



Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

04-43885

54. TÍTULO "Nuevos Compuestos y composiciones como Inhibidores
de Cathepsina S"

51. CLASIFICACIÓN INTERNACIONAL **COD 271b6; AGIK 31/4152;
AGIK 31/424 S**

71. SOLICITANTE **Aventis Pharmaceuticals Inc y Axys pharmaceutical Inc**

DOMICILIO **New Jersey, Estados Unidos y South San Francisco
CA 94080 Estados Unidos**

74. APODERADO **Gustavo Hernan Restrepo**

22. BOGOTÁ, D. C., **12 de Mayo de 2004**

PETITORIO


Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA Y COMERCIO
Radicación: 04043805 00000000 Folios: 252
Fecha (MD): 2004-05-12 16:11:24
Trámite: 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT

ENTRADA EN FASE NACIONAL

14-06-2004

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 USA y 180 Kimball
Way, South San Francisco, CA 94080 USA.
Nacionalidad o Domicilio: New Jersey, Estados
Unidos y South San
Lugar de Constitución: Francisco, CA 94080 USA
Estados Unidos
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 2878023 TP 5903

④ INVENTOR (ES) (72)

Nombre: LI, Jiayao
Dirección: 442 Milton Avenue, Apartment 3,
Nacionalidad o Domicilio San Bruno, CA 94066 Estados Unidos

⑤ PCT (86)

Solicitud Internacional No. PCT/US02/36396

Fecha Noviembre 14 de 2002

Publicación Internacional No. WO 03/042197 A1

Fecha Mayo 22 de 2003

⑥ Título (54)

"NUEVOS COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE
CATEPSINA S".

⑦ Clasificación Internacional (51)

