



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones



Organización CSA Ltda

NOV
27

SOLICITUD

PATENTE DE INVENCION

04-22770

21. EXPEDIENTE No.

54. TITULO "Nuevos compuestos y preparaciones como inhibidores de la captesina"

63. CLASIFICACION INTERNACIONAL AGIK31110; C07C 317/48

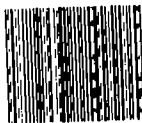
71. SOLICITANTE Aventis pharmaceuticals Inc. y Axy's Pharmaceuticals Inc.

DOMICILIO New Jersey, Estados Unidos de América y South San Francisco, Estados Unidos de América

74. APODERADO Gustavo Hollmann Restrepo

22. BOGOTA, D.C., 12 de Marzo de 2004

Industria y Comercio
SUPERINTENDENCIA



04 022770 00

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04022770 00000000 Folios: 154
Fecha (AMD): 2004-03-12 11:51:02
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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.
y AXYS PHARMACEUTICALS, INC.
Dirección: 300 Somerset Corporate Boulevard,
Bridgewater, NJ 08807-2854 Estados
Unidos de América y 180 Kimball Way,
Nacionalidad o Domicilio: New Jersey, Estados
Lugar de Constitución: Unidos de América y
Estados Unidos South San Francisco,
Estados Unidos de América
Teléfono: Fax:
E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

③ REPRESENTANTE
O APODERADO

Nombre: GUSTAVO HOLLMANN RESTREPO
Dirección: Cra. 11A No. 94-76-Of. 308
Teléfono: 6161948 Fax: 6163976
E-mail:

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☒
Cual _____
Número 2.878.023 TP 5903

④ INVENTOR (ES)
(72)

Nombre: GRAUPE, Michael
Dirección: 1131 Banyan Way,
Nacionalidad o Domicilio Pacifica, CA 94044 Estados Unidos

⑤ PCT (86)

Solicitud Internacional No. PCT/US02/29323 Fecha Septiembre 16 de 2002
Publicación Internacional No. WO 03/024924 A1 Fecha Marzo 27 de 2003

⑥ Título (54) "NUEVOS COMPUESTOS Y PREPARACIONES COMO INHIBIDORES DE LA
CATEPSINA".

⑦ Clasificación Internacional (51) C07C 317/48 ; A61K 31/10

⑧ Prioridad

SI ☒ NO ☐

(33) País de Origen
Estados Unidos

(32) Fecha

Septiembre 12, 2001

(31) Número de Solicitud

60/322,318

⑨ Comprobante de pago No. 04 - 20,027

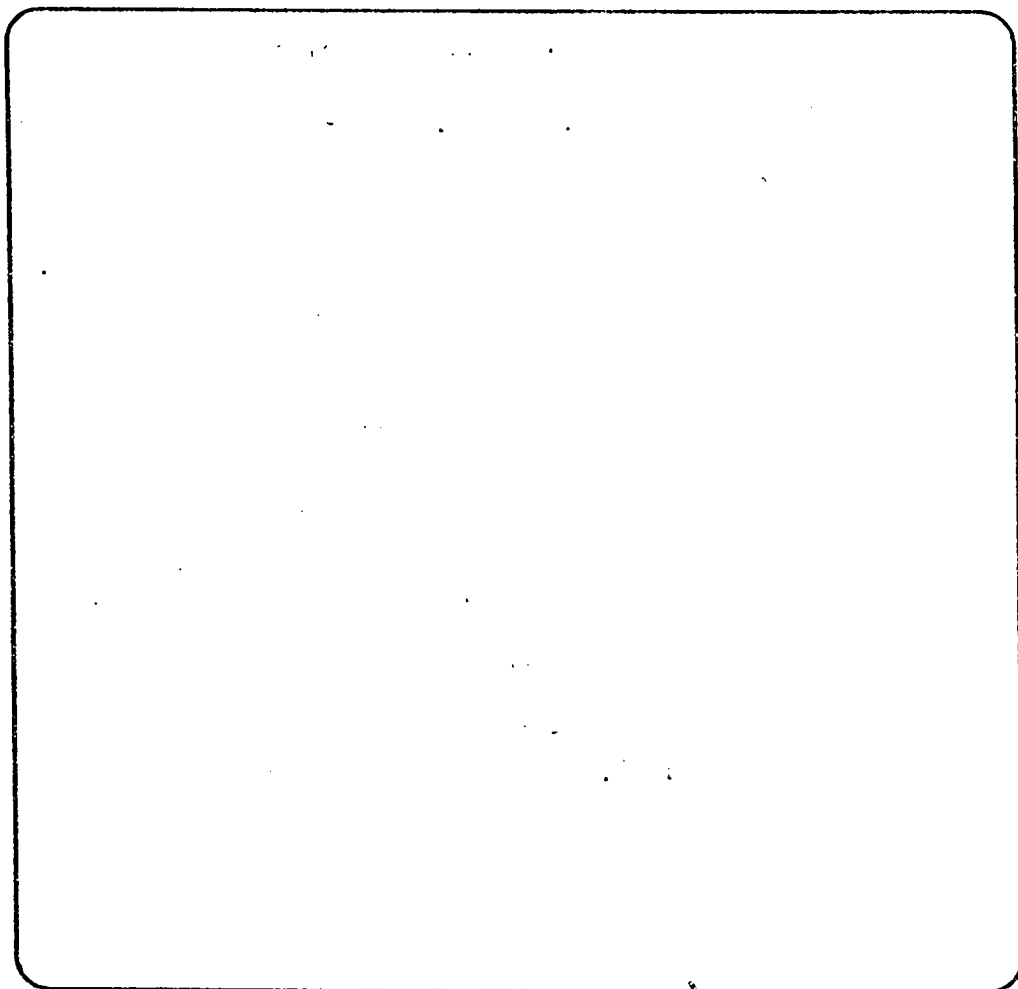
Fecha Marzo 11 de 2004

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar 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 CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: GUSTAVO HOLLMANN RESTREPO

FIRMA:

[Handwritten signature]

C.C. 2.930.616 de Bogotá T.P. 5903

Instrucciones para la presentación de los anexos, ver reverso de esta página.

Continuación nombre, dirección y domicilio de inventores:

<u>Nombre</u>	<u>Dirección</u>	<u>Domicilio</u>
PALMER, James, T.	131 Koch Road,	Corte Madera, CA 94925 Estados Unidos
ALDOUS, David J.	31 Dunbridge Lane,	Gillette, NJ 07933 Estados Unidos
THURAIRATNAM, Sukanthini	6 Smoke Rise Lane,	Bedminster, NJ 07921 Estados Unidos

Otros anexos que se acompañan a la solicitud.

Forma PCT/IB/304 correspondientes a la notificación y transmisión del documento de prioridad.

Forma PCT/RO/101 correspondiente a la solicitud internacional No. PCT/US02/29323.

Forma PCT/IB/308 correspondiente a la nota de información al solicitante de la comunicación de la solicitud internacional a las oficinas designadas.

Forma PCT/IB/332 referente a la información concerniente a las oficinas elegidas notificadas de su elección.

Forma PCT/IB/306 correspondiente al cambio de nombre de la sociedad CELERA, AN APPLERA CORPORATION BUSINESS a AXYS PHARMACEUTICALS INC.

SUPERINDUSTRIA Y COMERCIO

Radicacion : 04022770 00000000

Folios: 154

Fecha (AND): 2004-03-12 11:51:02

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

HIT : 800176089-2

RECIBO OFICIAL DE CAJA : 01 - 20.027
FECHA : MARZO 11 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	050-00110-6	24160758	11/03/2004	844,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL :	\$ 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

Ref. 55520

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

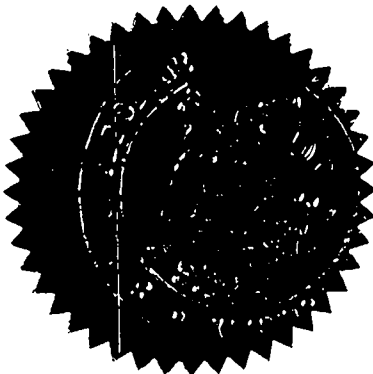
APOSTILLE

(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



John E McCormac



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, desisting, 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.

East Millstone, NJ



ROSS J. OEHLER
ASSISTANT 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, Cra 11ª No 94-76, Oficina 308, apoderado verdadero y legal, con poder especial, amplio y suficiente:

- 1) Para recabar 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 traspasos, 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 prescritos 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 creyeran 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

El Notario Cuarto del Circuito de Bogotá D.C. ha otorgado este poder en la forma y con el contenido que se indica.
- 5 MAR 2004
NOTARIO CUARTO (EJ)
RODRIGO LOPEZ

7

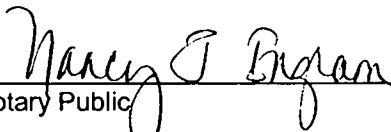
NOTARIAL CERTIFICATE (Corporation)

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, Expiration

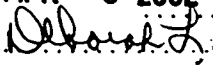
STATE OF NEW JERSEY }
COUNTY OF SOMERSET. } ss.:

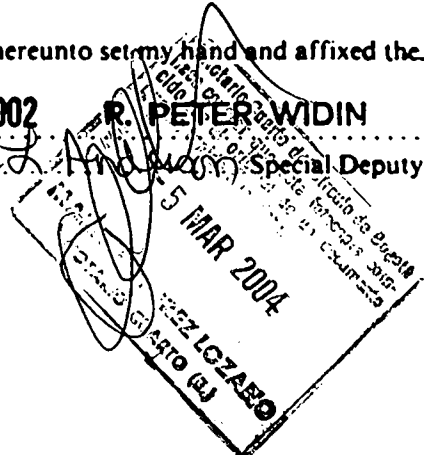
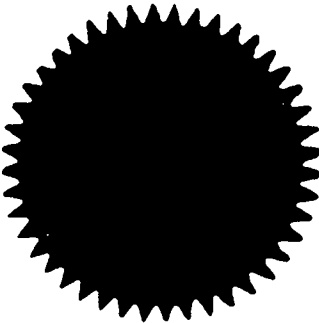
I, **PETER R. WIDIN**, Clerk of the County of Somerset and also Deputy Clerk of the Superior Court in and for said County, the same being a Court of Record, **Do Hereby Certify**, that

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.



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 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 coloqué 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.
JOSE MIGUEL MENDEZ

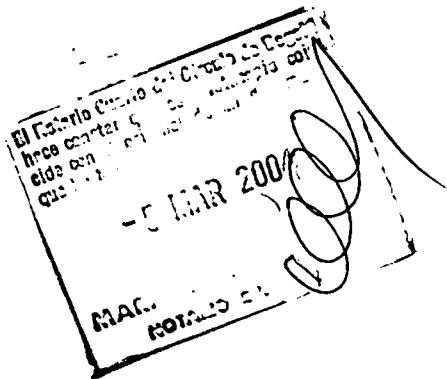
MINISTERIO DE RELACIONES
EXTERIORES

223893
J. A. Mendez
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2002 APR 22 P 12:19

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.



9

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.

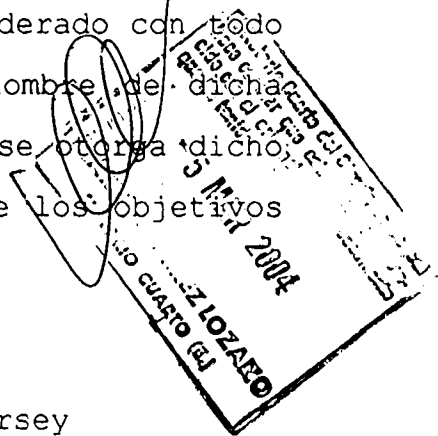
Certifico además que dicha autoridad, fechada el 29 de Noviem-
bre del 2000, se basa en una resolución de la Junta de Direc-
tores de la mencionada sociedad, documento que yo he tenido a
la vista, nombrando a la mencionada persona apoderado con todo
poder para firmar el instrumento adjunto en nombre 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)



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 March 2003 (27.03.2003)

PCT

(10) International Publication Number
WO 03/024924 A1

(51) International Patent Classification⁷: C07C 317/48,
317/50, C07D 207/24, 223/08, 295/20, 307/32, C07K
5/065, A61K 31/10, A61P 19/02, 29/00

(74) Agents: WANG, George, G. et al.; Aventis Pharmaceuti-
cals INC., P. O. Box 6800, Route 202-206, Bridgewater, NJ
08807-0800 (US).

(21) International Application Number: PCT/US02/29323

(22) International Filing Date:
16 September 2002 (16.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/322,318 14 September 2001 (14.09.2001) US

(71) Applicants (for all designated States except US):
AVENTIS PHARMACEUTICALS INC. [US/US];
300 Somerset Corporate Boulevard, Bridgewater, NJ
08807-2854 (US). CELERA, AN APPLERA CORPO-
RATION BUSINESS [US/US]; 180 Kimball Way, South
San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GRAUPE, Michael
[AT/US]; 1131 Banyan Way, Pacifica, CA 94044 (US).
PALMER, James, T. [US/US]; 131 Koch Road, Corte
Madera, CA 94925 (US). ALDOUS, David, J. [US/US];
31 Dunbridge Lane, Gillette, NJ 07933 (US). THU-
RAIRATNAM, Sukanthini [GB/US]; 6 Smoke Rise
Lane, Bedminster, NJ 07921 (US).

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

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

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report

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

(54) Title: NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

(57) Abstract: The present invention relates to compounds of formula I, where the variables are as defined in Claim 1, process for their preparation and their use as cathepsin S inhibitors.

WO 03/024924 A1



-1-

NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

THE INVENTION

This application is based on and claims priority from U.S. Provisional Application
5 S.N. 60/322,318 filed on September 14, 2001, incorporated herein by reference.

This Application relates to compounds and compositions for treating diseases
associated with cysteine protease activity, particularly diseases associated with activity of
cathepsin S.

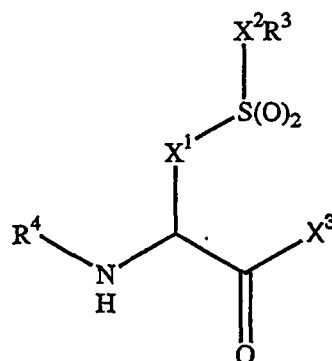
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DESCRIPTION OF THE FIELD

Cysteine proteases represent a class of peptidases characterized by the presence of
a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated
15 with the normal degradation and processing of proteins. The aberrant activity of cysteine
proteases, e.g., as a result of increase expression or enhanced activation, however, may
have pathological consequences. In this regard, certain cysteine proteases are associated
with a number of disease states, including arthritis, muscular dystrophy, inflammation,
tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic
20 leukodystrophy and others. An increase in cathepsin S activity contributes to the pathology
and/or symptomatology of a number of diseases. Accordingly, molecules that inhibit the
activity of cathepsin S protease are useful as therapeutic agents in the treatment of such
diseases.

SUMMARY OF THE INVENTION

This Application relates to compounds of Formula I:



I

in which:

X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond;

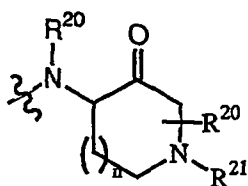
R^3 is $-\text{CR}^5=\text{CHR}^6$, $-\text{CR}^5(\text{CR}^6_3)_2$ or $-\text{CR}^7=\text{NR}^8$, wherein R^5 is hydrogen and R^6 is hydrogen or (C_{1-4}) alkyl or R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{3-12}) cycloalkenyl, hetero (C_{5-12}) cycloalkenyl, (C_{6-12}) aryl, hetero (C_{6-12}) aryl, (C_{9-12}) bicycloaryl or hetero (C_{8-12}) bicycloaryl and R^7 and R^8 together with the atoms to which R^7 and R^8 are attached form hetero (C_{5-12}) cycloalkenyl, hetero (C_{6-12}) aryl or hetero (C_{8-12}) bicycloaryl, wherein R^3 optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-\text{X}^4\text{NR}^9\text{R}^9$, $-\text{X}^4\text{OR}^9$, $-\text{X}^4\text{SR}^9$, $-\text{X}^4\text{C}(\text{O})\text{NR}^9\text{R}^9$, $-\text{X}^4\text{C}(\text{O})\text{OR}^9$, $-\text{X}^4\text{S}(\text{O})\text{R}^{10}$, $-\text{X}^4\text{S}(\text{O})_2\text{R}^{10}$ and $-\text{X}^4\text{C}(\text{O})\text{R}^{10}$, wherein X^4 is a bond or (C_{1-2}) alkylene, R^9 at each occurrence independently is hydrogen, (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{10} is (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl; and

R^4 is $-C(O)X^5R^{11}$ or $-S(O)_2X^5R^{11}$, wherein X^5 is a bond, $-O-$ or $-NR^{12}-$, wherein R^{12} is hydrogen or (C_{1-6}) alkyl, and R^{11} is (i) (C_{1-6}) alkyl optionally substituted by $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)R^{13}$, $-NR^{14}C(O)OR^{13}$, $-NR^{14}C(O)NR^{13}R^{14}$ or $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein R^{13} is
5 (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl and R^{14} at each occurrence independently is hydrogen or (C_{1-6}) alkyl, or (ii) (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or
10 hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl substituted by $-X^6OR^{15}$, $-X^6SR^{15}$, $-X^6S(O)R^{15}$, $-X^6S(O)_2R^{15}$, $-X^6C(O)R^{15}$, $-X^6C(O)OR^{15}$, $-X^6C(O)NR^{15}R^{16}$, $-X^6NR^{15}R^{16}$, $-X^6NR^{16}C(O)R^{15}$, $-X^6NR^{16}C(O)OR^{15}$, $-X^6NR^{16}C(O)NR^{15}R^{16}$, $-X^6NR^{16}C(O)OR^{16}$, $-X^6NR^{16}C(NR^{16})NR^{15}R^{16}$, wherein X^6 is a
15 bond or methylene, R^{15} is (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl and R^{16} is hydrogen or (C_{1-6}) alkyl; wherein R^4 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3}) alkyl, $-X^6NR^{17}R^{17}$,
20 $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$, $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$, $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$, $-X^6P(O)(OR^{18})OR^{17}$, $-X^6OP(O)(OR^{18})OR^{17}$, $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$, $-X^6S(O)_2R^{18}$ and $-X^6C(O)R^{18}$ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$,

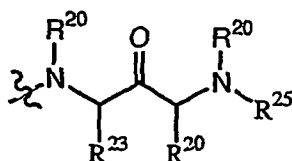
$-\text{NR}^{17}\text{C}(\text{NR}^{17})\text{NR}^{17}\text{R}^{17}$, $-\text{OR}^{17}$, $-\text{SR}^{17}$, $-\text{C}(\text{O})\text{OR}^{17}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{17}$, $-\text{S}(\text{O})_2\text{NR}^{17}\text{R}^{17}$,
 $-\text{P}(\text{O})(\text{OR}^{17})\text{OR}^{17}$, $-\text{OP}(\text{O})(\text{OR}^{17})\text{OR}^{17}$, $-\text{NR}^{17}\text{C}(\text{O})\text{R}^{18}$, $-\text{S}(\text{O})\text{R}^{18}$, $-\text{S}(\text{O})_2\text{R}^{18}$ and $-\text{C}(\text{O})\text{R}^{18}$,
 wherein X^6 is a bond or (C_{1-6}) alkylene, R^{17} at each occurrence independently is hydrogen,
 (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{18} is (C_{1-6}) alkyl or halo-substituted

5 (C_{1-3}) alkyl;

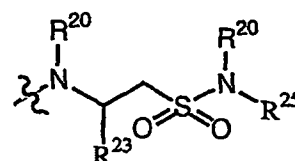
X^3 is a group of Formula (a), (b), (c), (d), (e), (f), (g) or (h):



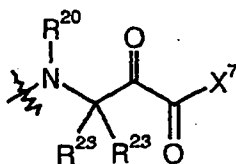
(a)



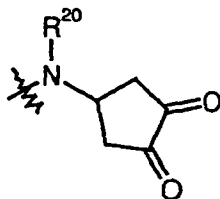
(b)



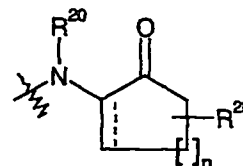
(c)



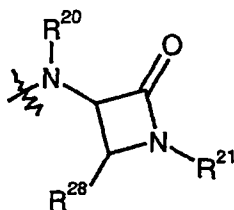
(d)



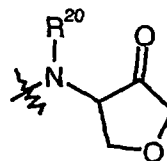
(e)



(f)



(g)



(h)

10

--- represents a single bond, or a double bond;

X^7 represents aryl, heteroaryl or $\text{NR}^{20}\text{R}^{25}$;

n is 0, 1 or 2;

R^{20} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl,

(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl and hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

R²¹ is selected from the group consisting of hydrogen, (C₁₋₉)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl, hetero(C₈₋₁₂)-bicycloaryl(C₀₋₃)alkyl, -C(O)R²⁶, -C(S)R²⁶, -S(O)₂R²⁶, -C(O)OR²⁶, -C(O)N(R²⁶)R²⁷, -C(S)N(R²⁶)R²⁷ and -S(O)₂N(R²⁷)R²⁶;

R²³ is selected from -H, (C₁₋₆)alkyl, (C₄₋₆)alkenyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵ wherein R¹⁵ is as described above;

R²⁵ is selected from hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₃)aryl(C₀₋₆)alkyl, -X⁴NHR¹⁵, -X⁴S(O)₂R²⁶ or -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷ wherein R¹⁵, R¹⁷ and X⁴ are as described above;

R²⁶ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl and hetero(C₈₋₁₂)-bicycloaryl(C₀₋₃)alkyl;

R²⁷ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

R²⁸ is R²⁰ or -O-C(=O)-R²⁹;

R²⁹ is (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl;

wherein X^3 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3}) alkyl, $-X^6NR^{17}R^{17}$, $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$,
 5 $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6C(O)R^{17}$, $-X^6OR^{15}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$,
 $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$, $-X^6P(O)(OR^8)OR^{17}$, $-X^6OP(O)(OR^8)OR^{17}$,
 $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$, $-X^6S(O)_2R^{18}$ and $-X^6C(O)R^{18}$ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$, $-NR^{17}C(NR^{17})NR^{17}R^{17}$, $-OR^{17}$,
 10 $-SR^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-P(O)(OR^{17})OR^{17}$, $-OP(O)(OR^{17})OR^{17}$,
 $-NR^{17}C(O)R^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$ and $-C(O)R^{18}$, wherein R^{15} , R^{17} , R^{18} and X^6 are as described above.

A second aspect of the invention is a pharmaceutical composition that contains a compound of Formula I or their *N*-oxide derivatives, individual isomers or mixture of
 15 isomers thereof, or pharmaceutically acceptable salts thereof, in admixture with one or more suitable excipients.

A third aspect of the invention is a method for treating a disease in an animal in which inhibition of cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a
 20 therapeutically effective amount of compound of Formula I or a *N*-oxide derivative, individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt thereof.

A fourth aspect of the invention is the processes for preparing compounds of Formula I and the *N*-oxide derivatives, prodrug derivatives, protected derivatives,

individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

5

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

10

"Alicyclic" means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures having properties resembling those of aliphatics and may be saturated or partially unsaturated with two or more double or triple bonds.

15

"Aliphatic" means a moiety characterized by a straight or branched chain arrangement of the constituent carbon atoms and may be saturated or partially unsaturated with two or more double or triple bonds.

20

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g., (C₁₋₆)alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g., as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g., (C₆₋₁₀)aryl(C₀₋₃)alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, and the like).

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g., (C₁₋₆)alkylene includes methylene (-CH₂-), ethylene (-CH₂CH₂-), trimethylene (-CH₂CH₂CH₂-), tetramethylene (-CH₂CH₂CH₂CH₂-) 2-butenylene (-CH₂CH=CHCH₂-),

5 2-methyltetramethylene (-CH₂CH(CH₃)CH₂CH₂-), pentamethylene (-CH₂CH₂CH₂CH₂CH₂-) and the like).

"Alkylidene" means a straight or branched saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C₁₋₆)alkylidene includes methylene (=CH₂), ethylidene (=CHCH₃), isopropylidene (=C(CH₃)₂),

10 propylidene (=CHCH₂CH₃), allylidene (=CH-CH=CH₂), and the like).

"Amino" means the radical -NH₂. Unless indicated otherwise, the compounds of the invention containing amino moieties include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

15 "Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

"Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are *sp*² hybridized and the total number of pi electrons is equal to 4n+2.

20 "Aryl" means a monocyclic or fused bicyclic ring assembly containing the total number of ring carbon atoms indicated, wherein each ring is comprised of 6 ring carbon atoms and is aromatic or when fused with a second ring forms an aromatic ring assembly. For example, optionally substituted (C₆₋₁₀)aryl as used in this Application includes, but is not limited to, biphenyl-2-yl, 2-bromophenyl, 2-bromocarbonylphenyl, 2-bromo-

5-fluorophenyl, 4-*tert*-butylphenyl, 4-carbamoylphenyl, 4-carboxy-2-nitrophenyl,
2-chlorophenyl, 4-chlorophenyl, 3-chlorocarbonylphenyl, 4-chlorocarbonylphenyl,
2-chloro-4-fluorophenyl, 2-chloro-6-fluorophenyl, 4-chloro-2-nitrophenyl, 6-chloro-
2-nitrophenyl, 2,6-dibromophenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl,
5 3,4-dichlorophenyl, 2-difluoromethoxyphenyl, 3,5-dimethylphenyl,
2-ethoxycarbonylphenyl, 2-fluorophenyl, 2-iodophenyl, 4-isopropylphenyl,
2-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl,
5-methyl-2-nitrophenyl, 4-methylsulfonylphenyl, naphth-2-yl, 2-nitrophenyl, 3-nitrophenyl,
4-nitrophenyl, 2,3,4,5,6-pentafluorophenyl, phenyl, 2-trifluoromethoxyphenyl,
10 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 2-trifluoromethylphenyl,
3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-trifluoromethylsulfanylphenyl,
4-trifluoromethylsulfanylphenyl, and the like. Optionally substituted (C₆₋₁₀)aryl as used
in this Application includes 3-acetylphenyl, 3-*tert*-butoxycarbonylaminomethylphenyl,
biphenyl-4-yl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-methoxyphenyl, naphth-2-yl,
15 3-phenoxyphenyl, phenyl, and the like.

"Bicycloaryl" means a bicyclic ring assembly containing the number of ring carbon
atoms indicated, wherein the rings are linked by a single bond or fused and at least one of
the rings comprising the assembly is aromatic, and any carbocyclic ketone, thioketone or
iminoketone derivative thereof (e.g., (C₉₋₁₀)bicycloaryl includes cyclohexylphenyl,
20 1,2-dihydronaphthyl, 2,4-dioxo-1,2,3,4-tetrahydronaphthyl, indanyl, indenyl,
1,2,3,4-tetrahydronaphthyl, and the like).

"Carbamoyl" means the radical -C(O)NH₂. Unless indicated otherwise, the
compounds of the invention containing carbamoyl moieties include protected derivatives
thereof. Suitable protecting groups for carbamoyl moieties include acetyl,

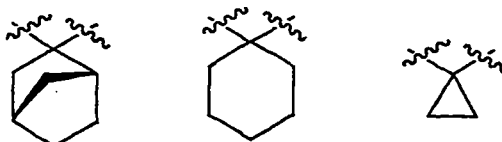
tert-butoxycarbonyl, benzyloxycarbonyl, and the like and both the unprotected and protected derivatives fall within the scope of the invention.

"Carbocyclic ketone derivative" means a derivative containing the moiety -C(O)- .

5 "Carboxy" means the radical -C(O)OH . Unless indicated otherwise, the compounds of the invention containing carboxy moieties include protected derivatives thereof. Suitable protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the like.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic
10 or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{3-10}) cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the
15 like).

"Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic ring or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, the instance wherein " R^1 and R^2 together with the carbon atom to which both R^1
20 and R^2 are attached form (C_{3-8}) cycloalkylene" includes, but is not limited to, the following:



"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

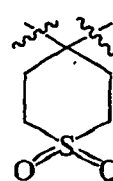
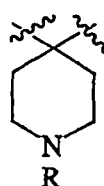
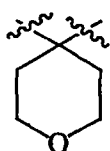
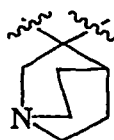
5 "Halo" means fluoro, chloro, bromo or iodo.

"Halo-substituted alkyl", as an isolated group or part of a larger group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (e.g. halo-substituted (C₁₋₃)alkyl includes chloromethyl, 10 dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

"Heteroatom moiety" includes -N=, -NR-, -N⁺(O)=, -O-, -S- or -S(O)₂-, wherein R is hydrogen, (C₁₋₆)alkyl or a protecting group.

"Heterocycloalkylene" means cycloalkylene, as defined in this Application, 15 provided that one or more of the ring member carbon atoms indicated, is replaced by heteroatom moiety selected from -N=, -NR-, -O-, -S- or -S(O)₂-, wherein R is hydrogen or (C₁₋₆)alkyl. For example, the instance wherein R¹ and R² together with the carbon atom to which both R¹ and R² are attached form hetero(C₃₋₈)cycloalkylene" includes, but is not limited to, the following:

20



in which R is hydrogen, (C₁₋₆)alkyl, or a protecting group.

"Heteroaryl" means aryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -N⁺(O⁻)=, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and each ring is comprised of 5 or 6 ring atoms. For example, optionally substituted hetero(C₅₋₁₃)aryl as used in this Application includes, but is not limited to, 4-amino-2-hydroxypyrimidin-5-yl, dibenzofuranyl, benzothiazol-2-yl, 1*H*-benzoimidazol-2-yl, 2-bromopyrid-5-yl, 5-bromopyrid-2-yl, 4-carbamoylthiazol-2-yl, 3-carboxypyrid-4-yl, 5-carboxy-2,6-dimethylpyrid-3-yl, 3,5-dimethylisoxazol-4-yl, 5-ethoxy-2,6-dimethylpyrid-3-yl, 5-fluoro-6-hydroxypyrimidin-4-yl, fur-2-yl, fur-3-yl, 5-hydroxy-4,6-dimethylpyrid-3-yl, 8-hydroxy-5,7-dimethylquinolin-2-yl, 5-hydroxymethylisoxazol-3-yl, 3-hydroxy-6-methylpyrid-2-yl, 3-hydroxypyrid-2-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, 1*H*-indol-3-yl, isothiazol-4-yl, isoxazol-4-yl, 2-methylfur-3-yl, 5-methylfur-2-yl, 1-methyl-1*H*-imidazol-2-yl, 5-methyl-3*H*-imidazol-4-yl, 5-methylisoxazol-3-yl, 5-methyl-2*H*-pyrazol-3-yl, 3-methylpyrid-2-yl, 4-methylpyrid-2-yl, 5-methylpyrid-2-yl, 6-methylpyrid-2-yl, 2-methylpyrid-3-yl, 2-methylthiazol-4-yl, 5-nitropyrid-2-yl, 2*H*-pyrazol-3-yl, 3*H*-pyrazol-4-yl, pyridazin-3-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 5-pyrid-3-yl-2*H*-[1,2,4]triazol-3-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1*H*-pyrrol-3-yl, quinolin-2-yl, 1*H*-tetrazol-5-yl, thiazol-2-yl, thiazol-5-yl, thien-2-yl, thien-3-yl, 2*H*-[1,2,4]triazol-3-yl, 3*H*-[1,2,3]triazol-4-yl, 5-trifluoromethylpyrid-2-yl, and the like. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. Optionally substituted hetero(C₅₋₁₀)aryl as used in this Application to define R⁴

includes benzofur-2-yl, fur-2-yl, fur-3-yl, pyrid-3-yl, pyrid-4-yl, quinol-2-yl, quinol-3-yl, thien-2-yl, thien-3-yl, and the like.

"Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, optionally substituted hetero(C₈₋₁₀)bicycloaryl as used in this Application includes, but is not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, and the like. In general, the term heterobicycloaryl as used in this Application includes, for example, benzo[1,3]dioxol-5-yl, 3,4-dihydro-2*H*-[1,8]naphthyridinyl, 3,4-dihydro-2*H*-quinolinyl, 2,4-dioxo-3,4-dihydro-2*H*-quinazolinyl, 1,2,3,4,5,6-hexahydro[2,2']bipyridinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, 5,6,7,8-tetrahydroquinolinyl, and the like.

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term hetero(C₅₋₁₀)cycloalkyl includes imidazolidinyl, morpholinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, and the like). Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. Both the unprotected and protected derivatives fall within the scope of the invention.

"Hydroxy" means the radical -OH. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable

protecting groups for hydroxy moieties include benzyl and the like.

"Iminoketone derivative" means a derivative containing the moiety $-C(NR)-$, wherein R is hydrogen or (C_{1-6}) alkyl.

"Isomers" mean compounds of Formula I having identical molecular formulae but
5 differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical
10 substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as ether an individual diastereomers or as a mixture of diastereomers, termed a "diastereomeric mixture". When
15 one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods
20 for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers. Thus, for example, the name morpholine-4-carboxylic acid [1-(1-

-15-

benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide is meant to include morpholine-4-carboxylic acid [S-1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide and morpholine-4-carboxylic acid [R-1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide and any mixture, racemic or otherwise, thereof.

"Ketone derivative" means a derivative containing the moiety -C(O)-. For example, for 2-acetoxy-azetidin-3-yl, the "carbocyclic ketone derivative" would be 2-acetoxy-4-oxo-azetidin-3-yl.

"Nitro" means the radical -NO₂.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "wherein within R³ and R⁴ any alicyclic or aromatic ring system may be substituted further by 1-5 radicals..." means that R³ and R⁴ may or may not be substituted in order to fall within the scope of the invention.

"Oxoalkyl" means alkyl, as defined above, wherein one of the number of carbon atoms indicated is replaced by an oxygen group (-O-), e.g., oxo(C₂₋₆)alkyl includes methoxymethyl, etc.

"N-oxide derivatives" means derivatives of compounds of Formula I in which nitrogens are in an oxidized state (i.e., O-N) and which possess the desired pharmacological activity.

"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

5 "Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, 10 heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 15 *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

20 Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the

like.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of Formula I. For example an ester of a compound of Formula I containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of Formula I containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of Formula I containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinate. Suitable esters of compounds of Formula I containing a carboxy group, are for example those described by F.J.Leinweber, Drug Metab. Res., 1987, 18, page 379. An especially useful class of esters of compounds of Formula I containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et al., J. Med. Chem., 1989, 32, page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylaminomethylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in

themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Therapeutically effective amount" means that amount which, when administered
5 to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thioketone derivative" means a derivative containing the moiety -C(S)-.

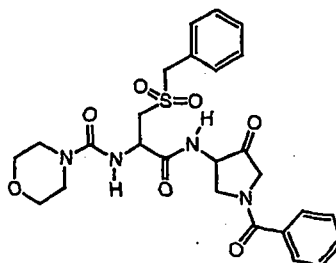
"Treatment" or "treating" means any administration of a compound of the present invention and includes:

- (1) preventing the disease from occurring in an animal which may be predisposed to
10 the disease but does not yet experience or display the pathology or symptomatology of the disease,
- (2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or
- 15 (3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

Nomenclature:

20 The compounds of Formula I and the intermediates and starting materials used in their preparation are named in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides, etc. Alternatively, the compounds are named by AutoNom 4.0 (Beilstein Information Systems, Inc.). For example, a compound of Formula I in which R³

is phenyl, R¹ is morpholine-4-carbonyl and X³ is 1-benzoyl-4-oxo-pyrrolidin-3-ylamino; that is, a compound having the following structure:



5 is named morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide.

Presently Preferred Embodiments:

While the broadest definition of the invention is set forth in the Summary of the
 10 Invention, certain aspects of the invention are preferred. For example, for a compound of
 Formula I, in which X¹ and X² are both methylene or X¹ is ethylene and X² is a bond; R³
 is -CR⁵=CHR⁶, -CR⁵(CR⁶)₂ or -CR⁷=NR⁸, wherein R⁵ is hydrogen and R⁶ is hydrogen
 or (C₁₋₄)alkyl or R⁵ and R⁶ together with the atoms to which R⁵ and R⁶ are attached form
 (C₃₋₁₂)cycloalkenyl, (C₆₋₁₂)aryl, hetero(C₆₋₁₂)aryl or (C₉₋₁₂)bicycloaryl and R⁷ and R⁸
 15 together with the atoms to which R⁷ and R⁸ are attached form hetero(C₅₋₁₂)cycloalkenyl or
 hetero(C₆₋₁₂)aryl, wherein R³ optionally is substituted by 1 to 5 radicals independently
 selected from a group consisting of (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl,
 -X⁴OR⁹ and -X⁴C(O)OR⁹, wherein X⁴ is a bond or (C₁₋₂)alkylene, R⁹ at each occurrence
 independently is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl; R⁴ is -C(O)X⁵R¹¹ or
 20 -S(O)₂X⁵R¹¹, wherein X⁵ is a bond, -O- or -NR¹²-, wherein R¹² is hydrogen or
 (C₁₋₆)alkyl, and R¹¹ is (i) (C₁₋₆)alkyl or (ii) hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl,

(C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl or (iii) hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl or phenyl(C₀₋₃)alkyl substituted by -X⁶OR¹⁵, -X⁶C(O)R¹⁵ or -X⁶NR¹⁶C(O)OR¹⁶, wherein X⁶ is a bond or methylene, R¹⁵ is phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹⁶ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, halo, -X⁶NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)OR¹⁷, -X⁶NC(O)R¹⁶ and -X⁶C(O)R¹⁸, R¹⁷ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁸ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl.

In particular, X³ is a group of Formula (a), (b) or (c) in which: n is 0, 1 or 2; R²⁰ is selected from the group consisting of hydrogen and (C₁₋₆)alkyl; R²¹ is selected from the group consisting of (C₁₋₉)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, -C(O)R²⁶, -S(O)₂R²⁶, -C(O)OR²⁶ and -C(O)N(R²⁶)R²⁷; R²³ is selected from (C₁₋₆)alkyl optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵ wherein R¹⁵ is as described above; R²⁵ is selected from (C₁₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, -X⁴S(O)₂R²⁶ or -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷ wherein R¹⁷ and X⁴ are as described above and R²⁶ is as described below; R²⁶ is selected from the group consisting of (C₁₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl and (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl; R²⁷ is (C₁₋₆)alkyl; herein X³ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, cyano, halo, -X⁶OR¹⁷, -X⁶C(O)R¹⁷ and -X⁶OR¹⁵.

R³ more preferably is selected from the group consisting of phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, vinyl, 2-difluoromethoxyphenyl, 1-oxy-pyridin-2-yl, 4-

methoxyphenyl, 4-methylphenyl, 2-methylphenyl, 4-chlorophenyl, 3,5-dimethylphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 2-bromophenyl, naphthalen-2-yl, 3,4-dichlorophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3-trifluoromethoxyphenyl, 2,3,4,5,6-pentafluoro-phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-cyano-phenyl, 2-trifluoromethylphenyl, 4-*tert*-butyl-phenyl, 3-chlorophenyl, 4-bromophenyl, 2-fluoro-3-chloro-phenyl, 2-fluoro-3-methyl-phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 3-bromophenyl, 2,5-dichlorophenyl, 2,6-difluorophenyl, 3-cyano-phenyl, 4-cyano-phenyl, 2-trifluoromethoxyphenyl, 2,3-difluorophenyl, biphenyl, 2-bromo-5-fluoro-phenyl, 4-fluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 2,4,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 2-chloro-5-trifluoromethylphenyl, 2,4-bis-trifluoromethylphenyl, 2,5,6-trifluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 2,3,5-trifluorophenyl, 2-fluoro-5-trifluoromethylphenyl, 5-fluoro-2-trifluoromethylphenyl, 4-fluoro-3-trifluoromethylphenyl, 2-methoxyphenyl, 3,5-bis-trifluoromethylphenyl, 4-difluoromethoxyphenyl, 3-difluoromethoxyphenyl, 2,6-dichlorophenyl, 4-carboxyphenyl, cyclohexyl, cyclopropyl, isopropyl, thiophen-2-yl, 5-chloro-thiophen-2-yl and 3,5-dimethyl-isoxazol-4-yl.

R^4 more preferably is selected from the group consisting of benzoyl, morpholine-4-carbonyl, acetyl, furan-3-carbonyl, 2-methoxy-benzoyl, 3-methoxy-benzoyl, naphthalene-2-carbonyl, benzo[1,3]dioxole-5-carbonyl, 3-pyridin-3-yl-acryloyl, benzofuran-2-carbonyl, furan-2-carbonyl, *tert*-butoxy-carbonyl, biphenyl-4-carbonyl, quinoline-2-carbonyl, quinoline-3-carbonyl, 3-acetyl-benzoyl, 4-phenoxy-benzoyl, 3-hydroxy-benzoyl, 4-hydroxy-benzoyl, pyridine-3-carbonyl, 3-(*tert*-butoxycarbonylamino-methyl)-benzoyl, 4-carbonyl-piperazine-1-carboxylic acid *tert*-butyl ester, 4-carbonyl-piperazine-1-carboxylic acid ethyl ester, 4-(furan-2-carbonyl)-piperazine-1-carbonyl, pyridine-4-carbonyl, 1-oxy-

- pyridine-4-carbonyl, 1-oxy-pyridine-3-carbonyl, thiophene-2-carbonyl, thiophene-3-carbonyl, 4-benzoyl-benzoyl, 5-methyl-thiophene-2-carbonyl, 3-chloro-thiophene-2-carbonyl, 3-bromo-thiophene-2-carbonyl, 4-chloro-benzoyl, 3-flouro-4-methoxy-benzoyl, 4-methoxy-benzoyl, 4-triflouromethoxy-benzoyl, 3,4-diflouro-benzoyl, 4-flouro-benzoyl,
- 5 3,4-dimethoxy-benzoyl, 3-methyl-benzoyl, 4-bromo-benzoyl, 4-triflouromethyl-benzoyl, 3-benzoyl-benzoyl, cyclopentane-carbonyl, benzo[b]thiophene-2-carbonyl, 3-chloro-benzo[b]thiophene-2-carbonyl, benzenesulfonyl, naphthalene-2-sulfonyl, 5-methyl-thiophene-2-sulfonyl, thiophene-2-sulfonyl, formamyl-methyl ester, 4-methyl-pentanoyl, formamyl-isobutyl ester, formamyl-monoallyl ester, formamyl-isopropyl ester, *N,N*-
- 10 dimethyl-formamyl, *N*-isopropyl-formamyl, *N*-pyridin-4-yl-formamyl, *N*-pyridin-3-yl-formamyl, 3-phenyl-acryloyl, 1H-indole-5-carbonyl, pyridine-2-carbonyl, pyrazine-2-carbonyl, 3-hydroxy-pyridine-2-carbonyl, 2-amino-pyridine-3-carbonyl, 2-hydroxy-pyridine-3-carbonyl, 6-amino-pyridine-3-carbonyl, 6-hydroxy-pyridine-3-carbonyl, pyridazine-4-carbonyl, 3-phenoxy-benzoyl and 1-oxo-1,3-dihydro-isoindole-2-carbonyl.
- 15 X^3 more preferably is selected from a group consisting of 4-amino-3-oxo-azepan-1-carboxylic acid benzyl ester, 4-amino-3-oxo-azepan-1-carboxylic acid isobutyl ester, 4-amino-1-benzoyl-azepan-3-one, 4-amino-1-benzenesulfonyl-azepan-3-one, 4-amino-1-(pyridine-2-sulfonyl)-azepan-3-one, 4-amino-1-(1-oxy-pyridine-2-sulfonyl)-azepan-3-one, 4-amino-1-(3,4-dichloro-benzenesulfonyl)-azepan-3-one, 4-amino-1-(2-flouro-
- 20 benzenesulfonyl)-azepan-3-one, 4-amino-1-(3,4-dimethoxy-benzenesulfonyl)-azepan-3-one, 4-amino-1-(2-cyano-benzenesulfonyl)-azepan-3-one, 4-amino-1-(naphthalene-1-sulfonyl)-azepan-3-one, 4-amino-1-(thiophene-2-sulfonyl)-azepan-3-one, 4-amino-1-(thiazole-2-sulfonyl)-azepan-3-one, 4-amino-1-(pyrrolidine-1-sulfonyl)-azepan-3-one, 4-amino-1-methanesulfonyl-azepan-3-one, 4-amino-1-(pyrrolidine-1-carbonyl)-azepan-3-

one, 4-amino-3-oxo-azepane-1-carboxylic-acid-dimethylamide, 4-amino-3-oxo-azepane-1-carboxylic-acid-benzylamide, 4-amino-1-benzyl-azepan-3-one, 4-amino-1-benzyl-piperidin-3-one, 4-amino-1-benzoyl-piperidin-3-one, 4-amino-1-benzoyl-pyrrolidin-3-one, 4-amino-1-benzyl-pyrrolidin-3-one, 4-amino-1-benzenesulfonyl-pyrrolidin-3-one, 4-amino-1-(5-methyl-hexyl)-pyrrolidin-3-one, 1-ethyl-2-oxo-3-(toluene-4-sulfonylamino)-butylamino, 1-ethyl-2-oxo-3-(4-phenoxy-benzenesulfonylamino)-propylamino, 1-ethyl-2-oxo-3-[4-(pyridin-3-yloxy)-benzenesulfonylamino]-propylamino, 3-(dibenzofuran-2-sulfonylamino)-1-ethyl-2-oxo-butylamino, 1-ethyl-3-[4-methyl-2-(4-methyl-pentanoylamino)-pentanoylamino]-2-oxo-propylamino, 5-amino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylamino, 5-benzyloxycarbonylamino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylamino, 1-[(4-methoxy-phenylsulfamoyl)-methyl]-3-phenyl-propylamino, 1-{[4-(1-hydroxy-ethyl)-phenylsulfamoyl]-methyl}-3-phenyl-propylamino, 1-[(4-acetyl-phenylsulfamoyl)-methyl]-3-phenyl-propylamino, 1-[(4-hydroxy-phenylsulfamoyl)-methyl]-3-phenyl-propylamino and 3-phenyl-1-[(2-phenylamino-ethylsulfamoyl)-methyl]-propylamino; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

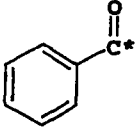
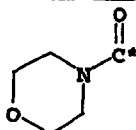
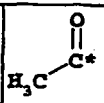
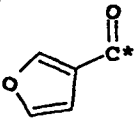
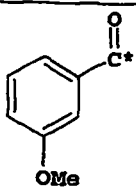
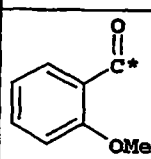
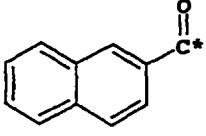
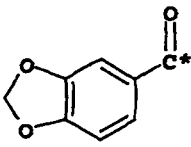
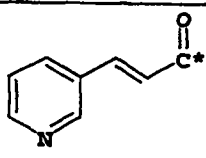
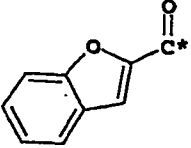
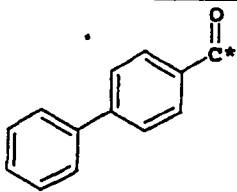
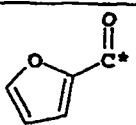
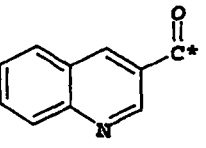
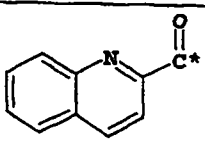
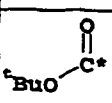
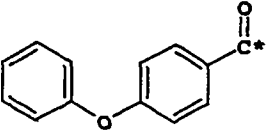
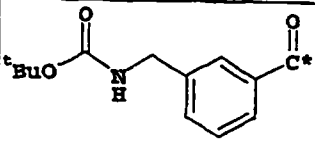
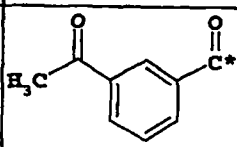
Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups.

