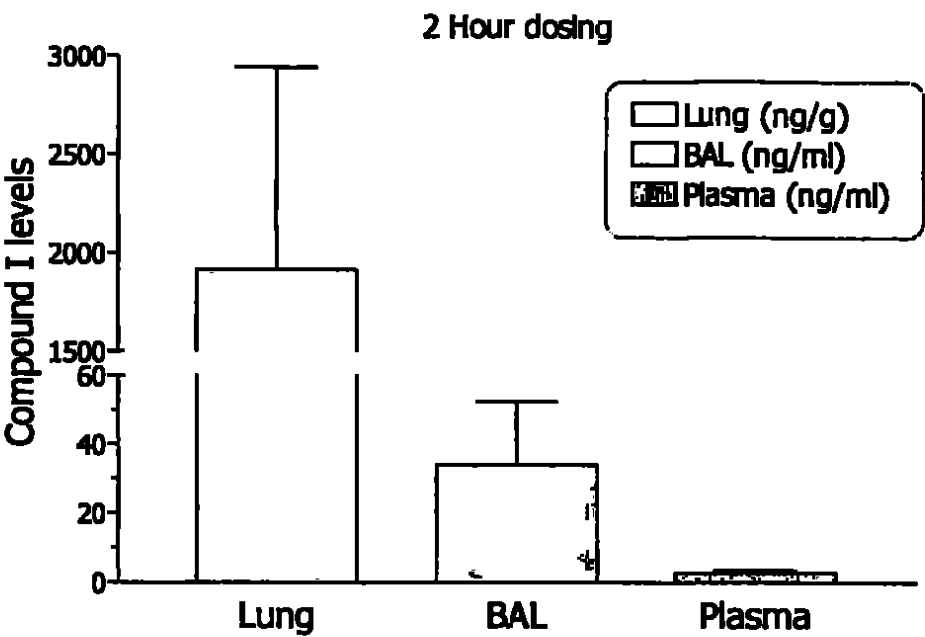
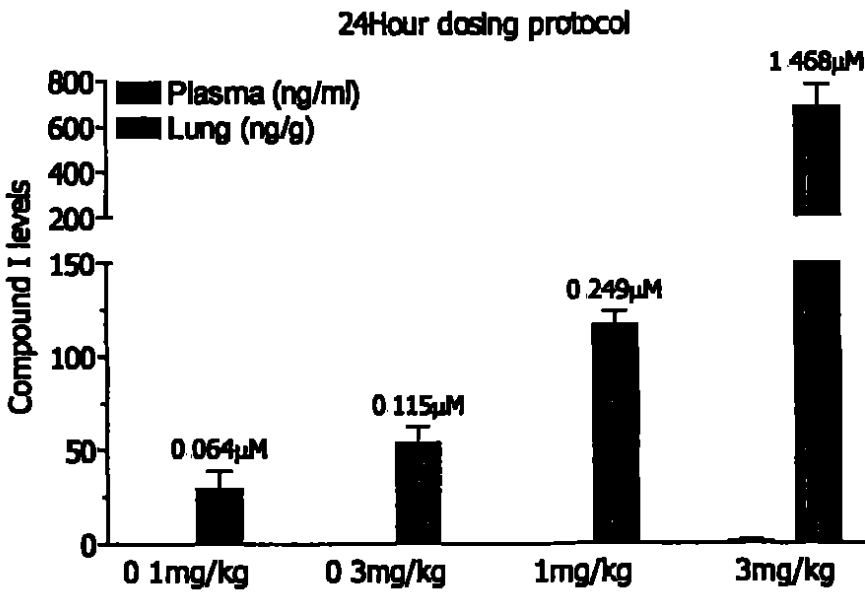


Figure II



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INTERNATIONAL SEARCH REPORT

Int. Application No
PC1/US2005/009899

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D409/06 A61K31/4535 A61P11/06		
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 A61K A61P		
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, WPI Data, PAJ BEILSTEIN Data 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 01/90101 A (AVENTIS PHARMACEUTICALS PRODUCTS INC, ASTLES, PETER, C, EASTWOOD, PAUL) 29 November 2001 (2001-11-29) Abstract, claims, examples, and the specific compound A3-B1-C90 & US 2003/187020 A1 (ASTLES PETER C ET AL) 2 October 2003 (2003-10-02)	1-26
☐ 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 doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (see 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 & document member of the same patent family		
Date of the actual completion of the international search 22 July 2005		Date of mailing of the international search report 03/08/2005
Name and mailing address of the ISA European Patent Office, P.B. 5518 Patentplan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 apo nl Fax (+31-70) 340-3016		Authorized officer Weisbrod T

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/009899

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos. because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 4-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound (I)
2. ☐ Claims Nos. because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Inter-
national Application No
PCT/US2005/009899

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			BR 0111206 A	15-04-2003
			CA 2409827 A1	29-11-2001
			CN 1439003 A	27-08-2003
			EP 1296972 A1	02-04-2003
			HU 0302485 A2	29-12-2003
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			ZA 200209484 A	23-02-2004
US 2003187020	A1	02-10-2003	AU 5741301 A	03-12-2001
			BR 0111206 A	15-04-2003
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			EP 1296972 A1	02-04-2003
			HU 0302485 A2	29-12-2003
			JP 2004510697 T	08-04-2004
			MA 25809 A1	01-07-2003
			MX PA02011400 A	23-05-2003
			NO 20025601 A	06-01-2003
			PL 360495 A1	06-09-2004
			WO 0190101 A1	29-11-2001
			ZA 200209484 A	23-02-2004

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PCT

(10) Número de Publicación Internacional
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(21)	Número de Solicitud Internacional	PCT/US2005/009899
(22)	Fecha de Presentación Internacional	24 Marzo 2005 (24 03 2005)
(25)	Idioma de Presentación	Inglés
(26)	Idioma de Publicación	Inglés
(30)	Datos de Prioridad	
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(81) Estados Designados (a menos que se indique de otra forma, para cada clase de protección nacional disponible) AE, AG, AL, AM, AT, AU, AZ BA, BB, BG, BR, BW, BY BZ, CA, CH CN CO CR, CU, CZ, DE, DK, DM, DZ, EC EE EG ES, FI, GB, GD GE GH, GM, HR HU ID, IL, IN IS JP KE, KG, KP KR KZ, LC, LK, LR, LS, LT, LU LV MA, MD MG MK, MN, MW MX, MZ, NA, NI NO NZ, OM PG PH PL, PT, RO RU SC, SD, SE, SG SK, SL, SM, SY TJ TM TN, TR, TT, TZ UA, UG, US UZ VC VN, YU, ZA, ZM ZW

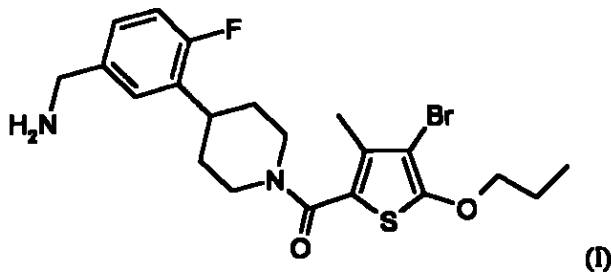
(84) Estados Designados (a menos que se indique de otra forma, para cada clase de protección regional disponible) ARIPO (BW, GH, GM, KE, LS MW, MZ, NA SD SL, SZ, TZ UG, ZM ZW), Euroasiática (AM, AZ, BY, KG KZ, MD, RU TJ TM), Europea (AT BE BG CH CY CZ, DE, DK, EE ES FI, FR, GB GR, HU IE, IS IT, LT, LU, MC NL, PL, PT, RO SE SI, SK, TR), OAPI (BF BJ CF CG, CI, CM GA, GN GQ, GW ML, MR, NE, SN, TD TG)

Publicada

Con reporte de búsqueda internacional

(54) Título [HIDROCLORURO DE [4-(5-AMINOMETIL-2-FLURO-FENIL)-PIPERIDIN-1-IL]-(4-BROMO-3-METIL-5-PROPOXI-TIOFEN-2-IL)-METANONA COMO UN INHIBIDOR DE LA TRIPTASA DE MASTOCITOS

(57) Resumen La presente invención incluye el compuesto de fórmula I



o un profármaco farmacéuticamente aceptable o solvato de dicho compuesto

Además la presente invención se refiere a una composición farmacéutica que comprende una cantidad farmacéuticamente eficaz del compuesto de fórmula I, y un vehículo farmacéuticamente aceptable

Además la presente invención se refiere al uso de un compuesto de fórmula I como inhibidor de triptasa, que comprende introducir el compuesto en una composición que comprende triptasa. Además la presente invención se refiere al uso de un compuesto de fórmula I para tratar a un paciente que padece o propenso a padecer una afección fisiológica que necesita la mejora de un inhibidor de triptasa que comprende administrar al paciente una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1

La presente invención también se refiere a la preparación de un compuesto de fórmula I

[HIDROCLORURO DE [4-(5 AMINOMETIL-2 FLUORO-FENIL)-PIPERIDIN 1 IL]-[4 BROMO-3 METIL-5 PROPOXI TIOFEN 2 IL]-METANONA COMO UN INHIBIDOR DE LA TRIPTASA DE MASTOCITOS

5 Campo de la invención

Esta invención se refiere a un compuesto de arilmetilamina sustituido, a su preparación, a una composición farmacéutica que comprende el compuesto, a su uso y a intermedios del mismo.

ANTECEDENTES DE LA INVENCION

10 Las afecciones inflamatorias mediadas por mastocitos, en particular el asma, suponen una preocupación cada vez mayor para la salud pública. El asma a menudo se caracteriza por el desarrollo progresivo de una hiperrespuesta de la tráquea y los bronquios tanto alérgenos inmunoespecíficos como estímulos químicos o físicos generalizados, lo cual conduce al inicio de una inflamación crónica. Los leucocitos que contienen receptores de IgE, particularmente los mastocitos y basófilos, están presentes en el epitelio y en el tejido de músculo liso subyacente de los bronquios. Estos leucocitos
15 inicialmente se activan por la unión de antígenos inhalados específicos a los receptores de IgE que después liberan varios mediadores químicos. Por ejemplo, la desgranulación de mastocitos conduce a la liberación de proteoglicanos, peroxidasa, arilsulfatasa B, quimasa y tripsina, lo cual produce una constricción de los bronquiolos.

La tripsina se almacena en los gránulos secretores de los mastocitos y es la proteasa secretora principal de los mastocitos humanos. La tripsina se ha implicado en diversos procesos biológicos incluyendo la degradación de neuropéptidos de vasodilatación y broncorelajación (Caughey et al J Pharmacol Exp Ther 1988, 244 páginas 133-137; Franconi et al J Pharmacol Exp Ther 1988, 248 páginas 947-951; y Tam, et al Am J Respir Cell Mol Biol 1990, 3 páginas 27-32) y la modulación de la respuesta bronquial a la histamina (Sekizawa, et al J Clin Invest. 1989, 83
25 páginas 175-179).

Como resultado, los inhibidores de tripsina pueden ser útiles como agentes antiinflamatorios (K Rice, P A. Sprengler Current Opinion in Drug Discovery and Development, 1999, 2(5) páginas 463-474) particularmente en el tratamiento del asma crónica (M Q Zhang, H Timmerman, Mediators Inflamm. 1997, 112 páginas 311-317), y también pueden ser útiles en el tratamiento o prevención de la rinitis alérgica (S J Wilson et al, Clin. Exp. Allergy 1998, 28 páginas 220-227), enfermedad inflamatoria del intestino (S C Bischoff et al, Histopathology 1996, 28, páginas 1-13), psoriasis (A. Naukkarinen et al Arch. Dermatol Res. 1993, 285 páginas 341-346), conjuntivitis (A.A.Iram et al, J Allergy Clin Immunol 1990, 86 páginas 34-40), dermatitis atópica (A. Jarvikallio et al Br J Dermatol 1997, 136, páginas 871-877), artritis reumatoide (L C Tetlow et al, Ann. Rheum. Dis. 1998, 54 páginas 549-555), osteoartritis (M G Buckley et al J Pathol 1998, 186 páginas 67-74),
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artritis gotosa, espondilitis reumatoide, y enfermedades de la destrucción del cartilago de las articulaciones.

Además se ha demostrado que la triptasa es un potente mitógeno para fibroblastos, lo que sugiere su implicación en la fibrosis pulmonar en el asma y en enfermedades pulmonares intersticiales (Ruoss et al. J Clin Invest. 1991 88, páginas 493-499).

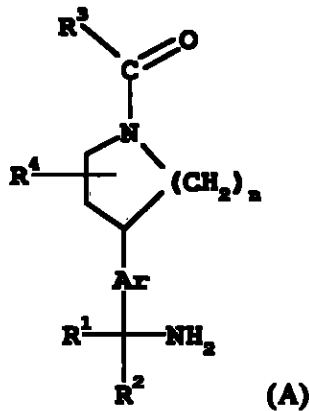
Por lo tanto, los inhibidores de triptasa pueden ser útiles en el tratamiento o prevención de afecciones fibróticas (J.A.Carns y A.F. Walls, J Clin. Invest. 1997 99 páginas 1313-1321) por ejemplo, fibrosis, esclerodermia, fibrosis pulmonar, cirrosis hepática, fibrosis de miocardio, neurofibromas y cicatrices hipertróficas.

Además, los inhibidores de triptasa pueden ser útiles en el tratamiento o prevención del infarto de miocardio, apoplejía, angina y otras consecuencias de la ruptura de placas ateroscleróticas (M. Jezioraka et al. J Pathol. 1997 182 páginas 115-122).

También se ha descubierto que la triptasa activa la prostomelina que a su vez activa la colagenasa, iniciándose de esta manera la destrucción del cartilago y el tejido conectivo periodontal, respectivamente.

Por lo tanto, los inhibidores de triptasa podrían ser útiles en el tratamiento o prevención de la artritis, enfermedad periodontal, retinopatía diabética y crecimiento tumoral (W.J. Beil et al., Exp Hematol. (1998) 26 páginas 158-169). Además, los inhibidores de triptasa pueden ser útiles en el tratamiento de la anafilaxia (L.B. Schwarz et al., J Clin Invest. 1995 96, páginas 2702-2710), esclerosis múltiple (M. Steinhoff et al., Nat. Med. (N.Y.), 2000 6(2), páginas 151-158), úlceras pépticas e infecciones por virus sincitiales.

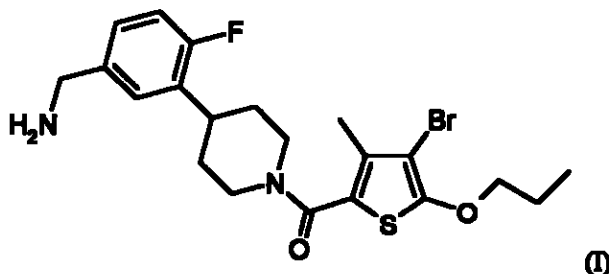
En la solicitud de Estados Unidos en trámite junto con la presente, con N° de serie 09/843 126 se presentan arilmetilaminas sustituidas representadas como los compuestos de fórmula (A), su preparación, composiciones farmacéuticas que contienen estos compuestos y su uso farmacéutico en el tratamiento de estados de enfermedad que pueden modularse por la inhibición de triptasa. Dentro de la descripción genérica de los compuestos de fórmula (A) de la solicitud de patentes de Estados Unidos con el N° de serie 09/843 126, se incluye el compuesto de la presente invención, de fórmula I. Sin embargo, el compuesto de fórmula I no se describe específicamente en la solicitud de Estados Unidos con el N° de serie 09/843 126.



Por consiguiente, lo que se necesita es un compuesto nuevo y útil que tenga propiedades farmacéuticas particularmente valiosas en su capacidad para inhibir la triptasa. Tal compuesto debe tener utilidad para tratar a un paciente que padece afecciones que pueden mejorar por medio de la administración de un inhibidor de triptasa, por ejemplo afecciones inflamatorias mediadas por mastocitos, inflamación y enfermedades o trastornos relacionados con la degradación de neuropeptidos vasodilatadores y broncorelajantes.

SUMARIO DE LA INVENCION

La presente invención incluye el compuesto de fórmula I



o un profármaco farmacéuticamente aceptable o solvato de dicho compuesto.

Además, la presente invención se refiere a una composición farmacéutica que comprende una cantidad farmacéuticamente eficaz del compuesto de fórmula I, y un vehículo farmacéuticamente aceptable.

Además, la presente invención se refiere al uso de un compuesto de fórmula I como inhibidor de triptasa, que comprende introducir el compuesto en una composición que comprende triptasa. Además, la presente invención se refiere al uso de un compuesto de fórmula I para tratar a un paciente que padece o propenso a padecer una afección fisiológica que necesita la mejora de un inhibidor de triptasa que comprende administrar al paciente una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1

La presente invención también se refiere a la preparación de un compuesto de fórmula I.

Breve descripción de los dibujos

Los aspectos, características y ventajas de la presente invención se entenderán mejor tras las siguientes descripciones detalladas consideradas junto con las figuras adjuntas, proporcionándose todas ellas sólo a modo de ilustración y sin limitar la presente invención, en las que:

5 Figura I Niveles de compuesto I en plasma, fluido de lavado broncoalveolar (BAL) y pulmón, medidos dos horas después de la dosificación del compuesto I a 1 mg/kg, p.o. Los valores son media $\pm$ SE de 6-8 animales

Figura II Niveles de compuesto I en plasma y en pulmón medidos 24 horas después de la dosificación. Los valores son la media $\pm$ SE de 3-4 animales

10 DESCRIPCIÓN DETALLADA

Definiciones

Como se ha usado anteriormente y a lo largo de la presente memoria descriptiva y la reivindicaciones adjuntas, se entenderá que las siguientes expresiones, a menos que se indique otra cosa, tienen los siguientes significados

15 Como se usa en este documento, se entiende que la expresión "compuesto de la presente invención" y expresiones equivalentes, incluyen el compuesto de fórmula I, como se ha descrito anteriormente en este documento, incluyendo la expresión el profármaco, la sal farmacéuticamente aceptable y el solvato, por ejemplo el hidrato. De forma similar se entiende que la referencia a los intermedios, se reivindiquen o no se reivindiquen, incluye las sales y solvatos cuando lo permita el
20 contexto. Por claridad, cuando el contexto lo permite, algunas veces ciertos casos particulares están indicados en el texto, pero estos casos son puramente ilustrativos y no pretenden excluir otros casos cuando el contexto lo permite.

Como se usa en este documento, el término "tratamiento o tratar" incluye la terapia profiláctica así como el tratamiento de una afección establecida.

25 "Paciente" significa un ser humano u otro mamífero

"Cantidad eficaz" pretende describir una cantidad de un compuesto eficaz para producir el efecto terapéutico deseado.

Profármaco significa un compuesto que es adecuado para administrarse a un paciente sin toxicidad indebida, irritación, respuesta alérgica y similares, y se puede convertir in vivo por medios
30 metabólicos (por ejemplo por hidrólisis) en el compuesto de la presente invención. En T. Higuchi y V. Stella Pro-drugs as Novel Delivery Systems, Vol. 14 de las A. C. S. Symposium Series, y en Edward B. Roche, ed. Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987 se proporciona una discusión minuciosa de profármacos.