C07D 271/06; A61K 31/4152; A61K 31/4245

⑧ Prioridad

SI ☒ NO ☐

(33) País de Origen

Estados Unidos

(32) Fecha

Noviembre 14, 2001

(31) Número de Solicitud

60/332,605

⑨ Comprobante de pago No. 04 - 36,221

Fecha Mayo 6 de 2004

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

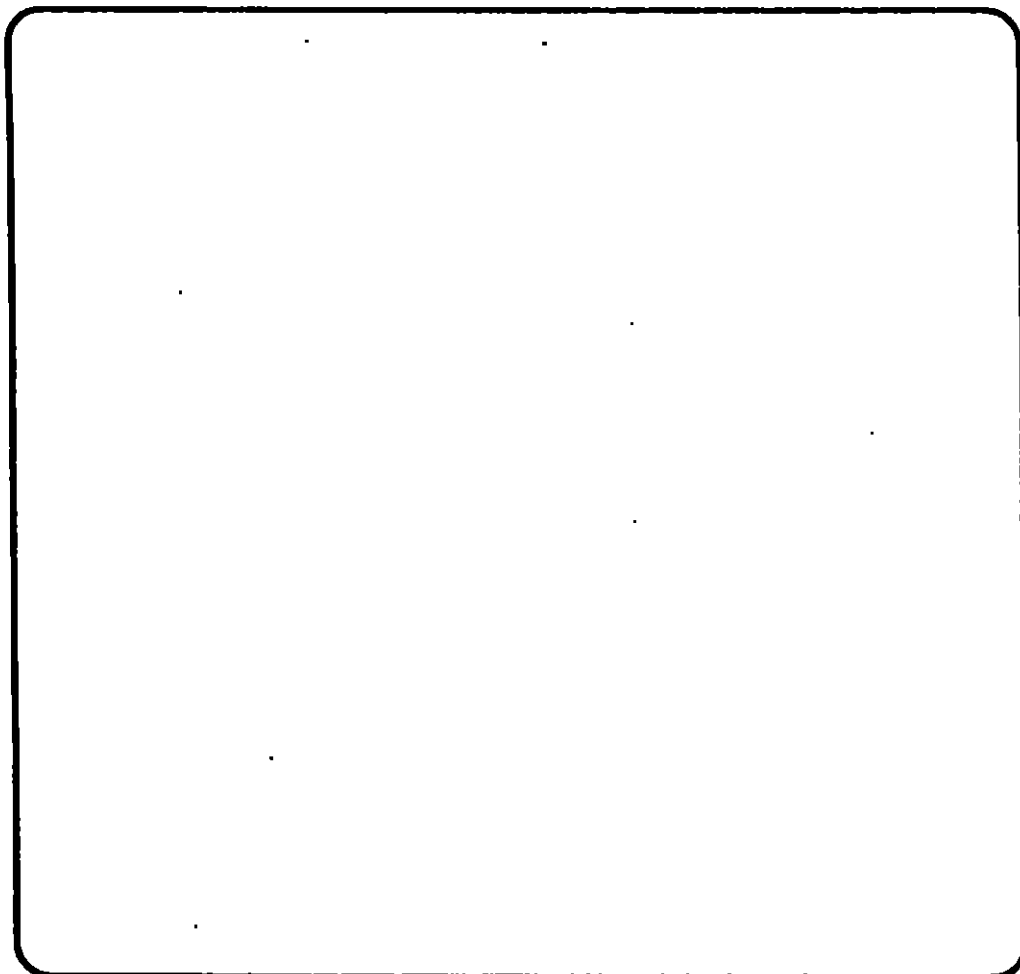
53-614

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:

C.C. 2.878.023 B/CS. T.P. 5903

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

**Continuación enumeración del nombre de los Inventores, con
Su correspondiente dirección, código postal y domicilio:**

<u>Nombre</u>	<u>Dirección</u>	<u>Domicilio</u>
ALDOUS, David J.	268 Gates Avenue,	Gillette, NJ 07933 Estados Unidos
THURAIRATNAM, Sukanthini,	6 Smoke Rise Lane,	Belminster, NJ 07921, Estados Unidos

Otros anexos que se acompañan a la solicitud.

Copia de la solicitud internacional.

Notificación concerniente a la transmisión del documento de prioridad (Forma PCT/IB/304).

Opinión escrita (Forma PCT/IPEA/408).

Respuesta a la opinión escrita de acuerdo con el artículo 34 (2) (d) PCT.

Segunda opinión escrita de acuerdo con el artículo 34 (2) (d) PCT.

Respuesta a la segunda opinión escrita.

Radicación : 04043085 00000000 Folios: 252
Fecha (AMD): 2004-05-12 16:11:24
Trámite : 011 PCT-PATENTE 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 36,221
FECHA : MAYO 6 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	030-00110-6	4991234	06/05/2004	7,005,000.00

***** 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.: 55614

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

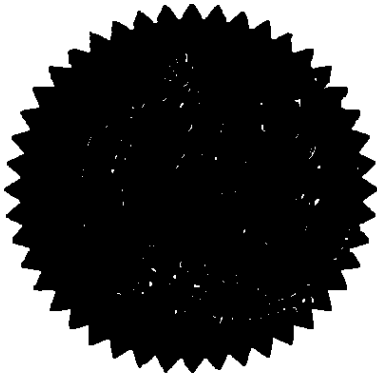
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

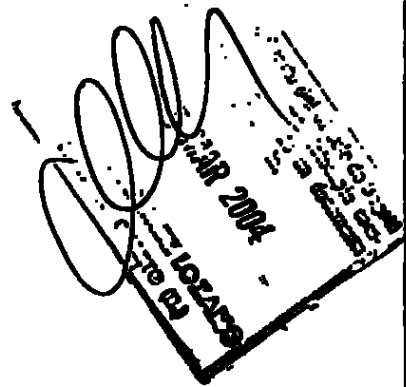
1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
R. PETER WIDIN
3. ACTING IN THE CAPACITY OF:
COUNTY CLERK
4. BEARS THE SEAL/STAMP OF:
COUNTY OF SOMERSET

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:

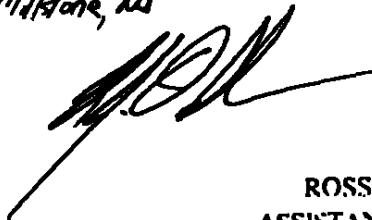
1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, utility models, industrial designs and models, commercial engravings and names, trademarks, slogans, health licenses, copyrights and domain 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 engravings 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 April 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 11^a 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 creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las facultades necesarias, y por este documento desde ahora declaro(amos) válido y bueno todo cuanto los apoderados hicieren en mi (nuestro) beneficio.