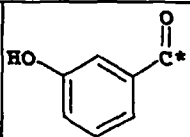
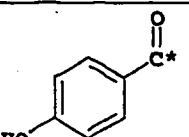
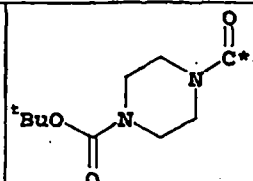
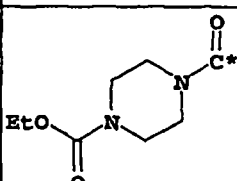
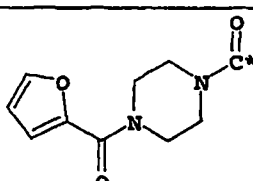
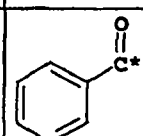
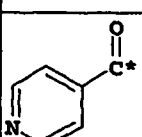
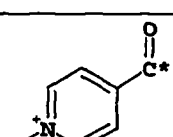
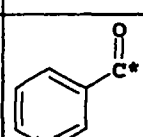
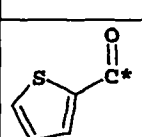
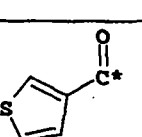
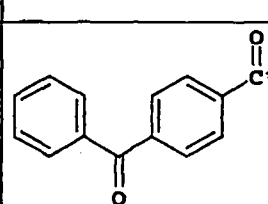
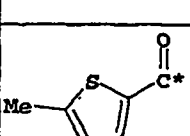
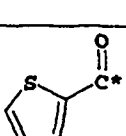
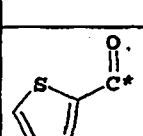
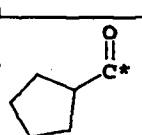
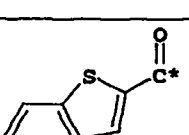
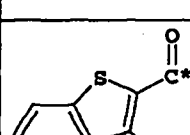
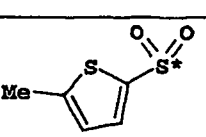
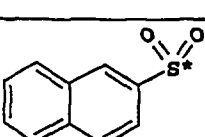
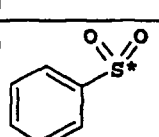
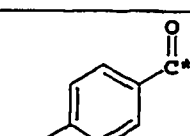
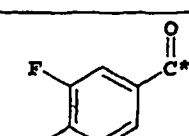
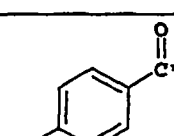
Particular compounds of the invention may be prepared by joining C* of one of the fragments (A1 to A72) shown in Table 1 to the nitrogen atom (*N) of one of the

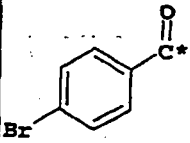
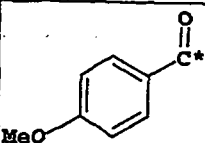
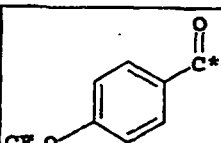
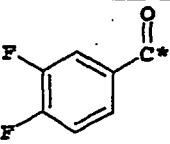
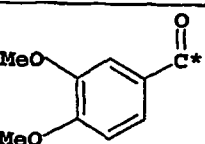
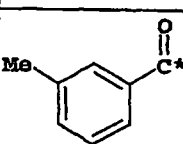
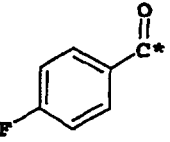
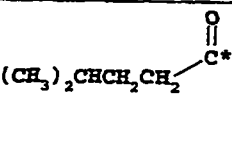
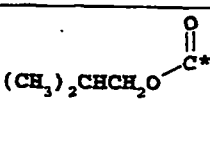
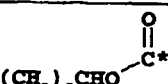
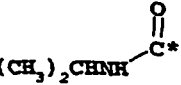
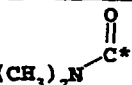
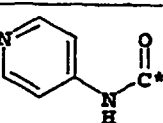
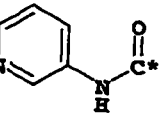
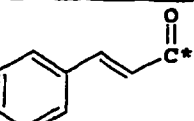
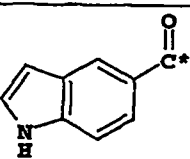
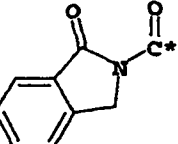
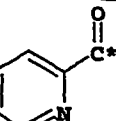
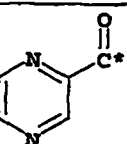
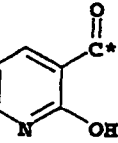
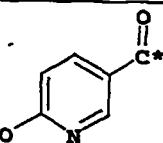
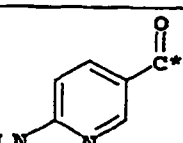
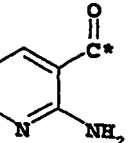
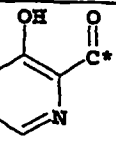
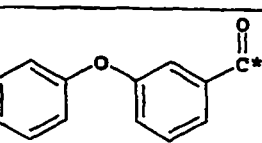
fragments (B1 to B80) shown in Table 2, and joining the methine carbon atom (CH*) of one of the fragments (B1 to B80) shown in Table 2 to the acyl carbon atom (C*) of one of the fragments (C1 to C37) depicted in Table 3.

5

TABLE 1

A1		A2		A3	
A4		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	
A16		A17		A18	

A19		A20		A21	
A22		A23		A24	
A25		A26		A27	
A28		A29		A30	
A31		A32		A33	
A34		A35		A36	
A37		A38		A39	
A40		A41		A42	

A43		A44		A45	
A46		A47		A48	
A49		A50		A51	
A52		A53		A54	
A55		A56		A57	
A58		A59		A60	
A61		A62		A63	
A64		A65		A66	
A67		A68		A69	

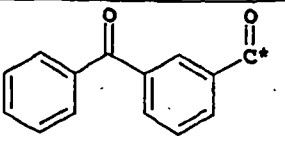
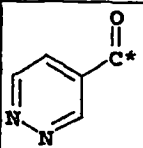
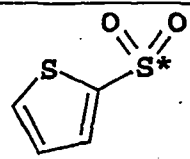
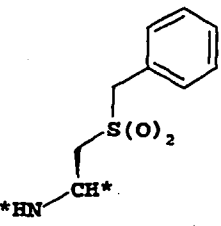
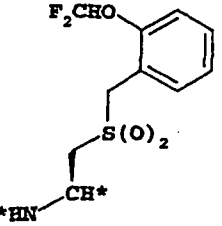
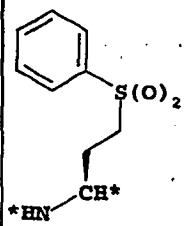
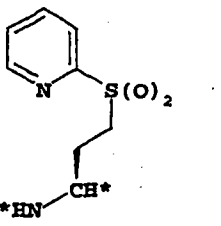
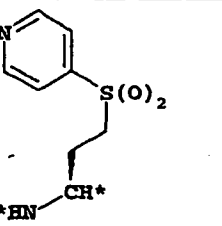
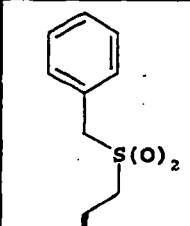
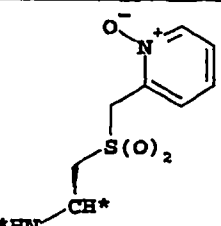
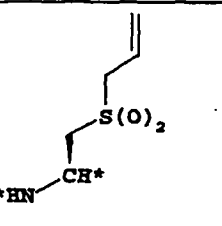
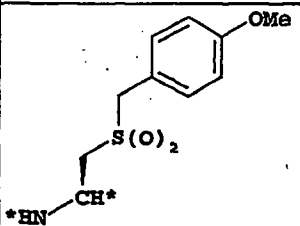
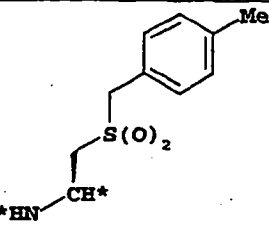
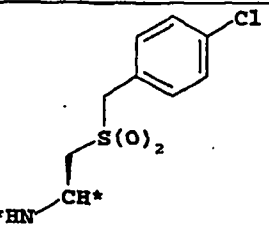
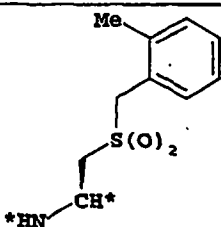
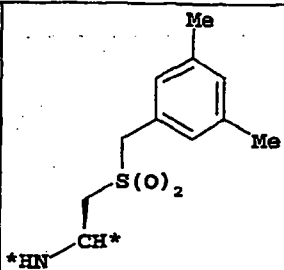
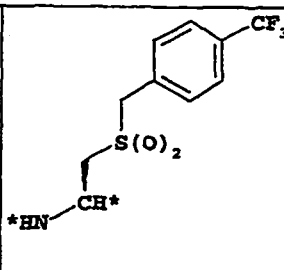
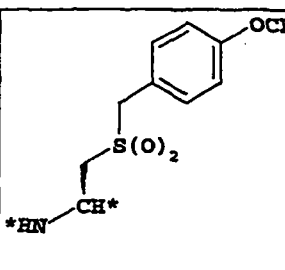
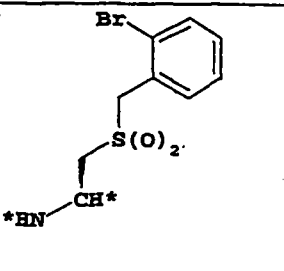
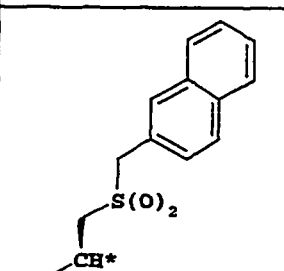
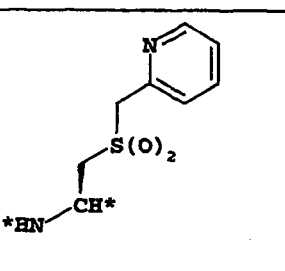
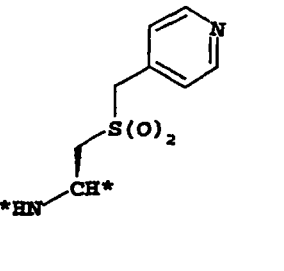
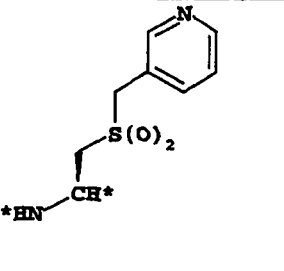
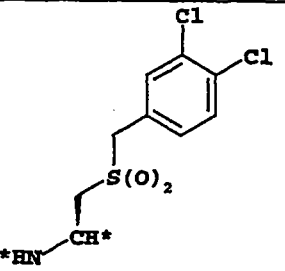
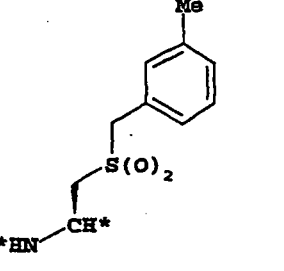
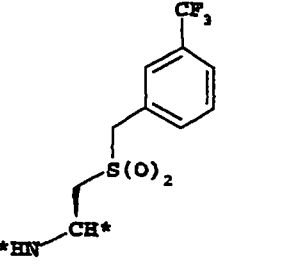
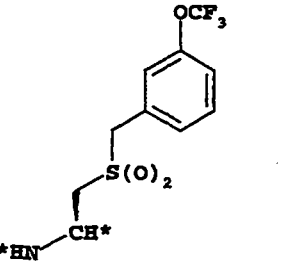
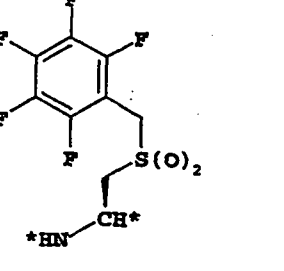
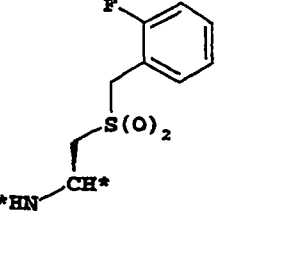
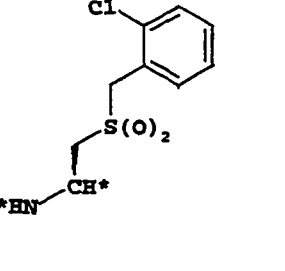
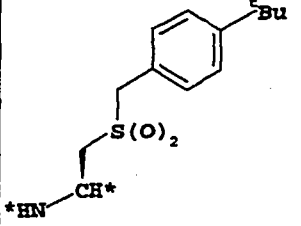
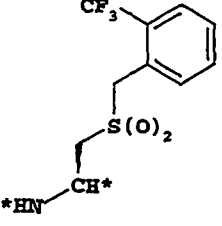
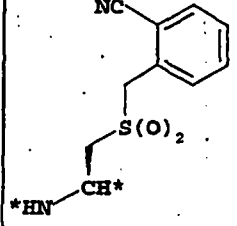
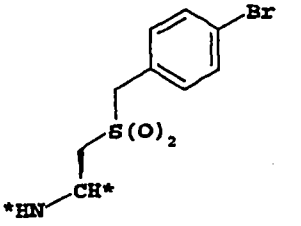
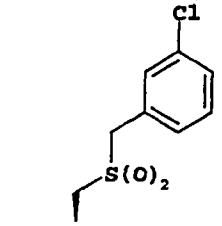
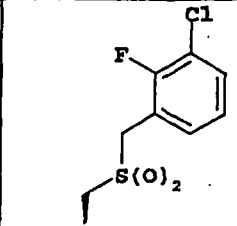
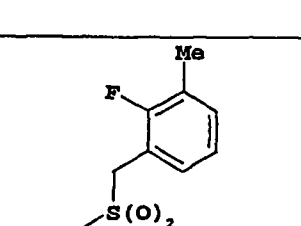
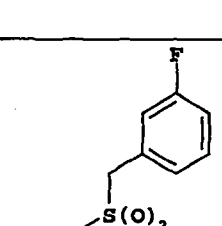
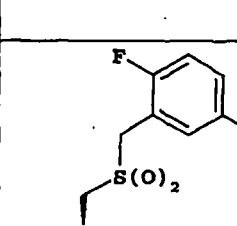
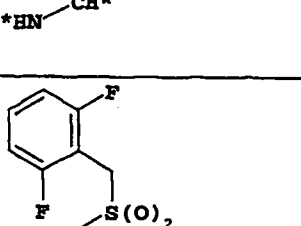
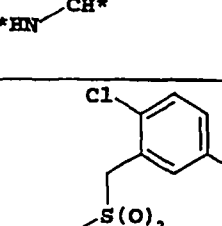
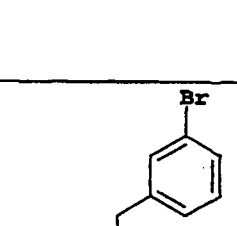
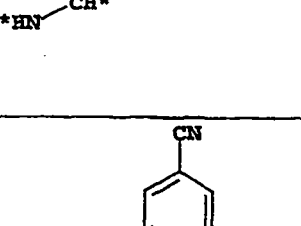
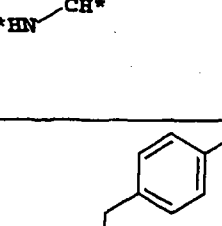
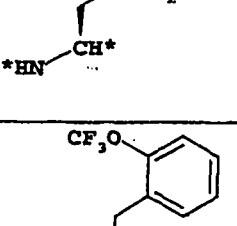
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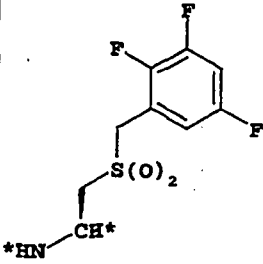
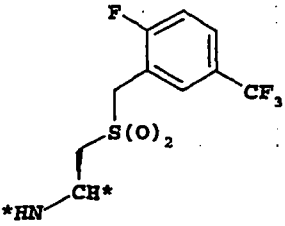
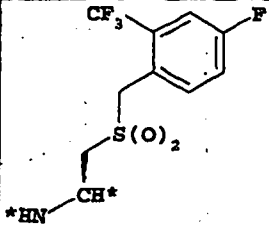
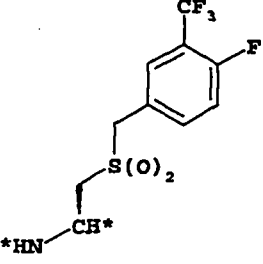
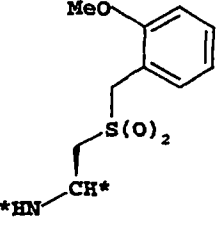
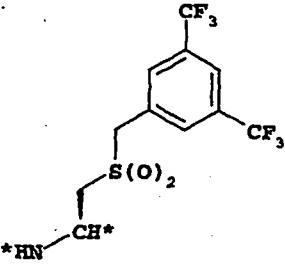
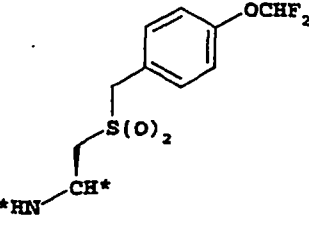
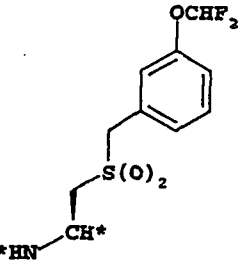
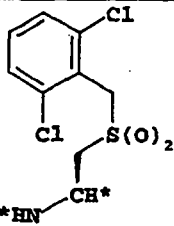
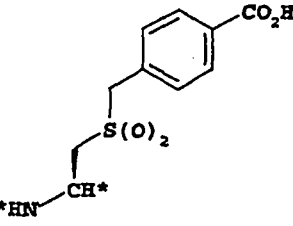
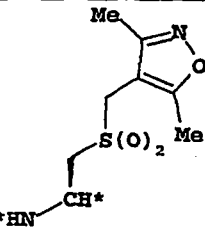
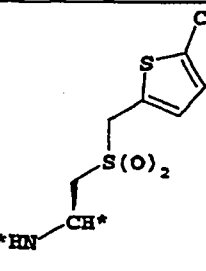
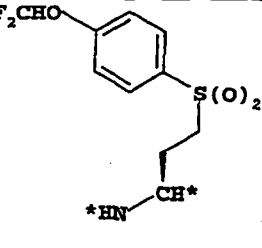
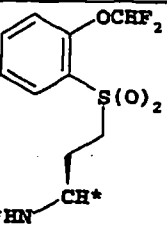
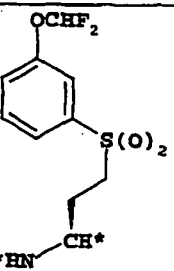
TABLE 2

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B16		B17		B18	
B19		B20		B21	
B22		B23		B24	
B25		B26		B27	

B28		B29		B30	
B31		B32		B33	
B34		B35		B36	
B37		B38		B39	
B40		B41		B42	

B43		B44		B45	
B46		B47		B48	
B49		B50		B51	
B52		B53		B54	
B55		B56		B57	

B58		B59		B60	
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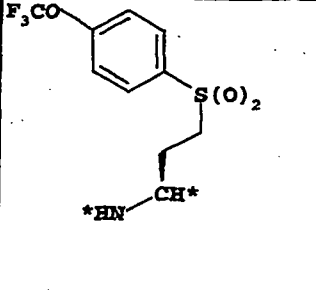
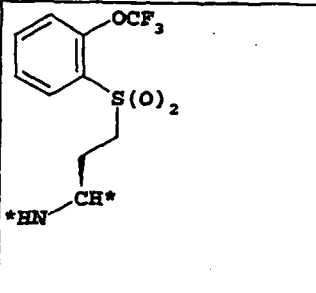
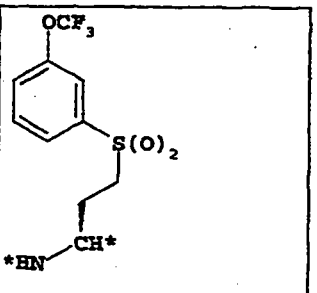
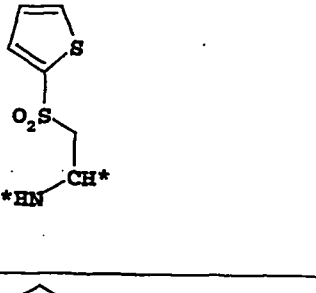
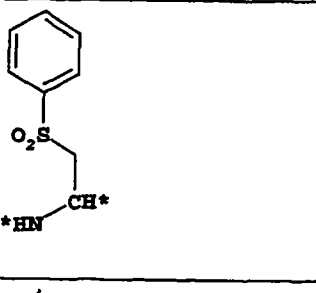
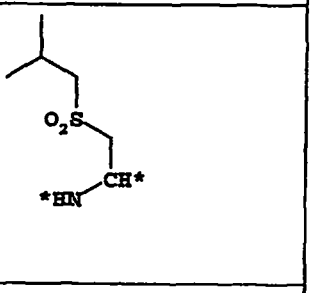
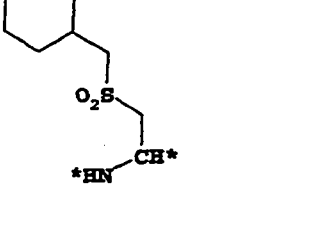
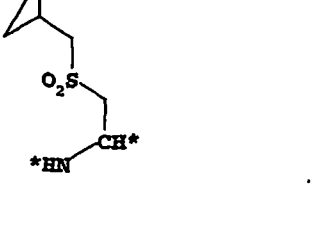
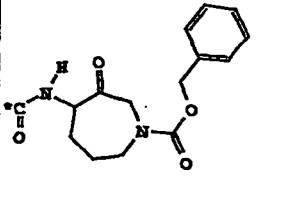
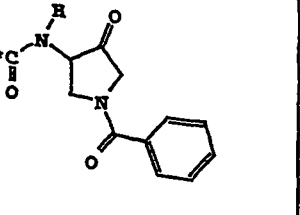
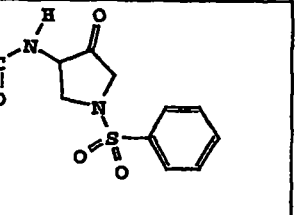
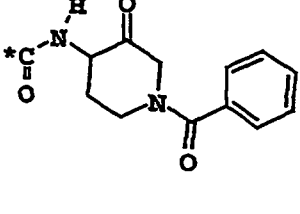
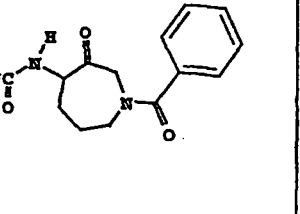
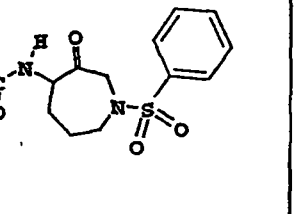
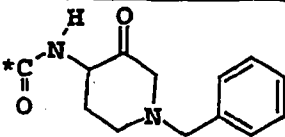
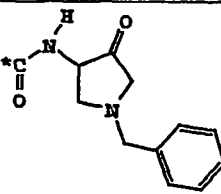
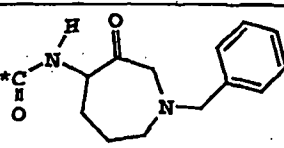
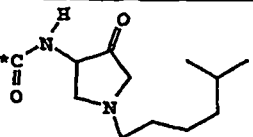
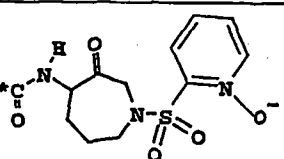
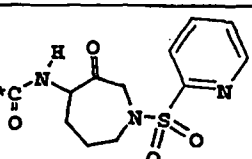
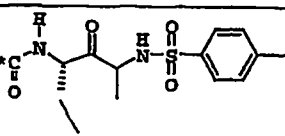
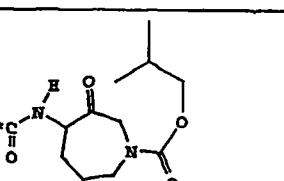
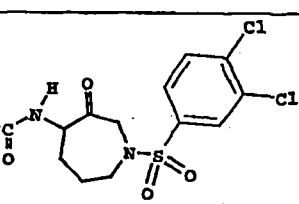
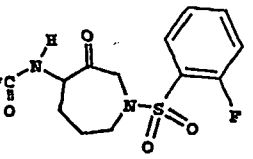
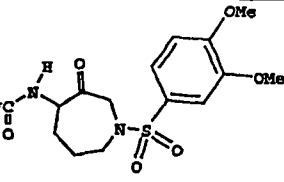
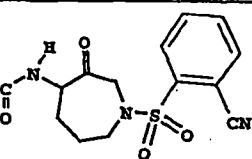
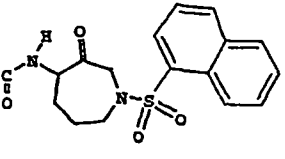
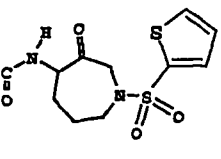
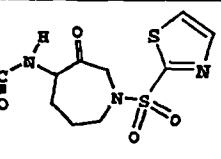
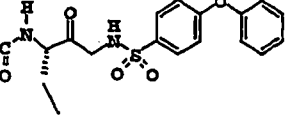
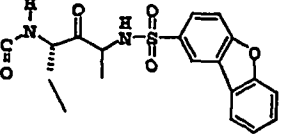
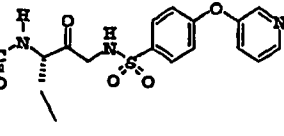
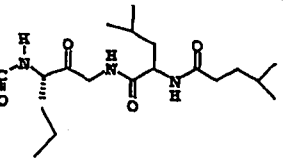
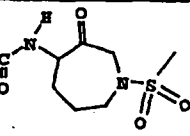
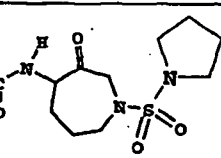
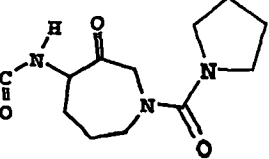
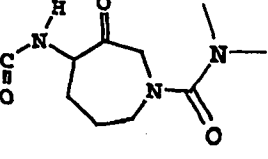
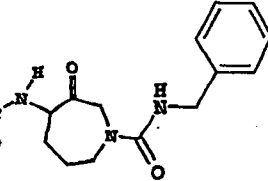
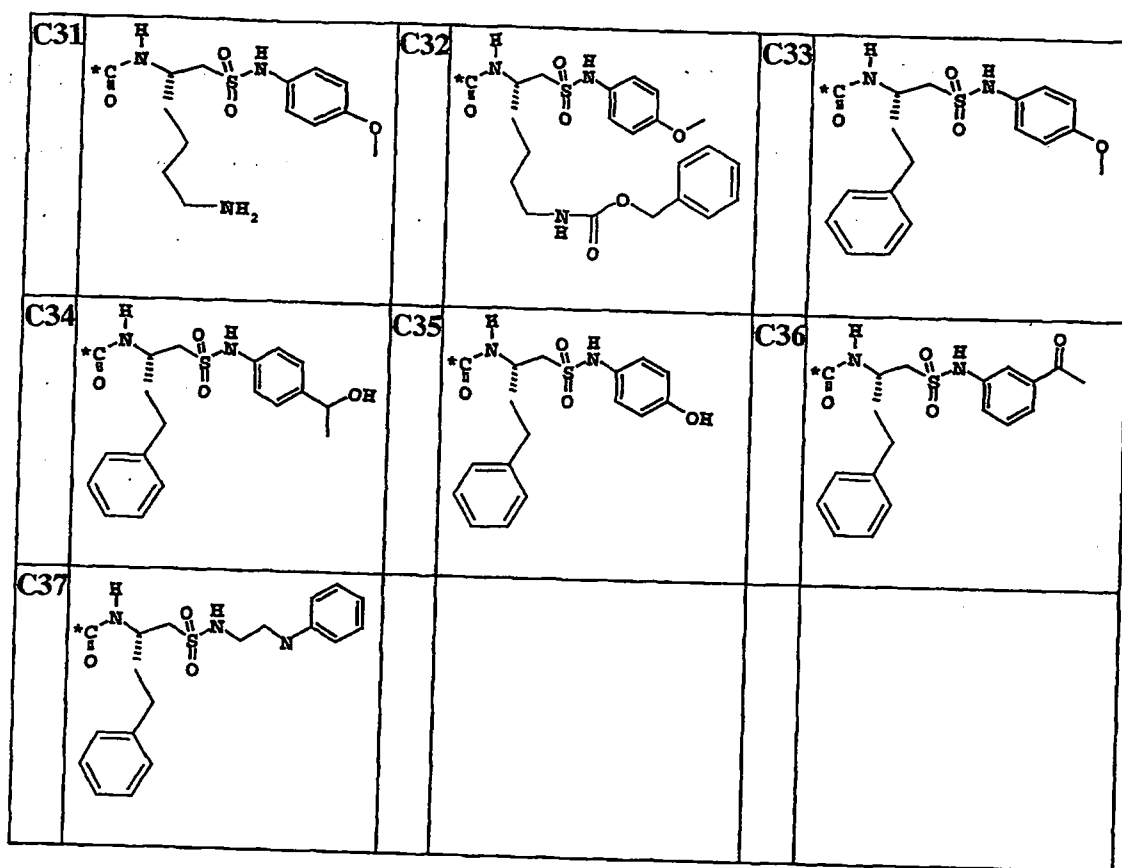
B73		B74		B75	
B76		B77		B78	
B79		B80			

TABLE 3

5

C1		C2		C3	
C4		C5		C6	

C7		C8		C9	
C10		C11		C12	
C13		C14		C15	
C16		C17		C18	
C19		C20		C21	
C22		C23		C24	
C25		C26		C27	
C28		C29		C30	



Pharmacology and Utility:

The compounds of the invention are selective inhibitors of cathepsin S and, as

5 such, are useful for treating diseases in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention are useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's

10 thyroiditis, allergic disorders, including, but not limited to, asthma, and allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts.

Cathepsin S also is implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway

elastolysis in asthma and bronchitis, pneumonitis and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

The cysteine protease inhibitory activities of the compounds of the invention can be determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease induced hydrolysis of a peptide based substrate. Details of assays for measuring protease inhibitory activity are set forth in Examples 14-17, *infra*.

Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I may range from about 1 micrograms per kilogram body weight ($\mu\text{g/kg}$) per day to about 1 milligram per kilogram body weight (mg/kg) per day, typically from about 10 $\mu\text{g/kg/day}$ to about 0.1 mg/kg/day . Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 100 $\mu\text{g/day}$ to about 100 mg/day , typically from about 1 $\mu\text{g/day}$ to about 10 mg/day . In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount

of a compound of Formula I for treating a given disease.

The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous).

- 5 Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the
- 10 active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and

15 semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula I in the composition may vary widely

20 depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in

a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I are described in Example 10, *infra*.

5

Chemistry:

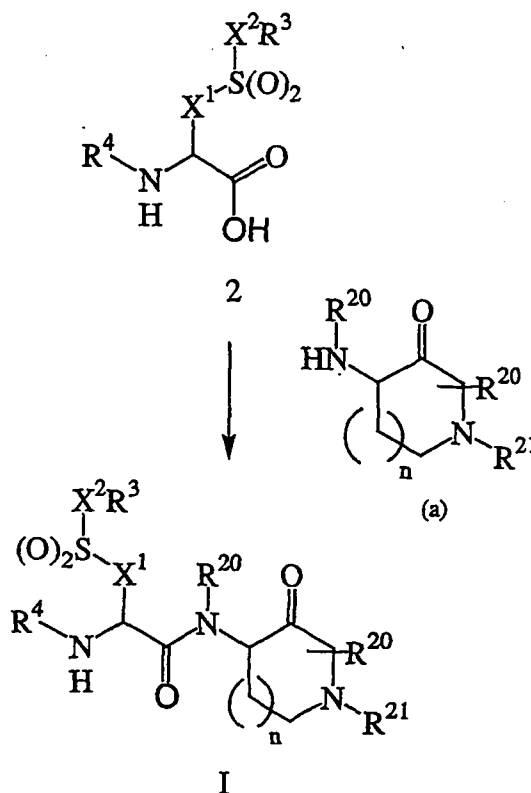
Processes for Making Compounds of Formula I:

Compounds of the invention may be prepared by the application or adaptation of
10 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.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these
15 are desired in the final product, 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.

Compounds of Formula I, in which X^3 is a compound of formula (a) (as defined in
20 the Summary of the Invention), can be prepared by proceeding as in the following Reaction Scheme 1:

Reaction Scheme 1



in which each X¹, X², R³, R⁴, R²⁰ and R²¹ are as defined for Formula I in the Summary of the Invention.

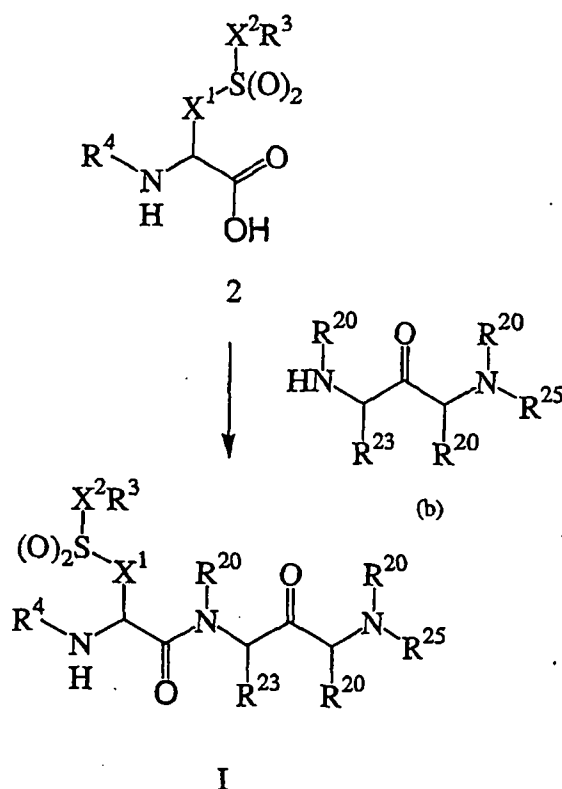
- 5 Compounds of Formula I can be prepared by condensing an acid of Formula 2 with an amino compound of formula (a). The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP[®]), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium
- 10 hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3, tetra-
- methyluroniumhexafluorophosphate (HATU), or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at

ambient temperature and requires 5 to 10 hours to complete.

An oxidation step, if required, can be carried out with an oxidizing agent (e.g., Oxone[®], metachloroperbenzoic acid or the like) in a suitable solvent (e.g., methanol, water, or the like, or any suitable combination thereof) at ambient temperature and requires 16 to 24 hours to complete. Detailed descriptions for the synthesis of a compound of Formula I by the processes in Reaction Scheme 1 are set forth in the Examples 1 to 11, *infra*.

Compounds of Formula I, where X^3 is a compound of formula (b) (as defined in the Summary of the Invention), can be prepared by proceeding as in the following Reaction Scheme 2:

Reaction Scheme 2



in which each X^1 , X^2 , R^3 , R^4 , R^{20} , R^{23} and R^{25} are as defined for Formula I in the Summary of the Invention.

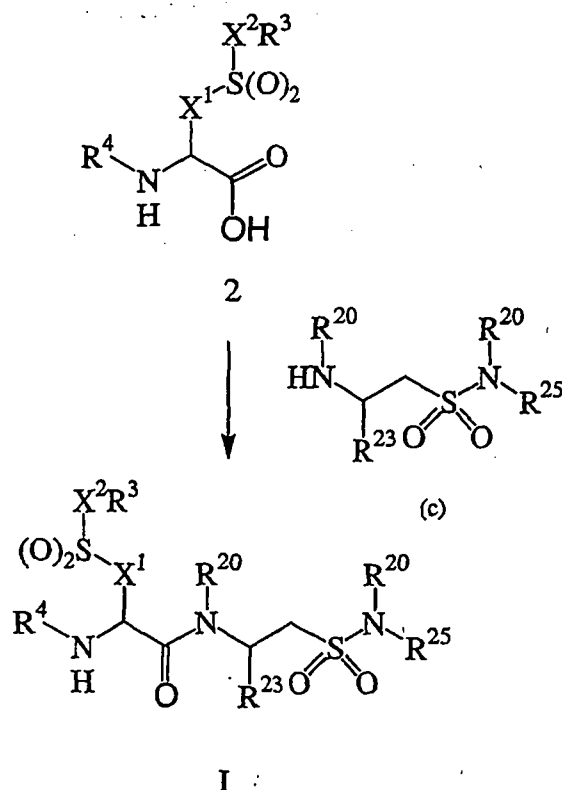
Compounds of Formula I can be prepared by condensing an acid of Formula 2 with an amino compound of formula (b). The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP[®]), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HATU), or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature and requires 5 to 10 hours to complete.

An oxidation step, if required, can be carried out with an oxidizing agent (e.g., Oxone[®], metachloroperbenzoic acid or the like) in a suitable solvent (e.g., methanol, water, or the like, or any suitable combination thereof) at ambient temperature and requires 16 to 24 hours to complete.

Compounds of Formula 1 in which X^3 is a compound of formula (c) (as defined in the Summary of the Invention), can be prepared by reacting a compound of Formula 2 with a compound of Formula (c) according to the following reaction scheme:

Reaction Scheme 3

-41-



in which each X^1 , X^2 , R^3 , R^4 , R^{20} , R^{23} and R^{25} are as defined for Formula I in the Summary of the Invention.

5

Additional Processes for Preparing Compounds of Formula I:

A compound of Formula I can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of Formula I can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this Application.

10

Alternatively, the salt forms of the compounds of Formula I can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of Formula I in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of Formula I in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

10 The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, 15 the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of Formula I can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.* (1994),

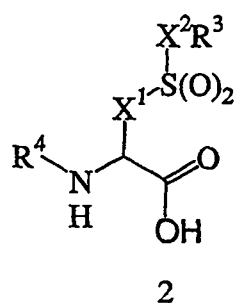
Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

- 5 Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.
- Compounds of the present invention may be conveniently prepared, or formed during the
- 10 process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.
- Compounds of Formula I can be prepared as their individual stereoisomers by reacting a
- racemic mixture of the compound with an optically active resolving agent to form a pair
- 15 of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily
- 20 separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of

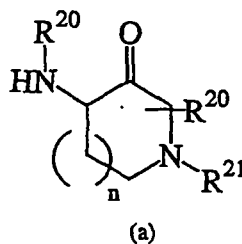
compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

In summary, the compounds of Formula I are made by a process which comprises:

- 5 (A) reacting a compound of Formula 2:

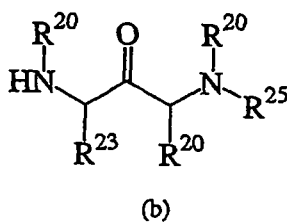


with a compound of the formula (a):



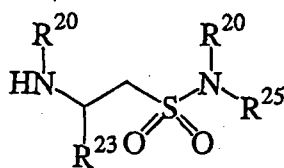
10 in which X^1 , X^2 , R^3 , R^4 , R^{20} and R^{21} are as defined in the Summary of the Invention for Formula I; or

- (B) reacting a compound of Formula 2 with a compound of the formula (b):



in which R^{20} , R^{23} and R^{25} are as defined in the Summary of the Invention for Formula I; or

(C) reacting a compound of Formula 2 with a compound of the formula (c):



(c)

5 in which R^{20} , R^{23} and R^{25} are as defined in the Summary of the Invention for Formula I; and

- (D) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;
- 10 (E) optionally converting a salt form of a compound of Formula I to non-salt form;
- (F) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;
- (G) optionally converting an *N*-oxide form of a compound of Formula I its unoxidized form;
- 15 (H) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;
- (I) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and
- (J) optionally converting a prodrug derivative of a compound of Formula I to its
- 20 non-derivatized form.

Examples:

The present invention is further exemplified, but not limited by, the following examples that illustrate the preparation of compounds of Formula I (Examples) and intermediates (References) according to the invention.

REFERENCE 1

3-amino-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

6-Oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (12.1g, 65.3mmol) was dissolved in a 8:1 methanol/water mixture (108mL). Ammonium chloride (15g) and sodium azide (21.4g, 329mmol) was added and the mixture was heated at 60°C overnight. After dilution with ether (500mL), the mixture was washed with saturated aqueous NaHCO₃ (200mL) and brine (200mL), dried with MgSO₄ and evaporated under vacuum. The crude product was dissolved in methanol (200mL). 10% Palladium on activated carbon (1.5g) was added and the mixture was stirred at ambient temperature under a hydrogen atmosphere until TLC analysis showed the disappearance of the starting material. The mixture was filtered through a pad of Celite and evaporated to dryness under vacuum. The product was purified by flash chromatography on silica gel. Eluent: 5% methanol in ethyl acetate to 20% methanol, 3% triethylamine in ethyl acetate. Yield: 4.3g 3-amino-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester as yellowish solid.

REFERENCE 2

4-Amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester

Sodium hydride (60% in mineral oil, 10g, 250mmol) was suspended in dry DMF. Allyl-carbamic acid benzyl ester (19.1g, 100mmol) was added drop wise at ambient temperature. After stirring for 5 minutes, 5-bromo-1-pentene (25g, 168mmol) was added drop wise. Stirring was continued at 50°C for 1 hour. The reaction was quenched with
5 water and then partitioned between diethyl ether and water. The ether layer was washed with water and brine, dried with MgSO_4 and evaporated under vacuum. Flash chromatography (ethyl acetate/hexane 1:9) gave allyl-pent-4-enyl-carbamic acid benzyl ester (15.5g).

Allyl-pent-4-enyl-carbamic acid benzyl ester (15.5g, 59.8mmol) was dissolved in
10 dichloromethane and bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (1g) was added. The mixture was refluxed under a nitrogen atmosphere until TLC analysis showed complete reaction. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (ethyl acetate/hexane 1:9) to give 2,3,4,7-Tetrahydro-azepine-1-carboxylic acid benzyl ester (7.8g).

15 To a solution of 2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (4.5g, 19.45mmol) in dichloromethane (50mL) was added *m*-chloroperbenzoic acid (60mmol). The mixture was stirred at ambient temperature for 16 hours. Saturated aqueous K_2CO_3 solution was added and the mixture was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous NaHCO_3 and brine, dried with MgSO_4
20 and evaporated under vacuum. The crude epoxide was dissolved in an 8:1 methanol/water mixture (100mL). Ammonium chloride (3.2g, 60mmol) and sodium azide (3.9g, 60mmol) were added and the mixture was heated at 60°C for 48 hours. Most of the solvent was removed under vacuum. The residue was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO_3 (200mL) and brine (200mL),

dried with MgSO_4 and evaporated under vacuum. Flash chromatography of the residue (hexane/ethyl acetate 3:1) gave 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester (3.3g).

To a solution of 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester (3.3g, 11.37mmol) in methanol (50mL) was added triethylamine (5mL) and 1,3-propanedithiol (3.42mL, 35mmol). The mixture was stirred at ambient temperature until TLC analysis showed complete consumption of the starting material. A white precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was triturated with a 1:1 hexane/diethyl ether mixture to remove excess dithiol and dried under vacuum to yield 4-amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester.