Realizaciones particulares o preferidas

35 Además, la presente invención se refiere al uso del compuesto de fórmula I para tratar a un paciente que padece una afección fisiológica que puede mejorarse por medio de la administración al

paciente de una cantidad terapéuticamente eficaz del compuesto de fórmula I. Las realizaciones particulares de afecciones fisiológicas que pueden tratarse con el compuesto de la presente invención incluyen, pero por supuesto sin limitación, enfermedades inflamatorias, por ejemplo inflamación de las articulaciones, artritis, artritis reumatoide, espondilitis reumatoide, artritis gotosa, artritis traumática, artritis por rubeola, artritis psoriásica, y otras enfermedades inflamatorias crónicas de las articulaciones. Otras realizaciones de afecciones fisiológicas que pueden tratarse por la presente invención incluyen afecciones fisiológicas tales como enfermedad pulmonar obstructiva crónica (COPD), exacerbaciones de COPD, destrucción del cartilago de las articulaciones, conjuntivitis ocular, conjuntivitis vernal, enfermedad inflamatoria del intestino, asma, rinitis alérgica, enfermedades pulmonares intersticiales, fibrosis esclerodermia, fibrosis pulmonar cirrótica hepática, fibrosis de miocardio, neurofibromas, cicatrices hipertróficas, diversas afecciones dermatológicas por ejemplo dermatitis atópica y psoriasis, infarto de miocardio, apoplejía, angina y otras consecuencias de la ruptura de placas ateroscleróticas, así como enfermedad periodontal, retinopatía diabética, crecimiento tumoral, anafilaxis, esclerosis múltiple, úlceras pépticas e infecciones por virus sincitiales.

En una realización particular la presente invención se refiere al uso de un compuesto de fórmula I para tratar a un paciente que padece asma, que comprende administrar al paciente una cantidad fisiológicamente eficaz del compuesto.

En otra realización particular la presente invención se refiere al uso de un compuesto de fórmula I para tratar a un paciente que padece COPD que comprende administrar al paciente una cantidad fisiológicamente eficaz del compuesto.

En otra realización particular la presente invención se refiere al uso de un compuesto de fórmula I para tratar a un paciente que padece exacerbaciones de COPD que comprende administrar al paciente una cantidad fisiológicamente eficaz del compuesto.

En otra realización particular la presente invención se refiere al uso de un compuesto de fórmula I para tratar a un paciente que padece rinitis alérgica, que comprende administrar al paciente una cantidad fisiológicamente eficaz del compuesto.

En otra realización particular la presente invención se refiere al uso de un compuesto de fórmula I para tratar a un paciente que padece inflamación de las articulaciones, que comprende administrar al paciente una cantidad fisiológicamente eficaz del compuesto.

En otra realización particular la presente invención se refiere al uso de un compuesto de fórmula I para tratar a un paciente que padece enfermedad inflamatoria del intestino que comprende administrar al paciente una cantidad fisiológicamente eficaz del compuesto.

Además la presente invención incluye una composición farmacéutica que comprende el compuesto de fórmula I, un segundo compuesto seleccionado entre el grupo que consiste en un agonista beta adrenérgico, un anticolinérgico, un corticosteroide anti-inflamatorio y un agente antiinflamatorio, y un vehículo farmacéuticamente aceptable de los mismos. En tal composición, el

compuesto de fórmula I y el segundo compuesto están presentes en cantidades que proporcionan una actividad terapéuticamente eficaz, es decir un efecto aditivo o sinérgico. Las enfermedades o trastornos inflamatorios particulares que pueden tratarse con tal composición farmacéutica incluyen, pero sin limitación, asma.

5 Además la presente invención se refiere a un método para tratar a un paciente que padece un trastorno inflamatorio, que comprende administrar al paciente el compuesto de fórmula I y un segundo compuesto seleccionado entre el grupo que consiste en un agonista beta adrenérgico, un anticolinérgico, un corticosteroide antiinflamatorio y un agente antiinflamatorio. En tal método, el compuesto de fórmula I y el segundo compuesto están presentes en cantidades que proporcionan una actividad terapéuticamente eficaz, es decir un efecto aditivo o sinérgico. En tal método de la presente invención, el compuesto de la presente invención puede administrarse al paciente antes que un segundo compuesto, el segundo compuesto puede administrarse al paciente antes que el compuesto de la presente invención, o el compuesto de la presente invención y el segundo compuesto pueden administrarse conjuntamente. Más adelante se describen ejemplos particulares de agonistas adrenérgicos, anticolinérgicos, corticosteroides antiinflamatorios y agentes antiinflamatorios que tienen aplicación de acuerdo con el método.

Composiciones farmacéuticas

20 Como se ha explicado anteriormente, el compuesto de la presente invención presenta actividad farmacológica útil y por consiguiente, puede incorporarse en una composición farmacéutica y usarse en el tratamiento de pacientes que padecen ciertos trastornos médicos. De esta manera, la presente invención proporciona, de acuerdo con un aspecto adicional, composiciones farmacéuticas que comprenden el compuesto de la invención y un vehículo farmacéuticamente aceptable del mismo. Como se usa en este documento, la expresión "farmacéuticamente aceptable" preferiblemente tiene significado aprobado por una agencia reguladora gubernamental, en particular el gobierno federal o un gobierno estatal, o indicado en la farmacopea de Estados Unidos u otra farmacopea reconocida generalmente para uso en animales, y más particularmente en seres humanos. En Remington's Pharmaceutical Sciences de E. W. Martin se describen vehículos farmacéuticos adecuados.

30 Las composiciones farmacéuticas de acuerdo con la presente invención pueden prepararse de acuerdo con los métodos habituales usando uno o más adyuvantes o excipientes farmacéuticamente aceptables. Los adyuvantes comprenden, entre otros diluyentes, cargas, aglutinantes, disgregantes, deslizantes, lubricantes, tensioactivos, medios acuosos estériles y diversos disolventes orgánicos no tóxicos. Las composiciones pueden presentarse en forma de comprimidos, cápsulas, píldoras, formulaciones de liberación sostenida, gránulos, polvos, soluciones o suspensiones acuosas, soluciones inyectables, elixires o jarabes, y pueden contener uno o más agentes seleccionados entre el grupo que comprende edulcorantes, aromatizantes, colorantes o estabilizadores para obtener preparaciones farmacéuticamente aceptables. La elección del vehículo y el contenido de la sustancia activa en el

vehículo generalmente se determinan de acuerdo con la solubilidad y propiedades químicas del compuesto activo, el modo particular de administración y las disposiciones a tener en cuenta en la práctica farmacéutica. Por ejemplo para preparar comprimidos pueden usarse excipientes tales como lactosa, celulosa microcristalina, almidón pregelatinizado, almidón no modificado, celulosa microcristalina silicificada, manitol, sorbitol, xilitol, dextratos, fructosa, citrato sódico, carbonato cálcico, fosfato dicálcico dihidrato, fosfato dicálcico anhidro, sulfato cálcico, junto con aglutinantes tales como polivinilpirrolidona, hidroxipropilmetil celulosa, etil celulosa, hidroxietil celulosa, metil celulosa, carboximetil celulosa sódica, almidón pregelatinizado, almidón, polietilenglicoles, poli(óxido de etileno), policarbofilos, gelatina y goma arábiga, y agentes disgregantes tales como croscarmelosa sódica, almidón glicolato sódico, crospovidona, almidón, celulosa microcristalina, ácidos alginicos y ciertos silicatos complejos junto con lubricantes tales como estearato de magnesio, estearato cálcico, ácido esteárico, aceite vegetal hidrogenado, aceite mineral, polietilenglicoles, ésteres de glicerilo de ácidos grasos, laurilsulfato sódico y deslizantes tales como dióxido de silicio, talco, almidón, junto con algunos agentes humectantes adecuados tales como laurilsulfato sódico, ésteres de sorbitán, ésteres de ácidos grasos o de ácido graso de polioxietileno, poloxámero, éter de polioxietileno, docusato sódico, aceite de ricino polietoxilado y cloruro de benzalconio. Para preparar una cápsula, es ventajoso usar cargas tales como lactosa, celulosa microcristalina, almidón pregelatinizado, almidón no modificado, celulosa microcristalina silicificada sola o una mezcla de dos o más cargas con y sin aglutinantes como se han descrito anteriormente junto con uno o más agentes humectantes adecuados, disgregantes, deslizantes, lubricantes, etc, como se ha indicado anteriormente. Cuando se usa suspensiones acuosas, pueden contener agentes emulsionantes o agentes que facilitan la suspensión. También pueden usar diluentes tales como sacarosa, etanol, polietilenglicol, propilenglicol, glicerol y cloroformo o mezclas de los mismos. Tales vehículos farmacéuticamente aceptables también pueden ser agua estéril y aceites, incluyendo los de petróleo, de origen vegetal o sintético tales como aceite de cacahuete, aceite de soja, aceite mineral, aceite de sésamo y similares. El agua es un vehículo preferido cuando la composición farmacéutica se administra por vía intravenosa. También pueden emplearse soluciones salinas y soluciones acuosas de dextrosa y glicerol como vehículos líquidos, particularmente para soluciones inyectables. Los excipientes farmacéuticos adecuados incluyen manitol, albúmina de suero humano (HSA), almidón, glucosa, lactosa, sacarosa, gelatina, malta, arroz, harina, carbonato cálcico, gel de sílice, carbonato de magnesio, estearato de magnesio, estearato sódico, monostearato de glicerol, talco, cloruro sódico, leche desnatada deshidratada, glicerol, propilenglicol, agua, etanol y similares. Estas composiciones pueden tomar la forma de soluciones, suspensiones, comprimidos, píldoras, cápsulas, polvos, formulaciones de liberación sostenida y similares.

Naturalmente, una composición farmacéutica de la presente invención contendrá una cantidad terapéuticamente eficaz del compuesto activo junto con una cantidad adecuada de vehículo para proporcionar la forma para la administración apropiada al paciente. Cuando la inyección intravenosa

es una muy eficaz de administración, pueden emplearse otros modos, tales como inyección o administración oral, nasal o parenteral, que se describe más adelante.

Métodos de Tratamiento

El compuesto de fórmula I posee actividad de inhibición de la tripsasa de acuerdo con ensayos descritos en la bibliografía y descritos más adelante en este documento, considerándose que los resultados de los ensayos se correlacionan con la actividad farmacológica en seres humanos y otros mamíferos. De esta manera, en una realización adicional, la presente invención se refiere al uso de la fórmula I o una composición que la comprende para tratar a un paciente que padece o propenso a padecer una afección que puede mejorar por medio de la administración de un inhibidor de tripsasa.

Por ejemplo, el compuesto de fórmula I es útil para tratar una enfermedad inflamatoria, por ejemplo inflamación de las articulaciones, incluyendo artritis, artritis reumatoide y otros estados artríticos tales como espondilitis reumatoide, artritis gotosa, artritis traumática, artritis por rubeola, artritis psoriática, osteoartritis u otra enfermedad inflamatoria crónica de las articulaciones, o enfermedades de la destrucción del cartilago de las articulaciones, conjuntivitis ocular conjuntivitis vernal enfermedad inflamatoria del intestino, asma, rinitis alérgica, enfermedades pulmonares intersticiales, fibrosis, esclerodermia, fibrosis pulmonar cirrosis hepática, fibrosis miocárdica, neurofibromas, cicatrices hipertróficas, diversas afecciones dermatológicas, por ejemplo, dermatitis atópicas y psoriasis, infarto de miocardio, apoplejía, angina, u otras consecuencias de la ruptura de placas ateroscleróticas así como enfermedad periodontal, retinopatía diabética, crecimiento tumoral, anafilaxis, esclerosis múltiple, úlceras pépticas o una infección producida por un virus sincitial.

De acuerdo con otra característica de la invención, se proporciona un método para el tratamiento de un paciente humano o animal que padece o propenso a padecer afecciones que pueden mejorar por medio de la administración de un inhibidor de tripsasa, por ejemplo las afecciones descritas anteriormente en este documento, que comprende administrar al paciente una cantidad eficaz de compuesto de la invención o una composición que contiene un compuesto de la invención.

Terapia de Combinación

Como se ha explicado anteriormente, dependiendo de la enfermedad que se vaya a tratar en combinación con el compuesto de fórmula I pueden emplearse otros agentes farmacéuticamente activos. Por ejemplo, en el tratamiento del asma, pueden incluirse agonistas beta-adrenérgicos tales como albuterol, terbutalina, formoterol, fenoterol o prenahina, así como anticolinérgicos tales como bromuro de ipratropio, corticosteroides anti-inflamatorios tales como dipropionato de beclometasona, triamcinolona acetónida, flunisolida o dexametasona, y agentes anti-inflamatorios tales como cromoglicato sódico y nedocromil sódico. De esta manera, la presente invención incluye una composición farmacéutica que comprende el compuesto de fórmula I y un segundo compuesto seleccionado entre el grupo que consiste en un agonista beta adrenérgico, un anticolinérgico, un corticosteroide anti-inflamatorio y un agente anti-inflamatorio y un vehículo farmacéuticamente

aceptable para los mismos. En este documento se describen vehículo farmacéuticos particulares que tienen aplicaciones en esta composición farmacéutica.

Además, la presente invención incluye un método para tratar un paciente que padece asma, que comprende administrar al paciente el compuesto de la presente invención y un segundo compuesto seleccionado entre el grupo que consiste en un agonista beta adrenérgico, un anticolinérgico, un corticosteroide anti-inflamatorio y un agente anti-inflamatorio. En tal método de combinación, el compuesto de la presente invención puede administrarse antes de la administración del segundo compuesto, el compuesto de la presente invención puede administrarse después de la administración del segundo compuesto, o el compuesto de la presente invención y el segundo compuesto puede administrarse conjuntamente.

Modos de Administración

De acuerdo con la invención, el compuesto de fórmula I, o una composición farmacéutica que comprende el compuesto, puede introducirse por vía parenteral, transmucosa, *por ejemplo* oral, nasal, pulmonar o rectal, o por vía transdérmica a un paciente.

Administración Oral

Para uso en este documento se contemplan formas de dosificación oral sólidas, que se describen en general en Remington's Pharmaceutical Sciences, 18^a Ed.1990 (Mack Publishing Co Easton PA 18042) en el capítulo 89 que se incorpora en este documento como referencia. Las formas de dosificación sólidas incluyen comprimidos, cápsulas, píldoras, troscos o grageas, obleas o gránulos. Además, puede usarse la encapsulación liposomal o en protenoides para formular las presentes composiciones (por ejemplo como microesferas proteínoides presentadas en la Patente de Estados Unidos N° 4 925 673). Puede usarse encapsulación liposomal y los liposomas pueden modificarse con diversos polímeros (*por ejemplo* Patente de Estados Unidos N° 5 013 556). Marshall, K. en *Modern Pharmaceutics* Editado por by G S. Banker y C T Rhodes Capítulo 10 1979 incorporado a este documento como referencia. En general, la formulación incluirá un compuesto de la presente invención e ingredientes inertes que permitan la protección frente al medio de estómago, y la liberación del material biológicamente activo, es decir un compuesto de la presente invención, en el intestino.

También se contemplan específicamente formas de dosificación oral del compuesto de la presente invención. Tal compuesto puede modificarse químicamente de forma que la administración oral sea más eficaz. Generalmente, la modificación química contemplada es la unión de al menos un resto a la propia molécula componente, donde dicho resto permite (a) la inhibición de la proteólisis, y (b) la absorción en la corriente sanguínea desde el estómago o el intestino. También se desea el aumento de la estabilidad global del compuesto de la presente invención y el aumento del tiempo de circulación en el cuerpo. Los ejemplos de tales restos incluyen: polietilenglicol, copolímeros de etilenglicol y propilenglicol, carboximetilcelulosa, dextrano, alcohol polivinílico, polivinilpirrolidona y

poliprolina. Abuchowski y Davis, 1981 "Soluble Polymer-Enzyme Adducts" en *Enzymes as Drugs* Hoenberg y Roberts, eds Wiley-Interscience, New York NY pág 367 383 Newmark, et al 1982 J Appl Biochem. 4 185 189 Otros polímeros que podría usarse son poli 1,3-dioxolano y poli 1,3 6-tioxocano. Para uso farmacéuticos, como se indicado anteriormente, se prefieren restos de polietilenglicol

Para compuesto de la presente invención, la localización de liberación puede ser el estómago el intestino delgado (el duodeno el yeyuno o el íleo) o el intestino grueso. Un especialista en la técnica dispone de formulaciones que no se disolverán en el estómago, liberando el material en el duodeno o en cualquier parte del intestino. Preferiblemente, la liberación, evitará los efectos perjudiciales del medio del estómago, bien por medio de la protección del compuesto de la presente invención o por medio de la liberación del compuesto más allá del medio del estómago, tal como en el intestino

Para asegurar una resistencia gástrica completa, es esencial un recubrimiento impermeable a un valor de pH de al menos 5.0. Son ejemplos de los ingredientes inertes más comunes que se usan como recubrimientos entéricos acetato trimelitato de celulosa (CAT), ftalato de hidroxipropilmetil celulosa (HPMCP), HPMCP 50 HPMCP 55 acetato ftalato de polivinilo (PVAP), Eudragit L30D Aquateric, acetato ftalato de celulosa (CAP), Eudragit L, Eudragit S, y goma laca. Estos recubrimientos pueden usarse como películas mixtas

También puede usarse un recubrimiento o mezcla de recubrimiento en comprimidos, que no están destinados para la protección frente al estómago. Este puede incluir recubrimientos de azúcar o recubrimientos que hacen que el comprimido sea más fácil de tragar. Las cápsulas pueden constar de una cubierta dura (tal como gelatina) para suministrar el agente terapéutico seco, es decir en forma de polvo. En el caso de las formas líquidas, puede usarse una cubierta de gelatina blanda. El material de la cubierta de obleas podría ser almidón espeso u otro papel comestible. En el caso de las píldoras, grageas, comprimidos moldeados o triturados de comprimidos, pueden usarse técnicas de amasado en húmedo.

El agente terapéutico puede incluirse en la formulación como multiparticulados finos en forma de gránulos o bolitas con un tamaño de partículas de aproximadamente 1 mm. La formulación del material para la administración en cápsulas también podría ser como un polvo, tabletas ligeramente comprimidas o incluso como comprimidos. El agente terapéutico podría prepararse por compresión.

Pueden incluirse agentes colorantes y aromatizantes. Por ejemplo, el compuesto de la presente invención puede formularse (tal como por medio de encapsulación en liposomas o microesferas) y después introducirse en un producto comestible, tal como una bebida refrigerada que contiene agentes colorantes y aromatizantes.

Se puede diluir o aumentar el volumen del agente terapéutico con un material inerte. Estos diluyentes podrían incluir carbohidratos, especialmente manitol, α -lactosa, lactosa anhidra, celulosa,

sacarosa, dextranos modificados y almidón. También pueden usarse ciertas sales inorgánicas como cargas, incluyendo trifosfato cálcico, carbonato de magnesio y cloruro sódico. Algunos diluyentes disponibles en el mercado son Fast Flo, Emdex, STA-Rx 1500 Emcompreas y Avicell.

5 En la formulación de los agentes terapéuticos en una forma de dosificación sólida pueden incluirse disgregantes. Los materiales usados como disgregantes incluyen, pero sin limitación almidón, incluyendo el disgregante comercial basado en almidón, Explotab. Pueden usarse almidón glicolato sódico, Amberlite, carboximetil celulosa sódica, ultramilopectina, alginato sódico, gelatina, piel de naranja, carboximetil celulosa ácida, esponja natural y bentonita. Otra forma de los disgregantes son las resinas de intercambio catiónico insolubles. Como disgregantes y como aglutinantes puede usarse
10 gomas en polvo y éstas pueden incluir gomas en polvo tales como agar Karaya o tragacanto. También son útiles como disgregantes el ácido algínico y su sal de sodio.

Puede usarse aglutinantes para mantener unido el agente terapéutico para formar un comprimido duro e incluyen materiales procedentes de productos naturales tales como goma arábiga, tragacanto, almidón y gelatina. Otros incluyen metil celulosa (MC), etil celulosa (EC) y carboximetil
15 celulosa (CMC). En soluciones alcohólicas para granular el agente terapéutico puede usarse tanto polivinilpirrolidona (PVP) como hidroxipropilmetil celulosa (HPMC).