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

Firmado en el

de
FEB 25 2002
- 5 MAR 2004
C. O. J. ALA 3

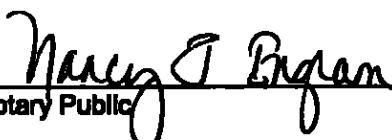
NOTARIAL CERTIFICATE (Corporation)

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

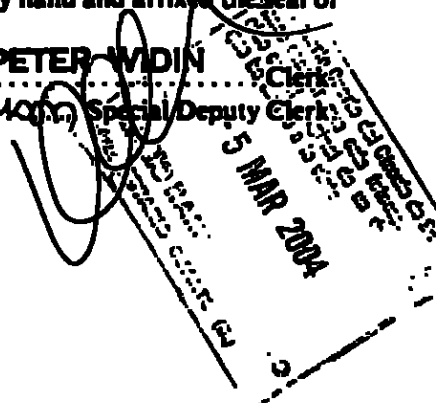
in and for said State, duly appointed, qualified, commissioned and sworn and authorized by law to take affidavits, acknowledgements or proofs of deeds or conveyances for lands, tenements or hereditaments and other instruments in writing in said State of New Jersey. And I further Certify, that I am well 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

by *Deborah L. Anderson* 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 Registrada, certifico, que Nathaniel Ingram, cuyo nombre aparece suscrito al certificado de reconocimiento, prueba o declaración del instrumento adjunto, era en el momento de tomar tal reconocimiento, prueba o declaración Notaria Pública en y para el Estado de New Jersey, debidamente nombrada, calificada, comisionada y juramentada y autorizada por la ley para tomar declaraciones, reconocimientos o pruebas de escrituras o traspasos de tierras, tenencias o herencias y otros instrumentos escritos en el mencionado Estado. Y certifico además que conozco bien la firma de dicha funcionaria y estoy convencido de que la firma que aparece en el mencionado certificado de reconocimiento, prueba o declaración es genuina.

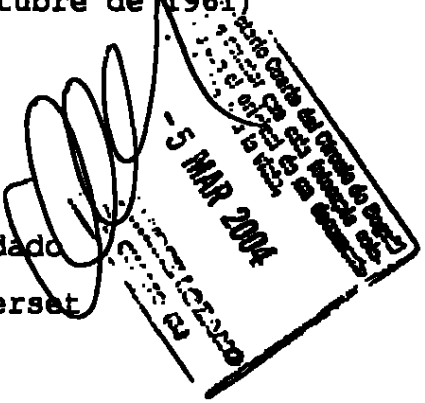
En testimonio de lo cual coloco mi firma y el sello del Condado el día de hoy 5 de Abril del 2002.

R. Peter Widin, Secretario
Deborah L. Anderson, Secretaria Especial Suplente
(Firma y Sello Oficial)

APOSTILLA

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

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



Confirmado

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

M. Méndez S.
JOS. MENDOZA
SECRETARIO DE ESTADO

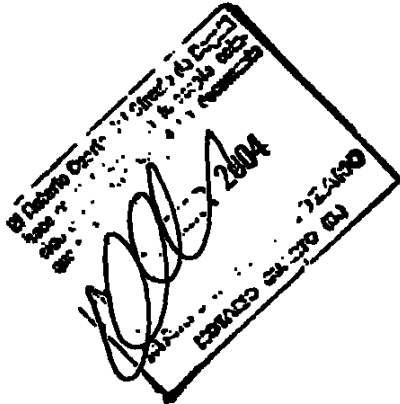
MINISTERIO DE RELACIONES
EXTERIORES

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

OFICINA DE
RESPONSABILIDAD DEL TEXTO

2002 APR 22 P 12 19

JEFE DE DELEGACIONES
SANTAFE DE BOGOTA S.C.