REFERENCE 3

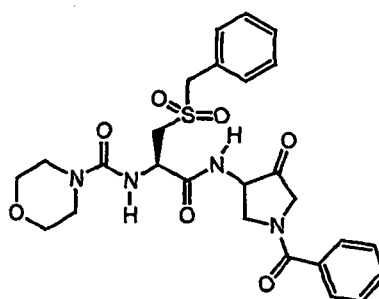
2S-Amino-N-(4-methoxyphenyl)-4-phenylbutane-1-sulfonamide hydrochloride

A solution comprised of crude *tert*-butyl 1-(4-methoxyphenylsulfamoylmethyl)-3-phenylpropylcarbamate (1.92 g, 4.42 mmol), prepared as in Reference Example 2, in DCM (10 mL) was treated with a 4M solution of hydrogen chloride in dioxane (11 mL). The mixture was stirred for 16 hours at room temperature and diluted with diethyl ether. A resulting precipitate was collected by filtration, washed several times with diethyl ether and hexane and pumped dry to provide 2S-amino-N-4-methoxyphenyl-4-phenylbutane-1-sulfonamide hydrochloride with quantitative mass recovery. ^1H NMR (DMSO): 2.05 (2H, m); 2.6-2.7 (2H, m); 3.4 (3H, m*); 3.72 (3H, s); 6.9 (2H, d, $J=7$ Hz); 7.25 (5H, m); 7.3 (2H, d, $J=7$ Hz); 8.5 (br. s); 10.0 (1H, s).

EXAMPLE 1

Morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 1)



5 2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (1g, 2.8mmol), 3-amino-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (700mg, 3.46mmol) prepared as in Reference 1, EDC (1.5g, 7.8mmol), and HOBt (1.5g, 9.6mmol) were combined. Dichloromethane (10mL) was added and then 4-methylmorpholine (1.5mL). The mixture was stirred at ambient temperature for 2 hours. After dilution with
10 ethyl acetate (200mL) the solution was washed with saturated aqueous NaHCO₃ (100mL) and brine (100mL), dried with MgSO₄ and evaporated under vacuum. 3-Hydroxy-4-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-pyrrolidine-1-carboxylic acid tert-butyl ester (1.05g, 1.94mmol) was obtained as yellowish foam and was dissolved in dichloromethane (6mL). Trifluoroacetic acid (6mL) was added and the
15 mixture was stirred at ambient temperature for 1 hour. Evaporation under vacuum gave crude morpholine-4-carboxylic acid [1-(4-hydroxy-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as TFA salt, which was used without further purification.

 Morpholine-4-carboxylic acid [1-(4-hydroxy-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide TFA salt (215mg, 0.39mmol) was dissolved in 1,4-
20

dioxane (20mL). Saturated aqueous NaHCO₃ solution (10mL) was added followed by benzoyl chloride (0.2mL, 1.72mmol). The mixture was stirred at ambient temperature for 1 hour and then extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (Eluent: 5% methanol in ethyl acetate to 20% methanol in ethyl acetate) to yield morpholine-4-carboxylic acid [1-(1-benzoyl-4-hydroxy-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (92mg).

Morpholine-4-carboxylic acid [1-(1-benzoyl-4-hydroxy-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (92mg, 0.169mmol) was dissolved in DMSO (5mL). Triethylamine (0.5mL) and then SO₃ pyridine complex (150mg) were added and the mixture was stirred at ambient temperature for 3 hours. After dilution with ethyl acetate (100mL), the solution was washed with water (50mL) and brine, dried with MgSO₄ and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (Eluent: 5% methanol in ethyl acetate) to yield morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as a mixture of diastereomers (Yellowish solid; 38mg); ¹H NMR: (DMSO) 8.50-8.35 (m, 1H), 7.55-7.34 (m, 10H), 7.16-6.95 (m, 1H), 4.80-4.65 (m, 1H), 4.54-4.22 (m, 3H), 3.98-3.25 (m, 14H); MS: (M+H)⁺ 543.

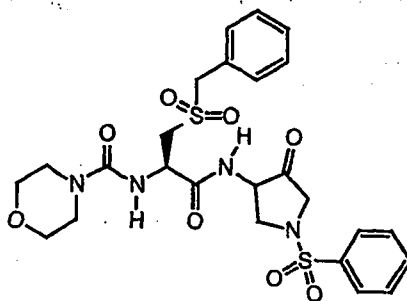
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EXAMPLE 2

Morpholine-4-carboxylic acid [1-(1-benzenesulfonyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 2)

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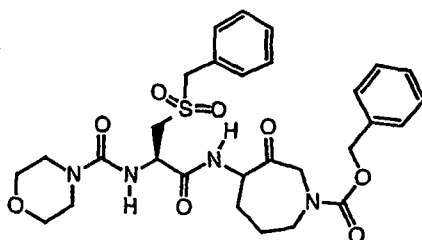


Morpholine-4-carboxylic acid [1-(1-benzenesulfonyl-4-oxo-pyrrolidin-3-ylcarbamoyl) 2-phenylmethanesulfonyl-ethyl]-amide was prepared following the procedure detailed in Example 1, substituting benzenesulfonyl chloride for benzoyl chloride; ¹H NMR: (DMSO) [8.35 (d, J=7.4Hz), 8.28 (d, J=7.6Hz), 1H], 7.87-7.62 (m, 5H), 7.41-7.32 (m, 5H), 7.06-6.98 (m, 1H), 4.72-4.60 (m, 1H), 4.45 (s, 2H), 4.42-4.23 (m, 1H), 3.92-3.79 (m, 2H), 3.55-3.20 (m, 11H), 3.06-2.97 (m, 1H). MS: (M+H)⁺ 579.

EXAMPLE 3

10 4-{2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester

(Compound 3)



Crude 4-amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester (150mg, 0.57mmol) prepared as in Reference 2, 2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (400mg, 1.12mmol), EDC (400mg, 2.1mmol), and HOBt (400mg, 2.5mmol) were combined. Dichloromethane (10mL) was added followed

by 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (100mL) the solution was washed with 1N HCl, saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and evaporated under vacuum.

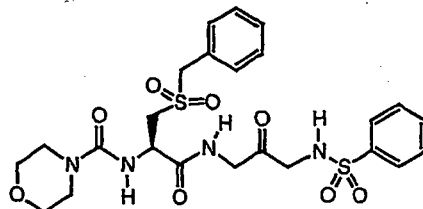
The residue was purified by flash chromatography (ethyl acetate/methanol 9:1) to yield 3-hydroxy-4-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionyl-amino}-azepane-1-carboxylic acid benzyl ester (320mg).

3-Hydroxy-4-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-azepane-1-carboxylic acid benzyl ester (100mg, 0.167mmol) was dissolved in DMSO (5mL). Triethylamine (0.3mL) and then SO₃ pyridine complex (150mg) were added and the mixture was stirred at ambient temperature for 3 hours. After dilution with ethyl acetate (100mL), the solution was washed with water (50mL) and brine, dried with MgSO₄ and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (Eluent: 5% methanol in ethyl acetate) to yield 4-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester (75mg); ¹H NMR: (DMSO) 8.23-8.08 (m, 1H), 7.40-7.29 (m, 10H), 7.06-6.98 (m, 1H), 5.20-5.09 (m, 2H), 4.79-4.65 (m, 1H), 4.52-4.31 (m, 3H), 4.02-3.80 (m, 2H), 3.62-3.23 (m, 11H), 3.00-2.78 (m, 1H), 1.88-1.55 (m, 4H); MS: (M+H)⁺ 601.

EXAMPLE 4

Morpholine-4-carboxylic acid [1-(3-benzenesulfonylamino-2-oxo-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 4)

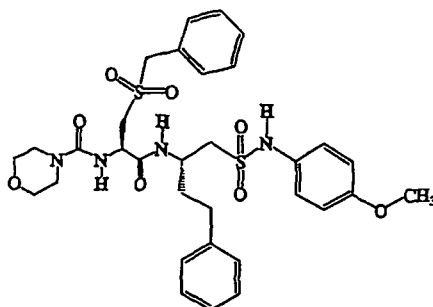


N-(3-Amino-2-hydroxy-propyl)-benzenesulfonamide TFA salt was prepared as outlined in Renee L. DesJarlais et al. *J. Am. Chem. Soc.* **1998**, *120*, 9114-9115.

2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (50mg, 0.14mmol), *N*-(3-amino-2-hydroxy-propyl)-benzenesulfonamide TFA salt (60mg, 0.17mmol), EDC (100mg, 0.52mmol), and HOBt (100mg, 0.64mmol) were combined. DMF (3mL) was added and then 4-methylmorpholine (0.3mL). The mixture was stirred at ambient temperature for 3 hours. After dilution with ethyl acetate (100mL) the solution was washed with 1N HCl, saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and evaporated under vacuum. The residue was dissolved in acetone (5mL). Jones reagent was added until the orange color persisted. The mixture was stirred for 2 hours, quenched with isopropanol, and diluted with ethyl acetate (100mL). The solution was washed with water, saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and evaporated under vacuum. The crude product was recrystallized from ethyl acetate/diethyl ether to give morpholine-4-carboxylic acid [1-(3-benzenesulfonylamino-2-oxo-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as white solid (19mg); ¹H NMR: (DMSO) 8.17 (t, J=5.7Hz, 1H), 7.93 (t, J=5.9Hz, 1H), 7.76-7.48 (m, 5H), 7.36-7.29 (m, 5H), 7.05 (d, J=8.1Hz, 1H), 4.68-4.59 (m, 1H), 4.45 (s, 2H), 3.89 (d, J=5.7Hz, 2H), 3.79-3.75 (m, 2H), 3.56-3.22 (m, 10H); MS: (M+H)⁺ 567.

N-{1*S*-[1*S*-(4-Methoxyphenylsulfamoylmethyl)-3-phenylpropylcarbamoyl] 2-benzylsulfonylethyl}-morpholine-4-carboxamide

(Compound 7)



5 A mixture comprised of 2*S*-morpholin-4-ylcarbonylamino-3-benzylsulfonyl-propionic acid (0.194 g, 0.599 mmol), 2*S*-amino-*N*-(4-methoxyphenyl)-4-phenylbutane-1-sulfonamide hydrochloride (0.222 g, 0.599 mmol), prepared as in Reference 3, and HATU (0.228 g, 0.599 mmol) in DMF (5 mL) was treated with 4-methylmorpholine (0.198 g, 1.80 mmol). The mixture was stirred at room temperature for approximately 12 hours and then
10 partitioned among a 4:1:2:3 mixture (100 mL total) of ethyl acetate, THF, water, and brine, respectively. The organic phase was separated and washed with saturated aqueous sodium bicarbonate (30 mL), brine (30 mL), dried (MgSO₄), filtered and concentrated. The residue was triturated with of 5:1 ether/ethyl acetate (100 mL), collected by filtration, washed with ether (30 mL), hexane (30 mL), and pumped dry to provide *N*-{1*S*-[1*S*-(4-methoxyphenylsulfamoylmethyl)-3-phenylpropylcarbamoyl]-2-benzylsulfonylethyl}-morpholine-4-carboxamide. TLC R_f (ethyl acetate): 0.65; ¹H NMR (DMSO): 1.74 (1H, m); 1.92 (1H, m); 2.39-2.61 (2H, m); 3.1-3.35 (2H, 2xddd*); 3.34 (4H, m); 3.42-3.65 (6H, m*); 3.72 (3H, s); 4.24 (1H, m); 4.51 (2H, s); 4.61 (1H, m); 6.88 (2H, d, J=9 Hz); 7.1-7.34 (8H, m); 7.4 (5H, s); 8.12 (1H, d, J=8.7 Hz); MS (M+1): 673.

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Proceeding as in Example 5 the following compounds of Formula I were prepared:

N-{1S-[5-amino-1S-(4-methoxyphenylsulfamoyl-methyl)pentylcarbamoyl]-2-benzylsulfonylethyl-morpholine-4-carboxamide hydrobromide (Compound 5); ¹H NMR (DMSO): 1.15-1.73 (6H, m*); 2.71 (2H, m); 3.05-3.25 (2H, 2xdd); 3.37 (4H, m); 3.45-3.6 (6H, m*); 3.72 (3H, s); 4.21 (1H, m); 4.49 (2H, dd); 4.5 (1H, m*); 6.89 (2H, d, J=8.9 Hz); 7.09 (1H, m*); 7.15 (2H, d, J=8.9 Hz); 7.39 (5H, s); 7.73 (3H, br. s); 8.03 (1H, d, J=8.6 Hz); 9.47 (1H, s); MS (M+1): 640, free base); and

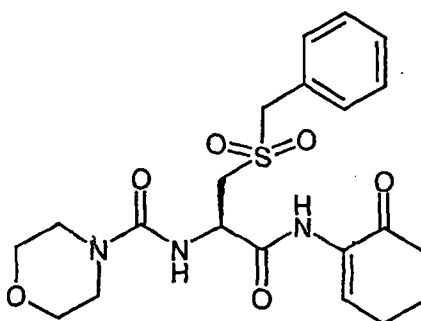
Benzyl 6-(4-methoxyphenylsulfamoyl)-5S-(2S-morpholin-4-ylcarbonylamino-3-benzylsulfonyl-propionylamino)hexylcarbamate (Compound 6); TLC R_f (ethyl acetate): 0.3; ¹H NMR (DMSO): 1.1-1.65 (6H, m); 2.94 (2H, q, J=6 Hz); 3.05-3.22 (2H, 2xdd); 3.34 (4H, m*); 3.35-3.59 (2H, m*); 3.53 (4H, br s); 3.71 (3H, s); 4.19 (1H, m*); 4.53 (2H, dd, J=15 Hz); 4.57 (1H, m*); 5.00 (2H, s); 6.89 (2H, d, J=8.4 Hz); 7.05 (1H, d, J=8 Hz); 7.15 (2H, d, J=8.4 Hz); 7.24 (1H, t); 7.3-7.45 (10H, 2xs); 7.99 (1H, J=8 Hz); MS (M+): 774.

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EXAMPLE 6

Morpholine-4-carboxylic acid [(R)-1-(6-oxo-cyclohex-1-enylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 8)



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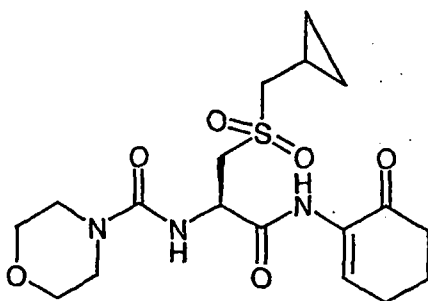
A solution of 2-amino-cyclohexane-1,3-diol (0.55 g) in dimethylformamide (30ml) was treated with diisopropylethylamine (1.6ml, 9.2mmol). After stirring at room temperature for 5 minutes the mixture was treated with (R)-2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (1.73g, 4.86mmol) followed by HATU (1.68g, 4.42mmol). This mixture was stirred at room temperature overnight and then evaporated. The residue was subjected to flash chromatography on silica eluting with ethyl acetate and then a mixture of ethyl acetate and methanol to give morpholine-4-carboxylic acid [(R)-1-(2,6-dihydroxy-cyclohexylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as a white solid (210mg). MS: 470 (MH⁺).

A solution of morpholine-4-carboxylic acid [(R)-1-(2,6-dihydroxy-cyclohexylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (90mg, 0.19mmol) in methylene chloride (6ml) was treated with Dess-Martin periodinane (162mg, 0.38mmol). After stirring at room temperature for 2 hours the reaction mixture was washed with a solution of Na₂S₂O₃ in water (0.26M), then with saturated aqueous bicarbonate solution then with water, then dried over Na₂SO₄ and then evaporated under reduced pressure. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and heptane to give morpholine-4-carboxylic acid [(R)-1-(6-oxo-cyclohex-1-enylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (8mg). ¹H NMR (CDCl₃) : 9.00 (s, 1H), 7.82 (t, J=5Hz, 1H), 7.53-7.38 (m, 5H), 6.06 (d, J=6Hz, 1H), 5.00 (m, 1H), 4.47-4.27 (m, 2H), 3.85 (m, 1H), 3.77-3.62 (m, 4H), 3.48-3.36 (m, 4H), 3.27 (m, 1H), 2.58-2.46 (m, 4H), 2.08-1.97 (m, 2H). MS: 450 (MH⁺).

EXAMPLE 7

Morpholine-4-carboxylic acid [(R)-2-cyclopropylmethanesulfonyl-1-(6-oxo-cyclohex-1-enylcarbamoyl)-ethyl]-amide

(Compound 9)



A mixture of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid (0.352g, 1.1 mmol) and N-cyclohexylcarbodiimide N'-methylpolystyrene (1.93 mmol/g, 1.03g) in DCM (10mL) was treated with
 10 hydroxybenzotriazole (0.27g, 2 mmol). After stirring at room temperature for 5 minutes the mixture was treated with 2-amino-cyclohexane-1,3-diol (0.0131g, 1 mmol) and stirring was continued for a further 2 days. The reaction mixture was treated with PS Trisamine (3.75 mmol/g, 1.3g) and after stirring at room temperature for 2 hours the resin was filtered off and washed with DCM. The combined filtrate plus washings were evaporated under
 15 reduced pressure to give morpholine-4-carboxylic acid [(R)-2-cyclopropylmethanesulfonyl-1-(2,6-dihydroxy-cyclohexylcarbamoyl)-ethyl]-amide (0.32g) as pale yellow thick oil. MS: 434 (MH⁺).

Dess Martin Periodinane (0.688 g, 1.62 mmol) was added to a solution of the [(R)-2-cyclopropylmethanesulfonyl-1-(2,6-dihydroxy-cyclohexylcarbamoyl)-ethyl]-amide
 20 (0.32g) in DCM (10mL) and the mixture was stirred at room temperature for 3 hours then

treated with resin bound $\text{Na}_2\text{S}_2\text{O}_3$ (1.5 mmol/g, 1.9g) and stirred at room temperature for a further 24 hours. The reaction mixture was diluted with DCM (20mL) , then filtered.

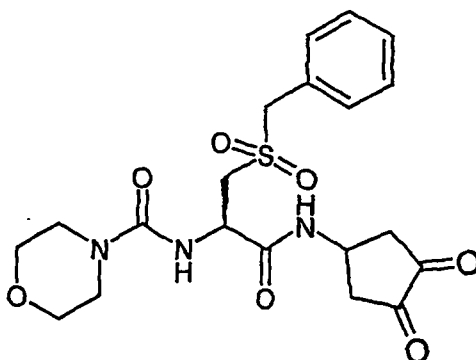
The filtrate was washed with a solution of 0.25 M $\text{Na}_2\text{S}_2\text{O}_3$, then with saturated NaHCO_3 , then dried (MgSO_4), and then evaporated under reduced pressure. The residue was

5 subjected to column chromatography eluting with a mixture of ethyl acetate and heptane to give morpholine-4-carboxylic acid [(R)-2-cyclopropylmethanesulfonyl-1-(6-oxo-cyclohex-1-enylcarbamoyl)-ethyl]-amide. ^1H NMR (CDCl_3): 9.00 (s, 1H), 7.78 (t, 1H), 6.18 (d, 1H), 4.9 (m, 1H), 3.85 (m, 1H), 3.77-3.62 (m, 4H), 3.58-3.45 (dd, 1H), 3.48-3.36 (m, 4H), 3.0 (d, 2H), 2.55-2.42 (m, 4H), 2.08-1.97 (m, 2H), 1.2 (m, 1H), 0.8-0.7 (m, 2H),
10 0.6-0.4 (m, 2H). MS: 414 (MH^+).

EXAMPLE 8

Morpholine-4-carboxylic acid [(R)-1-(3,4-dioxo-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 10)



15 A solution of 4-amino-cyclopentane-1, 2-diol; compound with trifluoroacetic acid (745mg, 3.23mmol) in DMF (15ml) was treated with DIPEA (1.12ml, 6.4mmol) and the mixture was stirred for 5 minutes at room temperature. Then (R)-2-[(Morpholine-4-

carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (1.15g, 3.23mmol) was added followed by HATU (1.23g, 3.24mmol). This mixture was stirred at room temperature overnight and then evaporated. The residue was subjected to flash chromatography on silica eluting with ethyl acetate and then with a mixture of ethyl acetate and methanol to give morpholine-4-carboxylic acid [(R)-1-(3,4-dihydroxy-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as a brown solid (680mg). LC/MS: RT=2.64min. (215 and 254nm), MH⁺=456.

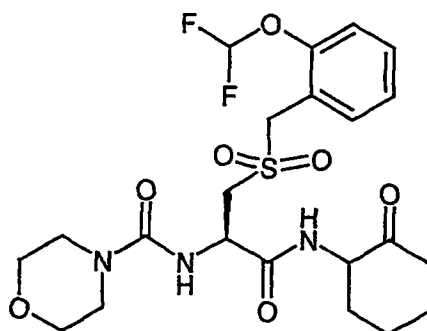
A solution of morpholine-4-carboxylic acid [(R)-1-(3,4-dihydroxy-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (670mg, 1.47mmol) in methylene chloride (40ml) was treated with Dess-Martin periodinane (624mg, 1.47mmol) and the reaction stirred at room temperature overnight. More Dess-Martin periodinane (642mg, 1.51mmol) was added and the reaction stirred at room temperature for 6 hours and then overnight. The reaction mixture was washed with a solution of Na₂S₂O₃ in water (0.26M), then with saturated aqueous bicarbonate solution, then with water, then dried over Na₂SO₄ and then evaporated under reduced pressure. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and heptane, then with ethyl acetate to give morpholine-4-carboxylic acid [(R)-1-(3,4-dioxo-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as an off white solid (45mg). ¹H NMR (CDCl₃): 7.50-7.38 (m, 5H), 6.62 (m, 1H), 5.91 (d, J=5Hz, 1H), 4.81 (m, 1H), 4.58-4.35 (m, 3H), 3.73-3.61 (m, 5H), 3.44-3.32 (m, 4H), 3.22 (m, 1H), 2.72-2.12 (m, 4H). MS: 452 (MH⁺).

EXAMPLE 9

Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-

oxo-cyclohexylcarbamoyl)-ethyl]-amide

(Compound 11)



- 5 3-(2-Difluoromethoxy-phenylmethanesulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid (100mg, 0.237mmol), 2-aminocyclohexanol (58mg, 0.5mmol), EDC (100mg, 0.52mmol), and HOBt (100mg, 0.64mmol) were combined. Dichloromethane (2mL) was added and then 4-methylmorpholine (0.2mL). The mixture was stirred at ambient temperature for 2h. After dilution with ethyl acetate (100mL) the solution was
- 10 washed with 1N aqu. HCl (30mL), sat. aqu. NaHCO₃ (30mL) and brine (30mL), dried with MgSO₄ and evaporated under vacuum. The crude product was dissolved in dichloromethane (10mL). Dess-Martin periodinane (300mg, 0.71mmol) was added, and the reaction mixture was stirred at ambient temperature for 1h. After dilution with ethyl acetate (100mL), the solution was washed with 0.26M Na₂S₂O₃ in sat. aqu. NaHCO₃
- 15 (30mL), sat. aqu. NaHCO₃ and brine, dried with MgSO₄, and evaporated under vacuum. Purification by flash-chromatography on silica gel (ethyl acetate/hexane) gave morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclohexylcarbamoyl)-ethyl]-amide (78mg, 0.151mmol) as a white solid. Mixture of diastereomers: ¹H NMR: (DMSO) [8.03 (d, J=7.2Hz), 7.96 (d, J=7.2Hz), 1H], 7.50-7.42 (m, 2H), 7.30-7.21 (m, 2H), 7.10 (t, J_{H,F}=74Hz, 1H), 7.03 (d, J=8.4Hz, 1H), 4.78-4.69 (m,
- 20 (m, 2H), 7.30-7.21 (m, 2H), 7.10 (t, J_{H,F}=74Hz, 1H), 7.03 (d, J=8.4Hz, 1H), 4.78-4.69 (m,

41
1H), 4.54 (s, 2H), 4.41-4.33 (m, 1H), 3.62-3.25 (m, 10H), 2.55-1.40 (m, 8H). MS: (M+H)⁺ 518.

By proceeding in similar manner to Example 9 but using 2-aminocyclopentanol

5 there was prepared morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclopentylcarbamoyl)-ethyl]-amide (Compound 12) as a mixture of diastereomers: ¹H NMR: (DMSO) [8.19 (d, J=8Hz), 7.15 (d, J=8Hz), 1H], 7.49-7.42 (m, 2H), 7.30-7.21 (m, 2H), 7.10 (t, J_{H,F}=74Hz, 1H), [7.02 (d, J=8.4Hz), 7.00 (d, J=8.4Hz), 1H], 4.77-4.70 (m, 1H), [4.53 (s), 4.52 (s), 2H], 4.10-3.91 (m, 1H), 10 3.60-3.23 (m, 10H), 2.28-1.70 (m, 6H). MS: (M+H)⁺ 504.

By proceeding in similar manner to Example 9 but using 2-aminocyclobutanol

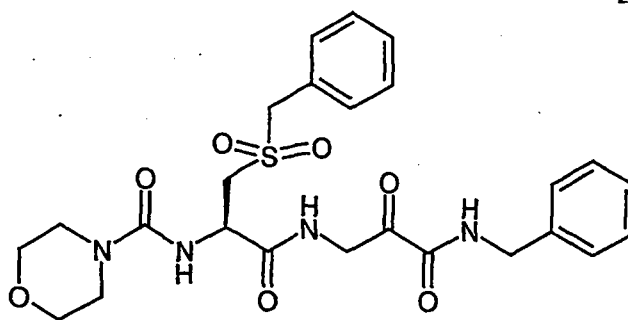
there was prepared morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclobutylcarbamoyl)-ethyl]-amide (Compound 13) 15 as a mixture of diastereomers: ¹H NMR: (DMSO) 8.49 (d, J=7.6Hz, 1H), 7.48-7.42 (m, 2H), 7.30-7.21 (m, 2H), 7.11 (t, J_{H,F}=74Hz, 1H), 7.02 (d, J=8.8Hz, 1H), 4.88-4.67 (m, 2H), 4.53 (s, 2H), 3.64-3.23 (m, 10H), 2.93-2.70 (m, 2H), 2.23-1.99 (m, 2H). MS: (M+H)⁺

20

EXAMPLE 10

(Morpholine-4-carboxylic acid [1-(2-benzylcarbamoyl-2-oxo-ethylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide)

(Compound 14)



Isoserine (3.11g, 29.6mmol) was dissolved in 1,4-dioxane/H₂O 3:1 (40mL). K₂CO₃ (0.5g) and NaHCO₃ (0.5g) was added. Di-*tert*-butyl dicarbonate (6.45g, 29.6mmol) was added and the mixture was stirred at ambient temperature over night. The reaction mixture
5 was extracted with dichloromethane (3x100mL). The combined organic phases were washed with brine, dried with MgSO₄, and evaporated under vacuum. The crude 3-*tert*-butoxycarbonylamino-2-hydroxy-propionic acid (4.76g, 23.2mmol) was obtained as a colorless oil, which solidified on standing, and was used without further purification.

10 3-*tert*-butoxycarbonylamino-2-hydroxy-propionic acid (1.5g, 7.31mmol), benzylamine (1.1mL, 10.0mmol), EDC (2.5g, 13.1mmol), and HOBt (2.0g, 12.8mmol) were combined. Dichloromethane (15mL) was added and then 4-methylmorpholine (2mL). The mixture was stirred at ambient temperature for 2h. After dilution with ethyl acetate (300mL) the solution was washed with 1N aqu. HCl (100mL), sat. aqu. NaHCO₃
15 (100mL) and brine (100mL), dried with MgSO₄ and evaporated under vacuum. Yield: 1.83g, 6.22mmol (2-Benzylcarbamoyl-2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester.

(2-Benzylcarbamoyl-2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester (0.2g, 0.68mmol) was dissolved in dichloromethane (2mL) and trifluoroacetic acid (2mL). After
20 stirring for 2h at ambient temperature, the solution was evaporated under vacuum and the

42

residue was dried under high vacuum. To this residue were added EDC (200mg, 1.05mmol), HOBt (200mg, 1.28mmol), 2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (200mg, 0.56mmol), dichloromethane (5mL) and 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2h.

5 After dilution with ethyl acetate (100mL) the solution was washed with 1N aqu. HCl (30mL), sat. aqu. NaHCO₃ (30mL) and brine (30mL), dried with MgSO₄ and evaporated under vacuum. The crude product was dissolved in dichloromethane (10mL). Dess-Martin periodinane (500mg, 1.18mmol) was added, and the reaction mixture was stirred at ambient temperature for 1h. After dilution with ethyl acetate (100mL), the solution was

10 washed with 0.26M Na₂S₂O₃ in sat. aqu. NaHCO₃ (30mL), sat. aqu. NaHCO₃ and brine, dried with MgSO₄, and evaporated under vacuum. The product (morpholine-4-carboxylic acid [1-(2-benzylcarbamoyl-2-oxo-ethylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide) was crystallized from ethyl acetate/diethylether and was obtained as a white solid (153mg, 0.29mmol). ¹H NMR: (DMSO) 9.24 (t, J=6.4Hz, 1H), 8.19 (t, J=5.6Hz, 1H),

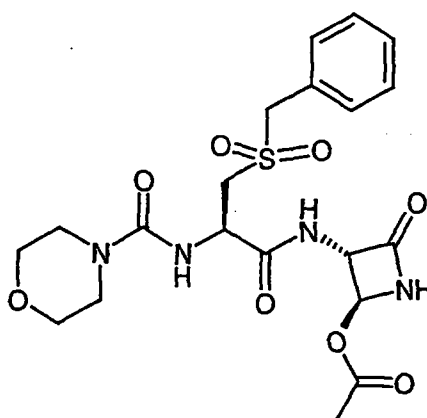
15 7.39-7.19 (m, 10H), 7.08 (d, J=8Hz, 1H), 4.83-4.76 (m, 1H), 4.49 (s, 2H), 4.48-4.33 (m, 2H), 4.31 (d, J=6.8Hz, 2H), 3.68-3.25 (m, 10H). MS: (M+H)⁺ 531.

EXAMPLE 11

Acetic acid 3-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-4-oxo-azetidin-2-yl ester

20

(Compound 15)



Acetic acid 3-benzyloxycarbonylamino-4-oxo-azetidin-2-yl ester was prepared as outlined in J.C. Arnould et al. *Eur. J. Med. Chem* **1992**, 27, 131-140.

5 Acetic acid 3-benzyloxycarbonylamino-4-oxo-azetidin-2-yl ester (100mg, 0.36mmol) was hydrogenated on a Parr shaker over 10% palladium on carbon (100mg) in ethyl acetate (20mL) at 50 psi for 5h. The mixture was filtered through Celite and evaporated. Acetic acid 3-amino-4-oxo-azetidin-2-yl ester was obtained in quantitative yield.

10

2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (100mg, 0.28mmol), acetic acid 3-amino-4-oxo-azetidin-2-yl ester (52mg, 0.36mmol), EDC (100mg, 0.52mmol), and HOBt (100mg, 0.64mmol) were combined. Dichloromethane (2mL) was added and then 4-methylmorpholine (0.2mL). The mixture
15 was stirred at ambient temperature for 2h. After dilution with ethyl acetate (100mL) the solution was washed with 1N aqu. HCl (30mL), sat. aqu. NaHCO₃ (30mL) and brine (30mL), dried with MgSO₄ and evaporated under vacuum. The residue was subjected to flash chromatography on silica gel (ethyl acetate) to give acetic acid 3-{2-[(morpholine-4-

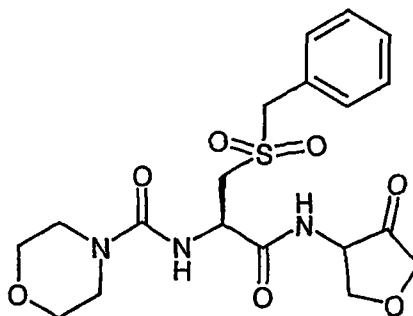
carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino]-4-oxo-azetidin-2-yl ester
(17mg, 0.035mmol). ¹H NMR: (DMSO) 9.18 (s, 1H), 8.72 (d, J=6.4Hz, 1H), 7.41-7.30
(m, 5H), 7.08 (m, 1H), 5.76 (s, 1H), 4.80-4.61 (m, 2H), 4.49 (s, 2H), 3.63-3.22 (m, 10H),
2.08 (s, 3H). MS: (M+H)⁺ 483.

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EXAMPLE 12

Morpholine-4-carboxylic acid [1-(4-oxo-tetrahydro-furan-3-ylcarbamoyl)-2-
phenylmethanesulfonyl-ethyl]-amide

(Compound 16)



10

4-Amino-tetrahydro-furan-3-ol was prepared as outlined in Marquis, Robert W. et al. *J. Med. Chem* **2001**, *44*, 725-736.

2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid
15 (100mg, 0.28mmol), 4-aminotetrahydrofuran-3-ol (100mg, 0.96mmol), EDC (200mg, 1.04mmol), and HOBt (200mg, 1.28mmol) were combined. DMF (2mL) was added and then 4-methylmorpholine (0.2mL). The mixture was stirred at ambient temperature for 2h. After dilution with ethyl acetate (100mL) the solution was washed with 1N aqu. HCl (30mL), sat. aqu. NaHCO₃ (30mL) and brine (30mL), dried with MgSO₄ and evaporated
20 under vacuum. The crude product was dissolved in dichloromethane (10mL). Dess-Martin

periodinane (300mg, 0.71mmol) was added, and the reaction mixture was stirred at ambient temperature for 1h. After dilution with ethyl acetate (100mL), the solution was washed with 0.26M Na₂S₂O₃ in sat. aqu. NaHCO₃ (30mL), sat. aqu. NaHCO₃ and brine, dried with MgSO₄, and evaporated under vacuum. Purification by flash-chromatography on silica gel (ethyl acetate) gave morpholine-4-carboxylic acid [1-(4-oxo-tetrahydro-furan-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (8.6mg, 0.020mmol) as a colorless glass. Mixture of diastereomers: ¹H NMR: (DMSO) [8.42 (d, J=6.8Hz), 7.15 (d, J=7.2Hz), 1H], 7.40-7.32 (m, 5H), [7.06 (d, J=8Hz), 7.05 (d, J=8Hz), 1H], 4.78-4.68 (m, 1H), [4.49 (s), 4.48 (s), 2H], 4.32-3.75 (m, 5H), 3.60-3.23 (m, 10H). MS: (M+H)⁺ 440.

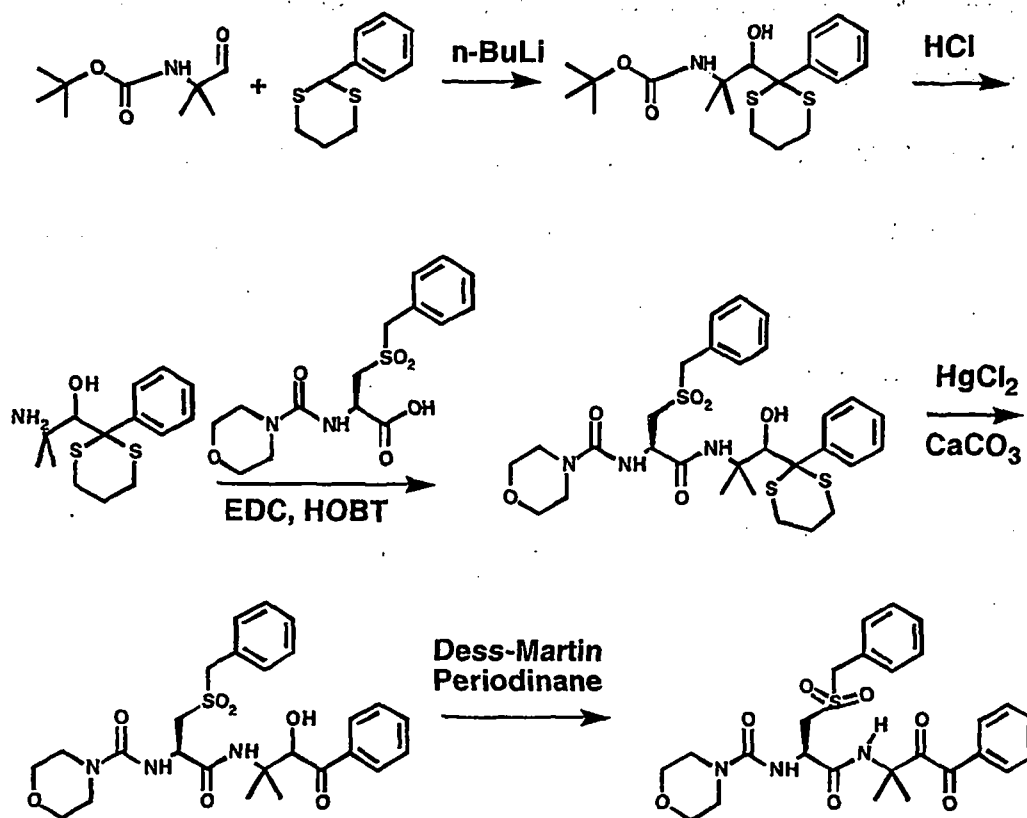
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EXAMPLE 13

Morpholine-4-carboxylic acid [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 17)

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Step 1 To a flask fitted with a septum and stirbar under a nitrogen atmosphere containing 4.1 g (20 mmol) of 2-phenyl-1,3-dithiane (Aldrich) was added dry distilled THF (20 mL). The solution was cooled to -30°C and n-butyl lithium (1.6M in

- 5 pentane, 16.8 mmol, 10.5 mL) was added slowly by syringe. The reaction mixture was warmed to -20°C and held at that temperature for 30 minutes, and then held at -10°C for 15 minutes. The yellow solution was cooled to -78°C and (1,1-dimethyl-2-oxo-ethyl)-carbamic acid *tert*-butyl ester (1.5 g, 8 mmol, in 5 mL THF) was added rapidly (over 30 seconds) and 60 seconds later a solution of 2 mL acetic acid and 5 mL THF
- 10 was added rapidly. The cooling bath was removed and 4 minutes later water was added and the mixture was extracted with ethyl acetate. The solvent was removed under reduced pressure and then recrystallized from 10 mL of ethyl acetate. The white crystals were washed three times with ethyl acetate and dried under reduced pressure to

afford [2-hydroxy-1,1-dimethyl-2-(2-phenyl-[1,3]dithian-2-yl)-ethyl]-carbamic acid *tert*-butyl ester (1.6g, 52%).

Step 2 To [2-hydroxy-1,1-dimethyl-2-(2-phenyl-[1,3]dithian-2-yl)-ethyl]-
5 carbamic acid *tert*-butyl ester (1 g, 2.6 mmol) in 4.8 mL dioxane at 10 °C was added
hydrochloric acid (4.8 mL, 4M in dioxane). The solution was warmed to 23 °C. After
2 hours the solution was concentrated to 4 ml and diluted with ether to afford a white
precipitate that was collected by filtration. The mother liquor was concentrated to a
paste and triturated with ether. The solids were combined to afford 726 mg of 2-amino-
10 2-methyl-1-(2-phenyl-[1,3]dithian-2-yl)-propan-1-ol (98% yield).

Step 3 2-Amino-2-methyl-1-(2-phenyl-[1,3]dithian-2-yl)-propan-1-ol and
2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid were
coupled using the standard peptide coupling conditions hereinbefore described to afford
15 morpholine-4-carboxylic acid {1-[2-hydroxy-1,1-dimethyl-2-(2-phenyl-[1,3]dithian-2-
yl)-ethylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide (270mg, 78%).

Step 4 To morpholine-4-carboxylic acid {1-[2-hydroxy-1,1-dimethyl-2-(2-
phenyl-[1,3]dithian-2-yl)-ethylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide (200
20 mg, 0.32 mmol) in 5.25 ml of 4:1 acetonitrile:water at 23 °C was simultaneously added
finely ground HgCl₂ (192 mg, 0.7 mmol) and finely ground calcium carbonate (80 mg,
0.8 mmol) with stirring. The mixture was stirred for 10 minutes and then diluted with
ethyl acetate. Methylene chloride was added and the organics were washed with water.
After separation the organic layer concentrated to a gum that solidified upon addition of

ether. The ether was removed under reduced pressure to afford a white solid. The solid was dissolved in a minimum of hot methylene chloride and filtered to remove insoluble material. The solution was concentrated to afford morpholine-4-carboxylic acid [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (165mg, 100% yield).

Step 5 [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide was oxidized in the usual manner to afford morpholine-4-carboxylic acid [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-

propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide. ¹HNMR: (CDCl₃) [8.0 (d, J = 8 Hz) 1H], 7.7-7.2 (m, 10H), [5.9 (d, J = 6Hz) 1H], [4.8 (d, J = 6Hz) 1H], [4.3 (d, J = 14, Hz) 1H], [4.1 (d, J = 14 Hz) 1H], 3.7 (m, 4H), 3.36 (m, 4H), [3.3 (d, J = 2 Hz) 1H], [3.29 (d, J = 2 Hz) 1H], 1.7(s, 6H). LCMS: elution time = 3.71 min. 527.6(M-1), 529.6(M+1). (MS: API 150EX. LC: HP Agilent 1100 Series. Column: Phenomenex, 5u ODS3 100A 100X3mm.; Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.).

By proceeding in a similar manner to Example 13 but using 3-(2-difluoromethoxy-phenylmethanesulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid in step 3 there was prepared morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(1,1-dimethyl-2,3-dioxo-3-phenyl-propylcarbamoyl)-ethyl]-amide. LC-MS: elution time = 3.95 min. 593.4(M-1),

596.2(M+1). (MS: API 150EX. LC: HP Agilent 1100 Series. Column: Phenomenex, 5u ODS3 100A 100X3mm.; Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then
5 gradient back to 100% A, 0% B from t = 7 to t = 15 min.)

EXAMPLE 14

Cathepsin S Assay

10 Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM). Human cathepsin S (0.158 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient
15 temperature. Z-Val-Val-Arg-AMC (9 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

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EXAMPLE 15

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-FR-AMC (20 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 16

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 17

Cathepsin L Assay

5 Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient
10 temperature. Z-Phe-Arg-AMC (1 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

 Some of the compounds of the invention tested according to the above-described
15 assays for protease inhibition were observed to exhibit selective cathepsin S inhibitory activity. The apparent inhibition constants (K_i) for compounds of the invention, against Cathepsin S, were in the range from about 10^{-10} M to about 10^{-7} M.