En las formulaciones del agente terapéutico se puede incluir un agente contra la fricción para impedir la adherencia durante el proceso de formulación. Pueden usarse lubricantes como una capa entre el agente terapéutico y la pared de la matriz, y estos pueden incluir, pero sin limitación, ácido
20 esteárico incluyendo sus sales de calcio y de magnesio, politetrafluoroetileno (PTFE), parafina líquida, aceites vegetales y ceras. También pueden usarse lubricantes solubles tales como laurilsulfato sódico, laurilsulfato de magnesio, polietilenglicol de diversos pesos moleculares, Carbowax 4000 y 6000.

Podían añadirse deslizantes que mejoren las propiedades de fluidez del fármaco durante la
25 formulación y que ayuden a la redistribución durante la compresión. Los deslizantes pueden incluir almidón, talco, sílice pirogénica y silicoaluminato hidratado.

Para ayudar a la disolución del agente terapéutico en el medio acuoso, podría añadirse un tensioactivo como agente humectante. Los tensioactivos pueden incluir detergentes amónicos tales como laurilsulfato sódico, dioctil sulfosuccinato sódico y dioctil sulfonato sódico. Podría usarse
30 detergentes catiónicos e incluirían cloruro de benzalconio o cloruro de bencetonio. La lista de detergentes no iónicos potenciales que podrían incluirse en la formulación como tensioactivos es laurómacrogol 400, estearato de polioxilo 40, polioxietileno-aceite de ricino hidrogenado 10, 50 y 60, monosteato de glicerol, polisorbato 40, 60, 65 y 80, éster de ácido graso de sacarosa, metilcelulosa y carboximetil celulosa. Estos tensioactivos podrían estar presentes en la formulación de un
35 compuesto de la presente invención solos o como una mezcla en diferentes relaciones.

Son aditivos que potencialmente aumentan la absorción del compuesto de la presente invención, por ejemplo, los ácidos grasos ácido oleico, ácido linoleico y ácido linolénico. Puede ser deseable una formulación oral de liberación controlada. El fármaco podría incorporarse en una matriz inerte que permita la liberación por mecanismos de difusión o infiltración, por ejemplo gomas. En la formulación también pueden incorporarse matrices de degeneración lenta. Algunos recubrimientos entéricos también tienen un efecto de liberación retardada.

Otra forma de liberación controlada de este agente terapéutico es por medio de un método basado en el sistema terapéutico Oros (Alza Corp.), es decir el fármaco se encierra en una membrana semipermeable que permite la entrada de agua y expulsa el fármaco a través de una sola abertura pequeña debido a efectos osmóticos.

Para la formulación pueden usarse otros recubrimientos. Estos incluyen una diversidad de azúcares que podrían aplicarse en una bandeja de recubrimiento. El agente terapéutico también podría proporcionarse en un comprimido recubierto con película y los materiales usados en este caso se dividen en dos grupos. Los primeros son los materiales no entéricos e incluyen metilcelulosa, etilcelulosa, hidroxietil celulosa, metilhidroxietil celulosa, hidroxipropil celulosa, hidroxipropil-metil celulosa, carboxi-metil celulosa sódica, povidona y los polietilenglicoles. El segundo grupo consta de los materiales entéricos que son comúnmente ésteres de ácido ftálico.

Podría usarse una mezcla de materiales para proporcionar el recubrimiento de película óptimo. El recubrimiento de película puede realizarse en un recubridor de bandeja o un lecho fluidizado o por medio de recubrimiento por compresión.

Administración Pulmonar

En el presente documento también se contempla la administración pulmonar del compuesto de la presente invención, sólo o en una composición farmacéutica. El compuesto se administra a los pulmones de un mamífero mientras se inhala y atraviesa el revestimiento del epitelio pulmonar hasta llegar a la corriente sanguínea. Otros informes de esto incluyen Adjei et al. 1990 Pharmaceutical Research, 7 565 569; Adjei et al. 1990 International Journal of Pharmaceutics, 63 135 144 (acetato de leuprolida); Braquet et al. 1989 Journal of Cardiovascular Pharmacology 13(suppl. 5) 143 146 (endotelina 1); Hubbard et al. 1989 Annals of Internal Medicine, Vol. III, pp. 206-212 (a1-antitripsina); Smith et al. 1989 J Clin. Invest. 84 1145 1146 (a1-proteinasa); Osweil et al. 1990 "Aerosolization of Proteins" Proceedings of Symposium on Respiratory Drug Delivery II, Keystone, Colorado, Marzo (hormona de crecimiento humana recombinante); Debs et al. 1988, J Immunol. 140.3482-3488 (interferón- γ factor de necrosis tumoral alfa) y Platz et al. Patente de Estados Unidos Nº 5 284 656 (factor estimulador de colonias de granulocitos). En la Patente de Estados Unidos Nº 5 451 569 expedida del 19 de septiembre de 1995 a Wong et al. se describe un método y composición para la administración pulmonar de fármacos para conseguir un efecto sistémico.

Para uso en la práctica de esta invención se contempla una amplia serie de dispositivos mecánicos diseñados para la administración pulmonar de productos terapéuticos, incluyendo pero sin limitación nebulizadores, inhaladores de dosis medidas, e inhaladores de polvo, con los que estarán familiarizados los especialistas en la técnica.

5 Algunos ejemplos específicos de dispositivos disponibles en el mercado adecuados para la práctica de esta invención son el nebulizador Ultravent fabricado por Mallinckrodt, Inc. St. Louis, Missouri el nebulizador Acorn II fabricado por Marquest Medical Products Englewood, Colorado el inhalador de dosis medidas Ventolin fabricado por Glaxo Inc. Research Triangle Park North Carolina y el inhalador de polvo Spinhaler fabricado por Fisons Corp. Bedford, Massachusetts, por
10 nombrar algunos.

Todos estos dispositivos requieren el uso de formulaciones adecuadas para la distribución del compuesto de la presente invención. Típicamente, cada formulación es específica para el tipo de dispositivo empleado y puede implicar el uso de un material propelente apropiado, además de los diluyentes, adyuvantes y/o vehículos habituales útiles en terapia. Además, se contempla el uso de
15 liposomas, microcápsulas o microesferas, complejos de inclusión u otros tipos de vehículos. Un compuesto modificado químicamente de la presente invención también puede prepararse en diferentes formulaciones dependiendo del tipo de modificación química o del tipo de dispositivo empleado.

Las formulaciones adecuadas para uso con un nebulizador en chorro o ultrasónico, típicamente comprenderán el compuesto de la presente invención disuelto en agua a una concentración
20 de aproximadamente 0.1 a 25 mg de compuesto por ml de solución. La formulación también puede incluir un tampón y un azúcar sencillo (*por ejemplo* para la estabilización y regulación de la presión osmótica). La formulación del nebulizador también puede contener un tensioactivo para reducir o prevenir la agregación inducida en la superficie del compuesto producida por la atomización de la solución para formar el aerosol.

25 Las formulaciones para uso con un dispositivo inhalador de dosis medida generalmente comprenderán un polvo finamente dividido que contiene el compuesto de la invención suspendido en un propelente con la ayuda de un tensioactivo. El propelente puede ser cualquier material convencional empleado para este fin, tal como un clorofluorocarburo, hidroclorofluorocarburo, hidrofluorocarburo o hidrocarburo, incluyendo triclourofluorometano, diclorodifluorometano, diclorotetrafluoroctanol y 1,1,1,2-tetrafluoroctano o combinaciones de los mismos. Los tensioactivos
30 adecuados incluyen trioleato de sorbitán y lecitina de soja. También puede ser útil como tensioactivo el ácido oleico.

Las formulaciones para distribuir desde un dispositivo inhalador de polvo comprenderán un polvo seco finamente dividido que contiene el compuesto de la invención, y también pueden incluir un
35 agente para proporcionar volumen, tal como lactosa, sorbitol, sacarosa o manitol en cantidades que facilitan la dispersión del polvo desde el dispositivo, por ejemplo, de 50 a 90% en peso de las

formulación. Lo más ventajoso es que el compuesto de la presente invención se prepare en forma particulada con un tamaño medio de partículas menor de 10 mm (o micrómetros) siendo el tamaño más preferiblemente de 0.5 a 5 mm, para proporcionar una administración eficaz en un sitio distal del pulmón.

5 Administración Nasal

También se contempla la administración nasal de compuesto de la presente invención. La administración nasal permite el paso del compuesto a la corriente sanguínea directamente después de administrar el producto terapéutico en la nariz, sin la necesidad de la deposición del producto en el pulmón. Las formulaciones para administración nasal incluyen las que tienen dextrano o

10 ciclodextrano.

Administración Transdérmica

En la técnica se conocen diversos y numerosos métodos para la administración transdérmica de un fármaco, por ejemplo, a través de un parche transdérmico, y tienen aplicaciones en la presente invención. Se describen parches transdérmicos, por ejemplo, en la Patente de Estados Unidos N° 5 407 713 expedida el 18 de abril de 1995 a Rolando et al. Patente de Estados Unidos N° 5 352 456 expedida el 4 de octubre de 1994 a Fallon et al. Patente de Estados Unidos N° 5 332 213 expedida el 9 de agosto de 1994 a D'Angelo et al. Patente de Estados Unidos N° 5 336 168 expedida el 9 de agosto de 1994 a Sibalis. Patente de Estados Unidos N° 5 290 561 expedida el 1 de marzo de 1994 a Farhadieh et al. Patente de Estados Unidos N° 5 254 346 expedida el 19 de octubre de 1993 a Tucker et al. Patente de Estados Unidos N° 5 164 189 expedida el 17 de noviembre de 1992 a Berger et al. Patente de Estados Unidos N° 5 163 899 expedida el 17 de noviembre de 1992 a Sibalis. Patente de Estados Unidos N° 5 088.977 y 5 087 240 ambas expedidas el 18 de febrero de 1992 a Sibalis. Patente de Estados Unidos N° 5 008 110 expedida el 16 de abril de 1991 a Benecke et al. y Patente de Estados Unidos N° 4 921 475 expedida el 1 de mayo de 1990 a Sibalis, incorporándose en este documento como referencia en su totalidad las descripciones de cada una de estas patentes.

25

Se apreciará fácilmente que la ruta de administración transdérmica puede mejorarse por medio del uso de un potenciador de la penetración dérmica, *por ejemplo* tales como los potenciadores descritos en la Patente de Estados Unidos N° 5 164 189 (*supra*) Patente de Estados Unidos N° 5 008 110 (*supra*) y Patente de Estados Unidos N° 4 879 119 expedida el 7 de noviembre de 1989 a Aruga et al. incorporándose en este documento como referencia en su totalidad las descripciones de cada una de estas patentes.

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Administración Tópica

Para la administración tópica, pueden usarse geles (basados en agua o en alcohol), cremas o pomadas que contienen compuestos de la invención. Los compuestos de la invención también pueden incorporarse en una base de gel o matriz para aplicación en un parche, que permite una liberación controlada del compuesto a través de la barrera transdérmica.

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47Administración rectal

Las composiciones sólidas para administración rectal incluyen supositorios formulados de acuerdo con métodos conocidos y que contienen el compuesto de la invención.

Dosificaciones

5 El porcentaje de ingrediente activo en la composición de la invención puede variarse, siendo necesario que constituya una proporción tal que se obtenga una dosificación adecuada. Evidentemente, puede administrarse varias formas de dosificación unitaria aproximadamente al mismo tiempo. La dosis empleada se determinará por el médico y depende del efecto terapéutico deseado, la vía de administración y la duración del tratamiento y el estado del paciente. En el adulto la dosis
10 generalmente son de aproximadamente 0.001 a aproximadamente 50 preferiblemente de aproximadamente 0.001 a aproximadamente 5 mg/kg de peso corporal al día por inhalación, de aproximadamente 0.01 a aproximadamente 100 preferiblemente de 0.1 a 70 y más especialmente de 0.5 a 10 mg/kg de peso corporal al día por administración oral, y de aproximadamente 0.01 a aproximadamente 10 preferiblemente de 0.01 a 1 mg/kg de peso corporal al día por administración
15 intravenosa. En cada caso particular las dosis se determinará de acuerdo con los factores característicos del sujeto a tratar tales como la edad, el peso, el estado general de salud y otras características que pueden influir sobre la eficacia del producto medicinal.

Además, el compuesto de acuerdo con la invención puede administrarse tan frecuentemente como sea necesario para obtener el efecto terapéutico deseado. Algunos pacientes pueden responder
20 rápidamente a una dosis mayor o menor y pueden considerarse adecuadas dosis de mantenimiento mucho más débiles. En el caso de otros pacientes, puede ser necesario proporcionar tratamientos a largo plazo en la proporción de 1 a 4 dosis al día, de acuerdo con los requisitos fisiológicos de cada paciente en particular. Generalmente, el producto activo puede administrarse por vía oral de 1 a 4 veces al día. Por supuesto, para algunos pacientes será necesario recetar no más de una o dos dosis al
25 día.

Naturalmente, un paciente en el que la administración del compuesto de la presente invención es un régimen terapéutico eficaz es preferiblemente un ser humano, pero puede ser cualquier animal. De esta manera, como puede apreciarse fácilmente por un especialista habitual en la técnica, los métodos y composiciones farmacéuticas de la presente invención son particularmente adecuados para
30 la administración a cualquier animal particularmente un mamífero, e incluyendo pero sin limitación animales domésticos, tales como gatos o perros, animales de granja tales como, pero sin limitación, vacas, caballos, cabras, ovejas y cerdos, animales silvestres (tanto en estado silvestre como en un zoológico, animales de investigación tales como ratones, ratas, conejos, cabras, ovejas, cerdos, perros, gatos, etc., especies aviarias tales como pollos, pavos, pájaros cantores, etc., es decir para uso
35 veterinario.

Detalles de Preparación

El compuesto de fórmula I puede prepararse por la aplicación o adaptación de métodos conocidos, por lo que se entiende métodos usados en este documento o descritos en la bibliografía, por ejemplo los descritos por R.C. Larock en *Comprehensive Organic Transformations*, VCH publishers 1989 o como se describe en este documento.

En las reacciones descritas en lo sucesivo puede ser necesario proteger grupos funcionales reactivos por ejemplo grupos amino para evitar su participación indeseada en reacciones. Pueden usarse grupos protectores convencionales de acuerdo con la práctica convencional, véase, por ejemplo T.W. Greene y P.G.M. Wuts en *Protective Groups in Organic Chemistry* John Wiley and Sons, 1991. En particular el compuesto de fórmula I puede prepararse como se muestra a lo largo de los Esquemas I-III.

Por ejemplo, el compuesto de la presente invención es un compuesto no quiral cuya preparación comprende una síntesis convergente. El Esquema I presentado a continuación muestra los procedimientos que culminan en la preparación de la amina 10. El Esquema II presentado a continuación muestra los procedimientos que culminan en la preparación del ácido 10. El Esquema III presentado a continuación muestra los procedimientos que culminan en la preparación del compuesto de fórmula I. Para producir el compuesto de fórmula I en una secuencia de dos etapas. La preparación de 10, 16 y el compuesto de fórmula I de la presente invención se describen, a su vez, a continuación.

El compuesto 2 se convierte en el compuesto 3 mediante la protección del grupo amino con un agente protector de amino tal como 1,2-bis(clorodimetilsilil)etano en presencia de una amina terciaria, tal como trietilamina, en un disolvente inerte adecuado tal como diclorometano, para producir el compuesto 3 protegido.

El compuesto 3 se convierte en el compuesto 5 por alquilación del compuesto 4 usando el compuesto 3 en condiciones de alquilación que comprenden una base fuerte tal como *n*-butilitio, en un disolvente aprótico, tal como tetrahidrofurano, para producir el compuesto 5 derivado de hidroxilo.

El compuesto 5 se convierte en el compuesto 6 por desprotección del grupo amino del mismo con un agente de desprotección, tal como un ácido inorgánico fuerte, tal como ácido fosfórico en presencia de un disolvente inerte, tal como heptano, para producir el compuesto 6 desprotegido.

El compuesto 6 se convierte en el compuesto 7 por deshidratación, usando un ácido inorgánico fuerte, tal como ácido fosfórico, y la posterior neutralización del producto usando una base inorgánica fuerte, tal como hidróxido sódico acuoso para producir el compuesto 7 deshidratado.

El compuesto 7 se convierte en el compuesto 8 por desprotección del grupo amino con un agente protector de amino tal como anhídrido de boc, en un sistema de disolventes mixto acuoso/orgánico, donde el disolvente orgánico es un disolvente orgánico polar tal como metanol, usando una base inorgánica fuerte, tal como hidróxido sódico acuoso para producir el compuesto 8 boc-prottegido.

El compuesto 8 se convierte en el compuesto 9 por hidrogenación usando un agente reductor tal como hidróxido de paladio sobre carbono (20%) en un sistema de disolventes mixto tal como ácido acético metanólico para producir la sal de piperidina desprotegida, compuesto 9

5 El compuesto 9 se convierte en su forma de base libre, compuesto 10 por neutralización usando una base inorgánica fuerte, tal como hidróxido sódico acuoso, para producir el compuesto final 10

El disulfuro de carbono se convierte en el compuesto 11 por acilación usando el agente de acilación cloroformato de propilo en presencia de una base inorgánica fuerte, tal como hidróxido potásico en n-propanol para producir el compuesto 11

10 El compuesto 11 se convierte en el compuesto 12 por alquilación de acetona con el compuesto 11 en presencia de una base fuerte tal como hidruro sódico para producir el compuesto alquilado 12

El compuesto 12 se convierte en el compuesto 13 por alquilación del compuesto 12 con acetato de α -bromo metilo en presencia de una amina terciaria tal como trietilamina para producir el compuesto alquilado 13

15 El compuesto 13 se convierte en el compuesto 14 por ciclación en condiciones de base fuerte, tal como metóxido sódico en presencia de un disolvente orgánico prótico tal como metanol para producir el compuesto 14 ciclado

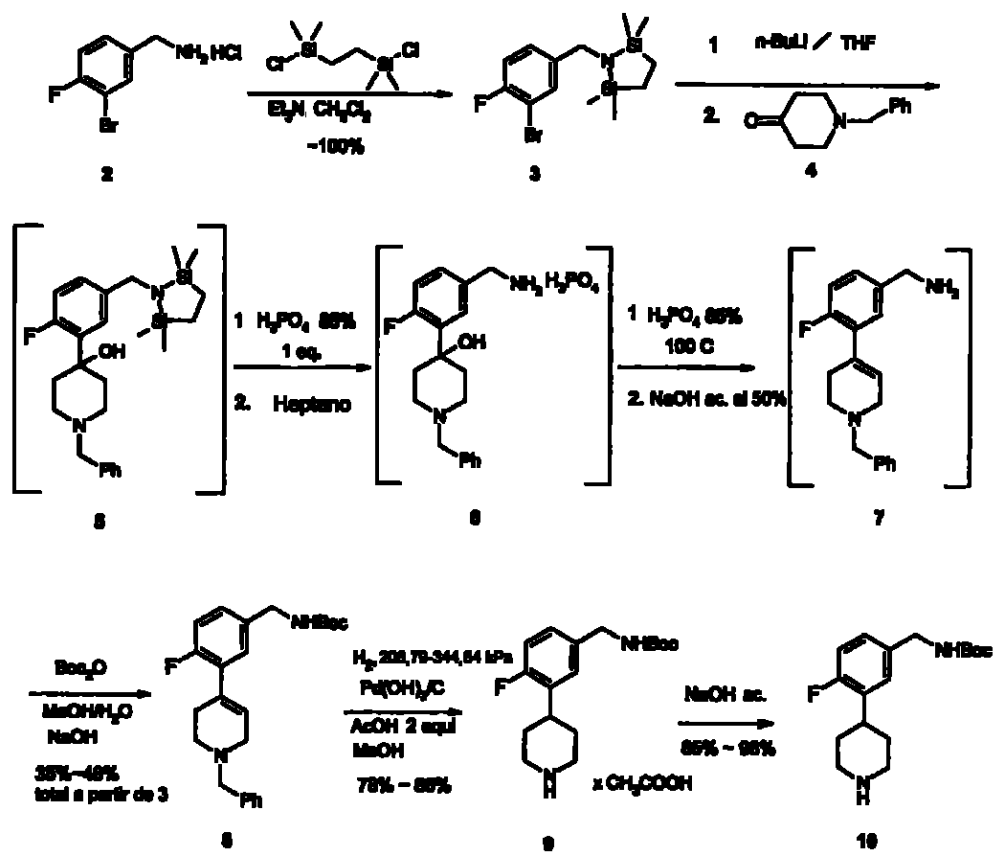
20 El compuesto 14 se convierte en el compuesto 15 por bromación en un disolvente orgánico inerte, tal como triclorometano o una mezcla de TBME/heptano para producir el compuesto 15 bromado