TRADUCCION OFICIAL DEL INGLES de las certificaciones y la Apostilla adjuntas al poder que la compañía AVENTIS PHARMACEUTICALS 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 compareció personalmente Ross J. Oehler, Secretario Suplente, quien yo sé o quien comprobó ante mí que es la persona mencionada en el adjunto poder y quien lo ejecutó, y él reconoció haber ejecutado dicho instrumento como un acto libre y voluntario 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 Estado de Delaware, Estados Unidos de América.

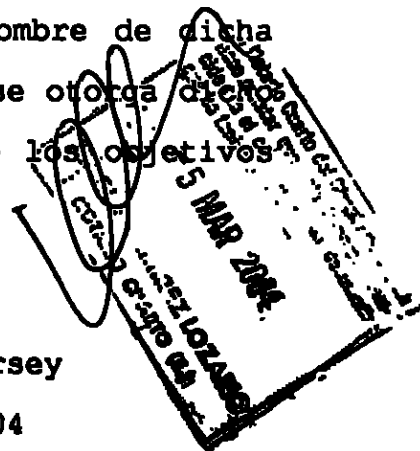
Certifico además que dicha autoridad, fechada el 29 de Noviembre del 2000, se basa en una resolución de la Junta de Directores de la mencionada sociedad, documento que yo he tenido a la vista, nombrando a la mencionada persona apoderado con todo poder para firmar el instrumento adjunto en nombre de dicha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





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*

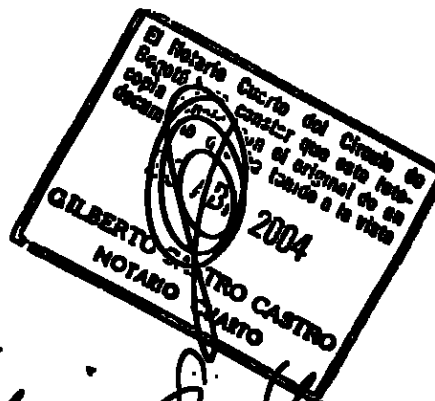


CERTIFIED

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 *[Signature]*
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,

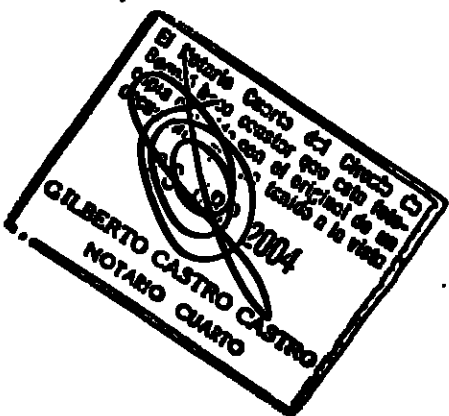
Do HEREBY CERTIFY, That MAURA LEE
whose name is subscribed to the Certificate of the proof or acknowledgment of the annexed instrument and thereon written, was at the time of taking such proof or acknowledgment, a Notary Public in and for said County, residing therein, duly commissioned and sworn, and 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