EXAMPLE 18

20 Representative Pharmaceutical Formulations Containing a Compound of Formula I

ORAL FORMULATION

	Compound of Formula I	10-100 mg
	Citric Acid Monohydrate	105 mg
	Sodium Hydroxide	18 mg
	Flavoring	
5	Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

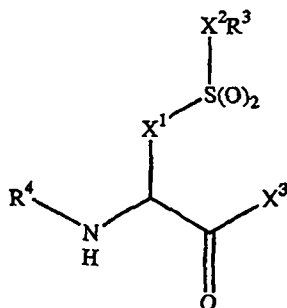
	Compound of Formula I	0.1-10 mg
	Dextrose Monohydrate	q.s. to make isotonic
10	Citric Acid Monohydrate	1.05 mg
	Sodium Hydroxide	0.18 mg
	Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

15	Compound of Formula I	1%
	Microcrystalline Cellulose	73%
	Stearic Acid	25%
	Colloidal Silica	1%.

WE CLAIM:

1. A compound of Formula I:



I

in which:

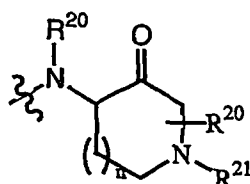
X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond;

- 10 R^3 is $-\text{CR}^5=\text{CHR}^6$, $-\text{CR}^5(\text{CR}^6_3)_2$ or $-\text{CR}^7=\text{NR}^8$, wherein R^5 is hydrogen and R^6 is hydrogen or (C_{1-4}) alkyl or R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{3-12}) cycloalkenyl, hetero (C_{5-12}) cycloalkenyl, (C_{6-12}) aryl, hetero (C_{6-12}) aryl, (C_{9-12}) bicycloaryl or hetero (C_{8-12}) bicycloaryl and R^7 and R^8 together with the atoms to which R^7 and R^8 are attached form hetero (C_{5-12}) cycloalkenyl, hetero (C_{6-12}) aryl or
- 15 hetero (C_{8-12}) bicycloaryl, wherein R^3 optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-\text{X}^4\text{NR}^9\text{R}^9$, $-\text{X}^4\text{OR}^9$, $-\text{X}^4\text{SR}^9$, $-\text{X}^4\text{C}(\text{O})\text{NR}^9\text{R}^9$, $-\text{X}^4\text{C}(\text{O})\text{OR}^9$, $-\text{X}^4\text{S}(\text{O})\text{R}^{10}$, $-\text{X}^4\text{S}(\text{O})_2\text{R}^{10}$ and $-\text{X}^4\text{C}(\text{O})\text{R}^{10}$, wherein X^4 is a bond or (C_{1-2}) alkylene, R^9 at each occurrence independently is hydrogen, (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl and
- 20 R^{10} is (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl; and

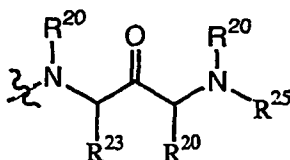
R^4 is $-C(O)X^5R^{11}$ or $-S(O)_2X^5R^{11}$, wherein X^5 is a bond, $-O-$ or $-NR^{12}-$, wherein R^{12} is hydrogen or (C_{1-6}) alkyl, and R^{11} is (i) (C_{1-6}) alkyl optionally substituted by $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)R^{13}$, $-NR^{14}C(O)OR^{13}$, $-NR^{14}C(O)NR^{13}R^{14}$ or $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein
 5 R^{13} is (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl and R^{14} at each occurrence independently is hydrogen or (C_{1-6}) alkyl, or (ii) (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or
 10 hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl substituted by $-X^6OR^{15}$, $-X^6SR^{15}$, $-X^6S(O)R^{15}$, $-X^6S(O)_2R^{15}$, $-X^6C(O)R^{15}$, $-X^6C(O)OR^{15}$, $-X^6C(O)NR^{15}R^{16}$, $-X^6NR^{15}R^{16}$, $-X^6NR^{16}C(O)R^{15}$, $-X^6NR^{16}C(O)OR^{15}$, $-X^6NR^{16}C(O)NR^{15}R^{16}$, $-X^6NR^{16}C(O)OR^{16}$, $-X^6NR^{16}C(NR^{16})NR^{15}R^{16}$, wherein X^6 is a
 15 bond or methylene, R^{15} is (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl and R^{16} is hydrogen or (C_{1-6}) alkyl; wherein R^4 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3}) alkyl, $-X^6NR^{17}R^{17}$,
 20 $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$, $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$, $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$, $-X^6P(O)(OR^{18})OR^{17}$, $-X^6OP(O)(OR^{18})OR^{17}$, $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$, $-X^6S(O)_2R^{18}$ and $-X^6C(O)R^{18}$ and when occurring within an aliphatic moiety are radicals independently selected from a group

consisting of cyano, halo, nitro, $-\text{NR}^{17}\text{R}^{17}$, $-\text{NR}^{17}\text{C}(\text{O})\text{OR}^{17}$, $-\text{NR}^{17}\text{C}(\text{O})\text{NR}^{17}\text{R}^{17}$, $-\text{NR}^{17}\text{C}(\text{NR}^{17})\text{NR}^{17}\text{R}^{17}$, $-\text{OR}^{17}$, $-\text{SR}^{17}$, $-\text{C}(\text{O})\text{OR}^{17}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{17}$, $-\text{S}(\text{O})_2\text{NR}^{17}\text{R}^{17}$, $-\text{P}(\text{O})(\text{OR}^{17})\text{OR}^{17}$, $-\text{OP}(\text{O})(\text{OR}^{17})\text{OR}^{17}$, $-\text{NR}^{17}\text{C}(\text{O})\text{R}^{18}$, $-\text{S}(\text{O})\text{R}^{18}$, $-\text{S}(\text{O})_2\text{R}^{18}$ and $-\text{C}(\text{O})\text{R}^{18}$, wherein X^6 is a bond or (C_{1-6}) alkylene, R^{17} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{18} is (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl;

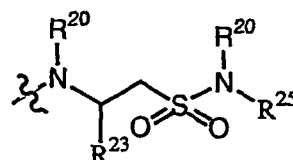
X^3 is a group of Formula (a), (b) or (c):



(a)



(b)



(c)

10

n is 0, 1 or 2;

R^{20} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl, (C_{0-6}) alkyl, (C_{6-12}) aryl, (C_{0-6}) alkyl and hetero (C_{5-12}) aryl, (C_{0-6}) alkyl;

15 R^{21} is selected from the group consisting of hydrogen, (C_{1-9}) alkyl, (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl, (C_{0-6}) alkyl, (C_{6-12}) aryl, (C_{0-6}) alkyl, hetero (C_{5-12}) aryl, (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl, (C_{0-3}) alkyl, hetero (C_{8-12}) -bicycloaryl, (C_{0-3}) alkyl, $-\text{C}(\text{O})\text{R}^{26}$, $-\text{C}(\text{S})\text{R}^{26}$, $-\text{S}(\text{O})_2\text{R}^{26}$, $-\text{C}(\text{O})\text{OR}^{26}$, $-\text{C}(\text{O})\text{N}(\text{R}^{26})\text{R}^{27}$, $-\text{C}(\text{S})\text{N}(\text{R}^{26})\text{R}^{27}$ and $-\text{S}(\text{O})_2\text{N}(\text{R}^{27})\text{R}^{26}$;

20 R^{23} is selected from (C_{1-6}) alkyl, (C_{4-6}) alkenyl, (C_{3-12}) cycloalkyl, (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl, (C_{0-6}) alkyl, (C_{6-12}) aryl, (C_{0-6}) alkyl or hetero (C_{5-12}) aryl, (C_{0-6}) alkyl

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optionally substituted with amino, -NHC(O)R^{15} or -R^{15} wherein R^{15} is as described above;

R^{25} is selected from hydrogen, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-13})\text{aryl}(\text{C}_{0-6})\text{alkyl}$, $\text{-X}^4\text{NHR}^{15}$, $\text{-X}^4\text{S(O)}_2\text{R}^{26}$ or $\text{-X}^4\text{C(O)R}^{17}\text{NR}^{17}\text{C(O)R}^{17}$ wherein R^{15} , R^{17} and X^4 are as

5 described above;

R^{26} is selected from the group consisting of hydrogen, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$, $(\text{C}_{9-12})\text{bicycloaryl}(\text{C}_{0-3})\text{alkyl}$ or hetero $(\text{C}_{8-12})\text{-bicycloaryl}(\text{C}_{0-3})\text{alkyl}$;

10 R^{27} is hydrogen, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$ or hetero $(\text{C}_{5-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$;

wherein X^3 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{1-6})\text{alkylidene}$, cyano, halo, nitro, halo-substituted

15 $(\text{C}_{1-3})\text{alkyl}$, $\text{-X}^6\text{NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{NR}^{17}\text{C(O)OR}^{17}$, $\text{-X}^6\text{NR}^{17}\text{C(O)NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{NR}^{17}\text{C(NR}^{17})\text{NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{OR}^{17}$, $\text{-X}^6\text{C(O)R}^{17}$, $\text{-X}^6\text{OR}^{15}$, $\text{-X}^6\text{SR}^{17}$, $\text{-X}^6\text{C(O)OR}^{17}$, $\text{-X}^6\text{C(O)NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{S(O)}_2\text{NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{P(O)(OR}^8\text{)OR}^{17}$, $\text{-X}^6\text{OP(O)(OR}^8\text{)OR}^{17}$, $\text{-X}^6\text{NR}^{17}\text{C(O)R}^{18}$, $\text{-X}^6\text{S(O)R}^{18}$, $\text{-X}^6\text{S(O)}_2\text{R}^{18}$ and $\text{-X}^6\text{C(O)R}^{18}$ and when occurring within

an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, $\text{-NR}^{17}\text{R}^{17}$, $\text{-NR}^{17}\text{C(O)OR}^{17}$, $\text{-NR}^{17}\text{C(O)NR}^{17}\text{R}^{17}$, $\text{-NR}^{17}\text{C(NR}^{17})\text{NR}^{17}\text{R}^{17}$, -OR^{17} , -SR^{17} , -C(O)OR^{17} , $\text{-C(O)NR}^{17}\text{R}^{17}$, $\text{-S(O)}_2\text{NR}^{17}\text{R}^{17}$, $\text{-P(O)(OR}^{17}\text{)OR}^{17}$, $\text{-OP(O)(OR}^{17}\text{)OR}^{17}$, $\text{-NR}^{17}\text{C(O)R}^{18}$, -S(O)R^{18} , $\text{-S(O)}_2\text{R}^{18}$ and -C(O)R^{18} , wherein R^{15} , R^{17} , R^{18} and X^6 are as described above; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the

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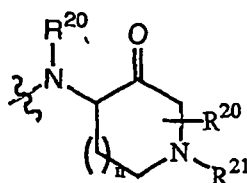
pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

5 2. The compound of claim 1 in which X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond; R^3 is $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$ or $-CR^7=NR^8$, wherein R^5 is hydrogen and R^6 is hydrogen or (C_{1-4}) alkyl or R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{3-12}) cycloalkenyl, (C_{6-12}) aryl, hetero (C_{6-12}) aryl or (C_{9-12}) bicycloaryl and R^7 and R^8 together with the atoms to which R^7 and R^8 are attached form
 10 hetero (C_{5-12}) cycloalkenyl or hetero (C_{6-12}) aryl, wherein R^3 optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, $-X^4OR^9$ and $-X^4C(O)OR^9$, wherein X^4 is a bond or (C_{1-2}) alkylene, R^9 at each occurrence independently is (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives,
 15 individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

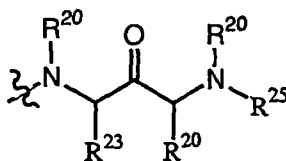
3. The compound of claim 2 in which R^4 is $-C(O)X^5R^{11}$ or $-S(O)_2X^5R^{11}$, wherein X^5
 20 is a bond, $-O-$ or $-NR^{12}-$, wherein R^{12} is hydrogen or (C_{1-6}) alkyl, and R^{11} is (i) (C_{1-6}) alkyl or (ii) hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl or (iii) hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl or phenyl (C_{0-3}) alkyl substituted by $-X^6OR^{15}$, $-X^6C(O)R^{15}$ or $-X^6NR^{16}C(O)OR^{16}$, wherein X^6 is a bond or methylene, R^{15} is phenyl (C_{0-3}) alkyl or

hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹⁶ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, halo, -X⁶NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)OR¹⁷, -X⁶NC(O)R¹⁶ and -X⁶C(O)R¹⁸, R¹⁷ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁸ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

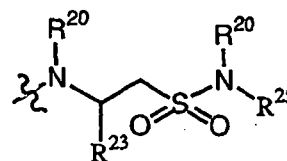
4. The compound of claim 3 in which X³ is a group of Formula (a), (b) or (c):



(a)



(b)



(c)

15

n is 0, 1 or 2;

R²⁰ is selected from the group consisting of hydrogen and (C₁₋₆)alkyl;

R²¹ is selected from the group consisting of (C₁₋₉)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, -C(O)R²⁶, -S(O)₂R²⁶, -C(O)OR²⁶ and -C(O)N(R²⁶)R²⁷;

20 R²³ is selected from (C₁₋₆)alkyl optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵ wherein R¹⁵ is as described above;

R^{25} is selected from (C_{1-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, $-X^4S(O)_2R^{26}$ or $-X^4C(O)R^{17}NR^{17}C(O)R^{17}$ wherein R^{17} and X^4 are as described above and R^{26} is as described below;

R^{26} is selected from the group consisting of (C_{1-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl and (C_{9-12}) bicycloaryl (C_{0-3}) alkyl;

R^{27} is (C_{1-6}) alkyl;

wherein X^3 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C_{1-6}) alkyl, cyano, halo, $-X^6OR^{17}$, $-X^6C(O)R^{17}$ and $-X^6OR^{15}$; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

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5. The compound of claim 4 in which R^3 is selected from the group consisting of phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, vinyl, 2-difluoromethoxyphenyl, 1-oxy-pyridin-2-yl, 4-methoxyphenyl, 4-methylphenyl, 2-methylphenyl, 4-chlorophenyl, 3,5-dimethylphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 2-bromophenyl, naphthalen-2-yl, 3,4-dichlorophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3-trifluoromethoxyphenyl, 2,3,4,5,6-pentafluoro-phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-cyano-phenyl, 2-trifluoromethylphenyl, 4-*tert*-butyl-phenyl, 3-chlorophenyl, 4-bromophenyl, 2-fluoro-3-chloro-phenyl, 2-fluoro-3-methyl-phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 3-bromophenyl, 2,5-dichlorophenyl, 2,6-difluorophenyl, 3-cyano-phenyl,

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4-cyano-phenyl, 2-trifluoromethoxyphenyl, 2,3-difluorophenyl, biphenyl, 2-bromo-5-fluoro-phenyl, 4-fluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 2,4,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 2-chloro-5-trifluoromethylphenyl, 2,4-bis-trifluoromethylphenyl, 2,5,6-trifluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 2,3,5-trifluorophenyl, 2-fluoro-5-trifluoromethylphenyl, 5-fluoro-2-trifluoromethylphenyl, 4-fluoro-3-trifluoromethylphenyl, 2-methoxyphenyl, 3,5-bis-trifluoromethylphenyl, 4-difluoromethoxyphenyl, 3-difluoromethoxyphenyl, 2,6-dichlorophenyl, 4-carboxyphenyl, cyclohexyl, cyclopropyl, isopropyl, thiophen-2-yl, 5-chloro-thiophen-2-yl and 3,5-dimethyl-isoxazol-4-yl.

6. The compound of claim 5 in which R⁴ is benzoyl, morpholine-4-carbonyl, acetyl, furan-3-carbonyl, 2-methoxy-benzoyl, 3-methoxy-benzoyl, naphthalene-2-carbonyl, benzo[1,3]dioxole-5-carbonyl, 3-pyridin-3-yl-acryloyl, benzofuran-2-carbonyl, furan-2-carbonyl, *tert*-butoxy-carbonyl, biphenyl-4-carbonyl, quinoline-2-carbonyl, quinoline-3-carbonyl, 3-acetyl-benzoyl, 4-phenoxy-benzoyl, 3-hydroxy-benzoyl, 4-hydroxy-benzoyl, pyridine-3-carbonyl, 3-(*tert*-butoxycarbonylamino-methyl)-benzoyl, 4-carbonyl-piperazine-1-carboxylic acid *tert*-butyl ester, 4-carbonyl-piperazine-1-carboxylic acid ethyl ester, 4-(furan-2-carbonyl)-piperazine-1-carbonyl, pyridine-4-carbonyl, 1-oxy-pyridine-4-carbonyl, 1-oxy-pyridine-3-carbonyl, thiophene-2-carbonyl, thiophene-3-carbonyl, 4-benzoyl-benzoyl, 5-methyl-thiophene-2-carbonyl, 3-chloro-thiophene-2-carbonyl, 3-bromo-thiophene-2-carbonyl, 4-chloro-benzoyl, 3-flouro-4-methoxy-benzoyl, 4-methoxy-benzoyl, 4-triflouromethoxy-benzoyl, 3,4-diflouro-benzoyl, 4-fluoro-benzoyl, 3,4-dimethoxy-benzoyl, 3-methyl-benzoyl, 4-bromo-benzoyl, 4-triflouromethyl-benzoyl, 3-benzoyl-

benzoyl, cyclopentane-carbonyl, benzo[b]thiophene-2-carbonyl, 3-chloro-benzo[b]thiophene-2-carbonyl, benzenesulfonyl, naphthalene-2-sulfonyl, 5-methylthiophene-2-sulfonyl, thiophene-2-sulfonyl, formamyl-methyl ester, 4-methyl-pentanoyl, formamyl-isobutyl ester, formamyl-monoallyl ester, formamyl-isopropyl ester, *N,N*-
5 dimethyl-formamyl, *N*-isopropyl-formamyl, *N*-pyridin-4-yl-formamyl, *N*-pyridin-3-yl-formamyl, 3-phenyl-acryloyl, 1H-indole-5-carbonyl, pyridine-2-carbonyl, pyrazine-2-carbonyl, 3-hydroxy-pyridine-2-carbonyl, 2-amino-pyridine-3-carbonyl, 2-hydroxypyridine-3-carbonyl, 6-amino-pyridine-3-carbonyl, 6-hydroxy-pyridine-3-carbonyl, pyridazine-4-carbonyl, 3-phenoxy-benzoyl and 1-oxo-1,3-dihydro-isoindole-2-carbonyl.

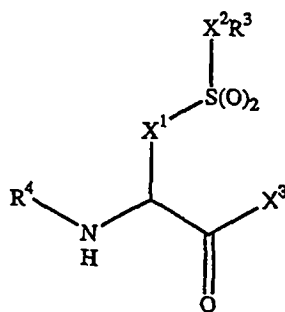
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7. The compound of claim 6 in which X^3 is selected from a group consisting of 4-amino-3-oxo-azepane-1-carboxylic acid benzyl ester, 4-amino-3-oxo-azepane-1-carboxylic acid isobutyl ester, 4-amino-1-benzoyl-azepan-3-one, 4-amino-1-benzenesulfonyl-azepan-3-one, 4-amino-1-(pyridine-2-sulfonyl)-azepan-3-one, 4-amino-1-(1-oxy-pyridine-2-sulfonyl)-azepan-3-one, 4-amino-1-(3,4-dichloro-benzenesulfonyl)-azepan-3-one, 4-amino-1-(2-flouro-benzenesulfonyl)-azepan-3-one, 4-amino-1-(3,4-dimethoxy-benzenesulfonyl)-azepan-3-one, 4-amino-1-(2-cyano-benzenesulfonyl)-azepan-3-one, 4-amino-1-(naphthalene-1-sulfonyl)-azepan-3-one, 4-amino-1-(thiophene-2-sulfonyl)-azepan-3-one, 4-amino-1-(thiazole-2-sulfonyl)-azepan-3-one, 4-amino-1-(pyrrolidine-1-sulfonyl)-azepan-3-one, 4-amino-1-methanesulfonyl-azepan-3-one, 4-amino-1-(pyrrolidine-1-carbonyl)-azepan-3-one, 4-amino-3-oxo-azepane-1-carboxylic-acid-dimethylamide, 4-amino-3-oxo-azepane-1-carboxylic-acid-benzylamide, 4-amino-1-benzyl-azepan-3-one, 4-amino-1-benzyl-piperidin-3-one, 4-amino-1-benzoyl-piperidin-3-one, 4-amino-1-benzoyl-pyrrolidin-3-one, 4-amino-1-benzyl-pyrrolidin-3-one, 4-amino-1-benzenesulfonyl-
- 15
- 20

pyrrolidin-3-one, 4-amino-1-(5-methyl-hexyl)-pyrrolidin-3-one, 1-ethyl-2-oxo-3-(toluene-4-sulfonylamino)-butylamino, 1-ethyl-2-oxo-3-(4-phenoxy-benzenesulfonylamino)-propylamino, 1-ethyl-2-oxo-3-[4-(pyridin-3-yloxy)-benzenesulfonylamino]-propylamino, 3-(dibenzofuran-2-sulfonylamino)-1-ethyl-2-oxo-butylamino, 1-ethyl-3-[4-methyl-2-(4-methyl-pentanoylamino)-pentanoylamino]-2-oxo-propylamino, 5-amino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylamino, 5-benzyloxycarbonylamino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylamino, 1-[(4-methoxy-phenylsulfamoyl)-methyl]-3-phenyl-propylamino, 1-{[4-(1-hydroxy-ethyl)-phenylsulfamoyl]-methyl}-3-phenyl-propylamino, 1-[(4-acetyl-phenylsulfamoyl)-methyl]-3-phenyl-propylamino, 1-[(4-hydroxy-phenylsulfamoyl)-methyl]-3-phenyl-propylamino and 3-phenyl-1-[(2-phenylamino-ethylsulfamoyl)-methyl]-propylamino.

8. The compound of claim 7 selected from the group consisting of morpholine-4-carboxylic acid (1-{5-amino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-amide, (6-(4-methoxy-phenylsulfamoyl)-5-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethane-sulfonyl-propionylamino}-hexyl)-carbamic acid benzyl ester, morpholine-4-carboxylic acid (1-{1-[(4-methoxy-phenylsulfamoyl)-methyl]-3-phenyl-propylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-amide, morpholine-4-carboxylic acid [1-(3-benzenesulfonylamino-2-oxo-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide, morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide, morpholine-4-carboxylic acid [1-(1-benzenesulfonyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide and 4-{2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.
- 5 10. A method for treating a disease in an animal in which inhibition of Cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or a *N*-oxide derivative or individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt or solvate of such compounds and the
- 10 *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.
11. The use of a compound of Claim 1 in the manufacture of a medicament for treating a disease in an animal in which Cathepsin S activity contributes to the pathology and/or
- 15 symptomology of the disease.
12. A process for preparing a compound of Formula I:



I

hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl substituted by -X⁶OR¹⁵, -X⁶SR¹⁵, -X⁶S(O)R¹⁵, -X⁶S(O)₂R¹⁵, -X⁶C(O)R¹⁵, -X⁶C(O)OR¹⁵, -X⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)R¹⁵, -X⁶NR¹⁶C(O)OR¹⁵, -X⁶NR¹⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)OR¹⁶, -X⁶NR¹⁶C(NR¹⁶)NR¹⁵R¹⁶, wherein X⁶ is a bond or methylene, R¹⁵ is (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹⁶ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, nitro, halo-substituted (C₁₋₃)alkyl, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷, -X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR¹⁸)OR¹⁷, -X⁶OP(O)(OR¹⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ and -X⁶C(O)R¹⁸ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷, -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷, -OP(O)(OR¹⁷)OR¹⁷, -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ and -C(O)R¹⁸, wherein X⁶ is a bond or (C₁₋₆)alkylene, R¹⁷ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁸ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl;

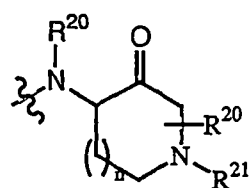
X³ is a group of Formula (a), (b) or (c):

in which:

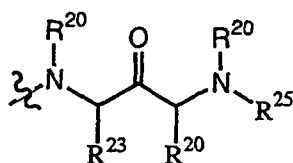
X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond;

R^3 is $-CR^5=CHR^6$, $-CR^5(CR^6)_2$ or $-CR^7=NR^8$, wherein R^5 is hydrogen and R^6 is
 5 hydrogen or (C_{1-4}) alkyl or R^5 and R^6 together with the atoms to which R^5 and R^6 are
 attached form (C_{3-12}) cycloalkenyl, hetero (C_{5-12}) cycloalkenyl, (C_{6-12}) aryl, hetero (C_{6-12}) aryl,
 (C_{9-12}) bicycloaryl or hetero (C_{8-12}) bicycloaryl and R^7 and R^8 together with the atoms to
 which R^7 and R^8 are attached form hetero (C_{5-12}) cycloalkenyl, hetero (C_{6-12}) aryl or
 hetero (C_{8-12}) bicycloaryl, wherein R^3 optionally is substituted by 1 to 5 radicals
 10 independently selected from a group consisting of (C_{1-4}) alkyl, cyano, halo, halo-substituted
 (C_{1-4}) alkyl, nitro, $-X^4NR^9R^9$, $-X^4OR^9$, $-X^4SR^9$, $-X^4C(O)NR^9R^9$, $-X^4C(O)OR^9$,
 $-X^4S(O)R^{10}$, $-X^4S(O)_2R^{10}$ and $-X^4C(O)R^{10}$, wherein X^4 is a bond or (C_{1-2}) alkylene, R^9 at
 each occurrence independently is hydrogen, (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl and
 R^{10} is (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl; and

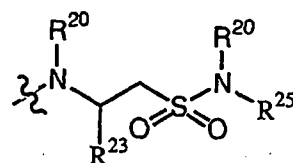
15 R^4 is $-C(O)X^5R^{11}$ or $-S(O)_2X^5R^{11}$, wherein X^5 is a bond, $-O-$ or $-NR^{12}-$, wherein
 R^{12} is hydrogen or (C_{1-6}) alkyl, and R^{11} is (i) (C_{1-6}) alkyl optionally substituted by $-OR^{13}$,
 $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$,
 $-NR^{14}C(O)R^{13}$, $-NR^{14}C(O)OR^{13}$, $-NR^{14}C(O)NR^{13}R^{14}$ or $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein
 R^{13} is (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl,
 20 hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or
 hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl and R^{14} at each occurrence independently is hydrogen
 or (C_{1-6}) alkyl, or (ii) (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl,
 (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or
 hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-3}) alkyl,



(a)



(b)



(c)

n is 0, 1 or 2;

R^{20} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl and hetero (C_{5-12}) aryl (C_{0-6}) alkyl;

R^{21} is selected from the group consisting of hydrogen, (C_{1-9}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl, hetero (C_{8-12}) -bicycloaryl (C_{0-3}) alkyl, $-C(O)R^{26}$, $-C(S)R^{26}$, $-S(O)_2R^{26}$, $-C(O)OR^{26}$, $-C(O)N(R^{26})R^{27}$, $-C(S)N(R^{26})R^{27}$ and $-S(O)_2N(R^{27})R^{26}$;

R^{23} is selected from (C_{1-6}) alkyl, (C_{4-6}) alkenyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl or hetero (C_{5-12}) aryl (C_{0-6}) alkyl optionally substituted with amino, $-NHC(O)R^{15}$ or $-R^{15}$ wherein R^{15} is as described above;

R^{25} is selected from hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, $-X^4NHR^{15}$, $-X^4S(O)_2R^{26}$ or $-X^4C(O)R^{17}NR^{17}C(O)R^{17}$ wherein R^{15} , R^{17} and X^4 are as described above;

R^{26} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl and hetero (C_{8-12}) -bicycloaryl (C_{0-3}) alkyl;

bicycloaryl(C₀₋₃)alkyl;

R²⁷ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

wherein X³ optionally further contains 1 to 5 substituents which when occurring

5 within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, nitro, halo-substituted

(C₁₋₃)alkyl, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷,

-X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)R¹⁷, -X⁶OR¹⁵, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷,

-X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR⁸)OR¹⁷, -X⁶OP(O)(OR⁸)OR¹⁷,

10 -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ and -X⁶C(O)R¹⁸ and when occurring within

an aliphatic moiety are radicals independently selected from a group consisting of cyano,

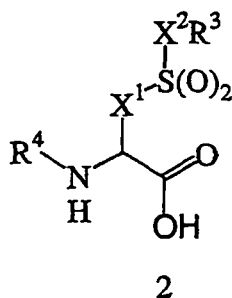
halo, nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷, -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷,

-OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷,

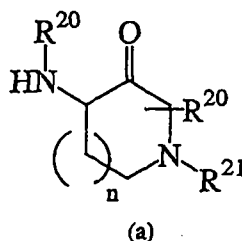
-OP(O)(OR¹⁷)OR¹⁷, -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ and -C(O)R¹⁸, wherein R¹⁵,

15 R¹⁷, R¹⁸ and X⁶ are as described above; said process comprising:

(A) reacting a compound of Formula 2:

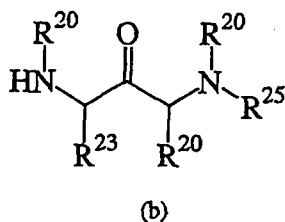


with a compound of the formula (a):



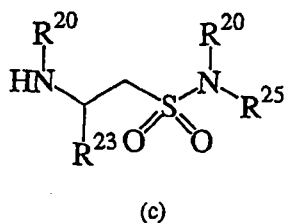
in which X^1 , X^2 , R^3 , R^4 , R^{20} and R^{21} are as defined in the Summary of the Invention for Formula I; or

- 5 (B) reacting a compound of Formula 2 with a compound of the formula (b):



in which R^{20} , R^{23} and R^{25} are as defined in the Summary of the Invention for Formula I; or

- 10 (C) reacting a compound of Formula 2 with a compound of the formula (c):



in which R^{20} , R^{23} and R^{25} are as defined in the Summary of the Invention for Formula I; and

- 15 (D) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;

(E) optionally converting a salt form of a compound of Formula I to non-salt form;

(F) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(G) optionally converting an *N*-oxide form of a compound of Formula I to its

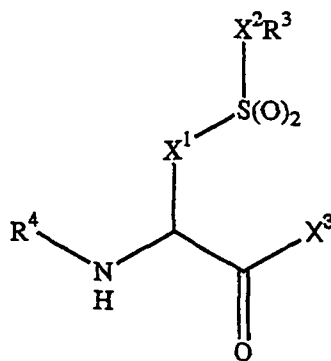
5 unoxidized form;

(H) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;

(I) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

10 (J) optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

13. A compound of Formula Ix:



Ix

in which:

X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond;

R^3 is $-\text{CR}^5=\text{CHR}^6$, $-\text{CR}^5(\text{CR}^6_3)_2$ or $-\text{CR}^7=\text{NR}^8$, wherein R^5 is hydrogen and R^6 is

hydrogen or (C₁₋₄)alkyl or R⁵ and R⁶ together with the atoms to which R⁵ and R⁶ are attached form (C₃₋₁₂)cycloalkenyl, hetero(C₅₋₁₂)cycloalkenyl, (C₆₋₁₂)aryl, hetero(C₆₋₁₂)aryl, (C₉₋₁₂)bicycloaryl or hetero(C₈₋₁₂)bicycloaryl and R⁷ and R⁸ together with the atoms to which R⁷ and R⁸ are attached form hetero(C₅₋₁₂)cycloalkenyl, hetero(C₆₋₁₂)aryl or hetero(C₈₋₁₂)bicycloaryl, wherein R³ optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR⁹R⁹, -X⁴OR⁹, -X⁴SR⁹, -X⁴C(O)NR⁹R⁹, -X⁴C(O)OR⁹, -X⁴S(O)R¹⁰, -X⁴S(O)₂R¹⁰ and -X⁴C(O)R¹⁰, wherein X⁴ is a bond or (C₁₋₂)alkylene, R⁹ at each occurrence independently is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁰ is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl; and

R⁴ is -C(O)X⁵R¹¹ or -S(O)₂X⁵R¹¹, wherein X⁵ is a bond, -O- or -NR¹²-, wherein R¹² is hydrogen or (C₁₋₆)alkyl, and R¹¹ is (i) (C₁₋₆)alkyl optionally substituted by -OR¹³, -SR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -C(O)OR¹³, -C(O)NR¹³R¹⁴, -NR¹³R¹⁴, -NR¹⁴C(O)R¹³, -NR¹⁴C(O)OR¹³, -NR¹⁴C(O)NR¹³R¹⁴ or -NR¹⁴C(NR¹⁴)NR¹³R¹⁴, wherein R¹³ is (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl and R¹⁴ at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or (ii) (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl substituted by -X⁶OR¹⁵, -X⁶SR¹⁵, -X⁶S(O)R¹⁵, -X⁶S(O)₂R¹⁵, -X⁶C(O)R¹⁵, -X⁶C(O)OR¹⁵, -X⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)R¹⁵, -X⁶NR¹⁶C(O)OR¹⁵, -X⁶NR¹⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)OR¹⁶, -X⁶NR¹⁶C(NR¹⁶)NR¹⁵R¹⁶, wherein X⁶ is a

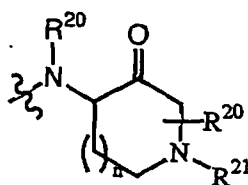
bond or methylene, R^{15} is (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl and R^{16} is hydrogen or (C_{1-6}) alkyl; wherein R^4 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of

5 (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3}) alkyl, $-X^6NR^{17}R^{17}$, $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$, $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$, $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$, $-X^6P(O)(OR^{18})OR^{17}$, $-X^6OP(O)(OR^{18})OR^{17}$, $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$, $-X^6S(O)_2R^{18}$ and $-X^6C(O)R^{18}$ and when occurring within an aliphatic moiety are radicals independently selected from a group

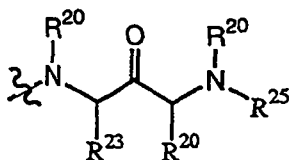
10 consisting of cyano, halo, nitro, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$, $-NR^{17}C(NR^{17})NR^{17}R^{17}$, $-OR^{17}$, $-SR^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-P(O)(OR^{17})OR^{17}$, $-OP(O)(OR^{17})OR^{17}$, $-NR^{17}C(O)R^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$ and $-C(O)R^{18}$, wherein X^6 is a bond or (C_{1-6}) alkylene, R^{17} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{18} is (C_{1-6}) alkyl or halo-substituted

15 (C_{1-3}) alkyl;

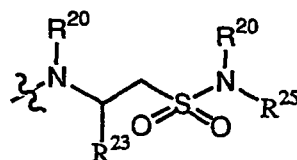
X^3 is a group of Formula (a), (b), (c), (d), (e), (f), (g) or (h):



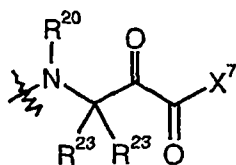
(a)



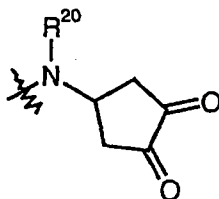
(b)



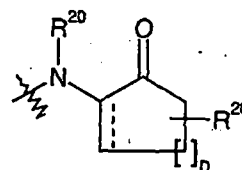
(c)



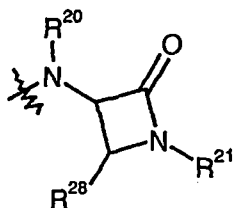
(d)



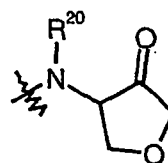
(e)



(f)



(g)



(h)

----- represents a single bond, or a double bond;

X^7 represents aryl, heteroaryl or $NR^{20}R^{25}$;

5 n is 0, 1 or 2;

R^{20} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl and hetero (C_{5-12}) aryl (C_{0-6}) alkyl;

10 R^{21} is selected from the group consisting of hydrogen, (C_{1-9}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl, hetero (C_{8-12}) -bicycloaryl (C_{0-3}) alkyl, $-C(O)R^{26}$, $-C(S)R^{26}$, $-S(O)_2R^{26}$, $-C(O)OR^{26}$, $-C(O)N(R^{26})R^{27}$, $-C(S)N(R^{26})R^{27}$ and $-S(O)_2N(R^{27})R^{26}$;

15 R^{23} is selected from $-H$, (C_{1-6}) alkyl, (C_{4-6}) alkenyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl or hetero (C_{5-12}) aryl (C_{0-6}) alkyl optionally substituted with amino, $-NHC(O)R^{15}$ or $-R^{15}$ wherein R^{15} is as described above;

R^{25} is selected from hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,

hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₃)aryl(C₀₋₆)alkyl, -X⁴NHR¹⁵, -X⁴S(O)₂R²⁶ or -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷ wherein R¹⁵, R¹⁷ and X⁴ are as described above;

R²⁶ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl and hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl;

R²⁷ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

R²⁸ is R²⁰ or -O-C(=O)-R²⁹;

R²⁹ is (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl;

wherein X³ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, nitro, halo-substituted (C₁₋₃)alkyl, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)R¹⁷, -X⁶OR¹⁵, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷, -X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR⁸)OR¹⁷, -X⁶OP(O)(OR⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ and -X⁶C(O)R¹⁸ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷, -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷, -OP(O)(OR¹⁷)OR¹⁷, -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ and -C(O)R¹⁸, wherein R¹⁵, R¹⁷, R¹⁸ and X⁶ are as

described above; or

one of *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers of compounds of formula Ix; or one of pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug
 5 derivatives, protected derivatives, individual isomers and mixtures of isomers formula Ix.

14. A compound of claim 13, wherein R²³ is selected from (C₁₋₆)alkyl, (C₄₋₆)alkenyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵
 10 wherein R¹⁵ is as described above;

15. A compound of claim 13, selected from the group consisting of:

Morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide;

15

Morpholine-4-carboxylic acid [1-(1-benzenesulfonyl-4-oxo-pyrrolidin-3-ylcarbamoyl) 2-phenylmethanesulfonyl-ethyl]-amide;

20

4-{2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester;

Morpholine-4-carboxylic acid [1-(3-benzenesulfonylamino-2-oxo-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide; or

25

N-{1*S*-[1*S*-(4-Methoxyphenylsulfamoylmethyl)-3-phenylpropylcarbamoyl] 2-benzylsulfonylethyl}-morpholine-4-carboxamide.

16. A compound of claim 13, selected from the group consisting of:

30

Morpholine-4-carboxylic acid [(*R*)-1-(6-oxo-cyclohex-1-enylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide;

Morpholine-4-carboxylic acid [(*R*)-2-cyclopropylmethanesulfonyl-1-(6-oxo-cyclohex-1-enylcarbamoyl)-ethyl]-amide;

Morpholine-4-carboxylic acid [(R)-1-(3,4-dioxo-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide;

- 5 Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclohexylcarbamoyl)-ethyl]-amide;

Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclopentylcarbamoyl)-ethyl]-amide;

10

Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclobutylcarbamoyl)-ethyl]-amide;

15

(Morpholine-4-carboxylic acid [1-(2-benzylcarbamoyl-2-oxo-ethylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide);

Acetic acid 3-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-4-oxo-azetidin-2-yl ester;

20

Morpholine-4-carboxylic acid [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide;

Morpholine-4-carboxylic acid [1-(4-oxo-tetrahydro-furan-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide; or

25

Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(1,1-dimethyl-2,3-dioxo-3-phenyl-propylcarbamoyl)-ethyl]-amide.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 02/29323

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C317/48 C07C317/50 C07D207/24 C07D223/08 C07D295/20
C07D307/32 C07K5/065 A61K31/10 A61P19/02 A61P29/00

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 C07C C07D C07K 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)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, 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.
A	WO 01 19796 A (AXYS PHARMARCEUTICALS) 22 March 2001 (2001-03-22) cited in the application page 2 -page 4; claims 1,11-13; examples ---	1-16
A	WO 96 30353 A (ARRIS PHARMACEUTICAL) 3 October 1996 (1996-10-03) page 3 -page 4; table 2 ---	1-16
A	WO 00 69855 A (MEDIVIR UK) 23 November 2000 (2000-11-23) page 2 -page 3 ---	13-16
A	WO 00 59881 A (NAEJA PHARMACEUTICAL) 12 October 2000 (2000-10-12) page 3 -page 4 -----	13-16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

5 December 2002

Date of mailing of the international search report

19/12/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

English, R

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-8,12-14

The scope of the claims 1-8,12-14, in as far as the expressions "prodrug derivatives" and "protected derivatives" are concerned, is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to these expressions.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/29323

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 claim 10 is 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/composition.
2. ☒ Claims Nos.: 1-8, 12-14
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 2 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.

II. INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No

PCT/US 02/29323

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0119796	A	22-03-2001	AU 7490900 A	17-04-2001
			AU 7703300 A	17-04-2001
			EP 1212302 A1	12-06-2002
			WO 0119808 A1	22-03-2001
			WO 0119796 A1	22-03-2001
WO 9630353	A	03-10-1996	AU 713492 B2	02-12-1999
			AU 5367496 A	16-10-1996
			CA 2216151 A1	03-10-1996
			CN 1184472 A ,B	10-06-1998
			CZ 9702981 A3	18-03-1998
			EP 0817778 A1	14-01-1998
			JP 11503417 T	26-03-1999
			NO 974403 A	17-11-1997
			NZ 305626 A	28-01-2000
			PL 322409 A1	19-01-1998
			TW 470750 B	01-01-2002
			WO 9630353 A1	03-10-1996
			US 5776718 A	07-07-1998
			ZA 9602336 A	31-07-1996
WO 0069855	A	23-11-2000	AU 4772200 A	05-12-2000
			BR 0010553 A	02-07-2002
			EP 1178986 A2	13-02-2002
			WO 0069855 A2	23-11-2000
WO 0059881	A	12-10-2000	AU 3570000 A	23-10-2000
			EP 1165506 A1	02-01-2002
			WO 0059881 A1	12-10-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference US20010143W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 02/ 29323	International filing date (day/month/year) 16/09/2002	(Earliest) Priority Date (day/month/year) 14/09/2001
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 6 sheets.

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

1. Basis of the report

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

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

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

☐ contained in the international application in written form.

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

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

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

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

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

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

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

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

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

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

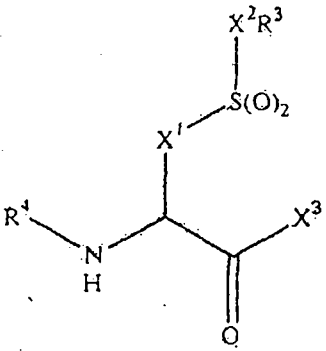
☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/ 29323

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The present invention relates to compounds of formula I, where the variables are as defined in Claim 1, process for their preparation and their use as cathepsin S inhibitors.



I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/29323

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C317/48 C07C317/50 C07D207/24 C07D223/08 C07D295/20
 C07D307/32 C07K5/065 A61K31/10 A61P19/02 A61P29/00

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 C07C C07D C07K 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)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, 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.
A	WO 01 19796 A (AXYS PHARMARCEUTICALS) 22 March 2001 (2001-03-22) cited in the application page 2 -page 4; claims 1,11-13; examples ---	1-16
A	WO 96 30353 A (ARRIS PHARMACEUTICAL) 3 October 1996 (1996-10-03) page 3 -page 4; table 2 ---	1-16
A	WO 00 69855 A (MEDIVIR UK) 23 November 2000 (2000-11-23) page 2 -page 3 ---	13-16
A	WO 00 59881 A (NAEJA PHARMACEUTICAL) 12 October 2000 (2000-10-12) page 3 -page 4 -----	13-16

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

Patent family members are listed in annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

5 December 2002

Date of mailing of the international search report

19/12/2002

Name and mailing address of the ISA

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Authorized officer

English, R

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-8,12-14

The scope of the claims 1-8,12-14, in as far as the expressions "prodrug derivatives" and "protected derivatives" are concerned, is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to these expressions.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/29323

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 claim 10 is 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/composition.
2. ☒ Claims Nos.: 1-8,12-14
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:

see FURTHER INFORMATION sheet PCT/ISA/210
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 2 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/US 02/29323

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0119796	A	22-03-2001	AU 7490900 A	17-04-2001
			AU 7703300 A	17-04-2001
			EP 1212302 A1	12-06-2002
			WO 0119808 A1	22-03-2001
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WO 9630353	A	03-10-1996	AU 713492 B2	02-12-1999
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			EP 0817778 A1	14-01-1998
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			NZ 305626 A	28-01-2000
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			TW 470750 B	01-01-2002
			WO 9630353 A1	03-10-1996
			US 5776718 A	07-07-1998
			ZA 9602336 A	31-07-1996
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			BR 0010553 A	02-07-2002
			EP 1178986 A2	13-02-2002
			WO 0069855 A2	23-11-2000
WO 0059881	A	12-10-2000	AU 3570000 A	23-10-2000
			EP 1165506 A1	02-01-2002
			WO 0059881 A1	12-10-2000

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL
TRATADO DE COOPERACIÓN DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual
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(43) Fecha de Publicación Internacional
27 Marzo 2003 (27.03.2003)

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207/24, 223/08, 295/20, 307/32,
C07K 5/065, A61K 31/10, A61P
19/02, 29/00

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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,
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GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), patente OAPI (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Declaración bajo la Regla 4.17:

de relación de inventores (Regla 4.17(iv)) solo para US.

Publicada:

- con reporte de búsqueda internacional

Para códigos de dos letras y otras abreviaturas, referirse a la "Notas de Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada número regular de la Gaceta del PCT.

(54) Título: COMPUESTOS Y COMPOSICIONES NOVEDOSOS COMO INHIBIDORES DE CATEPSINA

(57) Extracto: La presente invención se relaciona con compuestos de la fórmula I, donde las variables son como se definió en la Reivindicación 1, proceso para su preparación y su uso como inhibidores de catepsina S.

NUEVOS COMPUESTOS Y PREPARACIONES COMO INHIBIDORES DE LA CATEPSINA

LA INVENCION

5

Esta solicitud se refiere a compuestos y preparaciones para tratar enfermedades asociadas a la actividad de la cisteína proteasa, en particular enfermedades asociadas a la actividad de la catepsina S.

10

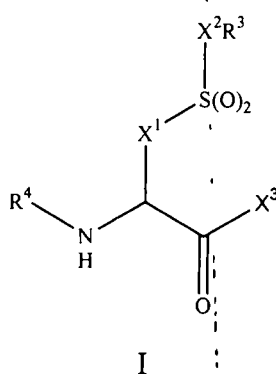
DESCRIPCIÓN DEL CAMPO DE LA INVENCION

Las cisteína proteasas representan una clase de peptidasas caracterizadas por la presencia de un residuo de cisteína en el sitio catalítico de la enzima. Las cisteína proteasas se asocian a la degradación y la transformación normales de las proteínas. Sin embargo, la actividad anormal de las cisteína proteasas, p. ej. como resultado de un aumento en la expresión o una mayor activación, puede tener consecuencias patológicas. A este respecto, ciertas cisteína proteasas se relacionan con una cantidad de enfermedades, entre las que se encuentran artritis, distrofia muscular, inflamación, tumor invasivo, glomerulonefritis, malaria, enfermedad periodontal, leucodistrofia metacromática y otras. Un aumento de la actividad de la catepsina S contribuye a la patología y/o sintomatología de una cantidad de enfermedades. En consecuencia, las moléculas que inhiben la actividad de la proteasa catepsina S son útiles como fármacos en el tratamiento de dichas enfermedades.