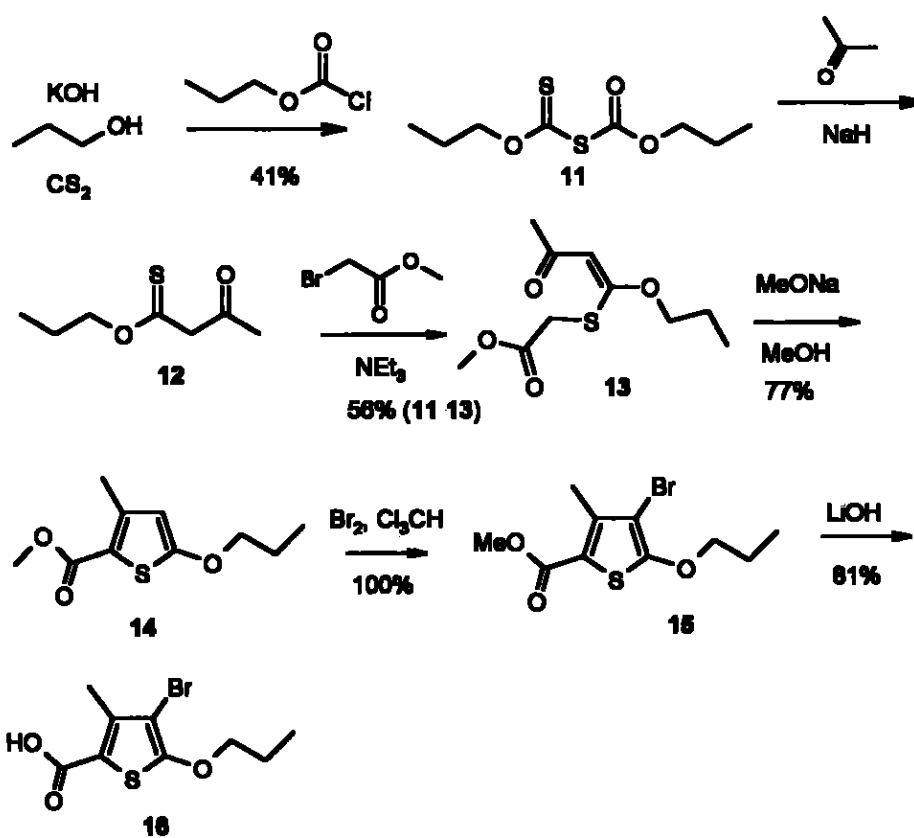
El compuesto 15 se convierte en el compuesto 16 por hidrolización usando una base inorgánica fuerte, tal como hidróxido de litio

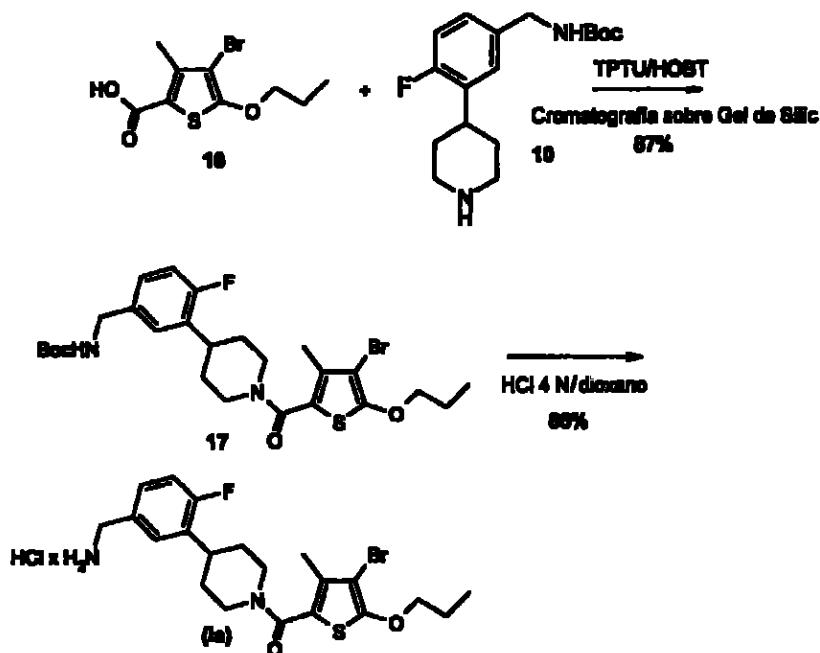
25 El compuesto 16 se convierte en el compuesto 17 por acoplamiento con el compuesto 10 usando un agente de acoplamiento tal como TPTU/HOBT o EDC en presencia de un disolvente inerte, tal como diclorometano y una amina terciaria tal como diisopropil etilamina en condiciones anhidras, para producir el compuesto 17 acoplado

El compuesto 17 se convierte en el compuesto I por desprotección en condiciones de ácido fuerte, tal como ácido clorhídrico, en presencia de un disolvente orgánico polar tal como dioxano, para producir el compuesto I desprotegido.

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49
50Esquema I

Esquema 2

Esquema 3

El compuesto de la presente invención es básico y tal compuesto es útil en forma de base libre o en forma de una sal de adición de ácidos farmacéuticamente aceptable del mismo.

- 5 Las sales de adición de ácidos pueden ser una forma más conveniente de uso y en la práctica, el uso de la forma de sal intrínsecamente equivale al uso de la forma de base libre. Los ácidos que pueden usarse para preparar las sales de adición de ácidos incluyen preferiblemente los que producen, en combinación con la base libre, sales farmacéuticamente aceptables, es decir sales cuyos aniones son no tóxicos para el paciente en dosis farmacéuticas de las sales, de forma que los efectos
- 10 inhibidores beneficiosos intrínsecos en la base libre no esté enmascarado por efectos secundarios atribuibles a los aniones. Aunque se prefieren las sales farmacéuticamente aceptables de dicho compuesto básico, las sales de adición de ácidos son útiles como fuentes de la forma de base libre aunque la sal particular per se, se desee sólo como un producto intermedio por ejemplo, cuando la sal se forma sólo con fines de purificación e identificación o cuando se usa como intermedio en la
- 15 preparación de una sal farmacéuticamente aceptable por procedimientos de intercambio iónico. Las sales farmacéuticamente aceptables dentro del alcance de la invención incluyen las derivadas de ácidos minerales y ácidos orgánicos e incluyen hidroháluros, *por ejemplo* hidrocloreuro e hidrobromuro, sulfatos, nitratos, sulfamatos, acetatos, citratos, lactatos, tartratos, malonatos, oxalatos, salicatos, propionatos, succinatos, fumaratos, maleatos, metilén-bis-*o*-hidroxinaftoatos, benzoatos, tosilatos, gentisatos, isctionatos, di-*p*-toluocitartratos, metanosulfonatos, etanosulfonatos, bencenosulfonatos, *p*-toluenosulfonatos, ciclohexilsulfamatos y quinatos. Una sal más particular del compuesto de fórmula I es la sal hidrocloreuro.
- 20

Además de ser útiles por sí mismas como compuesto activo, las sales del compuesto de la invención son útiles para la purificación del compuesto por ejemplo, por medio de la explotación de las diferencias de solubilidad entre las sales y el compuesto parental, productos secundarios y/o materiales de partida por técnicas bien conocidas para los especialistas en la técnica.

5 De acuerdo con otra característica de la invención, la sal de adición de ácidos del compuesto de esta invención puede prepararse por reacción de la base libre con el ácido apropiado por medio de la aplicación o adaptación de métodos conocidos. Por ejemplo, las sales de adición de ácidos del compuesto de esta invención pueden prepararse disolviendo la base libre en agua o en una solución acuosa del alcohol u otro disolvente adecuado que contenga el ácido apropiado y aislando la sal por
10 evaporación de la solución o por reacción de la base libre y el ácido en un disolvente orgánico, en cuyo caso la sal se separa directamente o puede obtenerse por concentración de la solución.

Las sales de adición de ácidos del compuesto de esta invención pueden regenerarse a partir de las sales por la aplicación o adaptación de métodos conocidos. Por ejemplo, el compuesto parental de la invención puede regenerarse a partir de sus sales de adición de ácidos por tratamiento con un álcali
15 por ejemplo, solución acuosa de bicarbonato sódico o solución acuosa de amoníaco.

Los materiales de partida e intermedios pueden prepararse por la aplicación o adaptación de métodos conocidos, por ejemplo, los métodos descritos en los ejemplos de referencia o sus equivalentes químicos evidentes.

La presente invención también se refiere algunos intermedios en los esquemas anteriores y como tales, los procesos descritos en este documento para su preparación constituyen características
20 adicionales de la presente invención.

Ejemplos

La presente invención pueden entenderse mejor haciendo referencia a los siguientes ejemplos no limitantes que se proporcionan a modo ejemplar de la invención. Los siguientes ejemplos se
25 presentan para ilustrar con más detalle realizaciones particulares de la invención. Sin embargo, no deben considerarse de ninguna manera limitantes del amplio alcance de la invención.

En los espectros de resonancia magnética nuclear (RMN) presentados más adelante, los desplazamientos químicos se expresan en ppm con respecto al tetrametilalano. Las abreviaturas tienen los siguientes significados: a = ancho, dd = doblete de dobletes, s = singlete, m = multiplete.
30

EJEMPLO 1

Etapas 1 Preparación de 1-(3-Bromo-4-fluoro-bencil)-2,2,5,5-tetrametil [1,2,5] azadiazolidina (Compuesto 3)

35 Se suspenden 110 g (0.46 mol) de hidrocloreto de 3-bromo-4-fluorobencilamina (2) en 900 ml de cloruro de metileno en un matraz de fondo redondo de tres bocas y de 2 l equipado con atmósfera de N₂, sensor de temperatura termopar recubierto de Teflón y agitador mecánico y se enfría

a -5°C en un baño de hielo. Se añaden un total de 144 g (1.42 mol, 3.1 equiv $d=0.7$) lo que produce una suspensión espesa. Después se añade gota a gota durante 1.5 horas una solución de 1.2 bis(clorodimetilsilil) etano (100 g, 0.46 mol) en 250 ml de cloruro de metileno mientras se mantiene la temperatura de la mezcla de reacción entre 5 y 8°C . La mezcla se agita durante 30 minutos y después
5 se calienta a temperatura ambiente. La suspensión de hidrocloreuro de trietilamina se retira por filtración. El filtrado se concentra al vacío (40°C <50 mbar), se añade 1 litro de pentano y el precipitado de $\text{Et}_3\text{N} \times \text{HCl}$ adicional que se forma se retira por filtración. El procedimiento se repite con 1 l más de pentano. El filtrado se concentra al vacío (40°C <5 mbar) hasta dar un líquido incoloro que solidifica tras un periodo de refrigeración, para dar 159 g (~100%) del compuesto 3 en forma de
10 un sólido cristalino blanco.

La finalización de la reacción debería controlarse usando ^1H NMR para asegurar que no queda esencialmente ningún resto de material de partida 2 y de hidrocloreuro de trietilamina según se ha consumido el *n*-butil litio en la etapa posterior por lo que da como resultado un menor rendimiento de la reacción.

15

Etapas 2 Preparación de 1-Benzil-4-[2-fluoro-5-(2,2,5,5-tetrametil-[1,2,5]-azadisilolidin-1-ilmetil)fenil]piperidin-4-ol (Compuesto 5)

Una solución del compuesto 3 (159 g, 0.4574 mol) en 1.5 l de THF se coloca en un matraz de fondo redondo, de tres bocas y de 5 l equipado con una atmósfera de N_2 , sensor de temperatura con termopar recubierto de Teflón y agitador mecánico y se enfría a -75°C . A esta solución agitada se le
20 añade gota a gota una solución 2.5 M de *n*-butil litio (192 ml, 0.48 mol 1.05 equiv) durante aproximadamente 1 hora mientras se mantiene la temperatura de la mezcla de reacción entre -72°C y -75°C . Después de 30 min, se añade gota a gota durante 1 hora una solución de 1-benzil-4-piperidona (Compuesto 4 88.2 g, 0.47 mol 1.02 equiv) en THF anhidro (350 ml + 50 ml de aclarado) mientras se
25 mantiene la temperatura de reacción por debajo de -70°C . Después de 20 min a una temperatura de -70°C a -75°C a la mezcla de reacción se le añaden 200 ml de metanol (cambia de color de naranja a amarillo) y después la mezcla se deja calentar a temperatura ambiente. La solución de reacción se concentra al vacío (50°C) para dar 295 g de un aceite pardo compuesto 5.

30 Etapas 3 Preparación de 4-(5-Aminometil-2-fluorofenil)-1-benzilpiperidin-4-ol (sal fosfato) (Compuesto 6)

El compuesto 5 bruto (~295 g) se diluye con 1 l de cloruro de metileno y se transfiere a un matraz de fondo redondo de tres bocas y de 3 litros equipado con sensor de temperatura termopar recubierto con Teflón y agitador mecánico. A esta solución se le añaden lentamente 53 g de H_3PO_4 al
35 85%(1 equiv) mientras se agita (exotérmica) y la mezcla se concentra al vacío (40°C). Se añade 1 l de cloruro de metileno y la mezcla se concentra al vacío (40°C 1 mbar) hasta dar una espuma amarilla.

que después se suspende en 1 l de heptano. Se forma un sólido y se aísla por filtración. El sólido castaño se seca para dar 190 g del compuesto 6. MS encontrado m/z 315 (M+H)

Etapa 4 Preparación de 3-(1-bencil 1,2,3,6-tetrahidro-piridin-4-il)-4-fluoro-bencilamina (Compuesto 7)

- Se transfiere un total de 190 g del compuesto 6 a un matraz de fondo redondo de tres bocas y de 2 l, equipado con sensor de temperatura termopar recubierto con Teflón y agitador mecánico. Se añade un total de 600 ml de H₃PO₄ al 85%. La suspensión resultante se calienta gradualmente a 100°C mientras se agita. La reacción se controla por HPLC con respecto a su finalización (típicamente de 2 a 3 horas). Una vez que la reacción se ha completado, la solución de reacción se enfría a temperatura ambiente y se diluye con 800 ml de agua. La capa acuosa se lava con éter (2 x 200 ml). Después, la capa acuosa se neutraliza con NaOH acuoso al 50% a pH > 9 mientras se mantiene la temperatura por debajo de 30 °C. Esta solución acuosa es un sistema tampón muy concentrado en el que el pH permanece sin cambios a aproximadamente 7-8 hasta que se alcanza el punto de neutralización. La confirmación de que la neutralización se ha completado se efectúa añadiendo unas pocas gotas de base a una pequeña muestra del líquido sobrenadante para asegurar que no se observa más precipitación. Una gran cantidad de la sal se retira por precipitación. La mezcla se filtra y el sólido se aclara con DCM (dicloruro de metileno) (aproximadamente 3 l) y 2 l de agua. La capa orgánica (fondo) se separa y se lava con agua (2 x 1 l). La solución orgánica se concentra al vacío (40°C) para dar 107 g de un aceite pardo, compuesto 7. MS encontrado m/z 297 (M+H).

Etapa 5 Preparación de éster terc-butílico del ácido [3-(1 Bencil 1,2,3,6-tetrahidropiridin-4-il)-4-fluoro-bencil]carbámico (Compuesto 8)

- A un matraz de fondo redondo, de 2 litros y 3 bocas, equipado con sensor de temperatura termopar recubierto con teflón y agitador mecánico se le añaden 50 g del compuesto 7 y una solución de metanol (800 ml) y agua (400 ml). Se añaden 36.8 g de anhídrido BOC y 2 ml de NaOH al 50% y la mezcla se agita a temperatura ambiente. El producto se retira por precipitación de la solución después de 2 horas de agitación. Si el producto de Boc no precipita, decantar la capa acuosa superior y añadir n-heptano al aceite para solidificar el producto. La mezcla se agita durante una noche a temperatura ambiente. El sólido se aísla por filtración y se suspende en 1.05 l de MeOH/agua (2 l en volumen) durante 4 horas. Después se aísla por filtración y se seca durante 4 días para dar 40 g (el rendimiento total es de aproximadamente 35% a 48% a partir del compuesto 3) de compuesto 8 en forma de un sólido amarillo claro. Pureza 96,3% por HPLC. MS m/z 397 (M+H). 398 (M+2H).

- Etapa 6 Preparación de éster terc-butílico del ácido 6 (4-Fluoro-3-piperidin-4-il-bencil)carbámico, sal acetato (Compuesto 9)**

Se cargan 64 g (0.16 mol) del compuesto 8, 6.4 g hidróxido de paladio/C 20%, 19.5 g (2 equiv) de ácido acético glacial y 250 ml de metanol en un recipiente de hidrogenación de 1 litro. El recipiente de la mezcla de reacción se purga (N_2 /vacío, 3 veces), después se carga H_2 a 275.71 kPa (40 psi) y se agita durante una noche a temperatura ambiente. El catalizador se retira por filtración y el filtrado se concentra al vacío (40°C) para producir un aceite. Se añaden 200 ml de éter isopropílico y se agita durante una noche. Un sólido blanco que precipita, se filtra, se aclara con éter isopropílico y se seca para dar 53.5 g de un sólido blanco con una pureza de 95.4 % por HPLC. El sólido se suspende en 500 ml de MTBE durante 5 horas, después se aísla por filtración y se suspende de nuevo en 500 ml de MTBE durante una noche. El sólido se aísla por filtración y se seca para producir 51.3 g (86.3%) de la sal acetato del compuesto 9 en forma de un sólido blanco. Análisis elemental. Calculado para $C_{17}H_{25}FN_2O_2$: C 61.94, H 7.93, N 7.6. Encontrado: C, 62.0; H 8.17; N 7.49. KF 0.34% de agua. HPLC: T_r 9.14 min, pureza 97 % por AUC. MS: m/z 309 (M+H), 310 (M+2H).

Etapas 7 Preparación de éster *tert*-butilico del ácido (4-Fluoro-3-pipendin-4-il bencil)carbámico (Compuesto 10)

Se disuelve la sal acetato del compuesto 9 (51 g) en 400 ml de agua y el pH se ajusta a 5 con HCl 2 N. La solución acuosa se lava con éter (2 x 200 ml). La capa acuosa se neutraliza a pH > 12 con NaOH ac. al 50% y se extrae con éter (2 x 300 ml). La capa orgánica se lava con agua y se seca sobre Na_2SO_4 y después se concentra hasta un aceite. Al aceite se le añaden 200 ml de n-pentano y se agita durante 3 horas. El producto sólido se aísla por filtración, se lava con n-pentano y se seca a temperatura ambiente con vacío doméstico durante 24 horas para producir 42 g del compuesto 10 (98%) en forma de un sólido blanco. MS (ESI) m/z 309 (M + H). Análisis elemental. Calculado para $C_{17}H_{25}FN_2O_2$: C 66.21, H 8.17, N 9.08. Encontrado sin corrección para agua: C 64.30, H 8.64, N 8.77. KF 2.57% de agua. HPLC: T_r 9.16 min, pureza 98.1 % por AUC.

Nota: Si la pureza de la sal acetato del compuesto 9 es menor del 95% por HPLC, puede usarse una solución de n-pentano y éter (hasta de 1 l en volumen) para solidificar el producto (base libre) a partir del aceite en lugar de sólo n-pentano. El producto es muy soluble en éter de forma que si se usa más éter se perderá más producto obteniéndose de esta manera un menor rendimiento.

EJEMPLO 2

Etapas 1 Preparación de sulfuro de bis(propoxitiocarbomilo) (compuesto 11)

Se añaden 84.2 g de hidróxido potásico en polvo (1.27 mol) a 530 ml de n-propanol colocado en un matraz de fondo redondo de tres bocas equipado con un agitador mecánico y un baño de refrigeración a temperatura ambiente. Después se añaden gota a gota durante 1 hora 80 ml de disulfuro

de carbono (1.33 mol) a la solución mediante un embudo adicional de presión equilibrada. Se continua agitando durante 3 horas. Se añaden 200 ml de agua. Se añaden gota a gota 73.5 g (0.6 mol) de cloroformato de propilo en forma pura mediante un embudo adicional de presión equilibrada. La mezcla se agita durante una noche a temperatura ambiente. La mezcla después se diluye con 400 ml de heptano. La capa acuosa se extrae dos veces con 100 ml de heptano. La capa orgánica combinada se lava con 100 ml de agua y 100 ml de salmuera y después se seca sobre carbonato potásico y se evapora. El propanol residual se retira adicionalmente por destilación a alto vacío para obtener un líquido amarillo transparente. Se disuelven 10 g del líquido amarillo transparente en 10 g de heptano y se purifica por cromatografía sobre gel de sílice, eluyendo con heptano para obtener 8.35 g del compuesto 11 (rendimiento de 41 %).

Etapas 2 Preparación de éster O-propílico del ácido 3-oxo-tiobutírico (Compuesto 12)

Se suspenden 1.82 g (4.5 mmol) de hidruro sodico en 40 ml de tolueno. A esta suspensión se le añade una solución de 4.76 g (20 mmol) del compuesto 11 en 10 ml de tolueno a 40°C con agitación. La reacción se inicia introduciendo una pequeña cantidad de hidruro potásico. Cuando se hace esto se forman burbujas y el color de la reacción cambia de amarillo a naranja. La mezcla de reacción se agita a 40°C durante una hora y después se enfría a 0°C en un baño de agua enfriada con hielo. Después, la mezcla de reacción se vierte en un vaso de precipitados que contiene 1 l de HCl 4 N hielo y 150 ml de éter. La capa orgánica se separa y se concentra. El producto bruto se purifica por cromatografía sobre gel de sílice, eluyendo con acetato de etilo al 5% en heptano para obtener éster O-propílico del ácido 3-oxo-tiobutírico (compuesto 12).

Etapas 3 Preparación de éster metílico del ácido (3-oxo-1-propoxi-but 1-enilsulfamilo)-acético (Compuesto 13)

Después, el compuesto 12 se disuelve en 40 ml de DMF y se enfría a 0°C. A esta solución se le añaden 4.6 g de acetato de α -bromo metilo en 5 ml de DMF y 5.2 ml de trietilamina. Instantáneamente se forma un precipitado blanco. Esta suspensión se agita a 0°C durante 2 horas y después se vierte en éter/agua enfriada con hielo. La capa orgánica se separa y se concentra. El producto bruto se purifica por cromatografía sobre gel de sílice y después se eluye con metanol al 3% en DCM para obtener 2.61 g del compuesto 13 (rendimiento de 56% en dos etapas).

Etapas 4 Preparación de éster metílico del ácido 3-metil-5-propoxi-tiufen-2-carboxílico (compuesto 14)

Una mezcla de 2.61 g (11.24) del compuesto 13 y 2 ml de metóxido sodico 0.5 M/metanol en 40 ml de metanol se calienta a 70-73°C durante 40 minutos. Después, la mezcla se vierte en éter/agua enfriada con hielo. La capa orgánica se separa y se concentra. El producto bruto se purifica por

cromatografía sobre gel de sílice, eluyendo con DCM para obtener 1.85 g (rendimiento de 76.8) del compuesto 14

5 Etapa 5 Preparación de éster metílico del ácido 4-bromo-3-metil-5-propoxi-tiofeno-2-carboxílico (compuesto 15)

10 A una solución de 1.22 g (5.7 mmol) del compuesto 14 en 20 ml de triclorometano se le añaden 11 ml de bromo 0.55 M/triclorometano a 0°C y se agita durante 10 minutos. La mezcla se inactiva con una solución acuosa de sulfuro sódico y se extrae con DCM. La capa orgánica se separa y se concentra. El producto bruto se purifica con una capa de carbonato potásico-gel de sílice con DCM para obtener 1.67 g (rendimiento de 100%) del compuesto 15

15 Etapa 6 Preparación de ácido 4-bromo-3-metil-5-propoxi-tiofeno-2-carboxílico (compuesto 16)

20 A una solución de 1.67 g del compuesto 15 (5.70 mmol) en 27 ml de dioxano se le añaden 10 ml de LiOH 2 M/agua y 9 ml de agua. La mezcla se agita a temperatura ambiente durante 4 horas. Después, la mezcla se diluye con 10 ml de agua y se extrae dos veces con 10 ml de éter. La solución acuosa se enfría en un baño de agua enfriada con hielo y se acidifica con HCl 4 M. El sólido blanco se recoge por filtración por succión para proporcionar 1.28 g (rendimiento de 80.5%) del compuesto 16

25 EJEMPLO 3

30 Etapa 1 Preparación de éster terc-butílico del ácido {3-[1-(4-bromo-3-metil-5-propoxi-tiofeno-2-carbonil)-piperidin-4-il]-4-fluoro-bencil}-carbámico (compuesto 17)

35 A una solución de 170 mg del compuesto 16 (0.61 mmol) en 25 ml de DCM en una atmósfera de N₂ se le añaden 170 mg de TPTU (0.61 mmol) y 80 mg de 1-hidrox-1H-benzotriazol (HOBt) (0.61 mmol). La mezcla se agita durante 3 minutos. Después, a la mezcla se le añade una solución de 200 mg (0.65 mmol) del compuesto 10 en 5 ml de DCM y 0.3 ml de diisopropil etilamina (1.2 mmol). La mezcla se agita a temperatura ambiente durante 24 horas. Después, la mezcla se lava con 20 ml de agua, se seca sobre sulfato sódico anhidro y se concentra. El aceite bruto se purifica por cromatografía sobre gel de sílice, eluyendo con metanol al 3% en DCM para obtener 0.3 g (rendimiento de 86.5%) del compuesto 17

40 ¹H RMN [CDCl₃] 7.14-7.04 (m, 2H), 6.95 (dd, H), 4.82 (s, H), 4.38 (d, 2H), 4.23 (d, 2H), 4.05 (t, 2H), 3.17-2.95 (m, 3H), 2.21 (s, 3H), 1.92-1.59 (m, 6H), 1.44 (s, 9H), 1.05 (t, 3H). MS(ESI+) 569 (M⁺+1)

Etapa 2 Preparación de hidrocloreuro de [4-(5-aminometil 2 fluoro-fenil)-piperidin 1-il]-(4-bromo-3-metil 5-propoxi-tiofen 2-il)-metazona (compuesto I)

Una solución de 0.25 g del compuesto 17 (0.44 mmol) en 8 ml de HCl 4 M/dioxano en una atmósfera de nitrógeno se agita a temperatura ambiente durante 3 horas. La solución se diluye con 30 ml de éter y se agita durante 5 min. El líquido se decanta del sólido. El sólido se lava con 30 ml de éter y el líquido se decanta de nuevo. Después, el sólido se disuelve en metanol al 3% en DCM y se purifica por cromatografía sobre gel de sílica, eluyendo con metanol al 3%-10% en DCM. Se obtiene el compuesto I 0.19 g (rendimiento de 86.4%) en forma de un sólido amorfo retirando el disolvente de las fracciones puras combinadas del producto por evaporación. El producto es un vidrio amorfo.

$^1\text{H RMN}$ [CDCl_3] δ (TMS) 8.62 (br s, 3H), 7.53-7.43 (m, H), 7.36-7.26 (m, H), 6.97 (dd, H), 4.22 (br d, 2H), 4.18-3.99 (m, 4H), 3.16-2.90 (m, 3H), 2.17 (s, 3H), 2.00-1.60 (m, 6H), 1.02 (t, 3H). MS(ESI+) 469 (M^++1). 100% de pureza por LC/MS (UV 220 nm y conteo iónico total).

ACTIVIDAD BIOLÓGICA

Las propiedades del compuesto de la presente invención se demuestran por 1) su potencia inhibidora de β -Tryptasa (valores de CI_{50} y K_i) y 2) su actividad medida en el modelo de hiperreactividad de las vías respiratorias de cobaya (DE_{50} Oral).

PROCEDIMIENTO DE ENSAYO IN VITRO

Como todas las acciones de la triptasa, como se ha descrito en la sección de antecedentes, dependen de su actividad catalítica, entonces los compuestos que inhiben su actividad catalítica inhibirán potencialmente las acciones de la triptasa. La inhibición de esta actividad catalítica puede medirse por medio del ensayo enzimático in vitro y el ensayo celular.

La actividad de inhibición de la triptasa se confirma usando triptasa aislada de pulmón humano o beta triptasa humana recombinante expresada en células de levadura. Se obtienen resultados esencialmente equivalentes usando la enzima nativa aislada o la enzima expresada. El procedimiento de ensayo emplea una microplaca de 96 pocillos (Costar 3590) usando L-piroglutamil L-prolil L-arginina-*para*-nitroamida (S2366 Quadrach) como sustrato (esencialmente como describe McEuen *et al.* Biochem Pharm, 1996 52 páginas 331-340). Los ensayos se realizan a temperatura ambiente usando sustrato 0.5 mM ($2 \times K_m$) y la microplaca se lee en un lector de microplacas (lector de placas Beckman Biomek) a una longitud de onda de 405 nm.

Materiales y Métodos para la Selección Primaria de la Triptasa (Ensayo Cromogénico)

Tampón de Ensayo

Tris (pH 8.2) 50 mM NaCl 100 mM Tween 20 al 0.05%, 50 $\mu\text{g/ml}$ de heparina.

Sustrato

S2366 (Soluciones madre de una concentración 2.5 mM)

Enzima

Soluciones madre de beta triptasa recombinante purificada de 310 µg/ml

5 Protocolo (Determinación de un solo punto)

- Añadir 60 µl de sustrato diluido (concentración final de 500 µM en tampón de ensayo) a cada pocillo
- Añadir compuesto por duplicado a una concentración final de 20 µM a un volumen de 20 µl
- Añadir enzima a una concentración final de 50 ng/ml en un volumen de 20 µl

10 • El volumen total de cada pocillo es de 100 µl

- Agitar brevemente para mezclar e incubar a temperatura ambiente en la oscuridad durante 30 minutos
- Leer las absorbancias a 405 nM

Cada placa tiene los siguientes controles

15 **Totales** 60 µl de sustrato, 20 µl de tampón (con una concentración final del 0.2% de DMSO), 20 µl de enzima**No específico** 60 µl de sustrato 40 µl de tampón (con DMSO al 0.2% DMSO)**Totales** 60 µl de sustrato, 20 µl de tampón (Sin DMSO) 20 µl de enzima**No específico** 60 µl de sustrato 40 µl de tampón (Sin DMSO)20 Protocolo (Determinación de CI_{50} y K_i)

El protocolo es esencialmente igual que el anterior con la excepción de que el compuesto se añade por duplicado a las siguientes concentraciones finales 0.01 0.03 0.1 0.3 1 3 10 µM (Todas las diluciones se realizan manualmente). Para cada ensayo, ya sea la determinación de un solo punto o del valor de CI_{50} , se usa un compuesto patrón para obtener el CI_{50} por comparación. A partir del valor de CI_{50} , la K_i puede calcularse usando la siguiente fórmula $K_i = CI_{50}/(1 + [Sustrato]/K_m)$

25 CI_{50} , la K_i puede calcularse usando la siguiente fórmula $K_i = CI_{50}/(1 + [Sustrato]/K_m)$

La potencia inhibidora de la β Triptasa para el compuesto de fórmula I corresponde a valores de CI_{50} y K_i de 76 nM y 15 nM respectivamente.

PROCEDIMIENTO DE ENSAYO IN VIVO30 Protocolo de ensayo.

Sensibilización y tratamiento con fármaco Se sensibilizan cobayas Hartley macho (225-250 g) con ovoalbúmina (0.5 ml de una solución al 1%, i.p. y s.c.). En el día 4 los animales recibieron una inyección de refuerzo (i.p.) de 0.5 ml de ovoalbúmina al 1%. En el día 21 los animales reciben por vía oral (2 ml/kg) vehículo (metilcelulosa al 0.5% / Tween 80 al 0.2%) o compuesto de ensayo dos horas antes de la exposición al antígeno. Treinta minutos antes de la exposición al antígeno, a los animales

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también se les inyecta mepiramina (30 mg/kg, i p) para impedir el colapso anafiláctico. Después los animales se exponen durante 5 minutos a un aerosol de solución salina (animales de control) u ovoalbumina al 1% usando un nebulizador de Vibrias Ultraneb.

- Medición de AHR. De dieciocho a veinticuatro horas después de la exposición, los animales se anestesian con una combinación de ketamina (133 mg/kg) y xilazina (24 mg/kg) administradas por vía intramuscular. Se preparan quirúrgicamente y después se montan en un pletismógrafo de cuerpo entero para medir la función pulmonar. Los animales se conectan a ventiladores Ugo-Basile que suministran un volumen corriente de 1 ml/100 g a una velocidad de 50 respiraciones/minuto a través de una cánula traqueal. También se cánula la vena yugular para la exposición a histamina. Se pone una cánula esofágica rellena con agua de tal forma que se pueda registrar la presión transpulmonar. La presión transpulmonar se mide como la diferencia entre las cánulas traqueal y esofágica usando un transductor de presión diferencial. El volumen, el flujo de aire y las señales de presión transpulmonar se controlan usando un sistema de análisis pulmonar (software Buxco XA) y se usan para calcular la resistencia pulmonar (cm H₂O/ml/s) y la complianza dinámica (ml/cm H₂O). La resistencia de las vías respiratorias y la complianza dinámica se calculan en una base de respiración por respiración. La histamina se administra por vía intravenosa y se evalúa la reactividad a concentraciones crecientes (0,3-20 µg/kg). Los valores de DE₅₀ se estiman a partir de los valores de área bajo la curva (AUC) obtenidos a partir de las curvas de dosis-respuesta a histamina individuales.

Niveles de fármaco en plasma y en pulmón

- Los niveles de compuesto en plasma y en pulmón se determinan en grupos satélite. Para la determinación de los niveles de fármaco se usan de tres a cuatro cobayas de cada uno de los grupos de tratamiento con fármaco experimental. En el punto de tiempo indicado (2 o 24 horas después de la dosificación), los animales se eutanizan y se obtienen muestras de un 1 ml de sangre por punción cardíaca y se recogen en jeringa recubiertas con heparina que contienen 20 µl (por 1 ml de sangre) de una solución de hidralazina 5 mM. El plasma se separa del componente celular de la sangre por centrifugación y se almacena a -20°C hasta que se ensaya. Las muestras de pulmón se disecan del tejido conectivo, se secan con papel secante, se pesan y se almacenan en viales de 20 ml que contienen 5 ml de una solución de hidralazina 5 mM en solución salina. Las muestras de plasma congelada después se transfieren en hielo seco al grupo Pilot PK para determinar los niveles de compuesto.

Resultados.

- La eficacia del compuesto II se perfila basándose en la Hiper-respuesta de las Vías Respiratorias (AHR) a la histamina en cobayas sensibilizadas por vía oral. El compuesto I no tiene ningún efecto sobre la resistencia basal de las vías respiratorias o la complianza pulmonar dinámica basal.

- La sensibilización y exposición individual con ovoalbumina tiene como resultado un aumento de la reactividad bronquial a la histamina como se indica por un desplazamiento hacia la izquierda en

la curva de dosis-respuesta del espasmogeno y también por un aumento significativo en el área bajo la curva (AUC) tanto para la resistencia de las vías respiratorias como para la complianza pulmonar. Los valores absolutos representan un aumento de la resistencia de las vías respiratorias y una reducción en la complianza pulmonar.

5 Tras la dosificación oral, 2 horas de la exposición a ovoalbumina, el compuesto I protege significativamente frente a la AHR estimulada por antígeno a la histamina con un valor de $DE_{30} = 0.1$ mg/kg medido por resistencia de las vías respiratorias y complianza pulmonar dinámica.

10 En animales separados, se miden los niveles de compuesto I en el fluido de lavado broncoalveolar (BAL), pulmón y plasma, dos horas después de la dosificación del compuesto (1 mg/kg, p.o.). Hay una cantidad apreciable de compuesto I en órganos diana tales como pulmón y BAL (sin tener en cuenta el factor de dilución para BAL). Los niveles del compuesto en plasma se detectan a un nivel mucho menor.

15 En animales satélite, los niveles de compuesto I, tanto en pulmón como en plasma, también se miden 24 horas después de la dosificación. Aunque no pudo detectarse en plasma, sin embargo, había una cantidad apreciable de compuesto I dependiente de la dosis detectada en el pulmón de cobaya 24 horas después de la dosificación. También se demuestra que el compuesto I posee una larga duración de la acción con un valor medio de DE_{30} de 0.4 mg/kg cuando se dosifica 24 horas antes de la exposición al antígeno. Esta larga duración de la acción está de acuerdo con su exposición prolongada.

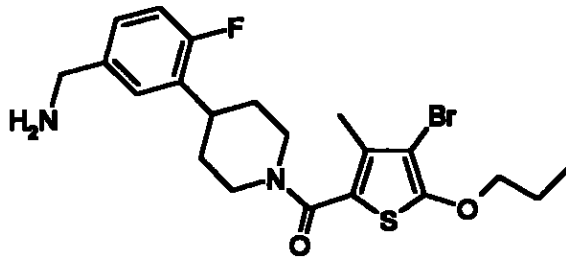
20 Los datos orales del compuesto de la presente invención en el modelo de cobaya de hiperrespuesta de las vías respiratorias demuestra claramente que el compuesto presenta actividad inhibidora de tripsina. Por consiguiente, el compuesto de la presente invención fácilmente tiene aplicación como agente farmacéutico para tratar una amplia diversidad de afecciones relacionadas con la tripsina, y naturalmente, en métodos para tratar tales afecciones en un paciente.

25 La presente invención no se limita en alcance por las realizaciones específicas descritas en este documento. De hecho, para los especialistas en la técnica serán evidentes diversas modificaciones de la invención además de las descritas en este documento por la descripción anterior y las figuras adjuntas. Tales modificaciones pretenden incluirse dentro del alcance de las reivindicaciones adjuntas.

En el presente documento se citan diversas publicaciones, cuyas descripciones se incorporan como referencia en su totalidad.