25

RESUMEN DE LA INVENCION

Esta solicitud se refiere a compuestos que tienen la fórmula I:



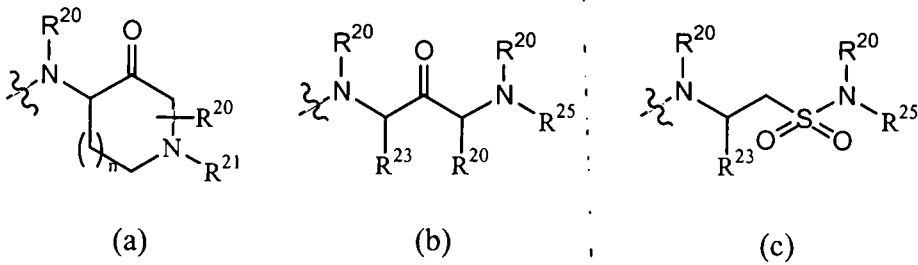
en la que:

- X^1 y X^2 son ambos metileno o X^1 es etileno y X^2 es un enlace;
- 5 R^3 es $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$ o $-CR^7=NR^8$, en los que R^5 es hidrógeno y R^6 es hidrógeno o un alquilo(C_{1-4}) o R^5 y R^6 junto con los átomos a los que R^5 y R^6 están unidos forman un cicloalquenilo(C_{3-12}), un heterocicloalquenilo(C_{5-12}), un arilo(C_{6-12}), un heteroarilo(C_{6-12}), un bicicloarilo(C_{9-12}) o un heterobicicloarilo(C_{8-12}) y R^7 y R^8 junto con los átomos a los que R^7 y R^8 están unidos forman un heterocicloalquenilo(C_{5-12}), un
- 10 heteroarilo(C_{6-12}) o un heterobicicloarilo(C_{8-12}), en los que R^3 está opcionalmente sustituido con 1 a 5 radicales elegidos independientemente entre un grupo que consiste en: un alquilo(C_{1-4}), un radical ciano, un halógeno, un alquilo(C_{1-4}) halo-sustituido, un radical nitro, $-X^4NR^9R^9$, $-X^4OR^9$, $-X^4SR^9$, $-X^4C(O)NR^9R^9$, $-X^4C(O)OR^9$, $-X^4S(O)R^{10}$, $-X^4S(O)_2R^{10}$ y $-X^4C(O)R^{10}$, en el que X^4 es un enlace o un alquilenio(C_{1-2}), R^9 cada vez
- 15 que está presente es independientemente hidrógeno, un alquilo(C_{1-3}) o un alquilo(C_{1-3}) halo-sustituido y R^{10} es un alquilo(C_{1-3}) o un alquilo(C_{1-3}) halo-sustituido; y
- R^4 es $-C(O)X^5R^{11}$ o $-S(O)_2X^5R^{11}$, en los que X^5 es un enlace, $-O-$ o $-NR^{12}-$, en el que R^{12} es hidrógeno o un alquilo(C_{1-6}), y R^{11} es (i) un alquilo(C_{1-6}) opcionalmente sustituido con $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$,
- 20 $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)R^{13}$, $-NR^{14}C(O)OR^{13}$, $-NR^{14}C(O)NR^{13}R^{14}$ o $-NR^{14}C(NR^{14})NR^{13}R^{14}$, en los que R^{13} es un cicloalquil(C_{3-12})alquilo(C_{0-3}), un heterocicloalquil(C_{5-12})alquilo(C_{0-3}), un aril(C_{6-12})alquilo(C_{0-3}), un heteroaril(C_{5-12})alquilo(C_{0-3}), un bicicloaril(C_{9-12})alquilo(C_{0-3}) o un heterobicicloaril(C_{8-12})alquilo(C_{0-3}) y R^{14} cada vez que está presente es
- 25 independientemente hidrógeno o un alquilo(C_{1-6}), o (ii) un cicloalquil(C_{3-12})alquilo(C_{0-3}), un heterocicloalquil(C_{5-12})alquilo(C_{0-3}), un aril(C_{6-12})alquilo(C_{0-3}), un heteroaril(C_{5-12})alquilo(C_{0-3}), un bicicloaril(C_{9-12})alquilo(C_{0-3}) o un

heterobícicloaril(C₈₋₁₂)alquilo(C₀₋₃) o (iii) un cicloalquil(C₃₋₆)alquilo(C₀₋₃), un heterocicloalquil(C₅₋₆)alquilo(C₀₋₃), un fenilalquilo(C₀₋₃) o un heteroaril(C₅₋₆)alquilo(C₀₋₃) sustituido con -X⁶OR¹⁵, -X⁶SR¹⁵, -X⁶S(O)R¹⁵, -X⁶S(O)₂R¹⁵, -X⁶C(O)R¹⁵, -X⁶C(O)OR¹⁵, -X⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)R¹⁵, -X⁶NR¹⁶C(O)OR¹⁵,
5 -X⁶NR¹⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)OR¹⁶, -X⁶NR¹⁶C(NR¹⁶)NR¹⁵R¹⁶, en los que X⁶ es un enlace o metileno, R¹⁵ es un cicloalquil(C₃₋₆)alquilo(C₀₋₃), un heterocicloalquil(C₅₋₆)alquilo(C₀₋₃), un fenilalquilo(C₀₋₃) o un heteroaril(C₅₋₆)alquilo(C₀₋₃) y R¹⁶ es hidrógeno o un alquilo(C₁₋₆); en los que R⁴ contiene además opcionalmente 1 a 5 sustituyentes que cuando están presentes dentro de un anillo alicíclico o aromático son
10 radicales elegidos independientemente entre un grupo que consiste en: un alquilo(C₁₋₆), un alquilideno(C₁₋₆), un radical ciano, un halógeno, un radical nitro, un alquilo(C₁₋₃) halo-sustituido, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷, -X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR¹⁸)OR¹⁷, -X⁶OP(O)(OR¹⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸,
15 -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ y -X⁶C(O)R¹⁸ y que cuando están presentes dentro de una porción alifática son radicales elegidos independientemente entre un grupo que consiste en: un radical ciano, un halógeno, un radical nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷, -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷, -OP(O)(OR¹⁷)OR¹⁷,
20 -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ y -C(O)R¹⁸; en los que X⁶ es un enlace o un alquileno(C₁₋₆), R¹⁷ cada vez que está presente es independientemente hidrógeno, un alquilo(C₁₋₆) o un alquilo(C₁₋₃) halo-sustituido y R¹⁸ es un alquilo(C₁₋₆) o un alquilo(C₁₋₃) halo-sustituido;

X³ es un grupo de fórmula (a), (b) o (c):

25



n es 0, 1 ó 2;

R^{20} se elige entre un grupo que consiste en: hidrógeno, un alquilo(C_{1-6}), un cicloalquil(C_{3-12})alquilo(C_{0-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un aril(C_{6-12})alquilo(C_{0-6}) y un heteroaril(C_{5-12})alquilo(C_{0-6});

5 R^{21} se elige entre el grupo que consiste en: hidrógeno, un alquilo(C_{1-9}), un cicloalquil(C_{3-12})alquilo(C_{0-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un aril(C_{6-12})alquilo(C_{0-6}), un heteroaril(C_{5-12})alquilo(C_{0-6}), un bicicloaril(C_{9-12})alquilo(C_{0-3}), un heterobicicloaril(C_{8-12})alquilo(C_{0-3}), $-C(O)R^{26}$, $-C(S)R^{26}$, $-S(O)_2R^{26}$, $-C(O)OR^{26}$, $-C(O)N(R^{26})R^{27}$, $-C(S)N(R^{26})R^{27}$ y $-S(O)_2N(R^{27})R^{26}$;

10 R^{23} se elige entre un alquilo(C_{1-6}), un alqueno(C_{4-6}), un cicloalquil(C_{3-12})alquilo(C_{0-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un aril(C_{6-12})alquilo(C_{0-6}) o un heteroaril(C_{5-12})alquilo(C_{0-6}) opcionalmente sustituido con un grupo amino, $-NHC(O)R^{15}$ o $-R^{15}$ en los que R^{15} es como se definió antes;

R^{25} se elige entre hidrógeno, un alquilo(C_{1-6}), un cicloalquil(C_{3-12})alquilo(C_{0-6}),
15 un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un aril(C_{6-12})alquilo(C_{0-6}), un heteroaril(C_{5-13})alquilo(C_{0-6}), $-X^4NHR^{15}$, $-X^4S(O)_2R^{26}$ o $-X^4C(O)R^{17}NR^{17}C(O)R^{17}$ en los que R^{15} , R^{17} y X^4 son como se los definió antes;

R^{26} se elige entre un grupo que consiste en: hidrógeno, un alquilo(C_{1-6}), un cicloalquil(C_{3-12})alquilo(C_{0-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un aril(C_{6-12})alquilo(C_{0-6}), un heteroaril(C_{5-12})alquilo(C_{0-6}), un bicicloaril(C_{9-12})alquilo(C_{0-3}) y un heterobicicloaril(C_{8-12})alquilo(C_{0-3});

R^{27} es hidrógeno, un alquilo(C_{1-6}), un cicloalquil(C_{3-12})alquilo(C_{0-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un aril(C_{6-12})alquilo(C_{0-6}) o un heteroaril(C_{5-12})alquilo(C_{0-6});

25 en los que X^3 contiene además opcionalmente 1 a 5 sustituyentes que cuando están presentes en un anillo alicíclico o aromático son radicales elegidos independientemente entre un grupo que consiste en: un alquilo(C_{1-6}), un alquilideno(C_{1-6}), un radical ciano, un halógeno, un radical nitro, un alquilo(C_{1-3}) halo-sustituido, $-X^6NR^{17}R^{17}$, $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$,
30 $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6C(O)R^{17}$, $-X^6OR^{15}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$,

-X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR⁸)OR¹⁷, -X⁶OP(O)(OR⁸)OR¹⁷,
 -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ y -X⁶C(O)R¹⁸ y cuando están presentes
 dentro de una porción alifática son radicales elegidos independientemente entre un grupo
 que consiste en: un radical ciano, un halógeno, un radical nitro, -NR¹⁷R¹⁷,
 5 -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷, -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -OR¹⁷, -SR¹⁷,
 -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷, -OP(O)(OR¹⁷)OR¹⁷,
 -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ y -C(O)R¹⁸, en los que R¹⁵, R¹⁷, R¹⁸ y X⁶ son
 como se los definió antes.

Un segundo aspecto de la invención es una preparación farmacéutica que contiene
 10 un compuesto de fórmula I o sus derivados *N*-óxido, cada uno de los isómeros o mezclas
 de isómeros de éstos, o las sales de los mismos aceptables desde el punto de vista
 farmacéutico, mezclados con uno o más excipientes adecuados.

Un tercer aspecto de la invención es un método para tratar una enfermedad en un
 animal en el cual la inhibición de la catepsina S puede prevenir, inhibir o mejorar la
 15 patología y/o la sintomatología de la enfermedad, dicho método consiste en la
 administración al animal de una cantidad terapéuticamente eficaz del compuesto de
 fórmula I, o de un derivado *N*-óxido, cada uno de los isómeros o mezcla de isómeros de
 éstos; o de una sal de los mismos aceptable desde el punto de vista farmacéutico.

Un cuarto aspecto de la invención es el proceso para preparar compuestos de
 20 fórmula I y los derivados *N*-óxidos, derivados profármaco, derivados protegidos, cada
 uno de los isómeros y mezclas de isómeros de éstos; y las sales de los mismos aceptables
 desde el punto de vista farmacéutico.

DESCRIPCIÓN DETALLADA DE LA INVENCION

25

Definiciones:

A menos que se indique de otra manera, los términos siguientes utilizados en la
 especificación y las reivindicaciones se definen a los efectos de esta solicitud y tienen los
 significados siguientes:

30

"Alicíclico" significa una porción caracterizada por una disposición de los átomos de carbono en estructuras cerradas no aromáticas con forma de anillo que tiene propiedades semejantes a las estructuras alifáticas y que puede ser saturada o parcialmente insaturada con dos o más enlaces dobles o triples.

- 5 "Alifático" significa una porción caracterizada por una disposición de los átomos de carbono constituyentes en una cadena lineal o ramificada que puede ser saturada o parcialmente insaturada con dos o más enlaces dobles o triples.

"Alquilo" presentado solo significa un radical alifático, lineal o ramificado, saturado o no saturado que tiene la cantidad de átomos de carbono indicada (p. ej.,
10 alquilo(C₁₋₆) comprende a: metilo, etilo, propilo, isopropilo, butilo, *sec*-butilo, isobutilo, *terc*-butilo, vinilo, alilo, 1-propenilo, isopropenilo, 1-butenilo, 2-butenilo, 3-butenilo, 2-metilalilo, etinilo, 1-propinilo, 2-propinilo y similares). Alquilo representado junto con otro radical (p. ej., como un arilalquilo) significa un radical divalente, alifático, lineal o ramificado, saturado o no saturado que tiene la cantidad de átomos indicada o cuando no
15 se indican los átomos significa un enlace (p. ej., aril(C₆₋₁₀)alquilo(C₀₋₃) comprende a: fenilo, bencilo, fenetilo, 1-feniletilo, 3-fenilpropilo y similares).

"Alquileno", a menos que se indique de otro modo, significa un radical divalente, alifático, lineal o ramificado, saturado o no saturado que tiene la cantidad de átomos de carbono indicada (p. ej.,
20 alquileno(C₁₋₆) comprende a: metileno (-CH₂-), etileno (-CH₂CH₂-), trimetileno (-CH₂CH₂CH₂-), tetrametileno (-CH₂CH₂CH₂CH₂-), 2-butenileno (-CH₂CH=CHCH₂-), 2-metiltetrametileno (-CH₂CH(CH₃)CH₂CH₂-), pentametileno (-CH₂CH₂CH₂CH₂CH₂-) y similares).

"Alquilideno" significa un radical divalente, alifático, lineal o ramificado, saturado o no saturado que tiene la cantidad de átomos de carbono indicada (p. ej.,
25 alquilideno(C₁₋₆) comprende a: metileno (=CH₂), etilideno (=CHCH₃), isopropilideno (=C(CH₃)₂), propilideno (=CHCH₂CH₃), alilideno (=CH'CH=CH₂) y similares).

"Amino" significa el radical -NH₂. A menos que se indique de otro modo, en los compuestos de la invención que contienen porciones amino se incluyen los derivados protegidos de éstos. Los grupos protectores adecuados para las porciones amino incluyen
30 acetilo, *terc*-butoxicarbonilo, benciloxicarbonilo y similares.

El término "animal" incluye mamíferos humanos y no humanos (p. ej., perros, gatos, conejos, ganado, caballos, ovejas, cabras, cerdos, ciervos y similares) y no mamíferos (p. ej., aves y similares).

"Aromático" significa una porción en la que los átomos constituyentes componen un anillo no saturado, todos los átomos del anillo forman orbitales híbridos sp^2 y la cantidad total de electrones pi es igual a $4n+2$.

"Ariilo" significa un anillo monocíclico o bicíclico fusionado que contiene en el anillo la cantidad total de átomos de carbono indicada, en el que cada anillo está constituido por 6 átomos de carbono y es aromático o cuando se fusiona con un segundo anillo forma un anillo aromático. Por ejemplo, un ariilo(C_{6-10}) opcionalmente sustituido como se usa en esta solicitud, comprende, entre otros a, bifenil-2-ilo, 2-bromofenilo, 2-bromocarbonilfenilo, 2-bromo-5-fluorofenilo, 4-*terc*-butilfenilo, 4-carbamoilfenilo, 4-carboxi-2-nitrofenilo, 2-clorofenilo, 4-clorofenilo, 3-clorocarbonilfenilo, 4-clorocarbonilfenilo, 2-cloro-4-fluorofenilo, 2-cloro-6-fluorofenilo, 4-cloro-2-nitrofenilo, 6-cloro-2-nitrofenilo, 2,6-dibromofenilo, 2,3-diclorofenilo, 2,5-diclorofenilo, 3,4-diclorofenilo, 2-difluorometoxifenilo, 3,5-dimetilfenilo, 2-etoxycarbonilfenilo, 2-fluorofenilo, 2-yodofenilo, 4-isopropilfenilo, 2-metoxifenilo, 4-metoxifenilo, 2-metilfenilo, 3-metilfenilo, 4-metilfenilo, 5-metil-2-nitrofenilo, 4-metilsulfonilfenilo, naft-2-ilo, 2-nitrofenilo, 3-nitrofenilo, 4-nitrofenilo, 2,3,4,5,6-pentafluorofenilo, fenilo, 2-trifluorometoxifenilo, 3-trifluorometoxifenilo, 4-trifluorometoxifenilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-trifluorometilsulfanilfenilo, 4-trifluorometilsulfanilfenilo y similares. Un ariilo(C_{6-10}) opcionalmente sustituido como se usa en esta solicitud comprende a 3-acetilfenilo, 3-*terc*-butoxicarbonilaminometilfenilo, bifenil-4-ilo, 3-hidroxifenilo, 4-hidroxifenilo, 3-metoxifenilo, naft-2-ilo, 3-fenoxifenilo, fenilo y similares.

"Bicicloarilo" significa un anillo bicíclico constituido por la cantidad de átomos de carbono indicada, en el que los anillos están unidos por un enlace simple o están fusionados y al menos uno de los anillos del compuesto es aromático, así como todos los derivados cetona carbocíclica, tiocetona e iminocetona de éstos (p. ej., bicicloarilo(C_{9-10})).

comprende a: ciclohexilfenilo, 1,2-dihidronaftilo, 2,4-dioxo-1,2,3,4-tetrahidronaftilo, indanilo, indenilo, 1,2,3,4-tetrahidronaftilo y similares).

"Carbamoilo" significa el radical $-C(O)NH_2$. A menos que se indique de otro modo, en los compuestos de la invención que contienen porciones carbamoilo se incluyen los derivados protegidos de éstos. Los grupos protectores de las porciones carbamoilo adecuados incluyen acetilo, *tert*-butoxicarbonilo, benciloxicarbonilo y similares, y tanto los derivados protegidos como los no protegidos se encuentran dentro del alcance de la invención.

"Derivado cetona carbocíclica" significa un derivado que contiene al grupo $-C(O)-$.

"Carboxilo" significa el radical $-C(O)OH$. A menos que se indique de otro modo, en los compuestos de la invención que contienen porciones carboxilo se incluyen los derivados protegidos de éstos. Los grupos protectores adecuados para las porciones carboxilo incluyen bencilo, *tert*-butilo y similares.

"Cicloalquilo" significa un anillo monocíclico, bicíclico fusionado o policíclico unido por puentes, saturado o parcialmente insaturado, que contiene la cantidad de átomos de carbono indicada, y todos los derivados cetona carbocíclica, tiocetona e iminocetona de éstos (p. ej., cicloalquilo(C_{3-10}) comprende a: ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclohexenilo, 2,5-ciclohexadienilo, biciclo[2.2.2]octilo, adamantan-1-ilo, decahidronaftilo, oxociclohexilo, dioxociclohexilo, tiociclohexilo, 2-oxobiciclo[2.2.1]hept-1-ilo y similares).

"Cicloalquilenos" significa un anillo monocíclico o policíclico unido por puentes, divalente, saturado o parcialmente insaturado, que contiene la cantidad de átomos de carbono indicada y todos los derivados cetona carbocíclica, tiocetona e iminocetona de éstos.

El término "enfermedad" incluye específicamente todo trastorno de la salud de un animal o de parte de éste así como todo trastorno que pueda ser causado por, o sea consecuencia de un tratamiento médico o veterinario aplicado al animal, es decir, los "efectos colaterales" de dicho tratamiento.

"Halógeno" significa flúor, cloro, bromo o yodo.

"Alquilo halo-sustituido", como grupo aislado o como parte de un grupo más grande, significa un "alquilo" sustituido con uno o más átomos de "halógeno", del modo en que dichos términos se definen en esta solicitud. Alquilo halo-sustituido incluye haloalquilo, dihaloalquilo, trihaloalquilo, perhaloalquilo y similares (p. ej., un alquilo(C₁₋₃) halo-sustituido incluye clorometilo, diclorometilo, difluorometilo, trifluorometilo, 2,2,2-trifluoroetilo, perfluoroetilo, 2,2,2-trifluoro-1,1-dicloroetilo y similares).

"Un grupo con heteroátomo" incluye -N=, -NR-, -N⁺(O⁻)=, -O-, -S- o -S(O)₂-, en el que R es hidrógeno, un alquilo(C₁₋₆) o un grupo protector.

10 "Heterocicloalquileno" significa un cicloalquileno, como se lo definió en esta solicitud, siempre que uno o más de los átomos de carbono indicados del anillo sea reemplazado por un grupo con un heteroátomo que se elige entre -N=, -NR-, -O-, -S- o -S(O)₂-, en el que R es hidrógeno o un alquilo(C₁₋₆). Por ejemplo, el caso en que R¹ y R² junto con el átomo de carbono al que ambos R¹ y R² están unidos forma un
15 "heterocicloalquileno(C₃₋₈)" que incluye entre otros los siguientes:

"Heteroarilo" significa un arilo, como se lo definió en esta solicitud, siempre que uno o más de los átomos de carbono indicados del anillo sea reemplazado por un grupo con un heteroátomo que se elige entre -N=, -NR-, -N⁺(O⁻)=, -O- o -S-, en el que R es hidrógeno, un alquilo(C₁₋₆), un grupo protector o representa la valencia libre que sirve de
20 punto de unión a un anillo nitrogenado, y cada anillo esté constituido por 5 ó 6 átomos. Por ejemplo, un heteroarilo(C₅₋₁₃) opcionalmente sustituido como se usa en esta solicitud comprende entre otros a: 4-amino-2-hidroxipirimidin-5-ilo, dibenzofuranilo, benzotiazol-2-ilo, 1*H*-benzoimidazol-2-ilo, 2-bromopirid-5-ilo, 5-bromopirid-2-ilo, 4-carbamoyltiazol-2-ilo, 3-carboxipirid-4-ilo, 5-carboxi-2,6-dimetilpirid-3-ilo,
25 3,5-dimetilisoxazol-4-ilo, 5-etoxi-2,6-dimetilpirid-3-ilo, 5-fluoro-6-hidroxipirimidin-4-ilo, fur-2-ilo, fur-3-ilo, 5-hidroxi-4,6-dimetilpirid-3-ilo, 8-hidroxi-5,7-dimetilquinolin-2-ilo, 5-hidroximetilisoxazol-3-ilo, 3-hidroxi-6-metilpirid-2-ilo, 3-hidroxipirid-2-ilo, 1*H*-imidazol-2-ilo, 1*H*-imidazol-4-ilo, 1*H*-indol-3-ilo, isotiazol-4-ilo, isoxazol-4-ilo, 2-metilfur-3-ilo, 5-metilfur-2-ilo, 1-metil-
30 1*H*-imidazol-2-ilo, 5-metil-3*H*-imidazol-4-ilo, 5-metilisoxazol-3-ilo, 5-metil-

2*H*-pirazol-3-ilo, 3-metilpirid-2-ilo, 4-metilpirid-2-ilo, 5-metilpirid-2-ilo, 6-metilpirid-2-ilo, 2-metilpirid-3-ilo, 2-metiltiazol-4-ilo, 5-nitropirid-2-ilo, 2*H*-pirazol-3-ilo, 3*H*-pirazol-4-ilo, piridazin-3-ilo, pirid-2-ilo, pirid-3-ilo, pirid-4-ilo, 5-pirid-3-ilo-2*H*-[1,2,4]triazol-3-ilo, pirimidin-4-ilo, pirimidin-5-ilo, 1*H*-pirrol-3-ilo, 5 quinolin-2-ilo, 1*H*-tetrazol-5-ilo, tiazol-2-ilo, tiazol-5-ilo, tien-2-ilo, tien-3-ilo, 2*H*-[1,2,4]triazol-3-ilo, 3*H*-[1,2,3]triazol-4-ilo, 5-trifluorometilpirid-2-ilo y similares. Los grupos protectores adecuados incluyen *tert*-butoxicarbonilo, benciloxicarbonilo, bencilo, 4-metoxibencilo, 2-nitrobencilo y similares. Un heteroarilo(C₅₋₁₀) opcionalmente sustituido como se usa en esta solicitud para definir a R⁴ incluye benzofur-2-ilo, fur-2-ilo, fur-3-ilo, pirid-3-ilo, pirid-4-ilo, quinol-2-ilo, quinol-3-ilo, tien-2-ilo, tien-3-ilo y similares.

"Heterobicicloarilo" significa un bicicloarilo, como se lo definió en esta solicitud, siempre que uno o más de los átomos de carbono indicados del anillo sea reemplazado por un grupo con un heteroátomo que se elige entre -N=, -NR-, -O- o -S-, en el que R es hidrógeno, un alquilo(C₁₋₆), un grupo protector o representa la valencia libre que sirve de punto de unión a un anillo nitrogenado, así como todos los derivados cetona carbocíclica, tiocetona e iminocetona de éstos. Por ejemplo, un heterobicicloarilo(C₈₋₁₀) opcionalmente sustituido como se usa en esta solicitud comprende entre otros a 2-amino-4-oxo-3,4-dihidropteridin-6-ilo y similares. En general, el término heterobicicloarilo como se usa en esta solicitud incluye, por ejemplo, benzo[1,3]dioxol-5-ilo, 3,4-dihidro-2*H*-[1,8]naftiridinilo, 3,4-dihidro-2*H*-quinolinilo, 2,4-dioxo-3,4-dihidro-2*H*-quinazolinilo, 1,2,3,4,5,6-hexahidro[2,2']bipiridinililo, 3-oxo-2,3-dihidrobenzo[1,4]oxazinilo, 5,6,7,8-tetrahidroquinolinilo y similares.

"Heterocicloalquilo" significa un cicloalquilo, como se lo definió en esta solicitud, siempre que uno o más de los átomos de carbono indicados del anillo sea reemplazado por un grupo con un heteroátomo que se elige entre -N=, -NR-, -O- o -S-, en el que R es hidrógeno, un alquilo(C₁₋₆), un grupo protector o representa la valencia libre que sirve de punto de unión a un anillo nitrogenado, así como todos los derivados cetona carbocíclica, tiocetona e iminocetona de éstos (p. ej., el término heterocicloalquil(C₅₋₁₀) incluye imidazolidinilo, morfolinilo, piperazinilo, piperidilo, pirrolidinilo, pirrolinilo,

quinuclidinilo y similares). Los grupos protectores adecuados incluyen *tert*-butoxicarbonilo, benciloxicarbonilo, bencilo, 4-metoxibencilo, 2-nitrobencilo y similares. Tanto los derivados protegidos como los no protegidos se encuentran dentro del alcance de la invención.

5 "Hidroxilo" significa el radical -OH. A menos que se indique de otro modo, en los compuestos de la invención que contienen radicales hidroxilo se incluyen los derivados protegidos de éstos. Los grupos protectores adecuados para el radical hidroxilo incluyen bencilo y similares.

10 "Derivado iminocetona" significa un derivado que contiene la porción -C(NR)-, en la que R es hidrógeno o un alquilo(C₁₋₆).

"Isómeros" significa compuestos de fórmula I que tienen idéntica fórmula molecular pero difieren en la naturaleza o secuencia de enlace de sus átomos o en la disposición de sus átomos en el espacio. Los isómeros que difieren en la disposición de sus átomos en el espacio se llaman "estereoisómeros". Los estereoisómeros que no son
15 imágenes especulares uno de otro se llaman "diastereoisómeros" y los estereoisómeros que son imágenes especulares no superponibles se llaman "enantiómeros" o a veces "isómeros ópticos". Un átomo de carbono unido a cuatro sustituyentes distintos se llama "centro quiral". Un compuesto con un centro quiral tiene dos formas enantioméricas de quiralidad opuesta y se llama "mezcla racémica". Un compuesto que tiene más de un
20 centro quiral tiene 2^{n-1} pares de enantiómeros, donde n es la cantidad de centros quirales. Los compuestos con más de un centro quiral pueden existir ya sea como cada uno de los diastereoisómeros o como una mezcla de diastereoisómeros, lo que se llama una "mezcla diastereoisomérica". Cuando hay un centro quiral presente, un estereoisómero se puede caracterizar por la configuración absoluta de su centro quiral. La configuración absoluta
25 se refiere a la disposición en el espacio de los sustituyentes unidos al centro quiral. Los enantiómeros se caracterizan por la configuración absoluta de sus centros quirales y se describen mediante las reglas de secuencia *R*- y *S*- de Cahn, Ingold y Prelog. Las convenciones de la nomenclatura estereoquímica, los métodos para la determinación de la estereoquímica y la separación de estereoisómeros son bien conocidas en la profesión
30 (p. ej., consulte "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley &

Sons, Nueva York, 1992). Se sabe que los nombres e ilustraciones utilizados en esta solicitud para describir a los compuestos de fórmula I tienen la intención de englobar a todos los posibles estereoisómeros. De este modo, por ejemplo, el nombre [1-(1-benzoil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico tiene la intención de incluir la [S-1-(1-benzoil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico y la [R-1-(1-benzoil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico y toda mezcla, racémica o de otro tipo, de éstas.

"Derivado cetona" significa un derivado que contiene al grupo -C(O)-. Por ejemplo, para el 2-acetoxi-azetidin-3-ilo, el "derivado cetona carbocíclica" sería el 2-acetoxi-4-oxo-azetidin-3-ilo.

"Nitro" significa el radical -NO₂.

"Opcional" u "opcionalmente" significa que el suceso o la circunstancia que se describen subsiguientemente pueden ocurrir o no, y que la descripción incluye casos en que el suceso o la circunstancia ocurren y casos en que no ocurren. Por ejemplo, la frase "en los que dentro de R³ y R⁴ cualquier anillo alicíclico o aromático pueden estar sustituidos además con 1 a 5 radicales..." significa que R³ y R⁴ pueden estar sustituidos o no de modo de encontrarse dentro del alcance de la invención.

"Oxoalquilo" significa un alquilo, como se definió antes, en el que uno de los átomos de carbono indicados es reemplazado por un grupo oxígeno (-O-), p. ej., un oxoalquilo(C₂₋₆) incluye metoximetilo, etc.

"Derivados N-óxido" significa derivados de los compuestos de fórmula I en los que los átomos de nitrógeno están en un estado oxidado (es decir, O-N) y que poseen la acción farmacológica deseada.

"Patología" de una enfermedad significa la naturaleza esencial, las causas y el avance de una enfermedad así como los cambios estructurales y funcionales resultantes de los procesos de la enfermedad.

"Aceptable desde el punto de vista farmacéutico" significa aquello que es útil en la elaboración de una preparación farmacéutica que es en general segura, no tóxica y que no es ni biológicamente ni de ninguna otra manera indeseable e incluye aquello que es

aceptable para uso veterinario así como para uso farmacéutico humano.

"Sales aceptables desde el punto de vista farmacéutico" significa sales de los compuestos de fórmula I que son aceptables desde el punto de vista farmacéutico, como se definió antes, y que poseen la acción farmacológica deseada. Dichas sales incluyen

5 sales de adición de ácido formadas con ácidos inorgánicos como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares; o con ácidos orgánicos como ácido acético, ácido propiónico, ácido hexanoico, ácido heptanoico, ácido ciclopentanpropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido malónico, ácido succínico, ácido málico, ácido maleico, ácido fumárico, ácido tartárico,

10 ácido cítrico, ácido benzoico, ácido *o*-(4-hidroxibenzoil)benzoico, ácido cinámico, ácido maléico, ácido metansulfónico, ácido etansulfónico, ácido 1,2-etandisulfónico, ácido 2-hidroxietansulfónico, ácido bencensulfónico, ácido *p*-clorobencensulfónico, ácido 2-naftalensulfónico, ácido *p*-toluensulfónico, ácido alcanforsulfónico, ácido 4-metilbicyclo[2.2.2]oct-2-en-1-carboxílico, ácido glucoheptónico, ácido

15 4,4'-metilenbis(3-hidrox-2-en-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido butilacético terciario, ácido laurilsulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico y similares.

Las sales aceptables desde el punto de vista farmacéutico incluyen las sales de

20 adición de base que se pueden formar cuando los protones ácidos presentes son capaces de reaccionar con bases orgánicas o inorgánicas. Entre las bases inorgánicas aceptables se encuentran hidróxido de sodio, carbonato de sodio, hidróxido de potasio, hidróxido de aluminio e hidróxido de calcio. Entre las bases orgánicas aceptables se encuentran etanolamina, dietanolamina, trietanolamina, trometamina, *N*-metilglucamina y similares.

25 "Profármaco" significa un compuesto que se puede transformar in vivo por medios metabólicos (p. ej. mediante hidrólisis) en un compuesto de fórmula I. Por ejemplo, un éster de un compuesto de fórmula I que contiene un grupo hidroxilo se puede transformar mediante hidrólisis in vivo en la molécula base. Alternativamente un éster de un compuesto de fórmula I que contiene un grupo carboxilo se puede transformar

30 mediante hidrólisis in vivo en la molécula base. Son ésteres adecuados de los compuestos

de fórmula I que contienen un grupo hidroxilo, por ejemplo, los acetatos, citratos, lactatos, tartratos, malonatos, oxalatos, salicilatos, propionatos, succinatos, fumaratos, maleatos, metilen-bis-b-hidroxinaftoatos, gentisatos, isetionatos, di-*p*-toluoltartratos, metansulfonatos, etansulfonatos, bencensulfonatos, *p*-toluensulfonatos, ciclohexilsulfamatos y quinatos. Son ésteres adecuados de los compuestos de fórmula I que contienen un grupo carboxilo, por ejemplo los descritos por F.J. Leinweber, *Drug Metab. Res.*, 1987, 18, página 379. Una clase especialmente útil de ésteres de los compuestos de fórmula I que contienen un grupo hidroxilo, se puede formar a partir de porciones ácidas elegidas entre las descritas por Bundgaard et al., *J. Med. Chem.*, 1989, 32, página 2503-2507, e incluyen (aminometil)-benzoatos sustituidos, por ejemplo dialquilamino-metilbenzoatos en los que dos grupos alquilo se pueden unir entre sí y/o interrumpirse a través de un átomo de oxígeno o de un átomo de nitrógeno opcionalmente sustituido, por ejemplo un átomo de nitrógeno alquilado, especialmente (morfolin-metil)benzoatos, p. ej. 3- o 4-(morfolinmetil)-benzoatos, y (4-alkilpiperazin-1-il)benzoatos, p. ej. 3- o 4-(4-alkilpiperazin-1-il)benzoatos.

"Derivados protegidos" significa derivados de compuestos de fórmula I en los que uno o más sitios reactivos están bloqueados con grupos protectores. Los derivados protegidos de los compuestos de fórmula I son útiles en la preparación de los compuestos de fórmula I o ellos mismos pueden ser inhibidores activos de la catepsina S. Una lista completa de grupos protectores adecuados se puede encontrar en T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

Una "cantidad terapéuticamente eficaz" significa la cantidad que, administrada a un animal para tratar una enfermedad, es suficiente para lograr el tratamiento de la misma.

"Derivado tioetona" significa un derivado que contiene al grupo -C(S)-.

"Tratamiento" o "tratar" significa la administración de un compuesto de la invención actual y consiste en:

- (1) evitar la aparición de la enfermedad en el animal que puede estar predispuesto a ella pero que aún no la sufre o no presenta la patología o la sintomatología de ésta,
- (2) inhibir la enfermedad en un animal que la está sufriendo o que presenta la

patología o la sintomatología de la enfermedad (es decir, detener el avance de la patología y/o la sintomatología), o

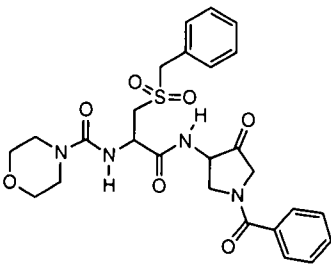
(3) mejorar a un animal que está sufriendo la enfermedad o que presenta la patología o la sintomatología de ésta (es decir, revertir la patología y/o la sintomatología).

5

Nomenclatura:

Los compuestos de fórmula I y los productos intermedios y materias primas utilizados en su preparación se nombran según las reglas de nomenclatura de la IUPAC en las que los grupos característicos se citan como grupo principal en orden decreciente de prioridad como sigue: ácidos, ésteres, amidas, etc. Alternativamente, los compuestos se nombran según AutoNom 4.0 (Beilstein Information Systems, Inc.). Por ejemplo, un compuesto de fórmula I en el que R³ es fenilo, R⁴ es morfolin-4-carbonilo y X³ es 1-benzoil-4-oxo-pirrolidin-3-ilamino; es decir, un compuesto que tiene la estructura siguiente:

10



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se nombra [1-(1-benzoil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico.

20 Materializaciones que se prefieren actualmente:

Aunque la definición más amplia de la invención está estipulada en el resumen de la invención, se prefieren ciertos aspectos de ésta. Por ejemplo, para un compuesto de fórmula I, en el que X¹ y X² son ambos metileno o X¹ es etileno y X² es un enlace; R³ es -CR⁵=CHR⁶, -CR⁵(CR⁶₃)₂ o -CR⁷=NR⁸, en los que R⁵ es hidrógeno y R⁶ es hidrógeno o un alquilo(C₁₋₄) o R⁵ y R⁶ junto con los átomos a los que R⁵ y R⁶ están unidos, forman un cicloalqueno(C₃₋₁₂), un arilo(C₆₋₁₂), un heteroarilo(C₆₋₁₂) o un bicicloarilo(C₉₋₁₂) y R⁷ y R⁸ junto con los átomos a los que R⁷ y R⁸ están unidos, forman un

25

heterocicloalquenilo(C₅₋₁₂) o un heteroarilo(C₆₋₁₂), en el que R³ está opcionalmente sustituido con 1 a 5 radicales elegidos independientemente entre un grupo que consiste en un alquilo(C₁₋₄), un radical ciano, un halógeno, un alquilo(C₁₋₄) halo-sustituido, -X⁴OR⁹ y -X⁴C(O)OR⁹, en los que X⁴ es un enlace o un alquilenio(C₁₋₂), R⁹ cada vez que

5 está presente es independientemente un alquilo(C₁₋₃) o un alquilo(C₁₋₃) halo-sustituido; R⁴ es -C(O)X⁵R¹¹ o -S(O)₂X⁵R¹¹, en los que X⁵ es un enlace, -O- o -NR¹²-, en el que R¹² es hidrógeno o un alquilo(C₁₋₆), y R¹¹ es (i) un alquilo(C₁₋₆) o (ii) un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₃), un aril(C₆₋₁₂)alquilo(C₀₋₃), un heteroaril(C₅₋₁₂)alquilo(C₀₋₃), un bicicloaril(C₉₋₁₂)alquilo(C₀₋₃) o un

10 heterobicicloaril(C₈₋₁₂)alquilo(C₀₋₃) o (iii) un heterocicloalquil(C₅₋₆)alquilo(C₀₋₃) o un fenilalquilo(C₀₋₃) sustituido con -X⁶OR¹⁵, -X⁶C(O)R¹⁵ o -X⁶NR¹⁶C(O)OR¹⁶, en los que X⁶ es un enlace o metileno, R¹⁵ es un fenilalquilo(C₀₋₃) o un heteroaril(C₅₋₆)alquilo(C₀₋₃) y R¹⁶ es hidrógeno o un alquilo(C₁₋₆); en el que R⁴ contiene además opcionalmente 1 a 5

15 sustituyentes que cuando están presentes dentro de un anillo alicíclico o aromático son radicales elegidos independientemente entre un grupo que consiste en: un alquilo(C₁₋₆), un halógeno, -X⁶NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)OR¹⁷, -X⁶NC(O)R¹⁶ y -X⁶C(O)R¹⁸, R¹⁷ cada vez que está presente es independientemente hidrógeno, un alquilo(C₁₋₆) o un alquilo(C₁₋₃) halo-sustituido y R¹⁸ es un alquilo(C₁₋₆) o un alquilo(C₁₋₃) halo-sustituido.

En particular, X³ es un grupo de fórmula (a), (b) o (c) en la que: n es 0, 1 ó 2; R²⁰ se

20 elige entre un grupo que consiste en hidrógeno y un alquilo(C₁₋₆); R²¹ se elige entre un grupo que consiste en un alquilo(C₁₋₉), un aril(C₆₋₁₂)alquilo(C₀₋₆), -C(O)R²⁶, -S(O)₂R²⁶, -C(O)OR²⁶ y -C(O)N(R²⁶)R²⁷; R²³ se elige entre un alquilo(C₁₋₆) opcionalmente sustituido con un grupo amino, -NHC(O)R¹⁵ o -R¹⁵ en los que R¹⁵ es como se definió antes; R²⁵ se elige entre un alquilo(C₁₋₆), un aril(C₆₋₁₂)alquilo(C₀₋₆), -X⁴S(O)₂R²⁶ o

25 -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷ en los que R¹⁷ y X⁴ son como se definieron antes y R²⁶ es como se define a continuación; R²⁶ se elige entre un grupo que consiste en un alquilo(C₁₋₆), un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₆), un aril(C₆₋₁₂)alquilo(C₀₋₆), un heteroaril(C₅₋₁₂)alquilo(C₀₋₆) y un bicicloaril(C₉₋₁₂)alquilo(C₀₋₃); R²⁷ es un alquilo(C₁₋₆); aquí X³ contiene además opcionalmente 1 a 5 sustituyentes que cuando están presentes

30 dentro de un anillo alicíclico o aromático son radicales elegidos independientemente

entre un grupo que consiste en: un alquilo(C₁₋₆), un radical ciano, un halógeno, -X⁶OR¹⁷, -X⁶C(O)R¹⁷ y -X⁶OR¹⁵.

R³ se elige más preferentemente entre un grupo que consiste en: fenilo, piridin-2-ilo, piridin-3-ilo, piridin-4-ilo, vinilo, 2-difluorometoxifenilo, 1-oxi-piridin-2-ilo, 4-
 5 metoxifenilo, 4-metilfenilo, 2-metilfenilo, 4-clorofenilo, 3,5-dimetilfenilo, 4-trifluorometilfenilo, 4-trifluorometoxifenilo, 2-bromofenilo, naftalen-2-ilo, 3,4-diclorofenilo, 3-metilfenilo, 3-trifluorometilfenilo, 3-trifluorometoxifenilo, 2,3,4,5,6-pentafluorofenilo, 2-fluorofenilo, 2-clorofenilo, 2-cianofenilo, 2-trifluorometilfenilo, 4-*tert*-butilfenilo, 3-clorofenilo, 4-bromofenilo, 2-fluoro-3-cloro-fenilo, 2-fluoro-3-metil-
 10 fenilo, 3-fluorofenilo, 2,5-difluorofenilo, 3-bromofenilo, 2,5-diclorofenilo, 2,6-difluorofenilo, 3-cianofenilo, 4-cianofenilo, 2-trifluorometoxifenilo, 2,3-difluorofenilo, bifenilo, 2-bromo-5-fluoro-fenilo, 4-fluorofenilo, 3,4-difluorofenilo, 2,4-difluorofenilo, 2,4,6-trifluorofenilo, 2,4,5-trifluorofenilo, 2,3,4-trifluorofenilo, 2-cloro-5-trifluorometilfenilo, 2,4-bis-trifluorometilfenilo, 2,5,6-trifluorofenilo, 2-fluoro-3-
 15 trifluorometilfenilo, 2-fluoro-4-trifluorometilfenilo, 2-fluoro-5-trifluorometilfenilo, 2,3,5-trifluorofenilo, 2-fluoro-5-trifluorometilfenilo, 5-fluoro-2-trifluorometilfenilo, 4-fluoro-3-trifluorometilfenilo, 2-metoxifenilo, 3,5-bis-trifluorometilfenilo, 4-difluorometoxifenilo, 3-difluorometoxifenilo, 2,6-diclorofenilo, 4-carboxifenilo, ciclohexilo, ciclopropilo, isopropilo, tiofen-2-ilo, 5-cloro-tiofen-2-ilo y 3,5-dimetil-
 20 isoxazol-4-ilo.

R⁴ se elige más preferentemente entre un grupo que consiste en benzoilo, morfolin-4-carbonilo, acetilo, furan-3-carbonilo, 2-metoxibenzoilo, 3-metoxibenzoilo, naftalen-2-carbonilo, benzo[1,3]dioxol-5-carbonilo, 3-piridin-3-il-acriloilo, benzofuran-2-carbonilo, furan-2-carbonilo, *tert*-butoxicarbonilo, bifenil-4-carbonilo, quinolin-2-carbonilo,
 25 quinolin-3-carbonilo, 3-acetilbenzoilo, 4-fenoxibenzoilo, 3-hidroxibenzoilo, 4-hidroxibenzoilo, piridin-3-carbonilo, 3-(*tert*-butoxicarbonilamino-metil)-benzoilo, éster *tert*-butilico del ácido 4-carbonil-piperazin-1-carboxílico, éster etílico del ácido 4-carbonil-piperazin-1-carboxílico, 4-(furan-2-carbonil)-piperazin-1-carbonilo, piridin-4-carbonilo, 1-oxi-piridin-4-carbonilo, 1-oxi-piridin-3-carbonilo, tiofen-2-carbonilo, tiofen-
 30 3-carbonilo, 4-benzoilbenzoilo, 5-metil-tiofen-2-carbonilo, 3-cloro-tiofen-2-carbonilo, 3-

bromo-tiofen-2-carbonilo, 4-clorobenzoilo, 3-fluoro-4-metoxi-benzoilo, 4-metoxibenzoilo, 4-trifluorometoxibenzoilo, 3,4-difluorobenzoilo, 4-fluorobenzoilo, 3,4-dimetoxibenzoilo, 3-metilbenzoilo, 4-bromobenzoilo, 4-trifluorometilbenzoilo, 3-benzoilbenzoilo, ciclopentancarbonilo, benzo[b]tiofen-2-carbonilo, 3-cloro-
 5 benzo[b]tiofen-2-carbonilo, bencensulfonilo, naftalen-2-sulfonilo, 5-metil-tiofen-2-sulfonilo, tiofen-2-sulfonilo, formamil-metil éster, 4-metil-pentanoilo, formamil-isobutil éster, formamil-monoalil éster, formamil-isopropil éster, *N,N*-dimetil-formamilo, *N*-isopropil-formamilo, *N*-piridin-4-il-formamilo, *N*-piridin-3-il-formamilo, 3-fenil-acrililo, 1H-indol-5-carbonilo, piridin-2-carbonilo, pirazin-2-carbonilo, 3-
 10 hidroxipiridin-2-carbonilo, 2-aminopiridin-3-carbonilo, 2-hidroxipiridin-3-carbonilo, 6-aminopiridin-3-carbonilo, 6-hidroxipiridin-3-carbonilo, piridazin-4-carbonilo, 3-fenoxibenzoilo y 1-oxo-1,3-dihidro-isoindol-2-carbonilo.