REIVINDICACIONES

1 Un compuesto de fórmula I



(I)

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o un profármaco, sal farmacéuticamente aceptable o solvato del mismo

2 El compuesto de la reivindicación 1 como una sal farmacéuticamente aceptable del mismo

3 El compuesto de la reivindicación 2 donde la sal farmacéuticamente aceptable es un hidrocloruro.

10 4 Un método para tratar a un paciente que padece o que es propenso a padecer una afección fisiológica en necesidad de mejora de un inhibidor de triptasa que comprende administrar al paciente una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1

5 El método de la reivindicación 4 donde la afección fisiológica se selecciona entre el grupo que consiste en enfermedad inflamatoria, una enfermedad de destrucción del cartílago de las articulaciones, conjuntivitis ocular, conjuntivitis vernal, enfermedad inflamatoria del intestino, asma, rinitis alérgica, enfermedad pulmonar intersticial, fibrosis, escleroderma, fibrosis pulmonar, cirrosis hepática, fibrosis de miocardio, neurofibroma, cicatrización hipertrófica, afección dermatológica, afección relacionada con la ruptura de placas ateroscleróticas, enfermedad periodontal, retinopatía diabética, crecimiento tumoral, anafilaxis, esclerosis múltiple, úlcera péptica e infección por virus sincitial.

20 6 El método de la reivindicación 5 donde la afección fisiológica es una enfermedad inflamatoria.

7 El método de la reivindicación 6, donde la enfermedad inflamatoria es inflamación de las articulaciones, artritis, artritis reumatoide, espondilitis reumatoide, artritis gotosa, artritis traumática, artritis de rubecola, artritis psoriática u osteoartritis.

25 8 El método de la reivindicación 5 donde la afección fisiológica es COPD

9 El método de la reivindicación 5 donde la afección fisiológica es exacerbaciones de COPD

10 El método de la reivindicación 5 donde la afección fisiológica es una afección dermatológica.

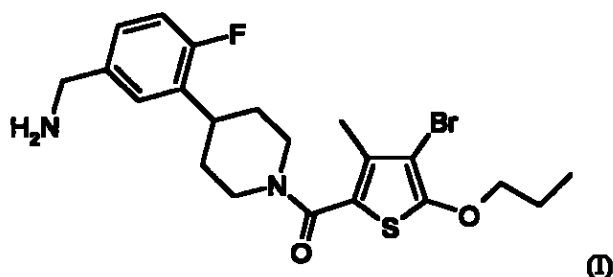
11 El método de la reivindicación 10 donde la afección dermatológica es dermatitis atópica o psoriasis.

30 12 El método de la reivindicación 5 donde la afección fisiológica está relacionada con la ruptura de placas ateroscleróticas.

- 13 El método de la reivindicación 12, donde la ruptura de placas ateroscleróticas es posterior a un infarto de miocardio, apoplejía o angina.
- 14 Un método para tratar a un paciente que padece asma, que comprende administrar al paciente una combinación de una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1 y un segundo compuesto seleccionado entre el grupo que consiste en un agonista beta adrenérgico, un anticolinérgico, corticosteroide anti-inflamatorio y un agente anti-inflamatorio.
- 15 El método de la reivindicación 4 donde la administración es tal que el compuesto de la reivindicación 1 se distribuye preferentemente en el tejido pulmonar en lugar de en el plasma.
- 16 Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1 y un vehículo farmacéuticamente aceptable del mismo.
- 17 Una composición farmacéutica que comprende un compuesto de la reivindicación 1 y una cantidad terapéuticamente eficaz de un segundo compuesto seleccionado entre el grupo que consiste en un agonista beta adrenérgico, un anticolinérgico, corticosteroide anti-inflamatorio y agente anti-inflamatorio y un vehículo farmacéuticamente aceptable.
- 18 La composición farmacéutica de la reivindicación 17 donde el segundo compuesto es un agonista beta adrenérgico.
- 19 La composición farmacéutica de la reivindicación 18 donde el agonista beta adrenérgico se selecciona entre albuterol, terbutalina, formoterol, fenoterol o prenalina.
- 20 La composición farmacéutica de la reivindicación 17 donde el segundo compuesto es un anticolinérgico.
- 21 La composición farmacéutica de la reivindicación 20 donde el anticolinérgico es bromuro de ipratropio.
- 22 La composición farmacéutica de la reivindicación 17 donde el segundo compuesto es un corticosteroide anti-inflamatorio.
- 23 La composición farmacéutica de la reivindicación 22 donde el corticosteroide anti-inflamatorio se selecciona entre dipropionato de beclometasona, triamcinolona acetomida, flumisolida o dexametasona.
- 24 La composición farmacéutica de la reivindicación 17 donde el segundo compuesto es un agente anti-inflamatorio.
- 25 La composición farmacéutica de la reivindicación 24 donde el agente anti-inflamatorio es cromoglicato sódico o nedocromil sódico.
- 26 La composición farmacéutica de la reivindicación 17 donde el segundo compuesto es un vehículo farmacéuticamente aceptable del mismo.

RESUMEN DE LA DESCRIPCIÓN

La presente invención incluye el compuesto de fórmula I



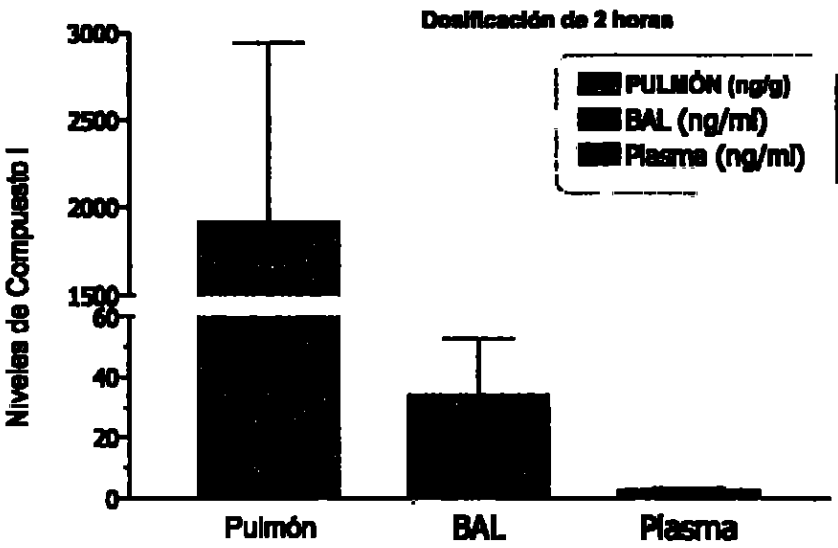
5 o un profármaco, farmacéuticamente aceptable o solvato de dicho compuesto.

Además, la presente invención se refiere a una composición farmacéutica que comprende una cantidad farmacéuticamente eficaz del compuesto de fórmula I y un vehículo farmacéuticamente aceptable.

10 Además, la presente invención se refiere al uso de un compuesto de fórmula I como inhibidor de triptasa, que comprende introducir el compuesto en una composición que comprende triptasa. Además, la presente invención se refiere al uso de un compuesto de fórmula I para tratar a un paciente que padece o propenso a padecer una afección fisiológica que necesita la mejora de un inhibidor de triptasa que comprende administrar al paciente una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1

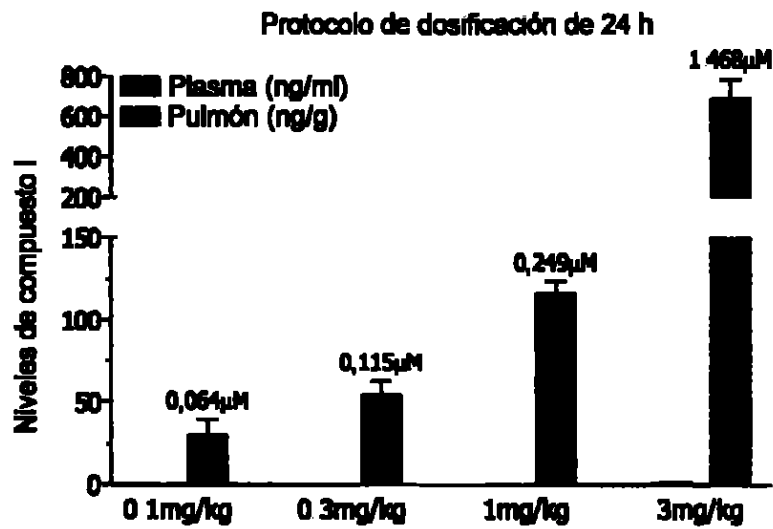
15 La presente invención también se refiere a la preparación de un compuesto de fórmula I

Figura I



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Figura II



PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form PCT/RO/101 PCT Request Prepared Using	PCT-SAFE [EASY mode] Version 3 50 (Build 0002 169)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	US20040013WO
I	Title of Invention	[4 - (5-AMINOMETHYL-2-FLUORO-PHENYL) - PIPERIDIN-1-YL] - (4-BROMO-3-METHYL-5-PROPOXY-THIOPHEN-2-YL) - METHANONE HYDROCHLORIDE AS AN INHIBITOR OF MAST CELL TRYPTASE
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	AVENTIS PHARMACEUTICALS INC
II-5	Address	300 Somerset Corporate Boulevard Bridgewater, New Jersey 08807-2854 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	(908) 231-3800
II-9	Facsimile No.	(908) 231-2626

69

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Original (for SUBMISSION)

III-1	Applicant and/or inventor	
III-1.1	This person is	applicant and inventor
III-1.2	Applicant for	US only
III-1.4	Name (LAST First)	GAO, Zhongli
III-1.5	Address	26 Running Brook Circle Flemington, NJ 08822 United States of America
III-1.6	State of nationality	US
III-1.7	State of residence	US
III-2	Applicant and/or inventor	
III-2.1	This person is	applicant and inventor
III-2.2	Applicant for	US only
III-2.4	Name (LAST First)	DAVIS, Larry
III-2.5	Address	7 Bird Lane Sergeantsville, NJ 08557 United States of America
III-2.6	State of nationality	US
III-2.7	State of residence	US
III-3	Applicant and/or inventor	
III-3.1	This person is	applicant and inventor
III-3.2	Applicant for	US only
III-3.4	Name (LAST First)	LEVELL, Julian
III-3.5	Address	8 Woodland Road Bernardsville, NJ 07924 United States of America
III-3.6	State of nationality	GB
III-3.7	State of residence	US
III-4	Applicant and/or inventor	
III-4.1	This person is	applicant and inventor
III-4.2	Applicant for	US only
III-4.4	Name (LAST First)	CZEKAJ, Mark
III-4.5	Address	3897 Charter Club Drive Doylestown, PA 18901 United States of America
III-4.6	State of nationality	US
III-4.7	State of residence	US

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III-5	Applicant and/or inventor	applicant and inventor
III-5-1	This person is	US only
III-5-2	Applicant for	US only
III-5-4	Name (LAST First)	SLEDESKI, Adam W
III-5-5	Address	24 Fisher Farm Road Belle Mead, NJ 08502 United States of America
III-5-6	State of nationality	PL
III-5-7	State of residence	US
IV 1	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
IV 1 1	Name (LAST First)	KNIGHT, Julie, Anne
IV 1-2	Address	Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
IV 1-3	Telephone No.	(908) 231-3679
IV 1-4	Facsimile No.	(908) 231-2626
IV-1-5	e-mail	julie.knight@aventis.com
IV 1-6	Agent's registration No.	48867
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	BARNEY Charlotte, L (35060); BENDER, Kelly (52610); BOLCSAK, James, W (39912); COPPOLA, William, C (41686); DAHLING, Gerald, V (29632); DARKES, Paul, R (33862); DOLAN, Peter, L (46307); GERMAN, Joel, B (48676); GUPTA, Balaram (40009); KIRK, Joseph, P, Jr (36844); KRUPEN, Karen, I (34647); KURYS, Barbara, E (34650); LIN, Jiang (51065); MOON, Carolyn, D (33022); NELLIGAN, Mark, C (36389); NEWMAN, Irving (22638); OEHLER, Ross, J (33270); ORT, Ronald, G (36969); PARKER, Raymond, S, III (34893); ROSSI, Joseph (47038); STRUPCZEWSKI, Joseph (50903)

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V	DESIGNATIONS	
V 1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI 1 1	Filing date	26 March 2004 (26 03 2004)
VI 1-2	Number	60/556,927
VI-1-3	Country	US
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s).	VI-1
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)
VIII	Declarations	Number of declarations
VIII-1	Declaration as to the identity of the inventor	-
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	1
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-

VII-3-1	Declaration. Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(II) and 51bis.1(a)(II)) Name	in relation to this international application AVENTIS PHARMACEUTICALS INC is entitled to claim priority of earlier application No 60/556,927 by virtue of the following
VIII-3-1(i) v)		an assignment from GAO, Zhongli to AVENTIS PHARMACEUTICALS INC , dated 04 June 2004 (04 06 2004)
VIII-3-1(i) v)		an assignment from DAVIS, Larry to AVENTIS PHARMACEUTICALS INC ; dated 02 June 2004 (02 06 2004)
VIII-3-1(i) v)		an assignment from LEVELL, Julian to AVENTIS PHARMACEUTICALS INC , dated 02 June 2004 (02 06 2004)
VIII-3-1(i) v)		an assignment from CZEKAJ, Mark to AVENTIS PHARMACEUTICALS INC , dated 07 June 2004 (07 06 2004)
VIII-3-1(i) v)		an assignment from SLEDESKI, Adam W to AVENTIS PHARMACEUTICALS INC , dated 10 June 2004 (10 06 2004)
VIII-3-1(i) x)	This declaration is made for the purposes of	all designations

VII-4-1	Declaration. Inventorship (only for the purposes of the designation of the United States of America) Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought This declaration is directed to the international application of which it forms a part (if filing declaration with application) I hereby declare that my residence, mailing address, and citizenship are as stated next to my name I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed
VII-4-1 1	Prior applications.	

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C F R § 1 56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon
VIII-4-1 1 1	Name (LAST First)	GAO, Zhongli
VIII-4-1 1-2	Residence: (city and either US State, if applicable or country)	Flemington,
VIII-4-1 1-3	Mailing address.	26 Running Brook Circle Flemington, NJ 08822 United States of America
VIII-4-1 1-4	Citizenship:	US
VIII-4-1 1-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor not that of the agent)	
VIII-4-1 1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

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Original (for SUBMISSION)

VIII-4-1 2-1	Name (LAST First)	DAVIS, Larry
VIII-4-1 2-2	Residence: (city and either US State, if applicable, or country)	Sergeantsville,
VIII-4-1 2-3	Mailing address:	7 Bird Lane Sergeantsville, NJ 08557 United States of America
VIII-4-1 2-4	Citizenship:	US
VIII-4-1 2-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor not that of the agent)	
VIII-4-1 2-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1 3-1	Name (LAST First)	LEVELL, Julian
VIII-4-1 3-2	Residence: (city and either US State, if applicable, or country)	Bernardsville,
VIII-4-1 3-3	Mailing address:	8 Woodland Road Bernardsville, NJ 07924 United States of America
VIII-4-1 3-4	Citizenship:	GB
VIII-4-1 3-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor not that of the agent)	
VIII-4-1 3-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

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Original (for SUBMISSION)

VIII-4-1 4-1	Name (LAST First)	CZEKAJ, Mark
VIII-4-1 4-2	Residence: (city and either US State, if applicable, or country)	Doylestown
VIII-4-1 4-3	Mailing address:	3897 Charter Club Drive Doylestown, PA 18901 United States of America
VIII-4-1 4-4	Citizenship:	US
VIII-4-1 4-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor not that of the agent)	
VIII-4-1 4-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1 5-1	Name (LAST First)	SLEDESKI, Adam, W
VIII-4-1 5-2	Residence: (city and either US State, if applicable, or country)	Belle Mead,
VIII-4-1 5-3	Mailing address:	24 Fisher Farm Road Belle Mead, NJ 08502 United States of America
VIII-4-1 5-4	Citizenship:	PL
VIII-4-1 5-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor not that of the agent)	
VIII-4-1 5-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

PCT REQUEST

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	10	✓
IX-2	Description	29	-
IX-3	Claims	2	-
IX-4	Abstract	1	✓
IX-5	Drawings	2	-
IX-7	TOTAL	44	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-18	Figure of the drawings which should accompany the abstract	2	
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST First)	KNIGHT, Julie, Anne	
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

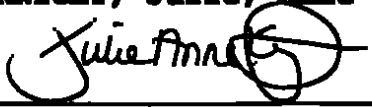
FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PCT (ANNEX FEE CALCULATION SHEET)

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(This sheet is not part of and does not count as a sheet of the International application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared Using	
0-4-1	PCT-SAFE [EASY mode] Version 3 50 (Build 0002 169)	
0-9	Applicant's or agent's file reference	
2	Applicant	
12	Calculation of prescribed fees	
12-1	Transmittal fee T	fee amount/multiplier
12-2-1	Search fee S	Total amounts (USD)
12-2-2	International search to be carried out by EP	
12-3	International filing fee (first 30 sheets) H1	1211
12-4	Remaining sheets	14
12-5	Additional amount (A) 13	
12-6	Total additional amount I2	182
12-7	H1 + I2 = I	1393
12-12	EASY Filing reduction R	-87
12-13	Total International filing fee (I-R) J	1306
12-14	Fee for priority document	
12-15	Number of priority documents requested	1
12-16	Fee per document (Q) 20	
12-17	Total priority document fee: P	20
12-18	TOTAL FEES PAYABLE (T+S+H+P)	3701
12-19	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions	
12-20-1	The receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
12-20-2	Authorization to charge the total fees indicated above	✓
12-20-3	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	✓
12-21	Authorization to charge the fee for priority document	✓
12-22	Deposit account No.	18-1982
12-23	Date	24 March 2005 (24 03 2005)
12-24	Name and signature	KNIGHT, Julie, Anne 

The present invention extends to the compound of formula I or a prodrug, pharmaceutically acceptable salt or solvate of said compound. Furthermore, the present invention is directed to a pharmaceutical composition comprising a pharmaceutically effective amount of the compound of formula I and a pharmaceutically acceptable carrier. Furthermore, the present invention is directed to the use of a compound of formula I as an inhibitor of tryptase comprising introducing the compound into a composition comprising tryptase. In addition, the present invention is directed to the use of a compound of formula I for treating a patient suffering from or subject to a physiological condition in need of amelioration of an inhibitor of tryptase comprising administering to the patient a therapeutically effective amount of the compound of Claim 1. The present invention is directed also to the preparation of a compound of formula I.

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13-2-1	Validation messages Request	Green? The title of the invention shall be short and precise Please verify
13-2-8	Validation messages Declarations	Green? Manually inputted data Please verify the contents of the information provided
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected

80-
81

PCT POWER OF ATTORNEY

Duplicate of Original

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 80.4)	
0-1 1	Prepared Using	PCT-SAFE [EASY mode] Version 3 50 (Build 0002 169)

PCT POWER OF ATTORNEY

Duplicate of Original

1	The undersigned applicant(s)	AVENTIS PHARMACEUTICALS INC ; GAO Zhongli DAVIS, Larry; LEVELL, Julian; CZEKAJ Mark; SLEDESKI Adam, W
1 1-1	hereby appoints (appoint) the following person	KNIGHT Julie, Anne Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1-2	hereby appoints (appoint) the following person	BARNEY, Charlotte L Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1-3	hereby appoints (appoint) the following person	BENDER Kelly Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1-4	hereby appoints (appoint) the following person	BOLCSAK James W Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1-5	hereby appoints (appoint) the following person	COPPOLA William C Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1-6	hereby appoints (appoint) the following person	DAHLING Gerald, V Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1 7	hereby appoints (appoint) the following person	DARKES, Paul R Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater New Jersey 08807-0800 United States of America
1 1-8	hereby appoints (appoint) the following person	DOLAN Peter L Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1-9	hereby appoints (appoint) the following person	GERMAN, Joel B Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater New Jersey 08807-0800 United States of America
1 1 10	hereby appoints (appoint) the following person	GUPTA, Balaram Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1 11	hereby appoints (appoint) the following person	KIRK Joseph, P Jr

PCT POWER OF ATTORNEY

Duplicate of Original

		Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1 12	hereby appoints (appoint) the following person	KRUPEN, Karen I Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1 13	hereby appoints (appoint) the following person	KURYS, Barbara E Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1 14	hereby appoints (appoint) the following person	LIN Jiang Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater New Jersey 08807-0800 United States of America
1 1 15	hereby appoints (appoint) the following person	MOON, Carolyn, D Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater New Jersey 08807-0800 United States of America
1 1 16	hereby appoints (appoint) the following person	NELLIGAN, Mark, C Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater New Jersey 08807-0800 United States of America
1 1 17	hereby appoints (appoint) the following person	NEWMAN Irving Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater New Jersey 08807-0800 United States of America
1-1-18	hereby appoints (appoint) the following person	OEHLEK Ross J Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater New Jersey 08807-0800 United States of America
1-1-19	hereby appoints (appoint) the following person	ORT, Ronald, G Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1-1-20	hereby appoints (appoint) the following person	PARKER Raymond, S , III Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater New Jersey 08807-0800 United States of America
1 1-21	hereby appoints (appoint) the following person	ROSSI, Joseph Aventis Pharmaceuticals Inc Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1 1-22	hereby appoints (appoint) the following person	STRUPCZEWSKI Joseph Aventis Pharmaceuticals Inc

PCT POWER OF ATTORNEY

Duplicate of Original

		Route 202-206 P O Box 6800 Bridgewater, New Jersey 08807-0800 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the International application identified below	
1-4-1	Title of invention	[4 - (5-AMINOMETHYL-2-FLUORO-PHENYL) -PIPER IDIN-1-YL] - (4-BROMO-3-METHYL-5-PROPOXY-T HIOPHEN-2-YL) -METHANONE HYDROCHLORIDE AS AN INHIBITOR OF MAST CELL TRYPTASE
1-4-2	Applicant's or agent's file reference	US20040013WO
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned	
2-1	Signature of applicant, agent or common representative	
2-1-1	Name	AVENTIS PHARMACEUTICALS INC
2-1-2	Name of signatory	Ross J Oehler
2-1-3	Capacity	Vice President
2-2	Signature of applicant, agent or common representative	
2-2-1	Name (LAST First)	GAO Zhongli
2-2-2	Name of signatory	
2-2-3	Capacity	
2-3	Signature of applicant, agent or common representative	
2-3-1	Name (LAST First)	DAVIS Larry
2-3-2	Name of signatory	
2-3-3	Capacity	
2-4	Signature of applicant, agent or common representative	
2-4-1	Name (LAST First)	LEVELL, Julian
2-4-2	Name of signatory	
2-4-3	Capacity	

PCT POWER OF ATTORNEY

Duplicate of Original

2-5	Signature of applicant, agent or common representative	
2-5-1	Name (LAST First)	CZEKAJ, Mark
2-5-2	Name of signatory	
2-5-3	Capacity	
2-6	Signature of applicant, agent or common representative	
2-6-1	Name (LAST First)	SLEDESKI, Adam, W
2-6-2	Name of signatory	
2-6-3	Capacity	
3	Date	24 March 2005 (24 03 2005)

PATENT COOPERATION TREATY

JAK 85

From the
INTERNATIONAL SEARCHING AUTHORITY

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86

To

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis 1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2005/009899International filing date (day/month/year)
24 03 2005Priority date (day/month/year)
26 03 2004International Patent Classification (IPC) or both national classification and IPC
C07D409/06 A61K31/4535 A61P11/06Applicant
AVENTIS PHARMACEUTICALS INC

1 This opinion contains indications relating to the following items

- ☒ Box No I Basis of the opinion
- ☒ Box No II Priority
- ☒ Box No III Non-establishment of opinion with regard to novelty Inventive step and industrial applicability
- ☐ Box No IV Lack of unity of invention
- ☒ Box No V Reasoned statement under Rule 43bis 1(a)(i) with regard to novelty Inventive step or industrial applicability citations and explanations supporting such statement
- ☐ Box No VI Certain documents cited
- ☒ Box No VII Certain defects in the international application
- ☒ Box No VIII Certain observations on the international application

2 FURTHER ACTION

If a demand for international preliminary examination is made this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority (IPEA). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66 1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together where appropriate with amendments before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220

3 For further details see notes to Form PCT/ISA/220

ACTION DUE

DUE DATE

DUE DATE

ATTY

Authorized Officer

Name and mailing address of the ISA

European Patent Office
D-80288 Munich
Tel +49 89 2399 0 Tx 523656 epmu d
Fax +49 89 2399 4465

Weisbrod T

Telephone No +49 89 2399-8931



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No
PCT/US2005/009899

86
87

Box No. I Basis of the opinion

- 1 With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b))
- 2 With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of
 - a type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b format of material
 - ☐ in written format
 - ☐ in computer readable form
 - c time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purposes of search
- 3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished
- 4 Additional comments

Box No. II Priority

- 1 ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date
- 2 ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date
- 3 Additional observations, if necessary

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No
PCT/US2005/009899

88

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel to involve an inventive step (to be non obvious) or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos 4-15

because

☒ the said international application or the said claims Nos 4-15 relate to the following subject matter which does not require an international preliminary examination (*specify*)

see separate sheet

☐ the description claims or drawings (*indicate particular elements below*) or said claims Nos are so unclear that no meaningful opinion could be formed (*specify*)

☐ the claims or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed

☐ no international search report has been established for the whole application or for said claims Nos

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing if in computer readable form only do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43b/s 1(a)(I) with regard to novelty inventive step or industrial applicability citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes	Claims	1-26
	No	Claims	
Inventive step (IS)	Yes	Claims	
	No	Claims	1-26
Industrial applicability (IA)	Yes	Claims	1-3, 16-26
	No	Claims	

2 Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

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

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description are made

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No

PCT/US2005/009899

Re Item I

Basis of the opinion

The application is directed to

- (i) the specific compound (I) prodrugs, pharmaceutical acceptable salts and solvates thereof (claims 1-2)
- (ii) therapeutic methods involving the compounds of claim 1 (claims 4-15) and
- (iii) pharmaceutical compositions comprising a compound of claim 1 (claims 16-26)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 4-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66 2(a)(II) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

- 1 Reference is made to the following document

D1 WO 01/90101 A 29 November 2001

- 2 Novelty

D1 relates to tryptase inhibitors which generally comprise the present compound (I) (cf. claims 1 and 36 in combination with page 10, lines 7-20 and page 12, lines 18-28). Compound (I) is however not specifically exemplified in document D1. Hence, the present claimed matter can be considered as a novel selection of the teaching of D1.

- 3 Inventive Step

- 40
91
- 3 1 The application describes the synthesis of the hydrochloride of the compound (I) and shows that it acts as an inhibitor of beta tryptase (page 27 lines 9 10)
- 3 2 In view of D1 as most relevant state of the art, the problem underlying the application may be seen in the provision of a further tryptase inhibitor. Since the present compound (I) is already generally comprised within the compounds of D1, its provision respectively selection from the compounds of D1, is obvious for the person skilled in the art in order to solve the problem posed. Hence, in the absence of any substantiated unexpected effect of the claimed parent compound (I) compared with the closest related compound of the prior art (i.e. the particularly preferred compound A3-B1 C90 according to page 49 of D1) no inventive activity would be seen in the claimed matter.

Independent from this reasoning it is noted that the therapeutic methods and pharmaceutical compositions of the claims 4-26 involve solvates of the present compound (I). However, it does not appear plausible that substantially all solvates of compound (I) were pharmaceutical acceptable, without being limitative e.g. the acetonitrile, dichloromethane, trichloromethane or tetrachloromethane solvates. It does not appear that therapeutic methods and pharmaceutical compositions that involve any solvate of compound (I) whatsoever would contribute to the solution of any relevant technical problem. Hence, no inventive step would be acknowledged for the claims 4-26 in as far as they refer to solvates of compound (I).

Thus, the claims 1-26 do not comply with the requirements of inventive step.

4 Industrial Applicability

For the assessment of the present claims 4-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the International application

The relevant background art disclosed in D1 is not mentioned in the description nor is this document identified therein (Rule 5 1(a)(ii) PCT)

Re Item VIII**Certain observations on the international application**

The application does not comply with the requirements of Article 6 PCT

- 1 Claim 4 is to be objected under Article 6 PCT because the therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition. The objection could be overcome by either introducing in the claims a list of pathological conditions cited in the application or by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition.
- 2 In addition, the expression "condition related to atherosclerotic plaque rupture" used in claims 5 and 12 has no clear meaning and renders these claims unclear.
- 3 The vague statement on page 28 lines 33-36 implies that the subject matter for which protection is sought might be different from what is defined in the claims, thereby resulting in a lack of clarity of the claims.

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22
93

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference US20040013WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below	
International application No. PCT/US2005/009899	International filing date (day/month/year) 24/03/2005	(Earliest) Priority Date (day/month/year) 26/03/2004
Applicant AVENTIS PHARMACEUTICALS INC		

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 4 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, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box II).

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

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 No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority because the applicant failed to suggest a figure.

☐ as selected by this Authority because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/009899

94

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/06 A61K31/4535 A61P11/06

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 A61K A61P

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, WPI Data PAJ, BEILSTEIN Data, 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 01/90101 A (AVENTIS PHARMACEUTICALS PRODUCTS INC, ASTLES, PETER, C EASTWOOD, PAUL) 29 November 2001 (2001-11-29) Abstract, claims examples, and the specific compound A3-B1-C90 & US 2003/187020 A1 (ASTLES PETER C ET AL) 2 October 2003 (2003-10-02)	1-26

☐ 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 relating 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.
- & document member of the same patent family

Date of the actual completion of the international search

22 July 2005

Date of mailing of the international search report

03/08/2005

Name and mailing address of the ISA

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

Authorized officer

Weisbrod, T

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/009899

94
95

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons.

- 1 ☒ Claims Nos.
because they relate to subject matter not required to be searched by this Authority namely
Although claims 4-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound (I)
- 2 ☐ Claims Nos.
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically
3. ☐ Claims Nos.
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a)

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application as follows.

- 1 ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
- 2 ☐ As all searchable claims could be searched without effort justifying an additional fee this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.
- 4 ☐ No required additional search fees were timely paid by the applicant. Consequently this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/009899

96

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0190101	A	29-11-2001	AU 5741301 A	03-12-2001
			BR 0111206 A	15-04-2003
			CA 2409827 A1	29-11-2001
			CN 1439003 A	27-08-2003
			EP 1296972 A1	02-04-2003
			HU 0302485 A2	29-12-2003
			JP 2004510697 T	08-04-2004
			MA 25809 A1	01-07-2003
			MX PA02011400 A	23-05-2003
			NO 20025601 A	06-01-2003
			PL 360495 A1	06-09-2004
			WO 0190101 A1	29-11-2001
			US 2003187020 A1	02-10-2003
			ZA 200209484 A	23-02-2004
US 2003187020	A1	02-10-2003	AU 5741301 A	03-12-2001
			BR 0111206 A	15-04-2003
			CA 2409827 A1	29-11-2001
			CN 1439003 A	27-08-2003
			EP 1296972 A1	02-04-2003
			HU 0302485 A2	29-12-2003
			JP 2004510697 T	08-04-2004
			MA 25809 A1	01-07-2003
			MX PA02011400 A	23-05-2003
			NO 20025601 A	06-01-2003
			PL 360495 A1	06-09-2004
			WO 0190101 A1	29-11-2001
			ZA 200209484 A	23-02-2004

PATENT COOPERATION TREATY

46 6
97

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From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis 1 and
Administrative Instructions, Section 422)

To

KNIGHT Julie Anne
Aventis Pharmaceuticals Inc
Route 202 206 || P O Box 8800
Bridgewater NJ 08807-0800
United States of America

Date of filing (day/month/year) 21 June 2005 (21 06 2005)	Applicant or agent's file reference US20040013WO	IMPORTANT NOTIFICATION
International application No. PCT/US 005/009899	International filing date (day/month/year) 24 March 2005 (24 03 2005)	

The following information has appeared on record concerning

☒ the inventor ☐ the agent ☐ the common representative

Name and Address HAADI AD EL Bidaoui 19 Battalion Drive Basking Ridge NJ 07920 United States of America	State of Nationality FR	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

The International Bureau hereby notifies the applicant that the following change has been recorded concerning

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address HAADI AD EL Bidaoui 19 Battalion Drive Basking Ridge NJ 07920 United States of America	State of Nationality FR	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

For the reasons necessary
The person identified in box 2 should be added to the record as applicant and inventor for
the United States of America only

For the reasons necessary
The person identified in box 2 should be added to the record as applicant and inventor for
the United States of America only

For the reasons necessary
The person identified in box 2 should be added to the record as applicant and inventor for
the United States of America only

☒ the International Preliminary Examining Authority ☐ the designated Offices concerned
☐ the national Searching Authority ☐ the elected Offices concerned
☐ other

The International Bureau of WIPO 41, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Mylène LACHAVANNE
Facsimile No. (41 22) 338 70 80	Telephone No. (41 22) 338 9521

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47 1(c))

To

RECEIVED

KNIGHT, Julie, Anne

Aventis Pharmaceuticals Inc.
Route 202 208||P O Box 6800
Bridgewater NJ 08807-0800
ETATS-UNIS D AMERIQUE

PATENT DEPT.

COMPUTER ENTERED

IMPORTANT NOTICE

Date of mailing (day/month/year)
27 July 2006 (27 07 2006)Applicant's or agent's file reference
US20040013WOInternational application No
PCT/US2005/009899International filing date (day/month/year)
24 March 2005 (24 03 2005)Priority date (day/month/year)
26 March 2004 (26 03 2004)

Applicant

AVENTIS PHARMACEUTICALS INC et al

- 1 ATTENTION For any designated Office(s) for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date) does not apply please see Form PCT/IB/308(First Notice) issued previously
- 2 Notice is hereby given that the following designated Office(s) for which the time limit under Article 22(1) as in force from 1 April 2002 does apply has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis 1. The International Bureau has effected that communication on the date indicated below
20 October 2005 (20.10.2005)

AU AZ BY CN CO DZ EP HU KG KP KR MD MK MZ NA PG RU SY TM US

In accordance with Rule 47 1(c-bis)(i) those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- 3 The following designated Offices for which the time limit under Article 22(1) as in force from 1 April 2002, does apply have not requested, as at the time of mailing of the present notice that the communication of the international application be effected under Rule 93bis 1

AE AG AL AM AP AT BA BB BG BR BW BZ CA CR CU CZ DE DK DM EA EC EE EG ES FI GB GD
GE GH GM HR ID IL IN IS JP KE KZ LC LK LR LS LT LV MA MG MN MW MX NI NO NZ OA OM PH
PL PT RO SC SD SG SK SL SM TJ TN TR TT UA UZ VC VN YU ZA ZW

In accordance with Rule 47 1(c-bis)(ii) those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will subject to what is said in the following paragraph be 30 MONTHS from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit) Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34 chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Philippe Becamel

Facsimile No. +41 22 338 82 70

e-mail pt12@wipo.int

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

KNIGHT Julie Anne
Aventis Pharmaceuticals Inc.
Route 202 208JP O Box 8800
Bridgewater NJ 08807-0800
ETATS-UNIS D'AMERIQUECOMPUTER L₁Date of mailing (day/month/year)
24 May 2005 (24 05 2005)Applicant's or agent's file reference
US20040013WOInternational application No.
PCT/US05/009899

International publication date (day/month/year)

International filing date (day/month/year)
24 March 2005 (24 03 2005)Priority date (day/month/year)
28 March 2004 (28 03 2004)

Applicant

AVENTIS PHARMACEUTICALS INC et al

1 By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR" in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2 (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(e) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity upon entry into the national phase to furnish the priority document within a time limit which is reasonable under the circumstances.

3 (If applicable) An asterisk () appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority application No.

Country or regional Office
or PCT receiving OfficeDate of receipt
of priority document

28 March 2004 (28 03 2004)

60/558 927

US

29 April 2005 (29 04 2005)

The International Bureau of WIPO
34 chemin des Colombettes
1211 Geneva 20 Switzerland

Authorized officer

Lachavanne Mylene

Facsimile No. +41 22 740 14 35

Facsimile No. +41 22 338 70 90
Telephone No. +41 22 338 9521

From the INTERNATIONAL BUREAU

PCTINFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Article 31(7) and Rule 61.3)

To

RECEIVED

APR 13 2006

KNIGHT Julie Anne
Aventis Pharmaceuticals Inc.
Route 202 206||P O Box 6800
Bridgewater NJ 08807-0800
ETATS-UNIS D'AMERIQUE**PATENT DEPT**

COMPUTER ENTERED



IMPORTANT INFORMATION

Date of mailing (day/month/year)

30 March 2006 (30 03 2006)

Applicant's or agent's file reference

US20040013WO

International application No.

PCT/US2005/009899

International filing date (day/month/year)

24 March 2005 (24 03 2005)

Priority date (day/month/year)

26 March 2004 (26 03 2004)

Applicant

AVENTIS PHARMACEUTICALS INC. et al

- 1 The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:
- EP AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LT LU MC NL PL PT RO SE
SI SK TR
National BG CA CN CZ DE JP KP KR MN NO PL RO RU SK SM US
- 2 The following Offices have waived the requirement for the notification of their election: the notification will be sent to them by the International Bureau only upon their request.
- AP BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW
EA AM AZ BY KG KZ MD RU TJ TM
OA BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
National AE AG AL AM AT AU AZ BA BB BR BW BY BZ CH CO CR CU DK DM DZ EC EE EG
ES FI GB GD GE GH GM HR HU ID IL IN IS KE KG KZ LC LK LR LS LT LU LV MA MD
MG MK MW MX MZ NA NI NZ OM PG PH PT SC SD SE SG SL SY TJ TM TN TR TT TZ UA
UG UZ VC VN YU ZA ZM ZW
- 3 Since the election(s) was (were) made after the expiration of 19 months from the priority date, the applicant is reminded that he must, subject to the following paragraph, enter the national phase within 20 months from the priority date (or later in some Offices) before some of the designated Offices in respect of which Article 22(1), as modified with effect of 1 April 2002, does not apply by paying the national fee(s) and furnishing, if prescribed, a translation of the international application.
- However, in respect of most other designated Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters, the *PCT Newsletter* and the WIPO Internet site, updated regularly.

The International Bureau of WIPO
34 chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Philippe Becamel

Facsimile No. +41 22 740 14 35

Facsimile No. +41 22 338 70 90

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PCT

In the
European Patent Office

Applicants File Reference
USAV2004/0013 WO

International Filing Date
24 March 2005 24/03/2005

International Application No
PCT/US2005/009899

Priority Date
26 March 2004 26/03/2004

Title of Invention

[4-(5 AMINOMETHYL-2 FLUORO PHENYL)-PIPERIDIN 1 YL] (4-BROMO-3 METHYL-5 PROPOXY THIOPHEN 2 YL) METHANONE HYDROCHLORIDE AS AN INHIBITOR OF MAST CELL TRYPTASE

Applicant(s) Aventis Pharmaceuticals Inc., et al

COMMUNICATION PURSUANT TO ARTICLE 34 AND
RESPONSE TO THE WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

European Patent Office
Erhardstr 27
D-80298 Munich, Germany

Dear Sirs

This paper is in response to the assertion in the Written Opinion of the International Searching Authority mailed on August 3 2005 regarding the lack of inventive step for the instant invention¹. In particular section 3.2 of the Written Opinion states in part

'3.2 In view of D1 as most relevant state of the art, the problem underlying the application may be seen in the provision of a further tryptase inhibitor. Since the present compound (I) is already generally comprised within the compounds of D1 its provision respectively selection from the compounds of D1 is obvious for the person skilled in the art in order to solve the problem posed. Hence in the absence of any substantiated unexpected effect of the claimed parent compound (I) compared with the closest related compound of the prior art (i.e. the particularly preferred compound A3 B1-C90 according to page 49 of D1) no inventive activity would be seen in the claimed matter.