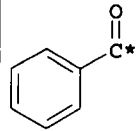
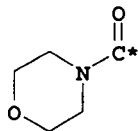
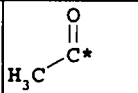
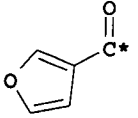
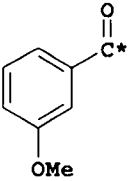
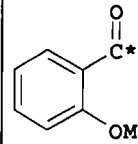
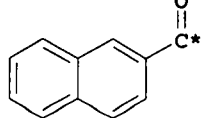
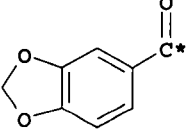
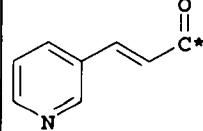
X^3 se elige más preferentemente entre un grupo que consiste en éster bencílico del ácido 4-amino-3-oxo-azepan-1-carboxílico, éster isobutílico del ácido 4-amino-3-oxo-
 15 azepan-1-carboxílico, 4-amino-1-benzoil-azepan-3-ona, 4-amino-1-bencensulfonil-azepan-3-ona, 4-amino-1-(piridin-2-sulfonil)-azepan-3-ona, 4-amino-1-(1-oxi-piridin-2-sulfonil)-azepan-3-ona, 4-amino-1-(3,4-dicloro-bencensulfonil)-azepan-3-ona, 4-amino-1-(2-fluoro-bencensulfonil)-azepan-3-ona, 4-amino-1-(3,4-dimetoxi-bencenesulfonil)-azepan-3-ona, 4-amino-1-(2-ciano-bencensulfonil)-azepan-3-ona, 4-amino-1-(naftalen-1-
 20 sulfonil)-azepan-3-ona, 4-amino-1-(tiofen-2-sulfonil)-azepan-3-ona, 4-amino-1-(tiazol-2-sulfonil)-azepan-3-ona, 4-amino-1-(pirrolidin-1-sulfonil)-azepan-3-ona, 4-amino-1-metansulfonil-azepan-3-ona, 4-amino-1-(pirrolidin-1-carbonil)-azepan-3-ona, dimetilamida del ácido 4-amino-3-oxo-azepan-1-carboxílico, bencilamida del ácido 4-amino-3-oxo-azepan-1-carboxílico, 4-amino-1-bencil-azepan-3-ona, 4-amino-1-bencil-
 25 piperidin-3-ona, 4-amino-1-benzoil-piperidin-3-ona, 4-amino-1-benzoil-pirrolidin-3-ona, 4-amino-1-bencil-pirrolidin-3-ona, 4-amino-1-bencensulfonil-pirrolidin-3-ona, 4-amino-1-(5-metil-hexil)-pirrolidin-3-ona, 1-etil-2-oxo-3-(toluen-4-sulfonilamino)-butilamino, 1-etil-2-oxo-3-(4-fenoxi-bencensulfonilamino)-propilamino, 1-etil-2-oxo-3-[4-(piridin-3-iloxi)-bencensulfonilamino]-propilamino, 3-(dibenzofuran-2-sulfonilamino)-1-etil-2-
 30 oxo-butilamino, 1-etil-3-[4-metil-2-(4-metil-pentanoilamino)-pentanoilamino]-2-oxo-

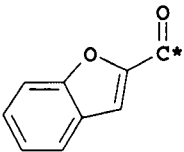
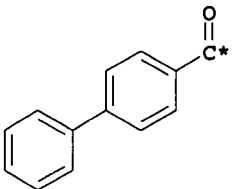
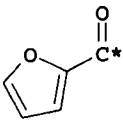
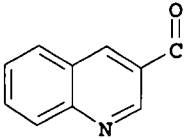
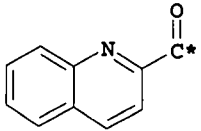
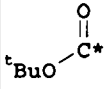
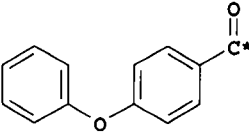
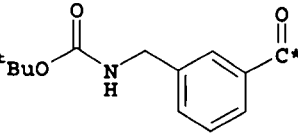
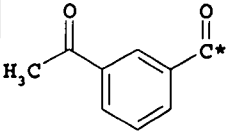
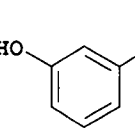
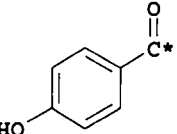
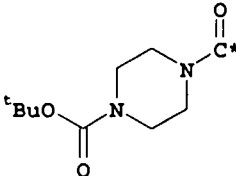
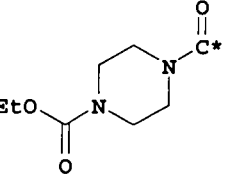
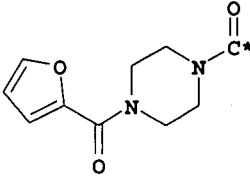
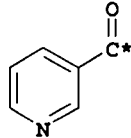
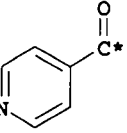
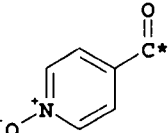
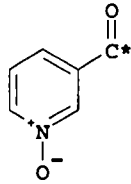
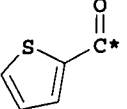
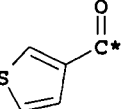
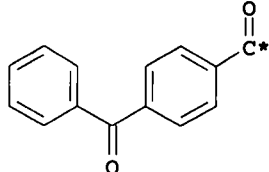
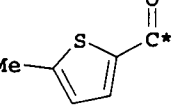
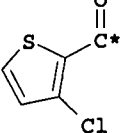
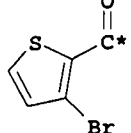
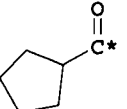
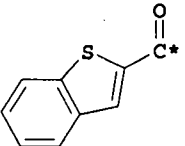
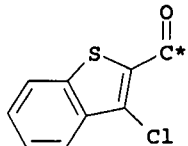
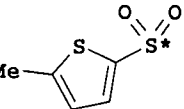
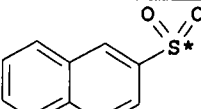
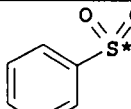
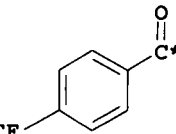
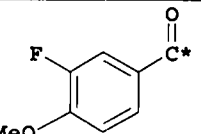
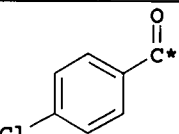
propilamino, 5-amino-1-[(4-metoxi-fenilsulfamoil)-metil]-pentilamino, 5-benciloxicarbonilamino-1-[(4-metoxi-fenilsulfamoil)-metil]-pentilamino, 1-[(4-metoxi-fenilsulfamoil)-metil]-3-fenil-propilamino, 1-{[4-(1-hidroxietyl)-fenilsulfamoil]-metil}-3-fenil-propilamino, 1-[(4-acetil-fenilsulfamoil)-metil]-3-fenil-propilamino, 1-[(4-hidroxi-fenilsulfamoil)-metil]-3-fenil-propilamino y 3-fenil-1-[(2-fenilamino-etilsulfamoil)-metil]-propilamino; y los derivados N-óxido, derivados profármaco, derivados protegidos, cada uno de los isómeros y mezclas de isómeros de éstos; y las sales y solvatos aceptables desde el punto de vista farmacéutico de dichos compuestos y los derivados N-óxido, derivados profármaco, cada uno de los isómeros y mezclas de isómeros de éstos.

Con relación a las materializaciones preferidas estipuladas antes se tiene la intención de incluir todas las combinaciones de los grupos específicos y preferidos.

Los compuestos específicos de la invención se eligen entre los compuestos formados mediante la unión del C* de uno de los fragmentos (A1 a A72) que se muestran en la tabla 1 al átomo de nitrógeno (*N) de uno de los fragmentos (B1 a B80) que se muestran en la tabla 2, y uniendo el átomo de carbono de la metina (CH*) de uno de los fragmentos (B1 a B80) que se muestran en la tabla 2 al átomo de carbono del acilo (C*) de uno de los fragmentos (C1 a C37) descritos en la tabla 3.

TABLA 1

A1		A2		A3	
A4		A5		A6	
A7		A8		A9	

A10		A11		A12	
A13		A14		A15	
A16		A17		A18	
A19		A20		A21	
A22		A23		A24	
A25		A26		A27	
A28		A29		A30	
A31		A32		A33	
A34		A35		A36	
A37		A38		A39	
A40		A41		A42	

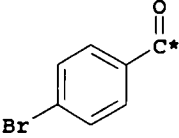
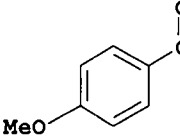
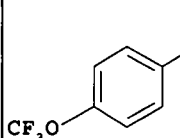
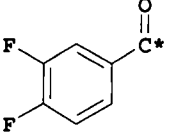
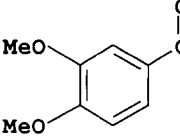
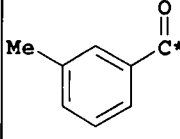
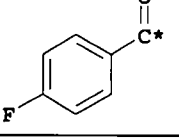
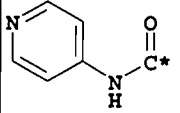
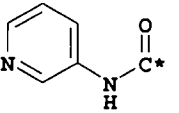
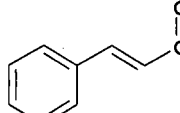
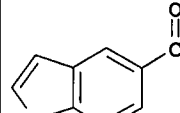
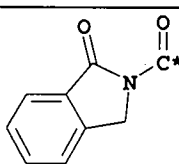
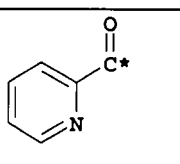
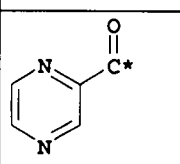
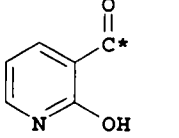
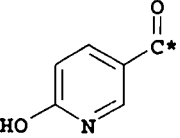
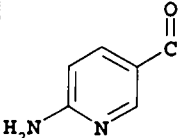
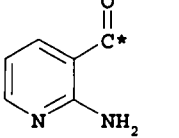
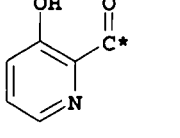
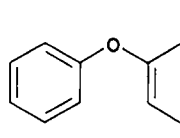
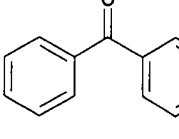
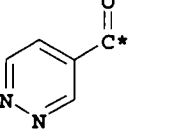
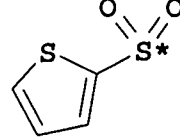
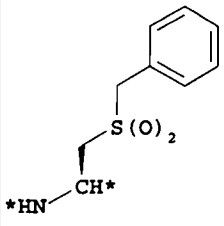
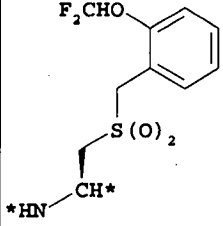
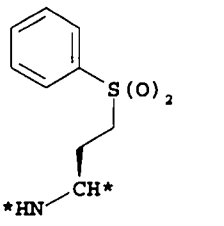
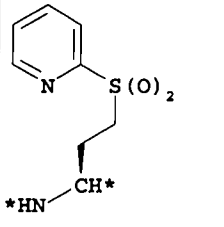
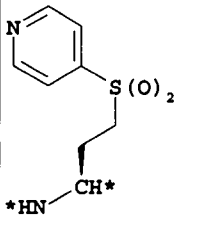
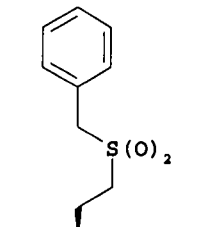
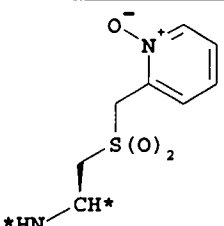
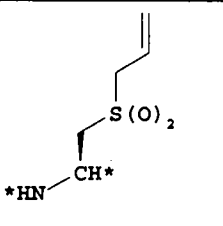
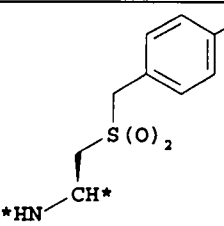
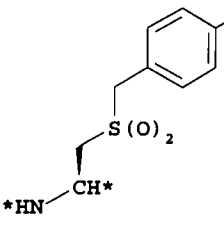
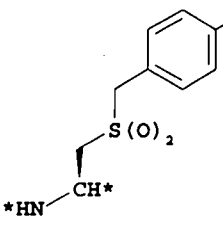
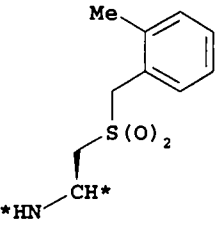
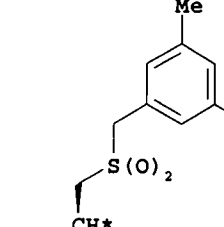
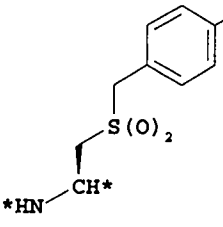
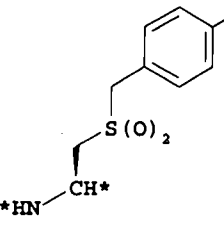
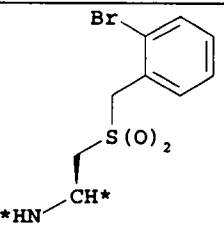
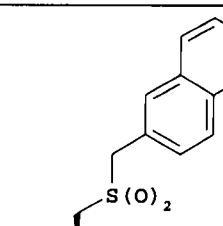
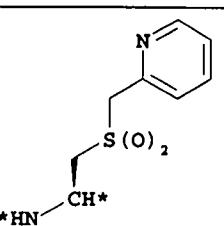
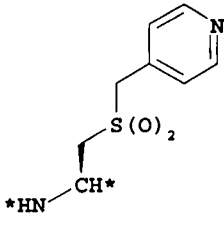
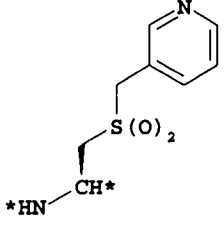
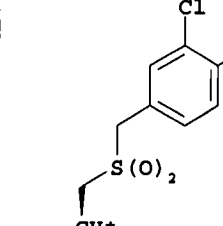
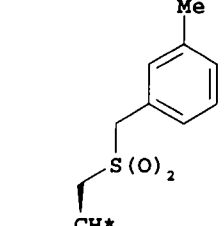
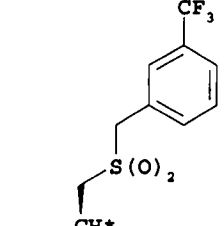
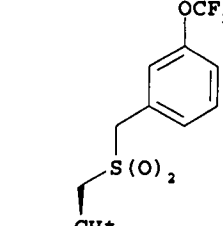
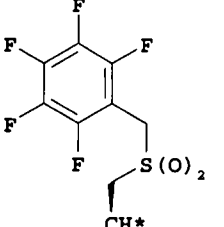
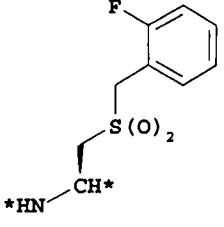
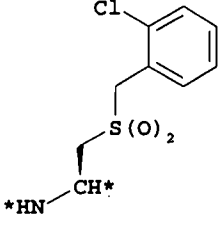
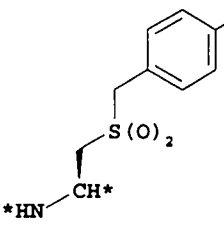
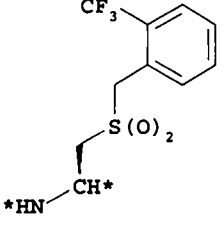
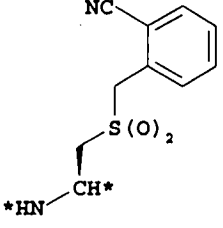
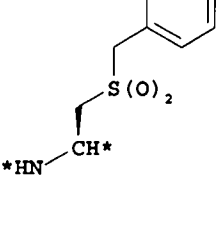
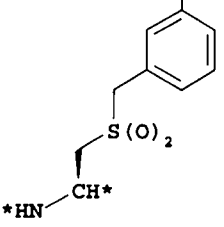
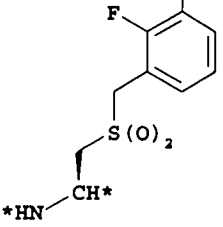
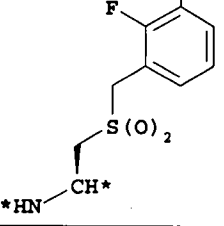
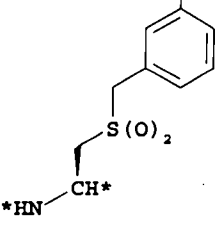
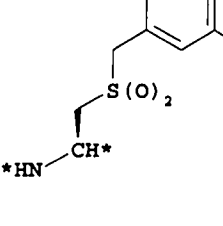
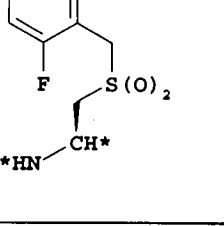
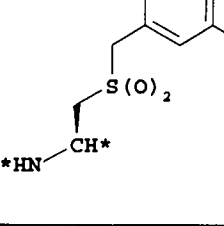
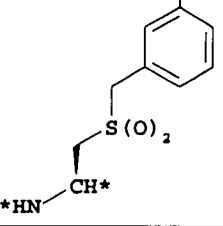
A43		A44		A45	
A46		A47		A48	
A49		A50	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{C}(=\text{O})^*$	A51	$(\text{CH}_3)_2\text{CHCH}_2\text{OC}(=\text{O})^*$
A52	$\text{CH}_3\text{OC}(=\text{O})^*$	A53	$\text{CH}_2=\text{CHCH}_2\text{OC}(=\text{O})^*$	A54	$(\text{CH}_3)_2\text{CHO-C}(=\text{O})^*$
A55	$(\text{CH}_3)_2\text{CHNH-C}(=\text{O})^*$	A56	$(\text{CH}_3)_2\text{N-C}(=\text{O})^*$	A57	
A58		A59		A60	
A61		A62		A63	
A64		A65		A66	
A67		A68		A69	
A70		A71		A72	

TABLE 2

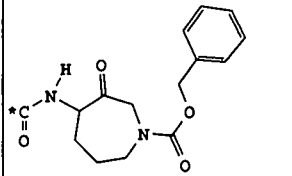
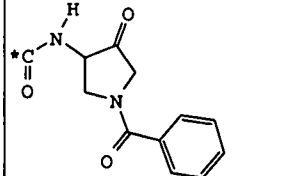
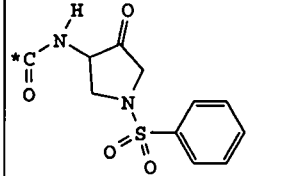
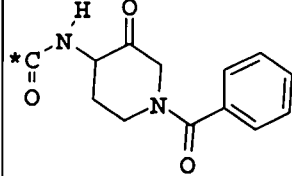
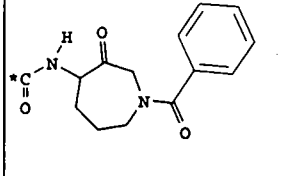
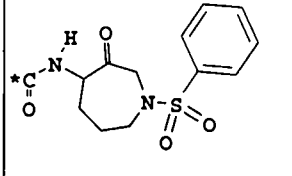
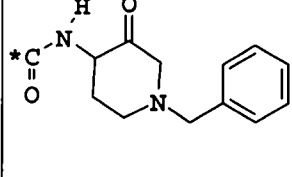
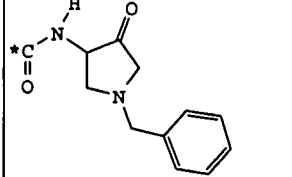
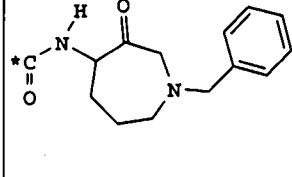
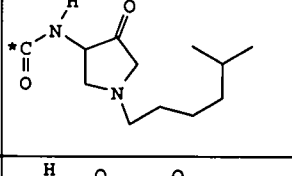
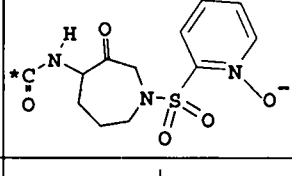
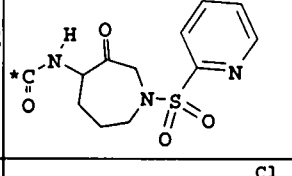
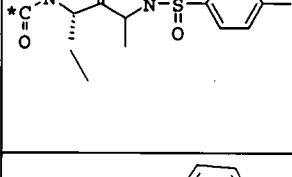
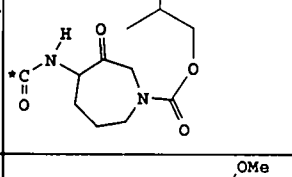
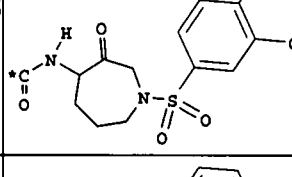
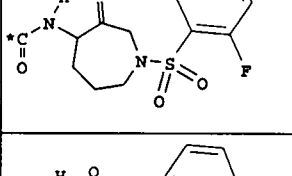
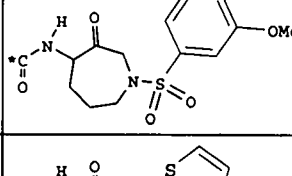
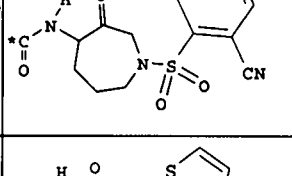
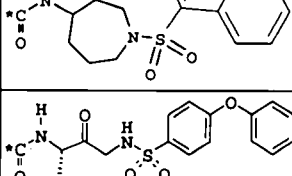
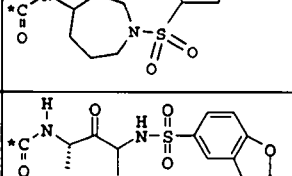
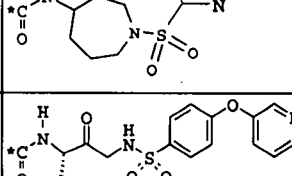
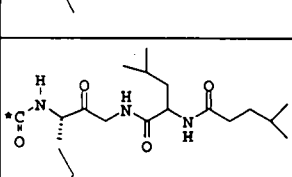
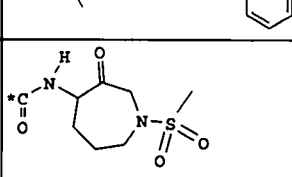
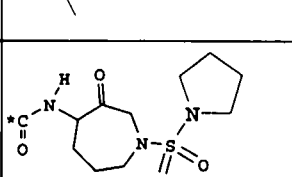
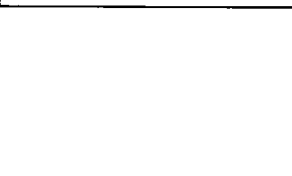
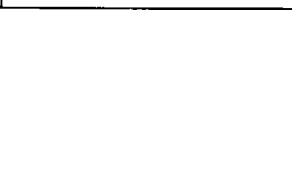
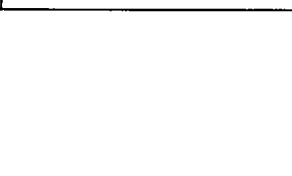
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B4		B5		B6	
B7		B8		B9	
B10		B11		B12	
B13		B14		B15	
B16		B17		B18	

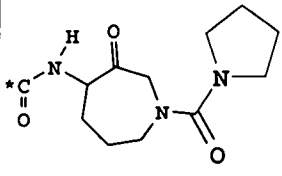
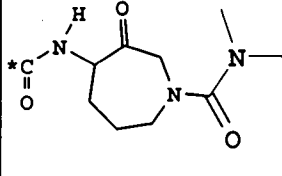
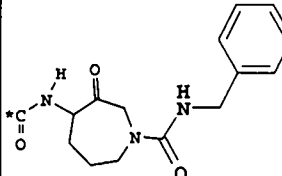
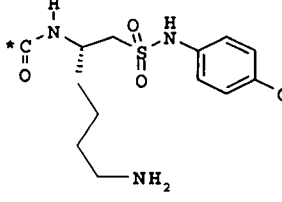
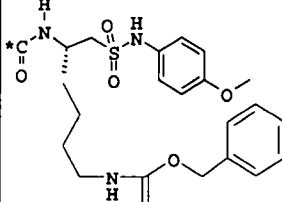
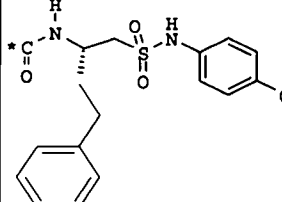
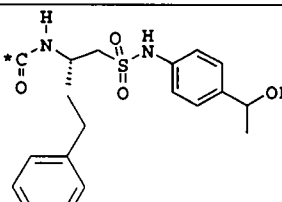
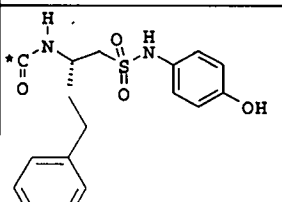
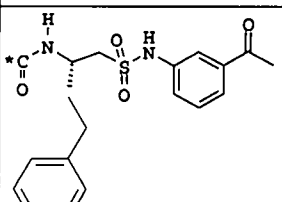
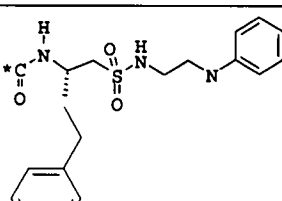
B19		B20		B21	
B22		B23		B24	
B25		B26		B27	
B28		B29		B30	
B31		B32		B33	
B34		B35		B36	
B37		B38		B39	

B40		B41		B42	
B43		B44		B45	
B46		B47		B48	
B49		B50		B51	
B52		B53		B54	
B55		B56		B57	
B58		B59		B60	

B61		B62		B63	
B64		B65		B66	
B67		B68		B69	
B70		B71		B72	
B73		B74		B75	
B76		B77		B78	
B79		B80			

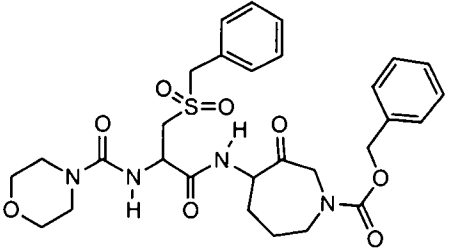
TABLE 3

C1		C2		C3	
C4		C5		C6	
C7		C8		C9	
C10		C11		C12	
C13		C14		C15	
C16		C17		C18	
C19		C20		C21	
C22		C23		C24	
C25		C26		C27	

C28		C29		C30	
C31		C32		C33	
C34		C35		C36	
C37					

Los compuestos combinaciones de “A”, “B” y “C” que se prefieren en particular se ilustran en la tabla 4, material que se presenta en disco compacto junto con esta solicitud y que se incorpora aquí como referencia. Dos copias del disco compacto (copia 1 y copia 2) cada una de las cuales contiene un archivo único de 2,58-mega bites denominado “Tabla 4”, ambas copias fueron creadas en formato ASCII el 13/09/2001.

De este modo, por ejemplo, en la tabla 4 el compuesto indicado como A2-B1-C1 es el producto de la combinación del grupo A2 de la tabla 1 con el B1 de la tabla 2 y el C1 de la tabla 3, concretamente el éster bencílico del ácido 4-{2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propionilamino}-3-oxo-azepan-1-carboxílico:



Farmacología y utilidad:

Los compuestos de la invención son inhibidores selectivos de la catepsina S y, como tales, son útiles para tratar enfermedades en las que la actividad de la catepsina S contribuye a la patología y/o la sintomatología de la enfermedad. Por ejemplo, los compuestos de la invención son útiles en el tratamiento de trastornos autoinmunes, incluidos entre otros, diabetes de aparición juvenil, esclerosis múltiple, pénfigo vulgar, enfermedad de Graves, miastenia grave, lupus eritematoso sistémico, artritis reumatoide y tiroiditis de Hashimoto, trastornos alérgicos incluida entre otros asma, y respuestas inmunitarias alogénicas, incluidos entre otros los trasplantes de órgano o los injertos de tejido.

La catepsina S también está implicada en trastornos que involucran una elastolisis excesiva como la enfermedad pulmonar obstructiva crónica (p. ej., enfisema), bronquiolitis, elastolisis de la vía aérea excesiva en asma y bronquitis, neumonitis y enfermedad cardiovascular como la ruptura de placa y ateroma. La catepsina S está implicada en la formación de fibrilla y por lo tanto, los inhibidores de la catepsina S son útiles en el tratamiento de la amiloidosis sistémica.

Se puede medir la inhibición de la proteasa cisteína por parte de los compuestos de la invención mediante métodos conocidos por los técnicos de la profesión. Se presentan ensayos *in vitro* adecuados para medir la actividad proteasa y la inhibición de ésta mediante los compuestos de prueba. De forma característica, el ensayo mide la hidrólisis inducida por la proteasa de un sustrato peptídico. En los ejemplos 6-9, más adelante, se exponen detalles de los ensayos para medir la inhibición de la proteasa.

Administración y preparaciones farmacéuticas:

En general, los compuestos de fórmula I se administrarán en cantidades terapéuticamente eficaces a través de cualquiera de los modos habituales y aceptables que se conocen en la profesión, ya sea solos o en combinación con uno o más fármacos. Una cantidad terapéuticamente eficaz puede variar ampliamente dependiendo de la gravedad de la enfermedad, la edad y el estado de salud del sujeto, la potencia de los compuestos utilizados y otros factores. Por ejemplo, las cantidades terapéuticamente eficaces de un

compuesto de fórmula I pueden abarcar desde aproximadamente 1 microgramo por kilogramo de peso corporal ($\mu\text{g/kg}$) por día hasta aproximadamente 1 miligramo por kilogramo de peso corporal (mg/kg) por día, habitualmente desde aproximadamente 10 $\mu\text{g/kg/día}$ hasta aproximadamente 0,1 mg/kg/día . Por lo tanto, una cantidad terapéuticamente eficaz para un paciente humano de 80 kg puede encontrarse en el intervalo entre 100 $\mu\text{g/día}$ y 100 mg/día , aproximadamente; habitualmente se encuentra entre 1 $\mu\text{g/día}$ y 10 mg/día , aproximadamente. En general, un técnico de la profesión, basándose en su propio conocimiento y en la información que divulga esta solicitud, será capaz de determinar una cantidad terapéuticamente eficaz de un compuesto de fórmula I para tratar una determinada enfermedad.

Los compuestos de fórmula I se pueden administrar como preparaciones farmacéuticas por alguna de las siguientes vías: oral, sistémica (p. ej., transdérmica, intranasal o mediante supositorio) o parenteral (p. ej., intramuscular, intravenosa o subcutánea). Las preparaciones pueden adoptar la forma de comprimidos, píldoras, cápsulas, semisólidos, polvos, formulaciones de liberación prolongada, soluciones, suspensiones, elixires, aerosoles o cualquier otra preparación apropiada y constan de, en general, un compuesto de fórmula I en combinación con al menos un excipiente aceptable desde el punto de vista farmacéutico. Los excipientes aceptables no son tóxicos, facilitan la administración y no afectan de manera adversa a los beneficios terapéuticos del principio activo. Tales excipientes pueden ser cualquier excipiente sólido, líquido, semisólido o en el caso de una preparación en aerosol, gaseoso que en general están a disposición de cualquier técnico de la profesión.

Entre los excipientes farmacéuticos sólidos se encuentran: almidón, celulosa, talco, glucosa, lactosa, sacarosa, gelatina, malta, arroz, harina, creta, sílica gel, estearato de magnesio, estearato de sodio, monoestearato de glicerol, cloruro de sodio, leche descremada desecada y similares. Los excipientes líquidos y semisólidos se pueden elegir entre: agua, etanol, glicerol, propilenglicol, y diversos aceites incluidos los de petróleo y de origen animal, vegetal o sintético (p. ej., aceite de maní, aceite de soja, aceite mineral, aceite de sésamo y similares). Los excipientes líquidos preferidos, en particular para las soluciones inyectables, incluyen agua, solución salina, solución acuosa de dextrosa y

glicoles.

La cantidad de un compuesto de fórmula I en la preparación puede variar mucho, dependiendo del tipo de formulación, del tamaño de una unidad de dosificación, del tipo de excipientes y de otros factores conocidos por los profesionales de las ciencias farmacéuticas. En general, una preparación de un compuesto de fórmula I para tratar una determinada enfermedad contendrá entre 0,01 % en peso y 10 % en peso, preferentemente entre 0,3 % en peso y 1 % en peso, de principio activo, siendo el resto de la preparación uno o más excipientes. Preferentemente la preparación farmacéutica se administra en una única forma de unidad de dosificación para tratamiento continuo o en una única forma de unidad de dosificación a voluntad cuando se necesita específicamente el alivio de los síntomas. En el ejemplo 10, más adelante, se describen formulaciones farmacéuticas representativas que contienen un compuesto de fórmula I.

15 Química:

Procesos para elaborar compuestos de fórmula I:

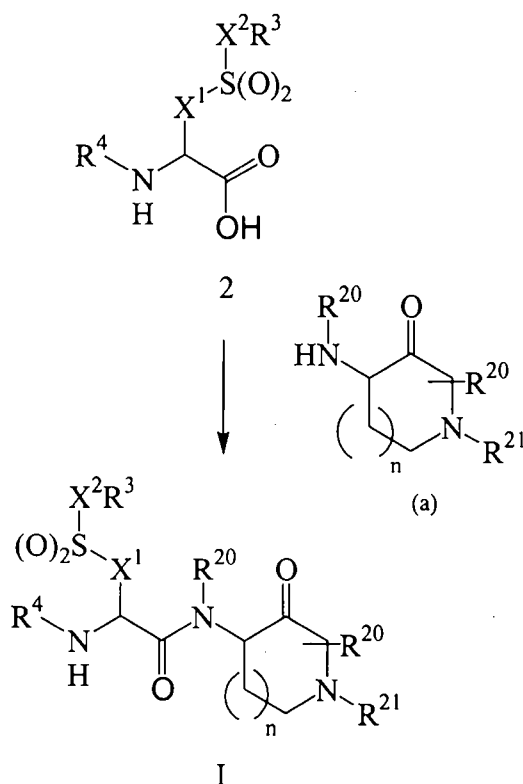
Los compuestos de la invención se pueden preparar mediante la aplicación o adaptación de métodos conocidos, es decir métodos usados hasta ahora o descritos en la bibliografía, por ejemplo los descritos por R.C. Larock en Comprehensive Organic Transformations, VCH publishers, 1989.

En las reacciones descritas a continuación puede ser necesario proteger los grupos funcionales reactivos, por ejemplo hidroxilo, amino, imino, tio o carboxilo, en el lugar que se quiere que se encuentren en el producto final, para evitar su participación no deseada en las reacciones. Se pueden usar los grupos protectores convencionales de acuerdo con la práctica estándar, por ejemplo consulte a T.W. Greene y P. G. M. Wuts en "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

Los compuestos de fórmula I, en los que X^3 es un compuesto de fórmula (a) (como se la definió en el resumen de la invención), se pueden preparar procediendo como

en el esquema de reacción 1 siguiente:

Esquema de reacción 1



5

en los que cada X^1 , X^2 , R^3 , R^4 , R^{20} y R^{21} es como se lo define para la fórmula I en el resumen de la invención.

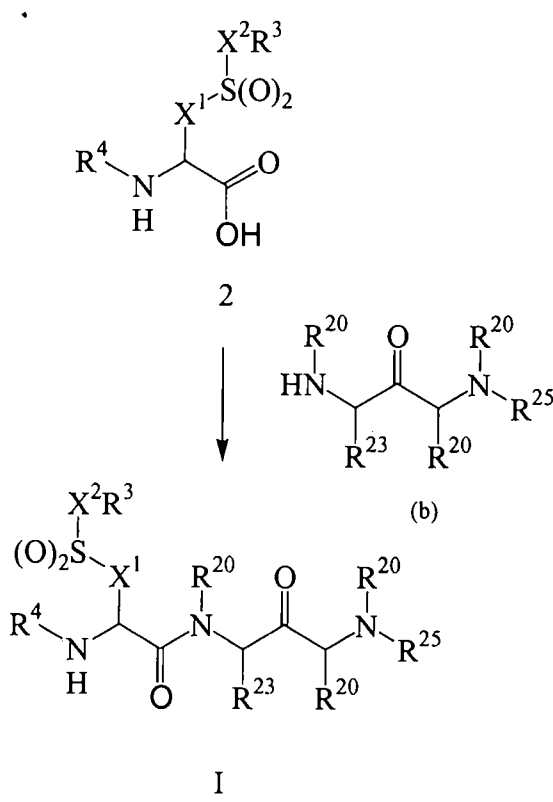
Los compuestos de fórmula I se pueden preparar condensando un ácido de fórmula 2 con un compuesto amino de fórmula (a). La reacción de condensación se puede llevar a cabo con un agente de acoplamiento adecuado (p. ej., hexafluorofosfato de benzotriazol-1-iloxitrispirrolidinofosfonio (PyBOP[®]), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI), hexafluorofosfato de *O*-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio (HBTU), 1,3-diciclohexilcarbodiimida (DCC), o similares) y opcionalmente un catalizador adecuado (p. ej., 1-hidroxibenzotriazol (HOBt), 1-hidroxi-7-azabenzotriazol (HOAt), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-1,1,3,3, tetra-metiluronio (HATU) o similares) y bases no nucleofílicas (p. ej., trietilamina, *N*-metilmorfolina, y similares, o cualquier combinación adecuada de éstas) a temperatura ambiente, siendo necesarias de 5 a 10 horas para que la reacción se complete. Si es necesario un paso de oxidación, se puede llevar a cabo con un

15

agente oxidante (p.ej., Oxone[®], ácido metacloroperbenzoico o similares) en un disolvente adecuado (p. ej., metanol, agua o similares, o cualquier combinación adecuada de éstos) a temperatura ambiente, siendo necesarias de 16 a 24 horas para que la reacción se complete. En los ejemplos 1 a 11, más adelante, se exponen descripciones detalladas de las síntesis de un compuesto de fórmula I mediante los procesos del esquema de reacción 1.

Los compuestos de fórmula I, en los que X³ es un compuesto de fórmula (b) (como se lo define en el resumen de la invención), se pueden preparar procediendo como en el esquema de reacción 2 siguiente:

Esquema de reacción 2



en los que cada X¹, X², R³, R⁴, R²⁰, R²³ y R²⁵ es como se lo define para la fórmula I en el resumen de la invención.

Los compuestos de fórmula I se pueden preparar condensando un ácido de fórmula 2 con un compuesto amino de fórmula (b). La reacción de condensación se puede llevar a cabo con un agente de acoplamiento adecuado (p. ej., hexafluorofosfato de

benzotriazol-1-iloxitrispirrolidinofosfonio (PyBOP[®]), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI), hexafluorofosfato de *O*-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio (HBTU), 1,3-diciclohexilcarbodiimida (DCC), o similares) y opcionalmente un catalizador adecuado (p. ej., 5 1-hidroxibenzotriazol (HOBt), 1-hidroxi-7-azabenzotriazol (HOAt), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-1,1,3,3, tetra-metiluronio (HATU) o similares) y bases no nucleofílicas (p. ej., trietilamina, *N*-metilmorfolina, y similares, o cualquier combinación adecuada de éstas) a temperatura ambiente, siendo necesarias de 5 a 10 horas para que la reacción se complete.

10 Si es necesario un paso de oxidación, se puede llevar a cabo con un agente oxidante (p.ej., Oxone[®], ácido metacloroperbenzoico o similares) en un disolvente adecuado (p. ej., metanol, agua o similares, o cualquier combinación adecuada de éstos) a temperatura ambiente, siendo necesarias de 16 a 24 horas para que la reacción se complete.

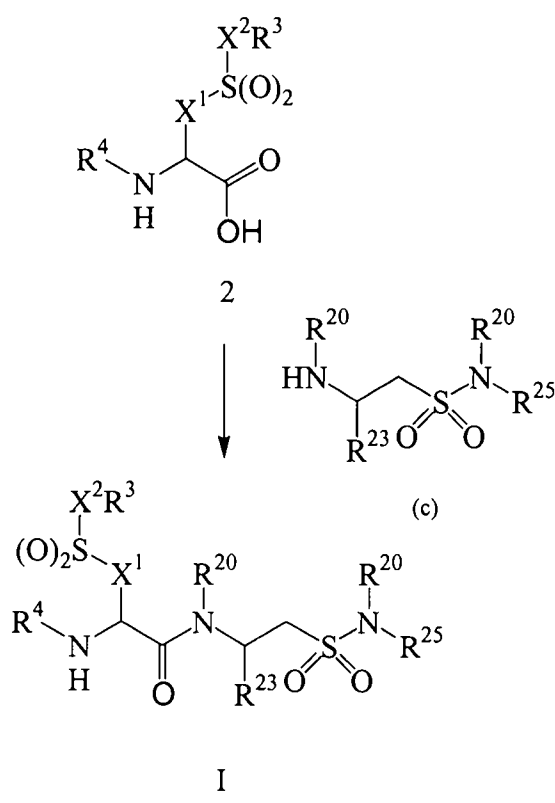
15 Los compuestos de fórmula 1 en los que X³ es un compuesto de fórmula (c) (como se lo define en el resumen de la invención), se pueden preparar haciendo reaccionar un compuesto de fórmula 2 con un compuesto de fórmula (c) según el esquema de reacción siguiente:

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Esquema de reacción 3



5 en los que cada X¹, X², R³, R⁴, R²⁰, R²³ y R²⁵ es como se lo define para la fórmula I en el resumen de la invención.

Otros procesos para elaborar compuestos de fórmula I:

10 Un compuesto de fórmula I se puede preparar como una sal de adición de ácido aceptable desde el punto de vista farmacéutico, haciendo reaccionar la forma base libre del compuesto con un ácido orgánico o inorgánico aceptable desde el punto de vista farmacéutico. Alternativamente, se puede preparar una sal de adición de base aceptable desde el punto de vista farmacéutico de un compuesto de fórmula I, haciendo reaccionar la forma ácido libre del compuesto con una base orgánica o inorgánica aceptable desde el

15 punto de vista farmacéutico. En la sección de definiciones de esta solicitud se estipulan los ácidos y bases orgánicos e inorgánicos adecuados para la preparación de las sales aceptables desde el punto de vista farmacéutico de los compuestos de fórmula I. Alternativamente, las sales de los compuestos de fórmula I se pueden preparar utilizando sales de las materias primas o de los productos intermedios.

Las formas ácido libre y base libre de los compuestos de fórmula I se pueden preparar a partir de la sal de adición de base o de la sal de adición de ácido correspondientes. Por ejemplo, un compuesto de fórmula I en forma de sal de adición de ácido se puede transformar en la base libre correspondiente tratándolo con una base adecuada (p. ej., solución de hidróxido de amonio, hidróxido de sodio y similares). Un
5 compuesto de fórmula I en forma de sal de adición de base se puede transformar en el ácido libre correspondiente tratándolo con un ácido adecuado (p. ej., ácido clorhídrico, etc.).

Los *N*-óxidos de los compuestos de fórmula I se pueden preparar con métodos
10 conocidos por los técnicos de la profesión. Por ejemplo, los *N*-óxidos se pueden preparar tratando una forma no oxidada del compuesto de fórmula I con un agente oxidante (p. ej., ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido *meta*-cloroperoxibenzoico o similares) en un disolvente orgánico inerte adecuado (p. ej., un hidrocarburo halogenado como el diclorometano) a aproximadamente 0° C.
15 Alternativamente, los *N*-óxidos de un compuesto de fórmula I se pueden preparar a partir del *N*-óxido de una materia prima apropiada.

Los compuestos de fórmula I en su forma no oxidada se pueden preparar a partir de *N*-óxidos de compuestos de fórmula I tratándolos con un agente reductor (p. ej., azufre, dióxido de azufre, trifenilfosfina, borohidruro de litio, borohidruro de sodio,
20 tricloruro de fósforo, tribromuro o similares) en un disolvente orgánico inerte adecuado (p. ej., acetonitrilo, etanol, solución acuosa de dioxano o similares) a una temperatura entre 0° y 80° C.

Los derivados profármaco de los compuestos de fórmula I se pueden preparar mediante métodos conocidos por los técnicos de la profesión (p. ej., por más detalles
25 consulte a Saulnier *et al.* (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). Por ejemplo, los profármacos apropiados se pueden preparar haciendo reaccionar un compuesto de fórmula I sin derivar con un agente carbamilante adecuado (p. ej., clorhidrato de 1,1-aciloxialquilcarbono, *para*-nitrofenil carbonato, o similares).

Los derivados protegidos de los compuestos de fórmula I se pueden preparar por
30 medios conocidos por los técnicos de la profesión. Se puede encontrar una descripción

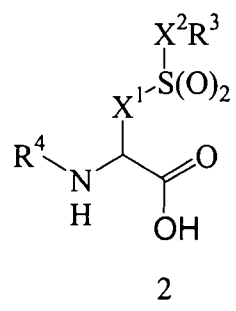
detallada de las técnicas aplicables para la preparación de grupos protectores y para su eliminación en T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

Los compuestos de la invención actual se pueden preparar convenientemente, o
5 formar durante el proceso de la invención, como solvatos (p. ej. hidratos). Los hidratos de los compuestos de la invención actual se pueden preparar convenientemente por recristalización de una mezcla disolvente acuosa y orgánica, utilizando disolventes orgánicos como la dioxina, el tetrahidrofurano o el metanol.

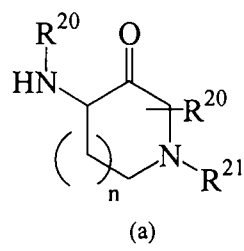
Los compuestos de fórmula I se pueden preparar como cada uno de sus
10 estereoisómeros haciendo reaccionar una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diastereoisómeros, separando los diastereoisómeros y recuperando el enantiómero ópticamente puro. Si bien la resolución de los enantiómeros se puede llevar a cabo utilizando derivados diastereoisoméricos de los compuestos de fórmula I, se prefieren los complejos
15 disociables (p. ej., sales diastereoisoméricas cristalinas). Los diastereoisómeros tienen diferentes propiedades físicas (p. ej., puntos de fusión, puntos de ebullición, solubilidades, reactividades, etc.) y se pueden separar fácilmente aprovechando estas diferencias. Los diastereoisómeros se pueden separar por cromatografía o
20 preferentemente por técnicas de separación y resolución basadas en las diferencias de solubilidad. Después el enantiómero ópticamente puro se recupera junto con el agente de resolución por cualquier medio práctico que no dé como resultado la racemización. Se puede encontrar una descripción más detallada de las técnicas aplicables para la resolución de estereoisómeros de compuestos de su mezcla racémica en Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley &
25 Sons, Inc. (1981).

En resumen, los compuestos de fórmula I se elaboran mediante un proceso que comprende:

(A) hacer reaccionar un compuesto de fórmula 2:

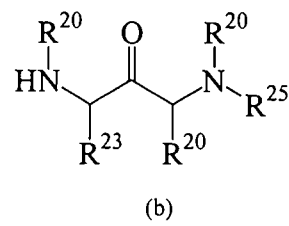


con un compuesto de fórmula (a):



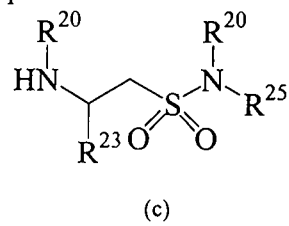
5 en los que X¹, X², R³, R⁴, R²⁰ y R²¹ son como se los define en el resumen de la invención para la fórmula I; o

(B) hacer reaccionar un compuesto de fórmula 2 con un compuesto de fórmula (b):



10 en los que R²⁰, R²³ y R²⁵ son como se los define en el resumen de la invención para la fórmula I; o

(C) hacer reaccionar un compuesto de fórmula 2 con un compuesto de fórmula (c):



15 en los que R²⁰, R²³ y R²⁵ son como se los define en el resumen de la invención para la fórmula I; y

(D) transformar opcionalmente un compuesto de fórmula I en una sal aceptable desde el punto de vista farmacéutico;

- (E) transformar opcionalmente un compuesto de fórmula I en forma de sal en un compuesto en una forma que no sea una sal;
- (F) transformar opcionalmente una forma no oxidada de un compuesto de fórmula I en un *N*-óxido aceptable desde el punto de vista farmacéutico;
- 5 (G) transformar opcionalmente una forma *N*-óxido de un compuesto de fórmula I en su forma no oxidada;
- (H) separar opcionalmente un isómero individual de un compuesto de fórmula I de una mezcla de isómeros;
- (I) transformar opcionalmente un compuesto de fórmula I sin derivar en un derivado profármaco aceptable desde el punto de vista farmacéutico; y
- 10 (J) transformar opcionalmente un derivado profármaco de un compuesto de fórmula I en su forma sin derivar.

Ejemplos:

- 15 La invención actual se explica más a fondo, pero no exclusivamente, mediante los ejemplos siguientes que ilustran la preparación de compuestos de fórmula I (ejemplos) y de productos intermedios (referencias) de acuerdo con la invención.

REFERENCIA 1

- 20 Éster terc-butilico del ácido 3-amino-4-hidroxi-pirrolidin-1-carboxílico

Se disuelve éster terc-butilico del ácido 6-oxa-3-aza-biciclo[3.1.0]hexan-3-carboxílico (12,1g; 65,3 mmol) en una mezcla metanol/agua 8:1 (108 mL). Se agrega cloruro de amonio (15 g) y azida de sodio (21,4 g; 329 mmol) y la mezcla se calienta a

25 60 °C durante toda la noche. Después de diluirla con éter (500 mL), la mezcla se lava con solución acuosa saturada de NaHCO₃ (200 mL) y solución saturada de cloruro de sodio (200 mL), se seca con MgSO₄ y se evapora bajo vacío. El producto crudo se disuelve en metanol (200 mL). Se agrega 10 % de paladio sobre carbono activado (1,5 g) y la mezcla se agita a temperatura ambiente bajo atmósfera de hidrógeno hasta que el

30 análisis por TLC (cromatografía en capa fina) muestra la desaparición de la materia

prima. Se filtra la mezcla a través de un tampón de Celite y se evapora a sequedad bajo vacío. El producto se purifica por cromatografía instantánea sobre sílica gel. Eluyente: metanol al 5 % en acetato de etilo:metanol al 20 %, trietilamina al 3 % en acetato de etilo. Rendimiento: 4,3 g de éster terc-butílico del ácido 3-amino-4-hidroxi-pirrolidin-1-carboxílico como un sólido amarillento.

REFERENCIA 2

Éster bencílico del ácido 4-amino-3-hidroxi-azepan-1-carboxílico

Se suspende hidruro de sodio (60 % en aceite mineral, 10 g, 250 mmol) en DMF seco. Se agrega gota a gota éster bencílico del ácido alilcarbámico (19,1 g; 100 mmol) a temperatura ambiente. Después de agitar durante 5 minutos, se agrega gota a gota 5-bromo-1-penteno (25 g, 168 mmol). Se continúa agitando a 50° C durante 1 hora. La reacción se enfría con agua y luego se reparte entre éter dietílico y agua. La capa etérea se lava con agua y solución saturada de cloruro de sodio, se seca con MgSO₄ y se evapora bajo vacío. La cromatografía instantánea (acetato de etilo/hexano 1:9) da como resultado éster bencílico del ácido alil-pent-4-enil-carbámico (15,5 g).

Se disuelve el éster bencílico del ácido alil-pent-4-enil-carbámico (15,5 g; 59,8 mmol) en diclorometano y se agrega dicloruro de bis(triciclohexilfosfina)benciliden rutenio(IV) (1 g). La mezcla se calienta a reflujo bajo atmósfera de nitrógeno hasta que el análisis por TLC muestra que la reacción se completó. Se evapora el disolvente bajo vacío y el residuo se purifica por cromatografía instantánea (acetato de etilo/hexano 1:9) para dar éster bencílico del ácido 2,3,4,7-tetrahidro-azepin-1-carboxílico (7,8 g).

A una solución de éster bencílico del ácido 2,3,4,7-tetrahidro-azepin-1-carboxílico (4,5 g; 19,45 mmol) en diclorometano (50 mL) se le agrega ácido m-cloroperbenzoico (60 mmol). La mezcla se agita a temperatura ambiente durante 16 horas. Se agrega solución acuosa saturada de K₂CO₃ y la mezcla se extrae con diclorometano. Las capas orgánicas combinadas se lavan con solución acuosa saturada de NaHCO₃ y solución saturada de cloruro de sodio, se secan con MgSO₄ y se evaporan bajo vacío. El epóxido crudo se disuelve en una mezcla metanol:agua 8:1 (100 mL). Se

agregan cloruro de amonio (3,2 g; 60 mmol) y azida de sodio (3,9 g; 60 mmol) y la mezcla se calienta a 60° C durante 48 horas. La mayor parte del disolvente se elimina bajo vacío. El residuo se extrae con acetato de etilo. Las capas orgánicas combinadas se lavan con solución acuosa saturada de NaHCO₃ (200 mL) y solución saturada de cloruro de sodio (200 mL), se secan con MgSO₄ y se evaporan bajo vacío. La cromatografía instantánea del residuo (hexano/acetato de etilo 3:1) da como resultado éster bencílico del ácido 4-azido-3-hidroxi-azepan-1-carboxílico (3,3 g).

A una solución del éster bencílico del ácido 4-azido-3-hidroxi-azepan-1-carboxílico (3,3 g; 11,37 mmol) en metanol (50 mL) se le agrega trietilamina (5 mL) y 1,3-propanoditiol (3,42 mL; 35 mmol). La mezcla se agita a temperatura ambiente hasta que el análisis por TLC muestra que se consumió toda la materia prima. Se elimina un precipitado blanco por filtración y el filtrado se evapora hasta sequedad. El residuo se tritura con una mezcla de hexano/éter dietílico 1:1 para eliminar el ditiol en exceso y se seca bajo vacío para obtener éster bencílico del ácido 4-amino-3-hidroxi-azepan-1-carboxílico.

REFERENCIA 3

Clorhidrato de 2S-amino-N-(4-metoxifenil)-4-fenilbutan-1-sulfonamida

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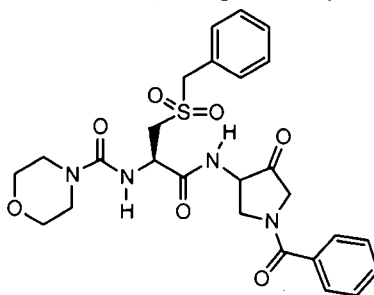
Una solución compuesta por 1-(4-metoxifenilsulfamoilmetil)-3-fenilpropilcarbamato de *terc*-butilo crudo (1,92 g; 4,42 mmol), preparada como en el ejemplo de referencia 2, en DCM (10 mL) se trata con una solución de ácido clorhídrico 4M en dioxano (11 mL). La mezcla se agita durante 16 horas a temperatura ambiente y se diluye con éter dietílico. El precipitado resultante se recoge por filtración, se lava varias veces con éter dietílico y hexano y se seca con bomba para obtener clorhidrato de 2S-amino-N-4-metoxifenil-4-fenilbutan-1-sulfonamida con recuperación cuantitativa de masa. ¹H NMR (DMSO): 2,05 (2H, m); 2,6-2,7 (2H, m); 3,4 (3H, m*); 3,72 (3H, s); 6,9 (2H, d, J=7 Hz); 7,25 (5H, m); 7,3 (2H, d, J=7 Hz); 8,5 (br. s); 10,0 (1H, s).

30

EJEMPLO 1

[1-(1-benzoil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida
del ácido morfolin-4-carboxílico.

(Compuesto 1)



5

Se combinan ácido 2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propiónico (1 g; 2,8 mmol), éster terc-butílico del ácido 3-amino-4-hidroxi-pirrolidin-1-carboxílico (700 mg; 3,46 mmol) preparados como en la referencia 1, EDC (1,5 g; 7,8 mmol) y HOBt (1,5 g; 9,6 mmol). Se agrega diclorometano (10 mL) y a continuación 4-metilmorfolina (1,5 mL). La mezcla se agita a temperatura ambiente durante 2 horas. Después de diluirla con acetato de etilo (200 mL), la solución se lava con solución acuosa saturada de NaHCO₃ (100 mL) y solución saturada de cloruro de sodio (100 mL), se seca con MgSO₄ y se evapora bajo vacío. Se obtiene éster terc-butílico del ácido 3-hidroxi-4-{2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propionilamino}-pirrolidin-1-carboxílico (1,05 g; 1,94 mmol) como una espuma amarillenta y se disuelve en diclorometano (6 mL). Se agrega ácido trifluoroacético (6 mL) y la mezcla se agita a temperatura ambiente durante 1 hora. La evaporación bajo vacío da como resultado [1-(4-hidroxi-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico crudo como sal trifluoroacética (TFA), que se usa sin una purificación posterior.

La sal TFA de [1-(4-hidroxi-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico (215 mg, 0,39 mmol) se disuelve en 1,4-dioxano (20 mL). Se agrega solución acuosa saturada de NaHCO₃ (10 mL) seguida de cloruro de benzoílo (0,2 mL; 1,72 mmol). La mezcla se agita a temperatura ambiente durante 1 hora y a continuación se extrae con acetato de etilo. Las capas orgánicas combinadas se lavan con solución acuosa saturada de NaHCO₃ y solución saturada de cloruro de sodio, se

25

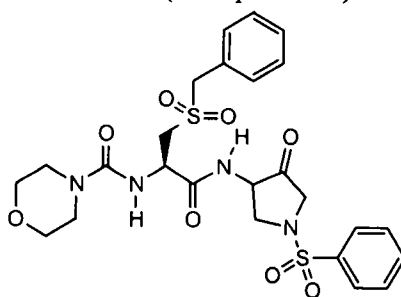
secan con MgSO_4 y se evaporan bajo vacío. El residuo se purifica por cromatografía instantánea sobre sílica gel (eluyente: metanol al 5 % en acetato de etilo:metanol al 20 % en acetato etilo) para producir la [1-(1-benzoil-4-hidroxi-pirrolidin-3-ilcarbamoil)-2-fenilmetan-sulfonil-etil]-amida del ácido morfolin-4-carboxílico (92 mg).

- 5 La [1-(1-benzoil-4-hidroxi-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico (92 mg; 0,169 mmol) se disuelve en DMSO (5 mL). Se agrega trietilamina (0,5 mL) y a continuación complejo SO_3 -piridina (150 mg) y la mezcla se agita a temperatura ambiente durante 3 horas. Después de diluirla con acetato de etilo (100 mL), la solución se lava con agua (50 mL) y solución saturada de
- 10 cloruro de sodio, se seca con MgSO_4 y se evapora bajo vacío. El residuo se purifica por cromatografía instantánea sobre sílica gel (eluyente: metanol al 5 % en acetato de etilo) para producir [1-(1-benzoil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico como una mezcla de diastereoisómeros (sólido amarillento; 38 mg); ^1H NMR: (DMSO) 8,50-8,35 (m, 1H); 7,55-7,34 (m, 10H); 7,16-6,95 (m, 1H); 4,80-4,65 (m, 1H); 4,54-4,22 (m, 3H); 3,98-3,25 (m, 14H); MS: $(\text{M}+\text{H})^+$
- 15 543.

EJEMPLO 2

20 [1-(1-bencensulfonil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico.

(Compuesto 2)



- Se preparó la [1-(1-bencensulfonil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico de acuerdo con el
- 25 procedimiento detallado en el ejemplo 1, sustituyendo el cloruro de bencensulfonilo por cloruro de benzoilo; ^1H NMR: (DMSO) [8,35 (d, $J=7,4\text{Hz}$); 8,28 (d, $J=7,6\text{Hz}$),

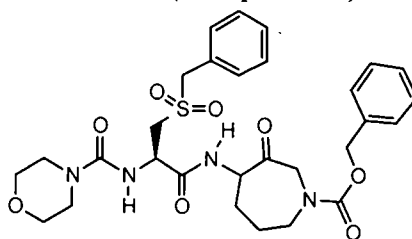
1H]; 7,87-7,62 (m, 5H); 7,41-7,32 (m, 5H); 7,06-6,98 (m, 1H); 4,72-4,60 (m, 1H); 4,45 (s, 2H); 4,42-4,23 (m, 1H); 3,92-3,79 (m, 2H); 3,55-3,20 (m, 11H); 3,06-2,97 (m, 1H). MS: (M+H)⁺ 579.

5

EJEMPLO 3

Éster bencílico del ácido 4-{2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propionilamino}-3-oxo-azepan-1-carboxílico

(Compuesto 3)



10

Se combinan éster bencílico del ácido 4-amino-3-hidroxi-azepan-1-carboxílico crudo (150 mg; 0,57 mmol) preparado como en la referencia 2, ácido 2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propiónico (400 mg; 1,12 mmol), EDC (400 mg; 2,1 mmol), y HOBt (400 mg; 2,5 mmol). Se agrega diclorometano (10 mL) seguido de 4-metilmorfolina (0,5 mL). La mezcla se agita a temperatura ambiente durante 2 horas. Después de diluirla con acetato de etilo (100 mL), la solución se lava con HCl 1 N, solución acuosa saturada de NaHCO₃ y solución saturada de cloruro de sodio, se seca con MgSO₄ y se evapora bajo vacío. El residuo se purifica por cromatografía instantánea (acetato de etilo/metanol 9:1) para producir el éster bencílico del ácido 3-hidroxi-4-{2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propionil-amino}-azepan-1-carboxílico (320 mg).

Se disuelve éster bencílico del ácido 3-hidroxi-4-{2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propionilamino}-azepan-1-carboxílico (100 mg; 0,167 mmol) en DMSO (5 mL). Se agrega trietilamina (0,3 mL) y a continuación complejo SO₃-piridina (150 mg) y la mezcla se agita a temperatura ambiente durante 3 horas. Después de diluirla con acetato de etilo (100 mL), la solución se lava con agua (50 mL) y solución saturada de cloruro de sodio, se seca con MgSO₄ y se evapora bajo vacío. El residuo se purifica por cromatografía instantánea sobre sílica gel (eluyente: metanol al 5

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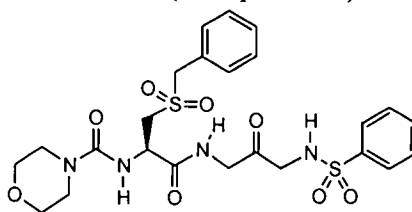
% en acetato de etilo) para producir éster bencílico del ácido 4-{2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propionilamino}-3-oxo-azepan-1-carboxílico (75 mg); ^1H NMR: (DMSO) 8,23-8,08 (m, 1H); 7,40-7,29 (m, 10H); 7,06-6,98 (m, 1H); 5,20-5,09 (m, 2H); 4,79-4,65 (m, 1H); 4,52-4,31 (m, 3H); 4,02-3,80 (m, 2H); 3,62-3,23 (m, 11H);
 5 3,00-2,78 (m, 1H); 1,88-1,55 (m, 4H); MS: (M+H) $^+$ 601.

EJEMPLO 4

[1-(3-bencensulfonilamino-2-oxo-propilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico

10

(Compuesto 4)



Se prepara la sal TFA de la *N*-(3-amino-2-hidroxi-propil)-bencensulfonamida como se indica en Renee L. DesJarlais et al. *J. Am. Chem. Soc.* **1998**, *120*, 9114-9115.

15 Se combinan ácido 2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propiónico (50 mg; 0,14 mmol), sal TFA de *N*-(3-amino-2-hidroxi-propil)-bencensulfonamida (60 mg; 0,17 mmol), EDC (100 mg; 0,52 mmol), y HOBt (100 mg; 0,64 mmol). Se agrega DMF (3 mL) y a continuación 4-metilmorfolina (0,3 mL). La mezcla se agita a temperatura ambiente durante 3 horas. Después de diluirla con acetato
 20 de etilo (100 mL), la solución se lava con HCl 1 N, solución acuosa saturada de NaHCO_3 y solución saturada de cloruro de sodio, se seca con MgSO_4 y se evapora bajo vacío. El residuo se disuelve en acetona (5 mL). Se agrega el reactivo de Jones hasta que persista el color naranja. La mezcla se agita durante 2 horas, se enfría con isopropanol y se diluye con acetato de etilo (100 mL). La solución se lava con agua, solución acuosa saturada de
 25 NaHCO_3 y solución saturada de cloruro de sodio, se seca con MgSO_4 y se evapora bajo vacío. El producto crudo se recrystaliza de acetato de etilo/éter dietílico para dar [1-(3-bencensulfonilamino-2-oxo-propilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico como un sólido blanco (19 mg); ^1H NMR: (DMSO) 8,17 (t, J=5,7

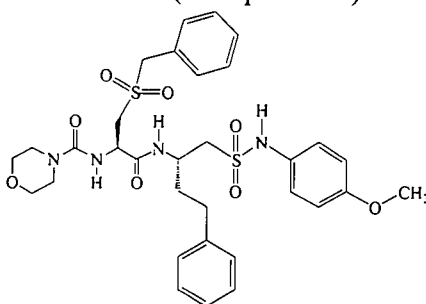
Hz, 1H); 7,93 (t, J=5,9 Hz, 1H); 7,76-7,48 (m, 5H); 7,36-7,29 (m, 5H); 7,05 (d, J=8,1 Hz, 1H); 4,68-4,59 (m, 1H); 4,45 (s, 2H); 3,89 (d, J=5,7 Hz, 2H); 3,79-3,75 (m, 2H); 3,56-3,22 (m, 10H); MS: (M+H)⁺ 567.

5

EJEMPLO 5

N-{1S-[1S-(4-metoxifenilsulfamoilmetil)-3-fenilpropilcarbamoil]-2-bencilsulfoniletil}-morfolin-4-carboxamida

(Compuesto 7)



10

Se trata una mezcla compuesta por ácido 2S-morfolin-4-ilcarbonilamino-3-bencilsulfonil-propiónico (0,194 g; 0,599 mmol), clorhidrato de 2S-amino-N-(4-metoxifenil)-4-fenilbutan-1-sulfonamida (0,222 g; 0,599 mmol), preparada como en la referencia 3, y HATU (0,228 g; 0,599 mmol) en DMF (5 mL) con 4-metilmorfolina (0,198 g; 1,80 mmol). La mezcla se agita a temperatura ambiente durante aproximadamente 12 horas y a continuación se reparte en una mezcla (100 mL total) de acetato de etilo, THF, agua y solución saturada de cloruro de sodio 4:1:2:3, respectivamente. La fase orgánica se separa y se lava con solución acuosa saturada de bicarbonato de sodio (30 mL) y solución saturada de cloruro de sodio (30 mL), se seca (MgSO₄), se filtra y se concentra. El residuo se tritura con éter/acetato de etilo 5:1 (100 mL), se recoge por filtración, se lava con éter (30 mL), hexano (30 mL), y se seca con bomba para obtener N-{1S-[1S-(4-metoxifenilsulfamoilmetil)-3-fenilpropilcarbamoil]-2-bencilsulfoniletil}-morfolin-4-carboxamida. TLC R_f (acetato de etilo): 0,65; ¹H NMR (DMSO): 1,74 (1H, m); 1,92 (1H, m); 2,39-2,61 (2H, m); 3,1-3,35 (2H, 2xdd*); 3,34 (4H, m); 3,42-3,65 (6H, m*); 3,72 (3H, s); 4,24 (1H, m); 4,51 (2H, s); 4,61 (1H, m); 6,88 (2H, d, J=9 Hz); 7,1-7,34 (8H, m); 7,4 (5H, s); 8,12 (1H, d, J=8,7 Hz); MS (M+1): 673.

Procediendo como en el ejemplo 5, se preparan los siguientes compuestos de fórmula I:

- bromhidruro de *N*-{1*S*-[5-amino-1*S*-(4-metoxifenilsulfamoil-metil)pentilcarbamoil]-2-bencilsulfonietil-morfolin-4-carboxamida (compuesto 5); ¹H NMR (DMSO): 1,15-1,73 (6H, m*); 2,71 (2H, m); 3,05-3,25 (2H, 2xdd); 3,37 (4H, m); 3,45-3,6 (6H, m*); 3,72 (3H, s); 4,21 (1H, m); 4,49 (2H, dd); 4,5 (1H, m*); 6,89 (2H, d, J=8,9 Hz); 7,09 (1H, m*); 7,15 (2H, d, J=8,9 Hz); 7,39 (5H, s); 7,73 (3H, br. s); 8,03 (1H, d, J=8,6 Hz); 9,47 (1H, s); MS (M+1): 640, base libre); y 6-(4-metoxifenilsulfamoil)-5*S*-(2*S*-morfolin-4-ilcarbonilamino-3-bencilsulfonil-propionilamino)hexilcarbamato de bencilo (compuesto 6); TLC R_f (acetato de etilo): 0,3; ¹H NMR (DMSO): 1,1-1,65 (6H, m); 2,94 (2H, q, J=6 Hz); 3,05-3,22 (2H, 2xdd); 3,34 (4H, m*); 3,35-3,59 (2H, m*); 3,53 (4H, br s); 3,71 (3H, s); 4,19 (1H, m*); 4,53 (2H, dd, J=15 Hz); 4,57 (1H, m*); 5,00 (2H, s); 6,89 (2H, d, J=8,4 Hz); 7,05 (1H, d, J=8 Hz); 7,15 (2H, d, J=8,4 Hz); 7,24 (1H, t); 7,3-7,45 (10H, 2xs); 7,99 (1H, J=8 Hz); MS (M+): 774.

15

EJEMPLO 6

Ensayo de catepsina S

- Se preparan soluciones de diversas concentraciones de los compuestos de prueba en 10 µL de dimetil sulfóxido (DMSO) y a continuación se diluyen en solución amortiguadora (40 µL, que contiene: MES, 50 mM (pH 6,5); EDTA, 2,5 mM; y NaCl, 100 mM). Se agrega catepsina S humana (0,158 pmoles en 25 µL de solución amortiguadora del ensayo) a las diluciones. Las soluciones del ensayo se mezclan durante 5 a 10 segundos en un agitador para placas, se cubren y se incuban durante 30 minutos a temperatura ambiente. Se agrega Z-Val-Val-Arg-AMC (9 nmoles en 25 µL de solución amortiguadora del ensayo) a las soluciones del ensayo y se sigue la hidrólisis espectrofotométricamente a (λ 460 nm) durante 5 minutos. Se calculan las constantes de inhibición aparente (K_i) a partir de las curvas de progreso de la enzima usando modelos matemáticos estándar.

30

EJEMPLO 7

Ensayo de catepsina B

Se preparan soluciones de diversas concentraciones de los compuestos de prueba en 10 μ L de dimetil sulfóxido (DMSO) y a continuación se diluyen en solución amortiguadora (40 μ L, que contiene: ácido *N,N*-bis(2-hidroxietil)-2-aminoetansulfónico (BES), 50 mM (pH 6); monolaurato de polioxietilensorbitan, 0,05 %; y ditioneitol (DTT), 2,5 mM). Se agrega catepsina B humana (0,025 pmoles en 25 μ L de solución amortiguadora del ensayo) a las diluciones. Las soluciones del ensayo se mezclan durante 5 a 10 segundos en un agitador para placas, se cubren y se incuban durante 30 minutos a temperatura ambiente. Se agrega Z-FR-AMC (20 nmoles en 25 μ L de solución amortiguadora del ensayo) a las soluciones del ensayo y se sigue la hidrólisis espectrofotométricamente a (λ 460 nm) durante 5 minutos. Se calculan las constantes de inhibición aparente (K_i) a partir de las curvas de progreso de la enzima usando modelos matemáticos estándar.

EJEMPLO 8

Ensayo de catepsina K

Se preparan soluciones de diversas concentraciones de los compuestos de prueba en 10 μ L de dimetil sulfóxido (DMSO) y a continuación se diluyen en solución amortiguadora (40 μ L, que contiene: MES, 50 mM (pH 5,5); EDTA, 2,5 mM; y DTT, 2,5 mM). Se agrega catepsina K humana (0,0906 pmoles en 25 μ L de solución amortiguadora del ensayo) a las diluciones. Las soluciones del ensayo se mezclan durante 5 a 10 segundos en un agitador para placas, se cubren y se incuban durante 30 minutos a temperatura ambiente. Se agrega Z-Phe-Arg-AMC (4 nmoles en 25 μ L de solución amortiguadora del ensayo) a las soluciones del ensayo y se sigue la hidrólisis espectrofotométricamente a (λ 460 nm) durante 5 minutos. Se calculan las constantes de inhibición aparente (K_i) a partir de las curvas de progreso de la enzima usando modelos matemáticos estándar.

EJEMPLO 9

Ensayo de catepsina L

Se preparan soluciones de diversas concentraciones de los compuestos de prueba en 10 µL de dimetil sulfóxido (DMSO) y a continuación se diluyen en solución amortiguadora (40 µL, que contiene: MES, 50 mM (pH 5,5); EDTA, 2,5 mM; y DTT, 2,5 mM). Se agrega catepsina L humana (0,05 pmoles en 25 µL de solución amortiguadora del ensayo) a las diluciones. Las soluciones del ensayo se mezclan durante 5 a 10 segundos en un agitador para placas, se cubren y se incuban durante 30 minutos a temperatura ambiente. Se agrega Z-Phe-Arg-AMC (1 nmoles en 25 µL de solución amortiguadora del ensayo) a las soluciones del ensayo y se sigue la hidrólisis espectrofotométricamente a (λ 460 nm) durante 5 minutos. Se calculan las constantes de inhibición aparente (K_i) a partir de las curvas de progreso de la enzima usando modelos matemáticos estándar.

Los compuestos de la invención se prueban de acuerdo con los ensayos descritos previamente para la inhibición de la proteasa y se observa si presentan acción inhibidora selectiva de la catepsina S. Por ejemplo, se encontró que los compuestos de la invención inhiben la actividad de la proteasa catepsina S a concentraciones que son por lo menos 50 veces menores que las concentraciones necesarias para producir una inhibición equivalente de la actividad de la proteasa catepsina K. Las constantes de inhibición aparente (K_i) de la actividad de la catepsina S para los compuestos de la invención, se encuentran en el intervalo entre aproximadamente 10⁻¹⁰ M y 10⁻⁷ M.

EJEMPLO 10

Formulaciones farmacéuticas representativas que contienen un compuesto de fórmula I

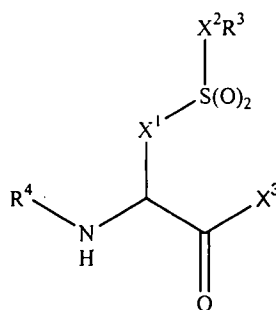
FORMULACIÓN ORAL

Compuesto de fórmula I	10-100 mg
Ácido cítrico monohidratado	105 mg

	Hidróxido de sodio	18 mg
	Saborizante	
	Agua	c.s para 100 mL
5	FORMULACIÓN INTRAVENOSA	
	Compuesto de fórmula I	0,1-10 mg
	Dextrosa monohidratada	c.s. para hacer isotónica
	Ácido cítrico monohidratado	1,05 mg
	Hidróxido de sodio	0,18 mg
10	Agua para inyección	c.s para 1,0 mL
	FORMULACIÓN EN COMPRIMIDOS	
	Compuesto de fórmula I	1 %
	Celulosa microcristalina	73 %
15	Ácido esteárico	25 %
	Sílica coloidal	1 %.

SE REIVINDICA:

1. Un compuesto de fórmula I:



I

en la que:

X^1 y X^2 son ambos metileno o X^1 es etileno y X^2 es un enlace;

- 10 R^3 es $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$ o $-CR^7=NR^8$, en los que R^5 es hidrógeno y R^6 es hidrógeno o un alquilo(C_{1-4}) o R^5 y R^6 junto con los átomos a los que R^5 y R^6 están unidos forman un cicloalqueno(C_{3-12}), un heterocicloalqueno(C_{5-12}), un arilo(C_{6-12}), un heteroarilo(C_{6-12}), un bicicloarilo(C_{9-12}) o un heterobicicloarilo(C_{8-12}) y R^7 y R^8 junto con los átomos a los que R^7 y R^8 están unidos forman un heterocicloalqueno(C_{5-12}), un heteroarilo(C_{6-12}) o un heterobicicloarilo(C_{8-12}), en el que R^3 está opcionalmente sustituido con 1 a 5 radicales elegidos independientemente entre un grupo que consiste en: un alquilo(C_{1-4}), un radical ciano, un halógeno, un alquilo(C_{1-4}) halo-sustituido, un radical nitro, $-X^4NR^9R^9$, $-X^4OR^9$, $-X^4SR^9$, $-X^4C(O)NR^9R^9$, $-X^4C(O)OR^9$, $-X^4S(O)R^{10}$, $-X^4S(O)_2R^{10}$ y $-X^4C(O)R^{10}$, en el que X^4 es un enlace o un alquilo(C_{1-2}), R^9 cada vez que está presente es independientemente hidrógeno, un alquilo(C_{1-3}) o un alquilo(C_{1-3}) halo-sustituido y R^{10} es un alquilo(C_{1-3}) o un alquilo(C_{1-3}) halo-sustituido; y

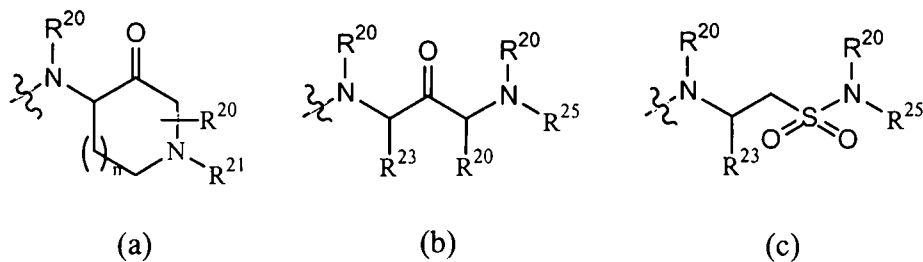
- 25 R^4 es $-C(O)X^5R^{11}$ o $-S(O)_2X^5R^{11}$, en los que X^5 es un enlace, $-O-$ o $-NR^{12}-$, en el que R^{12} es hidrógeno o un alquilo(C_{1-6}), y R^{11} es (i) un alquilo(C_{1-6}) opcionalmente sustituido con $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)R^{13}$, $-NR^{14}C(O)OR^{13}$, $-NR^{14}C(O)NR^{13}R^{14}$ o $-NR^{14}C(NR^{14})NR^{13}R^{14}$, en los que R^{13} es un cicloalquil(C_{3-12})alquilo(C_{0-3}), un heterocicloalquil(C_{5-12})alquilo(C_{0-3}), un aril(C_{6-12})alquilo(C_{0-3}), un

heteroaril(C₅₋₁₂)alquilo(C₀₋₃), un bicicloaril(C₉₋₁₂)alquilo(C₀₋₃) o un heterobicicloaril(C₈₋₁₂)alquilo(C₀₋₃) y R¹⁴ cada vez que está presente es independientemente hidrógeno o un alquilo(C₁₋₆), o (ii) un cicloalquil(C₃₋₁₂)alquilo(C₀₋₃), un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₃), un aril(C₆₋₁₂)alquilo(C₀₋₃), un

5 heteroaril(C₅₋₁₂)alquilo(C₀₋₃), un bicicloaril(C₉₋₁₂)alquilo(C₀₋₃) o un heterobicicloaril(C₈₋₁₂)alquilo(C₀₋₃) o (iii) un cicloalquil(C₃₋₆)alquilo(C₀₋₃), un heterocicloalquil(C₅₋₆)alquilo(C₀₋₃), un fenilalquilo(C₀₋₃) o un heteroaril(C₅₋₆)alquilo(C₀₋₃) sustituido con -X⁶OR¹⁵, -X⁶SR¹⁵, -X⁶S(O)R¹⁵, -X⁶S(O)₂R¹⁵, -X⁶C(O)R¹⁵, -X⁶C(O)OR¹⁵, -X⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)R¹⁵, -X⁶NR¹⁶C(O)OR¹⁵, 10 -X⁶NR¹⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)OR¹⁶, -X⁶NR¹⁶C(NR¹⁶)NR¹⁵R¹⁶, en los que X⁶ es un enlace o metileno, R¹⁵ es un cicloalquil(C₃₋₆)alquilo(C₀₋₃), un heterocicloalquil(C₅₋₆)alquilo(C₀₋₃), un fenilalquilo(C₀₋₃) o un heteroaril(C₅₋₆)alquilo(C₀₋₃) y R¹⁶ es hidrógeno o un alquilo(C₁₋₆); en los que R⁴ contiene además opcionalmente 1 a 5 sustituyentes que cuando están presentes dentro de un anillo alicíclico o aromático son

15 radicales elegidos independientemente entre un grupo que consiste en: un alquilo(C₁₋₆), un alquilideno(C₁₋₆), un radical ciano, un halógeno, un radical nitro, un alquilo(C₁₋₃) halo-sustituido, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷, -X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR¹⁸)OR¹⁷, -X⁶OP(O)(OR¹⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸, 20 -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ y -X⁶C(O)R¹⁸ y que cuando están presentes dentro de una porción alifática son radicales elegidos independientemente entre un grupo que consiste en: un radical ciano, un halógeno, un radical nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷, -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷, -OP(O)(OR¹⁷)OR¹⁷, 25 -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ y -C(O)R¹⁸, en los que X⁶ es un enlace o un alquileno(C₁₋₆), R¹⁷ cada vez que está presente es independientemente hidrógeno, un alquilo(C₁₋₆) o un alquilo(C₁₋₃) halo-sustituido y R¹⁸ es un alquilo(C₁₋₆) o un alquilo(C₁₋₃) halo-sustituido;

X³ es un grupo de fórmula (a), (b) o (c):



n es 0, 1 ó 2;

- 5 R^{20} se elige entre un grupo que consiste en: hidrógeno, un alquilo(C₁₋₆), un cicloalquil(C₃₋₁₂)alquilo(C₀₋₆), un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₆), un aril(C₆₋₁₂)alquilo(C₀₋₆) y un heteroaril(C₅₋₁₂)alquilo(C₀₋₆);

- R^{21} se elige entre el grupo que consiste en: hidrógeno, un alquilo(C₁₋₉), un cicloalquil(C₃₋₁₂)alquilo(C₀₋₆), un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₆), un aril(C₆₋₁₂)alquilo(C₀₋₆), un heteroaril(C₅₋₁₂)alquilo(C₀₋₆), un bicicloaril(C₉₋₁₂)alquilo(C₀₋₃), un heterobicicloaril(C₈₋₁₂)alquilo(C₀₋₃), -C(O)R²⁶, -C(S)R²⁶, -S(O)₂R²⁶, -C(O)OR²⁶, -C(O)N(R²⁶)R²⁷, -C(S)N(R²⁶)R²⁷ y -S(O)₂N(R²⁷)R²⁶;

- R^{23} se elige entre un alquilo(C₁₋₆), un alquenilo(C₄₋₆), un cicloalquil(C₃₋₁₂)alquilo(C₀₋₆), un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₆), un aril(C₆₋₁₂)alquilo(C₀₋₆) o un heteroaril(C₅₋₁₂)alquilo(C₀₋₆) opcionalmente sustituido con un grupo amino, -NHC(O)R¹⁵ o -R¹⁵ en los que R¹⁵ es como se definió antes;

- R^{25} se elige entre hidrógeno, un alquilo(C₁₋₆), un cicloalquil(C₃₋₁₂)alquilo(C₀₋₆), un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₆), un aril(C₆₋₁₂)alquilo(C₀₋₆), un heteroaril(C₅₋₁₃)alquilo(C₀₋₆), -X⁴NHR¹⁵, -X⁴S(O)₂R²⁶ o -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷ en los que R¹⁵, R¹⁷ y X⁴ son como se los definió antes;

- R^{26} se elige entre un grupo que consiste en: hidrógeno, un alquilo(C₁₋₆), un cicloalquil(C₃₋₁₂)alquilo(C₀₋₆), un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₆), un aril(C₆₋₁₂)alquilo(C₀₋₆), un heteroaril(C₅₋₁₂)alquilo(C₀₋₆), un bicicloaril(C₉₋₁₂)alquilo(C₀₋₃) o un heterobicicloaril(C₈₋₁₂)alquilo(C₀₋₃);

- 25 R^{27} es hidrógeno, un alquilo(C₁₋₆), un cicloalquil(C₃₋₁₂)alquilo(C₀₋₆), un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₆), un aril(C₆₋₁₂)alquilo(C₀₋₆) o un heteroaril(C₅₋₁₂)alquilo(C₀₋₆);

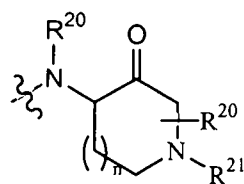
en el que X^3 contiene además opcionalmente 1 a 5 sustituyentes que cuando están presentes en un anillo alicíclico o aromático son radicales elegidos independientemente entre un grupo que consiste en: un alquilo(C_{1-6}), un alquilideno(C_{1-6}), un radical ciano, un halógeno, un radical nitro, un alquilo(C_{1-3}) halo-sustituido, $-X^6NR^{17}R^{17}$,
 5 $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$, $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$,
 $-X^6C(O)R^{17}$, $-X^6OR^{15}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$, $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$,
 $-X^6P(O)(OR^8)OR^{17}$, $-X^6OP(O)(OR^8)OR^{17}$, $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$,
 $-X^6S(O)_2R^{18}$ y $-X^6C(O)R^{18}$ y cuando están presentes dentro de una porción alifática son radicales elegidos independientemente entre un grupo que consiste en: un radical ciano,
 10 un halógeno, un radical nitro, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$,
 $-NR^{17}C(NR^{17})NR^{17}R^{17}$, $-OR^{17}$, $-SR^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$,
 $-P(O)(OR^{17})OR^{17}$, $-OP(O)(OR^{17})OR^{17}$, $-NR^{17}C(O)R^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$ y
 $-C(O)R^{18}$, en los que R^{15} , R^{17} , R^{18} y X^6 son como se los definió antes; y los derivados *N*-óxido, derivados profármaco, derivados protegidos, cada uno de los isómeros y mezclas
 15 de isómeros de éstos; y las sales y solvatos aceptables desde el punto de vista farmacéutico de dichos compuestos y los derivados *N*-óxido, derivados profármaco, derivados protegidos, cada uno de los isómeros y mezclas de isómeros de éstos.

2. El compuesto de la reivindicación 1 en el que X^1 y X^2 son ambos metileno o X^1
 20 es etileno y X^2 es un enlace; R^3 es $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$ o $-CR^7=NR^8$, en los que R^5
 es hidrógeno y R^6 es hidrógeno o un alquilo(C_{1-4}) o R^5 y R^6 junto con los átomos a los
 que R^5 y R^6 están unidos forman un cicloalqueno(C_{3-12}), un arilo(C_{6-12}), un
 heteroarilo(C_{6-12}) o un bicicloarilo(C_{9-12}) y R^7 y R^8 junto con los átomos a los que R^7 y R^8
 están unidos forman un heterocicloalqueno(C_{5-12}) o un heteroarilo(C_{6-12}), en los que R^3
 25 está opcionalmente sustituido con 1 a 5 radicales que se eligen independientemente entre
 un grupo que consiste en: un alquilo(C_{1-4}), un radical ciano, un halógeno, un alquilo(C_{1-4})
 halo-sustituido, $-X^4OR^9$ y $-X^4C(O)OR^9$, en los que X^4 es un enlace o un alquileno(C_{1-2}),
 R^9 cada vez que está presente es independientemente un alquilo(C_{1-3}) o un alquilo(C_{1-3})
 halo-sustituido; y los derivados *N*-óxido, derivados profármaco, derivados protegidos,
 30 cada uno de los isómeros y mezclas de isómeros de éstos; y las sales y solvatos

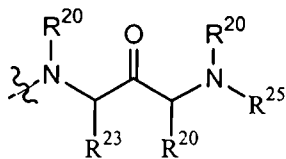
aceptables desde el punto de vista farmacéutico de dichos compuestos y los derivados *N*-óxido, derivados profármaco, derivados protegidos, cada uno de los isómeros y mezclas de isómeros de éstos.

- 5 3. El compuesto de la reivindicación 2 en el que R^4 es $-C(O)X^5R^{11}$ o $-S(O)_2X^5R^{11}$, en los que X^5 es un enlace, $-O-$ o $-NR^{12}-$, en el que R^{12} es hidrógeno o un alquilo(C_{1-6}), y R^{11} es (i) un alquilo(C_{1-6}) o (ii) un heterocicloalquil(C_{5-12})alquilo(C_{0-3}), un aril(C_{6-12})alquilo(C_{0-3}), un heteroaril(C_{5-12})alquilo(C_{0-3}), un bicicloaril(C_{9-12})alquilo(C_{0-3}) o un heterobicicloaril(C_{8-12})alquilo(C_{0-3}) o (iii) un heterocicloalquil(C_{5-6})alquilo(C_{0-3}) o un fenilalquilo(C_{0-3}) sustituido con $-X^6OR^{15}$, $-X^6C(O)R^{15}$ o $-X^6NR^{16}C(O)OR^{16}$, en los que X^6 es un enlace o metileno, R^{15} es un fenilalquilo(C_{0-3}) o un heteroaril(C_{5-6})alquilo(C_{0-3}) y R^{16} es hidrógeno o un alquilo(C_{1-6}); en el que R^4 contiene además opcionalmente 1 a 5 sustituyentes que cuando están presentes dentro de un anillo alicíclico o aromático son radicales que se eligen independientemente entre el grupo que
- 10 consiste en: un alquilo(C_{1-6}), un halógeno, $-X^6NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6C(O)OR^{17}$, $-X^6NC(O)R^{16}$ y $-X^6C(O)R^{18}$, R^{17} cada vez que está presente es independientemente hidrógeno, un alquilo(C_{1-6}) o un alquilo(C_{1-3}) halo-sustituido y R^{18} es un alquilo(C_{1-6}) o un alquilo(C_{1-3}) halo-sustituido; y los derivados *N*-óxido, derivados profármaco, derivados protegidos, cada uno de los isómeros y mezclas de isómeros de éstos; y las
- 15 sales y solvatos aceptables desde el punto de vista farmacéutico de dichos compuestos y los derivados *N*-óxido, derivados profármaco, derivados protegidos, cada uno de los isómeros y mezclas de isómeros de éstos.
- 20

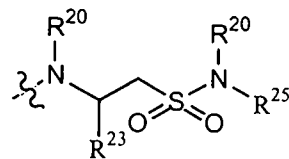
4. El compuesto de la reivindicación 3 en el que X^3 es un grupo con la fórmula (a),
- 25 (b) o (c):



(a)



(b)



(c)

n es 0, 1 ó 2;

R^{20} se elige entre el grupo consistente en hidrógeno y un alquilo(C_{1-6});

R^{21} se selecciona entre el grupo que consiste en: un alquilo(C_{1-9}), un aril(C_{6-12})alquilo(C_{0-6}), $-C(O)R^{26}$, $-S(O)_2R^{26}$, $-C(O)OR^{26}$ y $-C(O)N(R^{26})R^{27}$;

5 R^{23} se elige entre un alquilo(C_{1-6}) opcionalmente sustituido con un grupo amino, $-NHC(O)R^{15}$ o $-R^{15}$ en el que R^{15} es como se definió antes;

R^{25} se elige entre un alquilo(C_{1-6}), un aril(C_{6-12})alquilo(C_{0-6}), $-X^4S(O)_2R^{26}$ o $-X^4C(O)R^{17}NR^{17}C(O)R^{17}$ en los que R^{17} y X^4 son como se definieron antes y R^{26} es como se define a continuación;

10 R^{26} se elige entre un grupo que consiste en: un alquilo(C_{1-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un aril(C_{6-12})alquilo(C_{0-6}), un heteroaril(C_{5-12})alquilo(C_{0-6}) y un bicicloaril(C_{9-12})alquilo(C_{0-3});

R^{27} es un alquilo(C_{1-6});

en el que X^3 contiene además opcionalmente 1 a 5 sustituyentes que cuando están
15 presentes dentro de un anillo alicíclico o aromático son radicales que se eligen independientemente entre el grupo que consiste en: un alquilo(C_{1-6}), un radical ciano, un halógeno, $-X^6OR^{17}$, $-X^6C(O)R^{17}$ y $-X^6OR^{15}$; y los derivados *N*-óxido, derivados profármaco, derivados protegidos, cada uno de los isómeros y mezclas de isómeros de éstos; y las sales y solvatos aceptables desde el punto de vista farmacéutico de dichos
20 compuestos y los derivados *N*-óxido, derivados profármaco, derivados protegidos, cada uno de los isómeros y mezclas de isómeros de éstos.