First, Applicants disagree with the International Searching Authority's assertion that the only solution to be proffered regarding the technical problem in the instant case was to demonstrate that the instant claimed compound had improved β tryptase properties over the D1 Compound A3 B1-C90.

¹ On October 7 2005 this paper was prematurely submitted in response to the Written Opinion of the International Searching Authority dated August 3 2005. Thereafter Applicants acknowledged that the submission would be treated as informal correspondence and reserved the right to concurrently file such submission, or an amended version thereof concurrently with the filing of a timely Demand, for formal consideration.

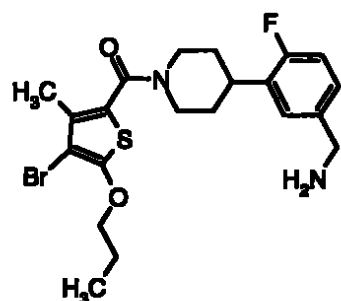
Applicants submit that a solution to a technical problem may be shown in two ways

- 1 finding an alternative compound to achieve the same effect as that of the known compound from the closest prior art, or
- 2 finding a compound with a different property or effect (e.g. improved biological activity, advantageous physical properties, etc.)

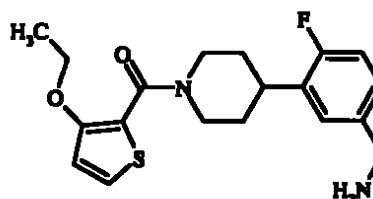
(A) Discovery of Compound I Being Significantly Structurally Distinguishable Over Cited Compound A3 B1 C90 Solves the Technical Problem for the Instant Case

The contention in the Written Opinion that Compound I of the present invention does not possess an inventive step is without merit. Applicants submit that reference D1 (WO 01/90101) does not teach or suggest to one skilled in the art, how to find Applicants' invention, i.e. a compound that concomitantly encompasses a thienyl ring that is tetra-substituted with a 3-methyl, 4-bromo, 5-propoxy and 2-carbonyl and that bears a phenyl moiety with a fluorine substituent in the para position relative to the amino-methyl substituent.

Furthermore, there are four significant structural differences between Compound I and Compound A3 B1 C90 as follows:



Compound I



Compound A3 B1 C90

(i) Compound I's alkoxy substituent is a propoxy group, whereas in Compound A3 B1 C90 the alkoxy substituent is an ethoxy group.

(ii) Compound I's alkoxy substituent is at the 5-position of the thienyl ring, whereas in Compound A3 B1 C90 the alkoxy substituent is at the 3-position of the thienyl ring.

(iii) Compound I has a bromo substituent on the thienyl ring, whereas Compound A3 B1 C90 does not bear a bromo substituent on the thienyl ring, and

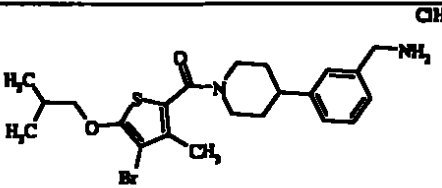
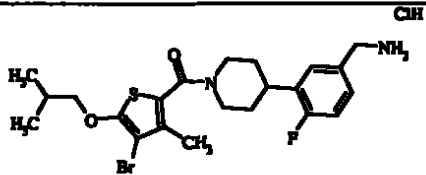
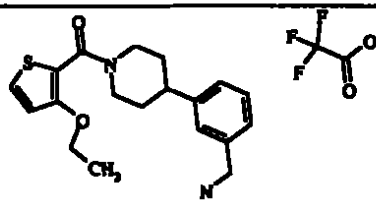
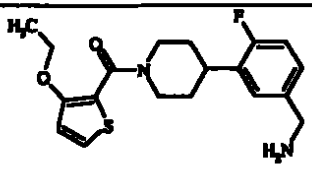
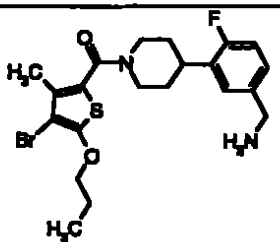
(iv) Compound I has a methyl substituent on the thienyl ring, whereas Compound A3 B1 C90 does not bear a methyl substituent on the thienyl ring.

Thus, Applicants submit that such is a solution to the technical problem in the instant case because nothing in Reference D1 provides any motivation for finding Compound I, or modifying Compound A3 B1-C90 to prepare Applicants' claimed Compound I having the particular combination of structural features noted above.

(B) Compound I Having Unexpected and Superior Properties Over Cited Compound A3-B1 C90 Solves the Technical Problem for the Instant Case

Compound A3 B1-C90 was noted in the Written Opinion as the closet related compound in cited reference D1 over which Applicants claimed Compound I should be distinguishable. However, no data is provided to support the contention in the Written Opinion that Applicants claimed Compound I is not inventive over Compound A3 B1-C90.

Applicants submit that data for other compounds bearing features related to Compound A3 B1-C90 and to Applicants claimed Compound I when considered together evidence that Applicants claimed Compound I has unexpected and superior properties over Compound A3 B1 C90. The relevant compound and data are shown in the following table.

COMPOUND IDENTIFIER	Structure	Tryptase K_i (nM)
A		109
B		1114
C (Example 61 of D1)		600
A3 B1-C90 (Cited as closest related compound from D1)		not determined
I Applicant's claimed compound		16

The sole structural difference between Compounds A and B above (which are structurally similar to Compound I) is the presence of a fluorine substituent in the para position relative to the aminomethyl group on the phenyl moiety. The β -tryptase inhibition data between the Compounds A and B are essentially the same, i.e., Compound A has a $K_i = 109$ nM versus Compound B having a $K_i = 1114$ nM. Such would lead one to conclude that the β -tryptase inhibitory activity remains essentially the same for compounds that differ structurally merely by the presence or absence of a fluoro substituent.

Also, the sole structural difference between Compound A3 B1-C90 and Compound C is the presence of a phenyl moiety with a fluorine substituent in the para position relative to the aminomethyl substituent. Thus, while no K_i data was determined for Compound A3-B1-C90 based on what was discussed above regarding the β -tryptase inhibitory activity of Compounds A and B, one skilled in the art would expect that Compound A3 B1-C90 would have essentially the same β -tryptase inhibitory activity as that of its des fluoro analog Compound C, i.e., a K_i of ~ 600 nM.

The fact that the β -tryptase activity of Compound A3 B1-C90 is expected to be about 600 nM and the activity for Compound I is 16 nM evidences an unexpected 38 fold superior activity for Applicants' claimed Compound I, over that expected for Compound A3 B1-C90.

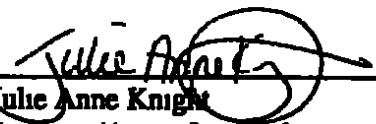
Thus, Applicants submit that such is also a solution to the technical problem in the instant case because nothing would have motivated one skilled in the art to make Compound I or expect its unexpected and superior activity.

For the foregoing reasons, Applicants respectfully request that the International Searching Authority reconsider its assertions regarding Inventive Step for the instant invention.

Respectfully submitted,

Dated: December 20, 2005

By


Julie Anne Knight
Attorney/Agent for Applicant

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Aventis Docket No. USAV2004/0013 WO

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PCT

In the
European Patent Office

Applicants File Reference
USAV2004/0013 WO

International Filing Date
24 March 2005 24/03/2005

International Application No.
PCT/US2005/009899

Priority Date
26 March 2004 26/03/2004

Title of Invention

[4-(5-AMINOMETHYL-2-FLUORO-PHENYL) PIPERIDIN 1 YL]-(4-BROMO-3-METHYL-5-PROPOXY THIOPHEN 2-YL)-METHANONE HYDROCHLORIDE AS AN INHIBITOR OF MAST CELL TRYPTASE

Applicant(s) Aventis Pharmaceuticals Inc., et al

**RESPONSE TO THE WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

European Patent Office
Erhardstr 27
D-80298 Munich, Germany

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First, Applicants disagree with the International Searching Authority's assertion that the only solution to be proffered regarding the technical problem in the instant case was to demonstrate that the instant claimed compound had improved β -tryptase properties over the D1 Compound A3 B1 C90.

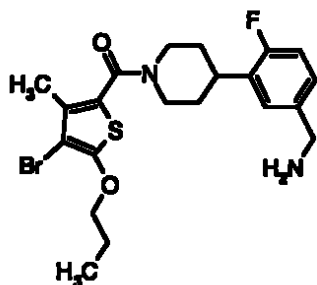
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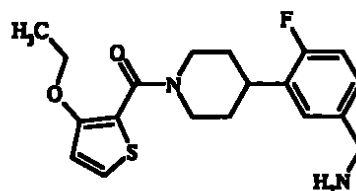
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Compound A3 B1 C90

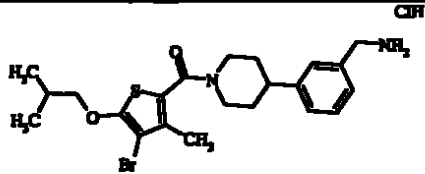
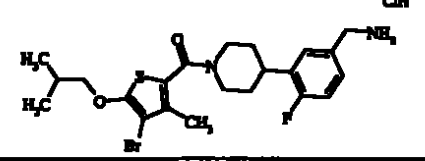
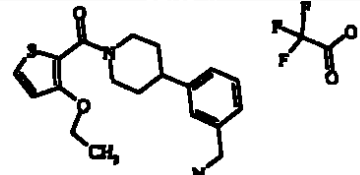
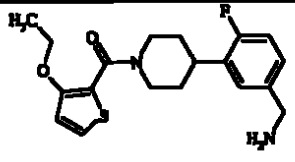
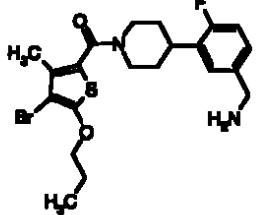
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Thus, Applicants submit that such is also a solution to the technical problem in the instant case because nothing would have motivated one skilled in the art to make Compound I, or expect its unexpected and superior activity.

For the forgoing reasons, Applicants respectfully request that the International Searching Authority reconsider its assertions regarding Inventive Step for the instant invention.

Respectfully submitted,

Dated: October 7, 2005

By _____
Julie Anne Knight
Attorney/Agent for Applicant

Aventis Pharmaceuticals Inc.
(a member of the sanofi-aventis group)
U.S. Patent Operations
Route #202-206 / P.O. Box 6800
Bridgewater, NJ 08807-0800
Telephone (908) 231-3679
Telefax (908) 231-2626
Aventis Docket No. USAV2004/0013 WO

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference USAV2004/0013 WO PCT	FOR FURTHER ACTION See Form PCT/PEAA18	
International application No. PCT/US2005/009899	International filing date (day/month/year) 24.03.2005	Priority date (day/month/year) 26.03.2004
International Patent Classification (IPC) or national classification and IPC INV C07D409/06 A61K31/4535 A61P11/06		
Applicant AVENTIS PHARMACEUTICALS INC et al		
1 This report is the International preliminary examination report established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2 This REPORT consists of a total of 7 sheets including this cover sheet. 3 This report is also accompanied by ANNEXES comprising a ☐ sent to the applicant and to the International Bureau a total of sheets as follows ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.18 and Section 807 of the Administrative Instructions) ☐ sheets which supersede earlier sheets but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed as indicated in Item 4 of Box No. I and the Supplemental Box. b ☐ (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) containing a sequence listing and/or tables related thereto in electronic form only as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions)		
4 This report contains indications relating to the following items ☒ Box No. I Basis of the report ☐ Box No. II Priority ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☒ Box No. VII Certain defects in the international application ☒ Box No. VIII Certain observations on the international application		
Date of submission of the demand 20.12.2005	Date of completion of this report 02.08.2006	
Name and mailing address of the International preliminary examining authority  European Patent Office D-80298 Munich Tel: +49 89 2399 0 Tlx: 523656 epmu d Fax: +49 89 2399 4485	Authorized officer Weisbrod T Telephone No. +49 89 2399-8931 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No
PCT/US2005/009899

Box No. III Non-establishment of opinion with regard to novelty Inventive step and Industrial applicability

1 The questions whether the claimed invention appears to be novel (to be non obvious) or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos 4-15

because

☒ the said international application or the said claims Nos 4-15 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the said claims Nos

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter 1(a) or (b) and 13ter 2

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions

☐ See separate sheet for further details

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**INTERNATIONAL PRELIMINARY REPORT
N PATENTABILITY**

International application No
PCT/US2005/009899

Box No. I Basis of the report

- 1 With regard to the ~~language~~ this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into ~~which is the language~~ of a translation furnished for the purposes of
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
- 2 With regard to the ~~elements~~ of the international application this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*

Description Pages

1-29 as originally filed

Claims, Numbers

1-28 as originally filed

Drawings, Sheets

1/2, 2/2 as originally filed

- ☐ a sequence listing and/or any related table(s) see Supplemental Box Relating to Sequence Listing

- 3 ☐ The amendments have resulted in the cancellation of
- ☐ the description pages
 - ☐ the claims Nos.
 - ☐ the drawings sheets/figs
 - ☐ the sequence listing *(specify)*
 - ☐ any table(s) related to sequence listing *(specify)*
- 4 ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made since they have been considered to go beyond the disclosure as filed as indicated in the Supplemental Box (Rule 70.2(c))
- ☐ the description pages
 - ☐ the claims Nos.
 - ☐ the drawings sheets/figs
 - ☐ the sequence listing *(specify)*
 - ☐ any table(s) related to sequence listing *(specify)*

* If item 4 applies some or all of these sheets may be marked superseded

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes	Claims	1-26
	No	Claims	
Inventive step (IS)	Yes	Claims	
	No	Claims	1-26
Industrial applicability (IA)	Yes	Claims	1-3, 18-26
	No	Claims	

2 Citations and explanations (Rule 70.7)

see separate sheet

Box No. VII Certain defects in the international application

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

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description and drawings or on the question whether the claims are fully supported by the description are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No

PCT/US2005/009899

Re Item I

Basis of the opinion

The application is directed to

- (i) the specific compound (I) prodrugs pharmaceutical acceptable salts, and solvates thereof (claims 1 2)
- (ii) therapeutic methods involving the compounds of claim 1 (claims 4-15) and
- (iii) pharmaceutical compositions comprising a compound of claim 1 (claims 16 26)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 4-15 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT. Consequently no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(i) PCT)

Re Item V

Reasoned statement under Rule 66 2(a)(ii) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

- 1 Reference is made to the following document

D1 WO 01/90101 A 29 November 2001

- 2 Novelty

D1 relates to tryptase inhibitors which generally comprise the present compound (I) (cf claims 1 and 36 in combination with page 10 lines 7-20 and page 12, lines 18 28). Compound (I) is however not specifically exemplified in document D1. Hence the present claimed matter can be considered as a novel selection of the teaching of D1.

- 3 Inventive Step

- 3.1 The application describes the synthesis of the hydrochloride of the compound (I) and shows that it acts as an inhibitor of beta tryptase (page 27, lines 9-10)

113
1/4

- 3 2 The present compound (I) is a selection of the beta tryptase inhibitors of the document D1. Merely as a solution of the problem of providing a further beta tryptase inhibitor, compound (I) is obvious in view of D1, because it is already generally comprised within the teaching of D1. Inventive step would only be acknowledged if the applicant was able to provide substantiated evidence that compound (I) exhibits an unexpected effect compared with the structurally closest related compound of D1, e.g. the particularly preferred compound A3-B1-C90 according to page 49 of D1.

In reply to the written opinion of the ISA, the applicant has tried to establish an inventive step by comparing data of certain compounds which bear structural features related to the present compound (I) and the compound A3-B1-C90 according to D1. In principle, such comparison might be suited to establish inventive step. However, the applicant has compared two hydrochlorides and one trifluoroacetate (example 61 of D1) with the free base of the present compound (I). Without experimental details of the test conditions employed, it is thus not evident whether the use of some tested compounds in their salt form and the use of the present compound (I) as free base affects the test results. In other words, it is not evident whether the data in the applicant's reply can be considered as a valid comparison.

Hence, claims 1-26 lack, at present, inventive step.

- 3 3 In addition, the therapeutic methods and pharmaceutical compositions of the claims 4-26 involve solvates of the present compound (I). However, it does not appear plausible that substantially all solvates of compound (I) were pharmaceutically acceptable without being limitative, e.g. the acetonitrile, dichloromethane, trichloromethane, or tetrachloromethane solvates. It does not appear that therapeutic methods and pharmaceutical compositions that involve any solvate of compound (I) whatsoever would contribute to the solution of any relevant technical problem. Hence, no inventive step would be acknowledged for the claims 4-26 in as far as they refer to solvates of compound (I).

4 Industrial Applicability

For the assessment of the present claims 4-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No

PCT/US2005/009899

claims to the use of a compound in medical treatment but may allow however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment

Re Item VII

Certain defects in the international application

The relevant background art disclosed in D1 is not mentioned in the description nor is this document identified therein (Rule 5 1(a)(ii) PCT)

Re Item VIII

Certain observations on the international application

The application does not comply with the requirements of Article 6 PCT

- 1 Claim 4 is to be objected under Article 6 PCT because the therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined real treatment of a pathological condition. The objection could be overcome by either introducing in the claims a list of pathological conditions cited in the application or by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition.
- 2 In addition, the expression "condition related to atherosclerotic plaque rupture" used in claims 5 and 12 has no clear meaning and renders these claims unclear.
- 3 The vague statement on page 28, lines 33-36 implies that the subject matter for which protection is sought might be different from what is defined in the claims, thereby resulting in a lack of clarity of the claims.

PATENT COOPERATION TREATY

+15

1/6

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

KNIGHT, Julie, Anne
Aventis Pharmaceuticals Inc
Route 202-206 P O Box 6800
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

COMPUTER ENTERED

Date of mailing
(day/month/year)

20-01 2006

Applicant's or agent's file reference
USAV2004/0013 WO PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US2005/009899

International filing date (day/month/year)

24/03/2005

Priority date (day/month/year)

26/03/2004

Applicant

AVENTIS PHARMACEUTICALS INC et al

- 1 The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application.

20/12/2005 ✓

- 2 This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

- 3 ☒ **ATTENTION:** That date of receipt is after the expiration of 19 months from the priority date. Consequently in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 20 months from the priority date (or later in some Offices). However in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II National Chapters and the WIPO Internet site.

- ☐ (if applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



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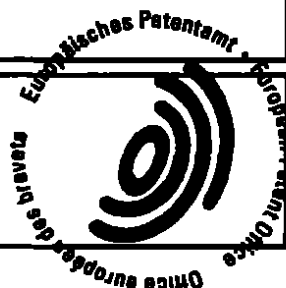
Authorized officer

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Form PCT/IPEA/402 (April 2002 reprint January 2004)

(17/01/2006)





Industria y Comercio

SUPERINTENDENCIA

117

Delegatura de Propiedad Industrial División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

PATENTE DE INVENCION ()	MODELO DE UTILIDAD ()	USUARIO ()	RADICADOR ()
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 ()

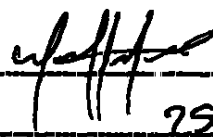
Indicación de que se solicita el registro de Diseño Industrial	()	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud	()	()
Representación grafica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
Comprobante de Pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

ESQUEMA DE TRAZADO ()

Indicación de que se solicita el registro de Diseño Industrial	()	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud	()	()
Representación gráfica del Esquema Trazado	()	()
Comprobante de Pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable

Fecha


25 de Sep 2006