5. El compuesto de la reivindicación 4 en el que R^3 se elige entre el grupo que consiste en: fenilo, piridin-2-ilo, piridin-3-ilo, piridin-4-ilo, vinilo, 2-
25 difluorometoxifenilo, 1-oxi-piridin-2-ilo, 4-metoxifenilo, 4-metilfenilo, 2-metilfenilo, 4-clorofenilo, 3,5-dimetilfenilo, 4-trifluorometilfenilo, 4-trifluorometoxifenilo, 2-bromofenilo, naftalen-2-ilo, 3,4-diclorofenilo, 3-metilfenilo, 3-trifluorometilfenilo, 3-trifluorometoxifenilo, 2,3,4,5,6-pentafluorofenilo, 2-fluorofenilo, 2-clorofenilo, 2-cianofenilo, 2-trifluorometilfenilo, 4-*terc*-butilfenilo, 3-clorofenilo, 4-bromofenilo, 2-
30 fluoro-3-cloro-fenilo, 2-fluoro-3-metilfenilo, 3-fluorofenilo, 2,5-difluorofenilo, 3-

bromofenilo, 2,5-diclorofenilo, 2,6-difluorofenilo, 3-cianofenilo, 4-cianofenilo, 2-trifluorometoxifenilo, 2,3-difluorofenilo, bifenilo, 2-bromo-5-fluorofenilo, 4-fluorofenilo, 3,4-difluorofenilo, 2,4-difluorofenilo, 2,4,6-trifluorofenilo, 2,4,5-trifluorofenilo, 2,3,4-trifluorofenilo, 2-cloro-5-trifluorometilfenilo, 2,4-bis-
 5 trifluorometilfenilo, 2,5,6-trifluorofenilo, 2-fluoro-3-trifluorometilfenilo, 2-fluoro-4-trifluorometilfenilo, 2-fluoro-5-trifluorometilfenilo, 2,3,5-trifluorofenilo, 2-fluoro-5-trifluorometilfenilo, 5-fluoro-2-trifluorometilfenilo, 4-fluoro-3-trifluorometilfenilo, 2-metoxifenilo, 3,5-bis-trifluorometilfenilo, 4-difluorometoxifenilo, 3-difluorometoxifenilo, 2,6-diclorofenilo, 4-carboxifenilo, ciclohexilo, ciclopropilo,
 10 isopropilo, tiofen-2-ilo, 5-cloro-tiofen-2-ilo y 3,5-dimetil-isoxazol-4-ilo.

6. El compuesto de la reivindicación 5 en el que R⁴ es benzoilo, morfolin-4-carbonilo, acetilo, furan-3-carbonilo, 2-metoxibenzoilo, 3-metoxibenzoilo, naftalen-2-carbonilo, benzo[1,3]dioxol-5-carbonilo, 3-piridin-3-il-acriloilo, benzofuran-2-carbonilo,
 15 furan-2-carbonilo, *terc*-butoxicarbonilo, bifenil-4-carbonilo, quinolin-2-carbonilo, quinolin-3-carbonilo, 3-acetilbenzoilo, 4-fenoxibenzoilo, 3-hidroxibenzoilo, 4-hidroxibenzoilo, piridin-3-carbonilo, 3-(*terc*-butoxicarbonilamino-metil)-benzoilo, éster *terc*-butílico del ácido 4-carbonil-piperazin-1-carboxílico, éster etílico del ácido 4-carbonil-piperazin-1-carboxílico, 4-(furan-2-carbonil)-piperazin-1-carbonilo, piridin-4-
 20 carbonilo, 1-oxi-piridin-4-carbonilo, 1-oxi-piridin-3-carbonilo, tiofen-2-carbonilo, tiofen-3-carbonilo, 4-benzoilbenzoilo, 5-metil-tiofen-2-carbonilo, 3-cloro-tiofen-2-carbonilo, 3-bromo-tiofen-2-carbonilo, 4-clorobenzoilo, 3-fluoro-4-metoxi-benzoilo, 4-metoxibenzoilo, 4-trifluorometoxibenzoilo, 3,4-difluorobenzoilo, 4-fluorobenzoilo, 3,4-dimetoxibenzoilo, 3-metilbenzoilo, 4-bromobenzoilo, 4-trifluorometilbenzoilo, 3-benzoilbenzoilo, ciclopentancarbonilo, benzo[b]tiofen-2-carbonilo, 3-cloro-benzo[b]tiofen-2-carbonilo, bencensulfonilo, naftalen-2-sulfonilo, 5-metil-tiofen-2-sulfonilo, tiofen-2-sulfonilo, formamil-metil éster, 4-metil-pentanoilo, formamil-isobutil éster, formamil-monoalil éster, formamil-isopropil éster, *N,N*-dimetil-formamilo, *N*-isopropil-formamilo, *N*-piridin-4-il-formamilo, *N*-piridin-3-il-formamilo, 3-fenil-acriloilo, 1H-indol-5-carbonilo, piridin-2-carbonilo, pirazin-2-carbonilo, 3-hidroxi-
 30

piridin-2-carbonilo, 2-amino-piridin-3-carbonilo, 2-hidroxi-piridin-3-carbonilo, 6-amino-piridin-3-carbonilo, 6-hidroxi-piridin-3-carbonilo, piridazin-4-carbonilo, 3-fenoxi-benzoilo y 1-oxo-1,3-dihidro-isoindol-2-carbonilo.

- 5 7. El compuesto de reivindicación 6 en el que X^3 se elige entre el grupo que consiste en: éster bencílico del ácido 4-amino-3-oxo-azepan-1-carboxílico, éster isobutílico del ácido 4-amino-3-oxo-azepan-1-carboxílico, 4-amino-1-benzoil-azepan-3-ona, 4-amino-1-bencensulfonil-azepan-3-ona, 4-amino-1-(piridin-2-sulfonil)-azepan-3-ona, 4-amino-1-(1-oxi-piridin-2-sulfonil)-azepan-3-ona, 4-amino-1-(3,4-dicloro-bencensulfonil)-azepan-3-ona, 4-amino-1-(2-fluoro-bencensulfonil)-azepan-3-ona, 4-amino-1-(3,4-dimetoxi-bencenesulfonil)-azepan-3-ona, 4-amino-1-(2-ciano-bencensulfonil)-azepan-3-ona, 4-amino-1-(naftalen-1-sulfonil)-azepan-3-ona, 4-amino-1-(tiofen-2-sulfonil)-azepan-3-ona, 4-amino-1-(tiazol-2-sulfonil)-azepan-3-ona, 4-amino-1-(pirrolidin-1-sulfonil)-azepan-3-ona, 4-amino-1-metansulfonil-azepan-3-ona, 4-amino-1-(pirrolidin-1-carbonil)-azepan-3-ona, dimetilamida del ácido 4-amino-3-oxo-azepan-1-carboxílico, bencilamida del ácido 4-amino-3-oxo-azepan-1-carboxílico, 4-amino-1-bencil-azepan-3-ona, 4-amino-1-bencil-piperidin-3-ona, 4-amino-1-benzoil-piperidin-3-ona, 4-amino-1-benzoil-pirrolidin-3-ona, 4-amino-1-bencil-pirrolidin-3-ona, 4-amino-1-bencensulfonil-pirrolidin-3-ona, 4-amino-1-(5-metil-hexil)-pirrolidin-3-ona, 1-etil-2-oxo-3-(toluen-4-sulfonilamino)-butilamino, 1-etil-2-oxo-3-(4-fenoxi-bencensulfonilamino)-propilamino, 1-etil-2-oxo-3-[4-(piridin-3-iloxi)-bencensulfonilamino]-propilamino, 3-(dibenzofuran-2-sulfonilamino)-1-etil-2-oxo-butilamino, 1-etil-3-[4-metil-2-(4-metil-pentanoilamino)-pentanoilamino]-2-oxo-propilamino, 5-amino-1-[(4-metoxi-fenilsulfamoil)-metil]-pentilamino, 5-benciloxicarbonilamino-1-[(4-metoxi-fenilsulfamoil)-metil]-pentilamino, 1-[(4-metoxi-fenilsulfamoil)-metil]-3-fenil-propilamino, 1-{[4-(1-hidroxi-etil)-fenilsulfamoil]-metil}-3-fenil-propilamino, 1-[(4-acetil-fenilsulfamoil)-metil]-3-fenil-propilamino, 1-[(4-hidroxi-fenilsulfamoil)-metil]-3-fenil-propilamino y 3-fenil-1-[(2-fenilamino-etilsulfamoil)-metil]-propilamino.

- 30 8. El compuesto de la reivindicación 7 que se elige entre el grupo que consiste en

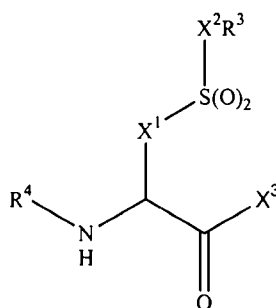
(1-{5-amino-1-[(4-metoxi-fenisulfamoil)-metil]-pentilcarbamoil}-2-fenilmetansulfonil-etil)-amida del ácido morfolin-4-carboxílico, éster bencílico del ácido (6-(4-metoxi-fenilsulfamoil)-5-{2-[(morfolin-4-carbonil)-amino]-3-fenilmetan-sulfonil-propionilamino}-hexil)-carbámico, (1-{1-[(4-metoxi-fenilsulfamoil)-metil]-3-fenil-propilcarbamoil}-2-fenilmetansulfonil-etil)-amida del ácido morfolin-4-carboxílico, [1-(3-bencensulfonilamino-2-oxo-propilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico, [1-(1-benzoil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico, [1-(1-bencensulfonil-4-oxo-pirrolidin-3-ilcarbamoil)-2-fenilmetansulfonil-etil]-amida del ácido morfolin-4-carboxílico y éster bencílico del ácido 4-{2-[(morfolin-4-carbonil)-amino]-3-fenilmetansulfonil-propionilamino}-3-oxo-azepan-1-carboxílico.

9. Una preparación farmacéutica que contiene una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1 en combinación con un excipiente aceptable desde el punto de vista farmacéutico.

10. Un método para tratar una enfermedad en un animal en el que la inhibición de la catepsina S puede evitar, inhibir o mejorar la patología y/o la sintomatología de dicha enfermedad, método que comprende la administración al animal de una cantidad terapéuticamente eficaz del compuesto de la reivindicación 1 o un derivado *N*-óxido o cada uno de los isómeros o mezclas de isómeros de éstos; o una sal o solvato aceptables desde el punto de vista farmacéutico de dichos compuestos y los derivados *N*-óxido, derivados profármaco, derivados protegidos, cada uno de los isómeros y mezclas de isómeros de éstos.

11. El uso de un compuesto de la reivindicación 1 en la elaboración de un medicamento para tratar una enfermedad en un animal en el que la actividad de la catepsina S contribuye a la patología y/o sintomatología de la enfermedad.

12. Un proceso para preparar un compuesto de fórmula I:



I

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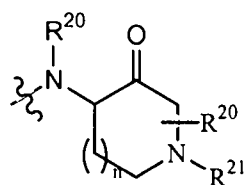
en la que:

X^1 y X^2 son ambos metileno o X^1 es etileno y X^2 es un enlace;

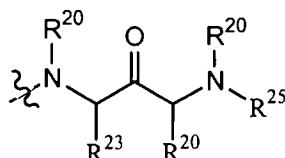
R^3 es $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$ o $-CR^7=NR^8$, en los que R^5 es hidrógeno y R^6 es hidrógeno o un alquilo(C_{1-4}) o R^5 y R^6 junto con los átomos a los que R^5 y R^6 están
 10 unidos forman un cicloalqueno(C_{3-12}), un heterocicloalqueno(C_{5-12}), un arilo(C_{6-12}), un heteroarilo(C_{6-12}), un bicicloarilo(C_{9-12}) o un heterobicicloarilo(C_{8-12}) y R^7 y R^8 junto con los átomos a los que R^7 y R^8 están unidos forman un heterocicloalqueno(C_{5-12}), un heteroarilo(C_{6-12}) o un heterobicicloarilo(C_{8-12}), en el que R^3 está opcionalmente sustituido con 1 a 5 radicales elegidos independientemente entre un grupo que consiste
 15 en: un alquilo(C_{1-4}), un radical ciano, un halógeno, un alquilo(C_{1-4}) halo-sustituido, un radical nitro, $-X^4NR^9R^9$, $-X^4OR^9$, $-X^4SR^9$, $-X^4C(O)NR^9R^9$, $-X^4C(O)OR^9$, $-X^4S(O)R^{10}$, $-X^4S(O)_2R^{10}$ y $-X^4C(O)R^{10}$, en el que X^4 es un enlace o un alquileno(C_{1-2}), R^9 cada vez que está presente es independientemente hidrógeno, un alquilo(C_{1-3}) o un alquilo(C_{1-3}) halo-sustituido y R^{10} es un alquilo(C_{1-3}) o un alquilo(C_{1-3}) halo-sustituido; y
 20 R^4 es $-C(O)X^5R^{11}$ o $-S(O)_2X^5R^{11}$, en los que X^5 es un enlace, $-O-$ o $-NR^{12}-$, en el que R^{12} es hidrógeno o un alquilo(C_{1-6}), y R^{11} es (i) un alquilo(C_{1-6}) opcionalmente sustituido con $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)R^{13}$, $-NR^{14}C(O)OR^{13}$, $-NR^{14}C(O)NR^{13}R^{14}$ o $-NR^{14}C(NR^{14})NR^{13}R^{14}$, en los que R^{13} es un cicloalquil(C_{3-12})alquilo(C_{0-3}), un
 25 heterocicloalquil(C_{5-12})alquilo(C_{0-3}), un aril(C_{6-12})alquilo(C_{0-3}), un heteroaril(C_{5-12})alquilo(C_{0-3}), un bicicloaril(C_{9-12})alquilo(C_{0-3}) o un heterobicicloaril(C_{8-12})alquilo(C_{0-3}) y R^{14} cada vez que está presente es

independientemente hidrógeno o un alquilo(C₁₋₆), o (ii) un cicloalquil(C₃₋₁₂)alquilo(C₀₋₃), un heterocicloalquil(C₅₋₁₂)alquilo(C₀₋₃), un aril(C₆₋₁₂)alquilo(C₀₋₃), un heteroaril(C₅₋₁₂)alquilo(C₀₋₃), un bicicloaril(C₉₋₁₂)alquilo(C₀₋₃) o un heterobicicloaril(C₈₋₁₂)alquilo(C₀₋₃) o (iii) un cicloalquil(C₃₋₆)alquilo(C₀₋₃), un heterocicloalquil(C₅₋₆)alquilo(C₀₋₃), un fenilalquilo(C₀₋₃) o un heteroaril(C₅₋₆)alquilo(C₀₋₃) sustituido con -X⁶OR¹⁵, -X⁶SR¹⁵, -X⁶S(O)R¹⁵, -X⁶S(O)₂R¹⁵, -X⁶C(O)R¹⁵, -X⁶C(O)OR¹⁵, -X⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)R¹⁵, -X⁶NR¹⁶C(O)OR¹⁵, -X⁶NR¹⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)OR¹⁶, -X⁶NR¹⁶C(NR¹⁶)NR¹⁵R¹⁶, en los que X⁶ es un enlace o metileno, R¹⁵ es un cicloalquil(C₃₋₆)alquilo(C₀₋₃), un heterocicloalquil(C₅₋₆)alquilo(C₀₋₃), un fenilalquilo(C₀₋₃) o un heteroaril(C₅₋₆)alquilo(C₀₋₃) y R¹⁶ es hidrógeno o un alquilo(C₁₋₆); en los que R⁴ contiene además opcionalmente 1 a 5 sustituyentes que cuando están presentes dentro de un anillo alicíclico o aromático son radicales elegidos independientemente entre un grupo que consiste en: un alquilo(C₁₋₆), un alquilideno(C₁₋₆), un radical ciano, un halógeno, un radical nitro, un alquilo(C₁₋₃) halo-sustituido, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷, -X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR¹⁸)OR¹⁷, -X⁶OP(O)(OR¹⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ y -X⁶C(O)R¹⁸ y que cuando están presentes dentro de una porción alifática son radicales elegidos independientemente entre un grupo que consiste en: un radical ciano, un halógeno, un radical nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷, -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷, -OP(O)(OR¹⁷)OR¹⁷, -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ y -C(O)R¹⁸, en los que X⁶ es un enlace o un alquileno(C₁₋₆), R¹⁷ cada vez que está presente es independientemente hidrógeno, un alquilo(C₁₋₆) o un alquilo(C₁₋₃) halo-sustituido y R¹⁸ es un alquilo(C₁₋₆) o un alquilo(C₁₋₃) halo-sustituido;

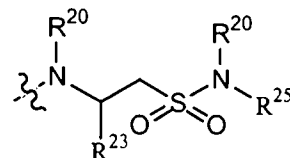
X³ es un grupo de fórmula (a), (b) o (c):



(a)



(b)



(c)

n es 0, 1 ó 2;

R^{20} se elige entre un grupo que consiste en: hidrógeno, un alquilo(C_{1-6}), un
5 cicloalquil(C_{3-12})alquilo(C_{0-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un
aril(C_{6-12})alquilo(C_{0-6}) y un heteroaril(C_{5-12})alquilo(C_{0-6});

R^{21} se elige entre el grupo que consiste en: hidrógeno, un alquilo(C_{1-9}), un
cicloalquil(C_{3-12})alquilo(C_{0-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un
aril(C_{6-12})alquilo(C_{0-6}), un heteroaril(C_{5-12})alquilo(C_{0-6}), un bicicloaril(C_{9-12})alquilo(C_{0-3}),
10 un heterobicicloaril(C_{8-12})alquilo(C_{0-3}), $-C(O)R^{26}$, $-C(S)R^{26}$, $-S(O)_2R^{26}$, $-C(O)OR^{26}$,
 $-C(O)N(R^{26})R^{27}$, $-C(S)N(R^{26})R^{27}$ y $-S(O)_2N(R^{27})R^{26}$;

R^{23} se elige entre un alquilo(C_{1-6}), un alquenilo(C_{4-6}), un
cicloalquil(C_{3-12})alquilo(C_{0-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un
aril(C_{6-12})alquilo(C_{0-6}) o un heteroaril(C_{5-12})alquilo(C_{0-6}) opcionalmente sustituido con un
15 grupo amino, $-NHC(O)R^{15}$ o $-R^{15}$ en los que R^{15} es como se definió antes;

R^{25} se elige entre hidrógeno, un alquilo(C_{1-6}), un cicloalquil(C_{3-12})alquilo(C_{0-6}),
un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un aril(C_{6-12})alquilo(C_{0-6}), un heteroaril
(C_{5-13})alquilo(C_{0-6}), $-X^4NHR^{15}$, $-X^4S(O)_2R^{26}$ o $-X^4C(O)R^{17}NR^{17}C(O)R^{17}$ en los que R^{15} ,
 R^{17} y X^4 son como se los definió antes;

20 R^{26} se elige entre un grupo que consiste en: hidrógeno, un alquilo(C_{1-6}), un
cicloalquil(C_{3-12})alquilo(C_{0-6}), un heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un
aril(C_{6-12})alquilo(C_{0-6}), un heteroaril(C_{5-12})alquilo(C_{0-6}), un bicicloaril(C_{9-12})alquilo(C_{0-3})
y un heterobicicloaril(C_{8-12})alquilo(C_{0-3});

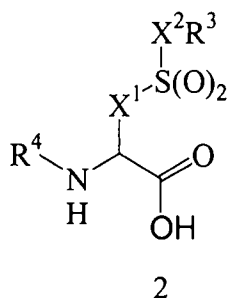
R^{27} es hidrógeno, un alquilo(C_{1-6}), un cicloalquil(C_{3-12})alquilo(C_{0-6}), un
25 heterocicloalquil(C_{5-12})alquilo(C_{0-6}), un aril(C_{6-12})alquilo(C_{0-6}) o un
heteroaril(C_{5-12})alquilo(C_{0-6});

en el que X^3 contiene además opcionalmente 1 a 5 sustituyentes que cuando están

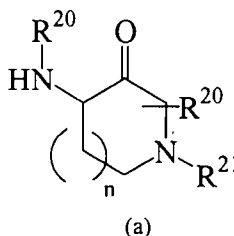
presentes en un anillo alicíclico o aromático son radicales elegidos independientemente entre un grupo que consiste en: un alquilo(C₁₋₆), un alquilideno(C₁₋₆), un radical ciano, un halógeno, un radical nitro, un alquilo(C₁₋₃) halo-sustituido, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷,
 5 -X⁶C(O)R¹⁷, -X⁶OR¹⁵, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷, -X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR⁸)OR¹⁷, -X⁶OP(O)(OR⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ y -X⁶C(O)R¹⁸ y cuando están presentes dentro de una porción alifática son radicales elegidos independientemente entre un grupo que consiste en un radical ciano, un halógeno, un radical nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷,
 10 -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷, -OP(O)(OR¹⁷)OR¹⁷, -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ y -C(O)R¹⁸, en los que R¹⁵, R¹⁷, R¹⁸ y X⁶ son como se los definió antes; comprendiendo dicho proceso:

(A) hacer reaccionar un compuesto de fórmula 2:

15

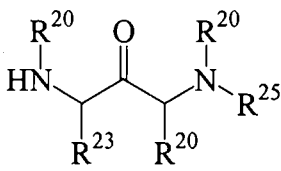


con un compuesto de fórmula (a):



20 en los que X¹, X², R³, R⁴, R²⁰ y R²¹ son como se los define en el resumen de la invención para la fórmula I; o

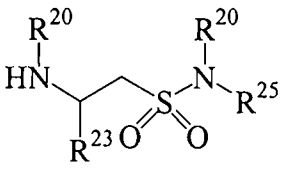
(B) hacer reaccionar un compuesto de fórmula 2 con un compuesto de fórmula (b):



(b)

en los que R²⁰, R²³ y R²⁵ son como se los define en el resumen de la invención para la fórmula I; o

- 5 (C) hacer reaccionar un compuesto de fórmula 2 con un compuesto de fórmula (c):



(c)

en los que R²⁰, R²³ y R²⁵ son como se los define en el resumen de la invención para la fórmula I; y

10

- (D) transformar opcionalmente un compuesto de fórmula I en una sal aceptable desde el punto de vista farmacéutico;
- (E) transformar opcionalmente un compuesto de fórmula I en forma de sal en un compuesto en una forma que no sea una sal;
- 15 (F) transformar opcionalmente una forma no oxidada de un compuesto de fórmula I en un *N*-óxido aceptable desde el punto de vista farmacéutico;
- (G) transformar opcionalmente una forma *N*-óxido de un compuesto de fórmula I en su forma no oxidada;
- (H) separar opcionalmente un isómero individual de un compuesto de fórmula I de
- 20 una mezcla de isómeros;
- (I) transformar opcionalmente un compuesto de fórmula I sin derivar en un derivado profármaco aceptable desde el punto de vista farmacéutico; y
- (J) transformar opcionalmente un derivado profármaco de un compuesto de fórmula I en su forma sin derivar;

25

RESUMEN DE LA DIVULGACIÓN DE INFORMACIÓN

La invención actual se refiere a nuevos inhibidores selectivos de la catepsina S,
5 las sales y *N*-óxidos de éstos aceptables desde el punto de vista farmacéutico, sus usos
como fármacos y sus métodos de elaboración.

PCT REQUEST

US20010143WO

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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	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.06.2002)
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	US20010143WO
I	Title of invention	NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS
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, NJ 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
II-10	e-mail	george.wang@aventis.com
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant only
III-1-2	Applicant for	all designated States except US
III-1-4	Name	CELERA, AN APPLERA CORPORATION BUSINESS
III-1-5	Address:	180 Kimball Way South San Francisco, CA 94080 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

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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)	GRAUPE, Michael
III-2-5	Address:	1131 Banyan Way Pacifica, CA 94044 United States of America
III-2-6	State of nationality	AT
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)	PALMER, James, T.
III-3-5	Address:	131 Koch Road Corte Madera, CA 94925 United States of America
III-3-6	State of nationality	US
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)	ALDOUS, David, J.
III-4-5	Address:	31 Dunbridge Lane Gillette, NJ 07933 United States of America
III-4-6	State of nationality	US
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	THURAIRATNAM, Sukanthini
III-5-5	Address:	6 Smoke Rise Lane Bedminster, NJ 07921 United States of America
III-5-6	State of nationality	GB
III-5-7	State of residence	US

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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)	WANG, George, G.
IV-1-2	Address:	AVENTIS PHARMACEUTICALS INC. P. O. Box 6800 Route 202-206 Bridgewater, NJ 08807-0800 United States of America
IV-1-3	Telephone No.	(908) 231-2843
IV-1-4	Facsimile No.	(908) 231-2626
IV-1-5	e-mail	george.wang@aventis.com
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	BARNEY, Charlotte, L.; COPPOLA, William, C.; DAHLING, Gerald, V.; DARKES, Paul, R.; DOLAN, Peter, L.; GUPTA, Balaram; KIRK, Joseph, P., Jr.; KNIGHT, Julie, Anne; KRUPEN, Karen, I.; KURYS, Barbara, E.; LIN, Jiang; MARTIN, Lawrence, L.; MOON, Carolyn, D.; NELLIGAN, Mark, C.; NEWMAN, Irving; OEHLER, Ross, J.; ORT, Ronald, G.; PARKER, Raymond, S., III; STRUPCZEWSKI, Joseph; WILLE, Louis, J.
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT

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V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	14 September 2001 (14.09.2001)
VI-1-2	Number	60/322,318
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	-
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	-

VIII-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.
VIII-4-1 -1	Prior applications:	60/322,318, US, 14 September 2001 (14.09.2001)

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		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:	GRAUPE, Michael
VIII-4-1 -1-2	Residence: (city and either US State, if applicable, or country)	San Mateo, California
VIII-4-1 -1-3	Mailing address:	2027 Edison Street Apartment 219 San Mateo, CA 94044 United States of America
VIII-4-1 -1-4	Citizenship:	AT
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) - printed on 16.09.2002 02:48:36 PM

VIII-4-1 -2-1	Name:	PALMER, James, T.
VIII-4-1 -2-2	Residence: (city and either US State, if applicable, or country)	Corte Madera, California
VIII-4-1 -2-3	Mailing address:	131 Koch Road Corte Madera, CA 94925 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:	ALDOUS, David, J.
VIII-4-1 -3-2	Residence: (city and either US State, if applicable, or country)	Gillette, New Jersey
VIII-4-1 -3-3	Mailing address:	31 Dunbridge Lane Gillette, NJ 07933 United States of America
VIII-4-1 -3-4	Citizenship:	US
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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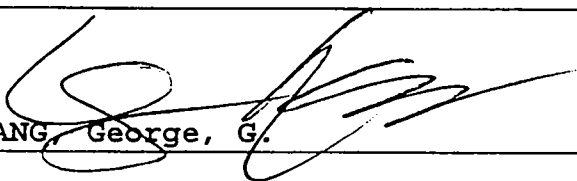
Original (for SUBMISSION) - printed on 16.09.2002 02:48:36 PM

VIII-4-1 -4-1	Name:	THURAIRATNAM, Sukanthini
VIII-4-1 -4-2	Residence: (city and either US State, if applicable, or country)	Bedminster, New Jersey
VIII-4-1 -4-3	Mailing address:	6 Smoke Rise Lane Bedminster, NJ 07921 United States of America
VIII-4-1 -4-4	Citizenship:	GB
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)	

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	9	-
IX-2	Description	73	-
IX-3	Claims	23	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	106	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
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)	WANG, George, G.	

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	
------	--	--

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Wang, George G.
AVENTIS PHARMACEUTICALS INC.
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

file

NO ACTION

DATE

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))

USA 2001/0143-WO

Date of mailing
(day/month/year) 25-04-2003

Applicant's or agent's file reference <i>US 20010143WO</i>		IMPORTANT NOTIFICATION
<i>US 20010143WO</i>		
International application No. PCT/US 02/ 29323	International filing date (day/month/year) 16/09/2002	Priority date (day/month/year) 14/09/2001
Applicant AVENTIS PHARMACEUTICALS INC.		

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:

10/04/2003

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, the election(s) made in the demand does (do) 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)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (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/ European Patent Office D-80298 Munich Tel. (+ 49-89) 2399-0, Tx: 523656 epmu d Fax: (+ 49-89) 2399-4465	Authorized officer CHURCHER G Tel. (+ 49-89) 2399-2545
--	---



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference US20010143W0	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US 02/ 29323	International filing date (<i>day/month/year</i>) 16/09/2002	Priority date (<i>day/month/year</i>) 14/09/2001
International Patent Classification (IPC) or national classification and IPC C07C317/48		
Applicant AVENTIS PHARMACEUTICALS INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u> 2 </u> sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consists of a total of <u> </u> sheets. 3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application
--

Date of submission of the demand 10/04/2003	Date of completion of this report 22/04/2003
Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer VERHULST W Tel. (+49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No PCT/ US 02/ 29323

I. Basis of the report

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

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

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

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

TRATADO DE COOPERACIÓN DE PATENTES
PCT
REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 PCT y Regla 70)

Referencia de archivo del solicitante o agente
US20010143WO

PARA ACCIÓN ADICIONAL Ver Notificación de Transmisión del Reporte de Examen Preliminar Internacional (Forma PCT/IPEA/416)

Solicitud internacional No. PCT/FR 02/29323

Fecha de presentación internacional (día/mes/año) 16/09/2002

Fecha de prioridad (día/mes/año) 14/09/2002

Clasificación Internacional de Patentes (IPC) o tanto clasificación nacional como IPC
C07C317/48

Solicitante
AVENTIS PHARMACEUTICALS INC.

1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad Internacional de Examen Preliminar y es transmitida al solicitante de acuerdo con el Artículo 36.
2. Este REPORTE consiste de un total de 2 hojas, incluyendo esta hoja de cubierta

Este reporte también está acompañado por ANEXOS, es decir, hojas de la descripción, reivindicaciones y/o dibujos que ha sido corregidos y son la base para este reporte y/o hojas que contienen rectificaciones hechas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT).

Estos anexos consisten de un total de hojas.

3. Este reporte contiene indicaciones relacionadas con los siguientes ítems:

I	X	Base de la opinión
II		Prioridad
III	X	No establecimiento de opinión con respecto a novedad, paso inventivo y aplicabilidad industrial
IV		Falta de unidad de invención
V	X	Declaración motivada bajo la Regla 66.2(a)(ii) con respecto a novedad, paso inventivo o aplicabilidad industrial: citas y explicaciones que sustentan cada declaración
VI		Algunos documentos citados
VII		Algunos defectos en la solicitud internacional
VIII		Algunas observaciones sobre la solicitud internacional

Fecha de presentación de la solicitud 10/04/2003

Fecha de completado el reporte 22/04/2003

Nombre y dirección de envío del IPEA

Oficina Europea de Patentes

D-80298 Munich

Tel.: (+49-89) 2399-0, Tx: 523656 epmu d

Fax: (+49-89) 2399-4465

Funcionario autorizado

VERHULST W

Tel.: (+49-89) 2399 2828

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No. PCT/US 02/ 29323

I. Base del reporte

El presente reporte de examen preliminar internacional se basa en la solicitud tal como fue presentada inicialmente.

III. No establecimiento de opinión con respecto a novedad, altura inventiva y aplicabilidad industrial

La pregunta de si la invención reivindicada parece ser novedosa, involucra una altura inventiva, o es aplicable industrialmente no han sido sujeto del examen preliminar internacional con respecto a las reivindicaciones las cuales no han sido sometidas a búsqueda (Artículo 17(2)(a) o (3) y Regla 66.1(e) PCT); ver también reporte de búsqueda internacional).

V. Declaración motivada de acuerdo con la Regla 66.2(a)(ii) con respecto a novedad, paso inventivo o aplicabilidad industrial.

En la extensión en que se ha llevado a cabo el examen preliminar (ver ítem III arriba), se puntualiza lo siguiente:

A la luz de los documentos citados en el reporte de búsqueda internacional, se considera que la invención tal como se define en las reivindicaciones independientes, la cual ha sido el sujeto de un reporte de búsqueda internacional, cumple con los criterios enunciados en el artículo 33(1) PCT, es decir parece que es nueva, implica una actividad inventiva y es aplicable industrialmente.

Formulario PCT/409PE2 (EPO-03-2002) P20761

G. WANG
COMPUTER ENTERED
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PCT

PCT COOPERATION TREATY

PCT/US02/29323

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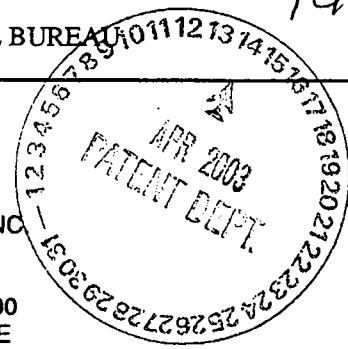
From the INTERNATIONAL BUREAU

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

WANG, George, G.
Aventis Pharmaceuticals INC
P. O. Box 6800
Route 202-206
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE



Date of mailing(day/month/year) 27 March 2003 (27.03.03)		
Applicant's or agent's file reference US20010143WO		
IMPORTANT NOTICE		
International application No. PCT/US02/29323	International filing date(day/month/year) 16 September 2002 (16.09.02)	Priority date(day/month/year) 14 September 2001 (14.09.01)
Applicant AVENTIS PHARMACEUTICALS INC., et al		

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

KP, KR, US

In accordance with Rule 47.1(c), third sentence, 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).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 27 March 2003 (27.03.03) under No. 03/024924

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

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, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 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>.

For filing a **demand for international preliminary examination**, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

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

Judith Zahra

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

PATENT COOPERATION TREATY

PCT

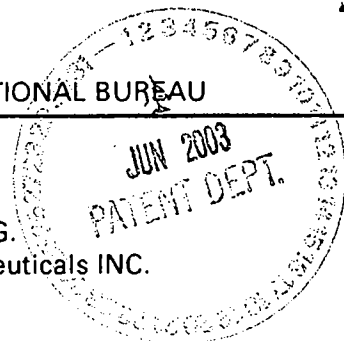
INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

WANG, George, G.
Aventis Pharmaceuticals INC.
P. O. Box 6800
Route 202-206
Bridgewater, NJ 08807-0800
United States of America



Date of mailing (day/month/year) 12 May 2003 (12.05.03)		
Applicant's or agent's file reference US20010143WO		IMPORTANT INFORMATION
International application No. PCT/US02/29323	International filing date (day/month/year) 16 September 2002 (16.09.02)	Priority date (day/month/year) 14 September 2001 (14.09.01)
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,IE,IT,LU,MC,NL,PT,SE,SK,TR
National : AU,BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK,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 : GH,GM,KE,LS,MW,MZ,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,AZ,BA,BB,BR,BY,BZ,CH,CO,CR,CU,CZ,DK,DM,DZ,EC,EE,
ES,FI,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,
MK,MW,MX,MZ,NZ,OM,PH,PT,SD,SE,SG,SI,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,VC,VN,
YU,ZA,ZM,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

NO ACTION DUE file in USA 2001/0143-WO

DUE DATE 6/3/03

DKTD BY G. WANG

ATTY

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: SUAREZ Javier
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338 9999

PATENT COOPERATION TREATY

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PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

WANG, George, G.
Aventis Pharmaceuticals INC.
P. O. Box 6800
Route 202-206
Bridgewater, NJ 08807-0800
United States of America

DEC 2002
Patent Dept.

Date of mailing (day/month/year) 21 November 2002 (21.11.02)	
Applicant's or agent's file reference US20010143WO	IMPORTANT NOTIFICATION
International application No. PCT/US02/29323 ✓	International filing date (day/month/year) 16 September 2002 (16.09.02) ✓
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 14 September 2001 (14.09.01) ✓
Applicant AVENTIS PHARMACEUTICALS INC. et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- 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). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) 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.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) 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.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
14 Sept 2001 (14.09.01)	60/322,318	US	30 Sept 2002 (30.09.02) ✓

p

ACTION DUE

file

DUE DATE

yes 12/9/02

G. WANG

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

Facsimile No. (41-22) 740.14.35

Authorized officer

PETRESKA Gorica

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

150

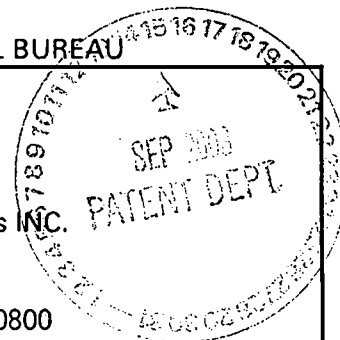
PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WANG, George, G.
Aventis Pharmaceuticals INC.
P. O. Box 6800
Route 202-206
Bridgewater, NJ 08807-0800
United States of America



Date of mailing (day/month/year) 02 September 2003 (02.09.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference US20010143WO	
International application No. PCT/US02/29323	International filing date (day/month/year) 16 September 2002 (16.09.02)

1. The following indications appeared on record concerning:		
☒ the applicant	☐ the inventor	☐ the agent
☐ the common representative		
Name and Address CELERA, AN APPLERA CORPORATION BUSINESS 180 Kimball Way South San Francisco, CA 94080 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. 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 AXYS PHARMACEUTICALS, INC. 180 Kimball Way South San Francisco, CA 94080 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary:		
ACTION DUE <u>file</u> DATE <u>9/15/03</u> DKTD BY <u>JES</u> BY <u>11/1/03</u>		
4. A copy of this notification has been sent to:		
☒ the receiving Office	☐ the designated Offices concerned	
☐ the International Searching Authority	☒ the elected Offices concerned	
☒ the International Preliminary Examining Authority	☒ other: CELERA	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Junko TAKEUCHI (Fax: 338 71 30) Telephone No. (41-22) 338 8446
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State of California

SECRETARY OF STATE

APOSTILLE

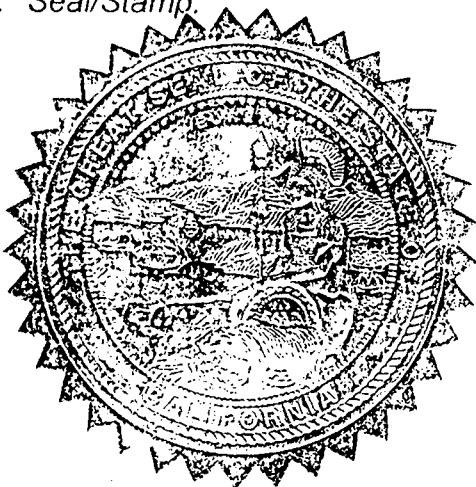
(Convention de La Haye du 5 octobre 1961)

1. Country: United States of America
This public document
2. has been signed by MADELEINE BRULEY
3. acting in the capacity of DEPUTY CLERK, County of SAN MATEO, State of California
4. bears the seal/stamp of the County of SAN MATEO, State of California

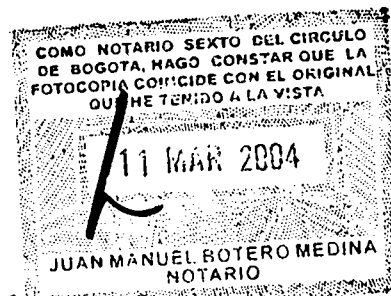


CERTIFIED

5. At San Francisco, California
6. The 20TH day of JANUARY, 2004
7. by Deputy Secretary of State, State of California
8. No. 59957
9. Seal/Stamp:



10. Signature



Kevin Shelley
KEVIN SHELLEY
Secretary of State

BY

Deputy

STATE OF CALIFORNIA
COUNTY OF SAN MATEO SS

I, WARREN SLOCUM, Assessor-County Clerk-Recorder, County of San Mateo, State of California, having by law a seal,

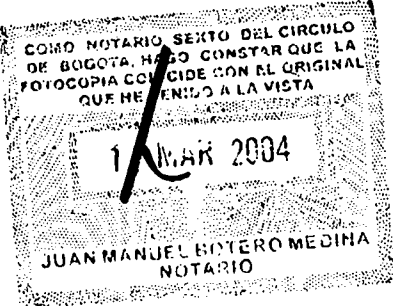
Do HEREBY CERTIFY, That MAURA LEE
whose name is subscribed to the Certificate of the proof or acknowledgment of the annexed instrument and thereon written, was at the time of taking such proof or acknowledgment, a Notary Public in and for said County, residing therein, duly commissioned and sworn, and duly authorized by the laws of said state to administer oaths, take acknowledgments and proofs of deeds or conveyances for land, tenements or hereditaments in said State, to be recorded therein. And further that I am well acquainted with the handwriting of such Notary Public, and verily believe that the signature to said Certificate of proof or acknowledgment is genuine, and that said instrument is executed and acknowledged according to the laws of said State. I further certify that an impression of the seals of Notaries Public is not required by law to be filed in my office.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the seal of the

Assessor-County Clerk-Recorder, this 20 day of January, 20 04
Year

WARREN Slocum
WARREN SLOCUM, Assessor-County Clerk-Recorder

By Madeleine Bruley
Deputy Clerk for the County of San Mateo
Madeleine Bruley



CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California }
County of San Mateo } ss.

On January 13, 2004, before me, Maura Lee
Date Name and Title of Officer (e.g., "Jane Doe, Notary Public")
personally appeared Wayne W. Montgomery
Name(s) of Signer(s)

☒ personally known to me
☐ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.



WITNESS my hand and official seal.
Maura Lee
Signature of Notary Public

Place Notary Seal Above

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

Description of Attached Document

Title or Type of Document: Power of Attorney (Columbia)

Document Date: January 13, 2004 Number of Pages: 1

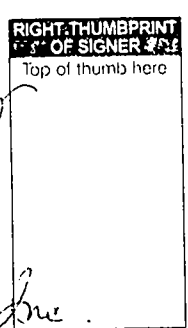
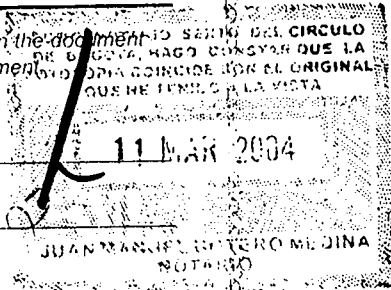
Signer(s) Other Than Named Above: No Other Signers

Capacity(ies) Claimed by Signer

Signer's Name: Wayne W. Montgomery

- ☐ Individual
- ☒ Corporate Officer — Title(s): Assistant Secretary
- ☐ Partner — ☐ Limited ☐ General
- ☐ Attorney in Fact
- ☐ Trustee
- ☐ Guardian or Conservator
- ☐ Other:

Signer Is Representing: Celera Genomics Cxys Pharm, Inc.



G. HOLLMANN RESTREPO
ABOGADOS LTDA

The undersigned, acting on behalf of and representing of, AXYS PHARMACEUTICALS, INC., domiciled in,

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, desisting, transacting, compromising, substituting and revoking substitutions, taking notifications, and appointing judicial or extra-judicial attorneys.

Signed in on this 13 day of Jan. of 2004
So. San Francisco

Wayne W. Montgomery

Wayne W. Montgomery
Assistant Secretary

G. HOLLMANN RESTREPO
ABOGADOS LTDA

Yo (nosotros), obrando en nombre propio y representación de, AXYS PHARMACEUTICALS, INC., con domicilio en,

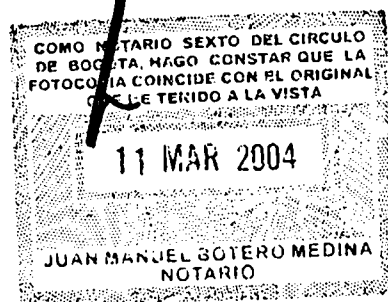
nombro(amos) a **GUSTAVO HOLLMANN RESTREPO** y/o **LUIS PATIÑO LEYVA**, con domicilio en Bogotá D.C., República de Colombia, Cra 11ª No 94-76, Oficina 308, apoderado verdadero y legal, con poder especial, amplio y suficiente:

1) Para recabar 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 traspasos, 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 prescritos 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 creyeran 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



REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial () ()
- Datos de identificación del solicitante o de la persona que presenta la solicitud. () ()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. () ()
- Comprobante de pago de las tasas establecidas () ()

COMPLETA () INCOMPLETA ()

ESQUEMA DE TRAZADO ()

- Indicación de que solicita el registro de un Esquema de trazado. () ()
- Datos de identificación del solicitante o de la persona que presenta La solicitud. () ()
- Representación gráfica del esquema de trazado () ()
- Comprobante de pago de las tasas establecidas. () ()

COMPLETA () INCOMPLETA ()

Firma Responsable:



SUPERINDUSTRIA Y COMERCIO

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Folios: 154

Fecha:

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