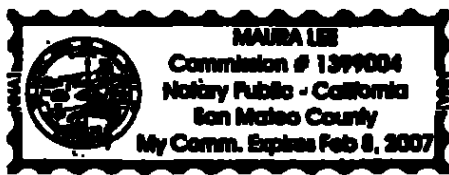
ALIF RNIA ALL-PURPOSE A KN WLEDGMENT

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: 2

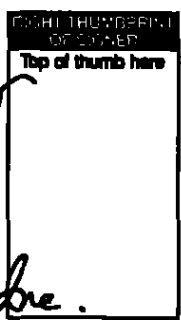
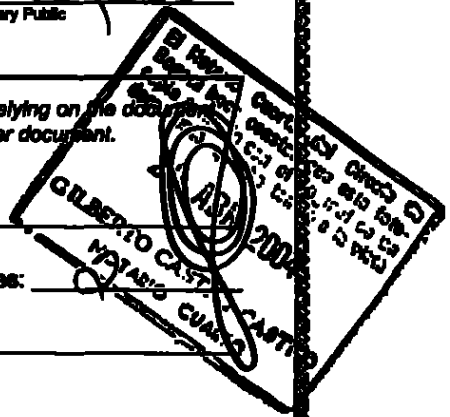
Signer(s) Other Than Named Above: No Other Signers

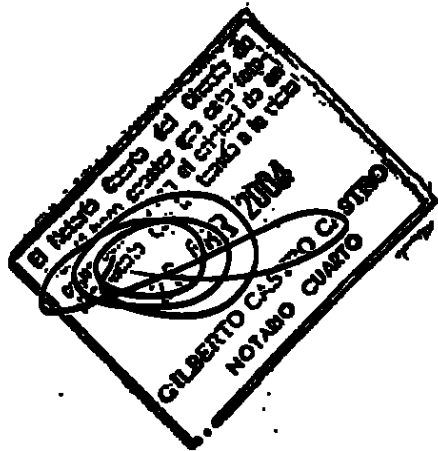
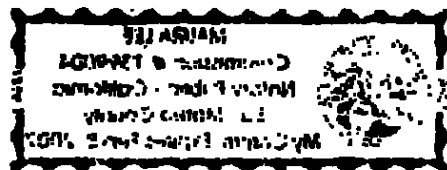
Capacity(ies) Claimed by Signer

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: Genera Genomics Axxys Pharm, Inc.





G. HOLLMANN RESTREPO
ABOGADOS LTDAG. 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 engravings 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 engravings 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

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

nombre(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 enseñanza 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.

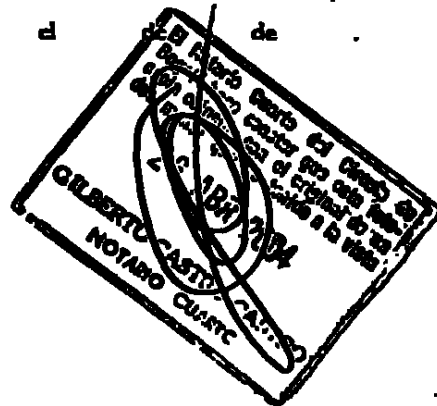
A este efecto, lo facultamos para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la Ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir 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 creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las facultades necesarias, y por este documento desde ahora declaro(amos) válido y bueno todo cuanto los apoderados hicieren en mi (nuestro) beneficio.

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

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de



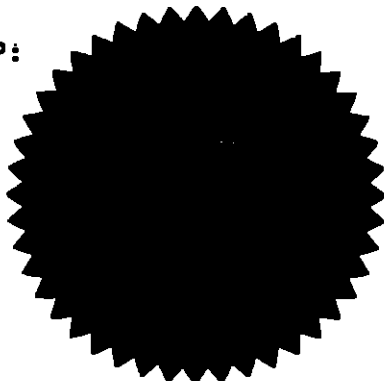
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
NANCY J INGRAM
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
NANCY J INGRAM, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 15TH DAY OF APRIL 2004
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A195400
9. SEAL/STAMP:
10. SIGNATURE



John E McCormac

NOTARIAL TRUE COPY

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

TO ALL TO WHOM THESE PRESENTS SHALL COME,

I Do Hereby Certify under the Oath of my Office and Seal that the annexed document(s) are TRUE COPIES of the original document(s) which I have compared.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the Seal under the Oath of my Office

At Bridgewater, New Jersey, United States of America

this 11th day of March, 2004.

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
 Date, if any, Title or
 Jurisdiction Area

Docket No. USAV2001/0197 *Co*

G. Wang 16 ✓



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Assistant Secretary and Commissioner
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SEPTEMBER 26, 2003

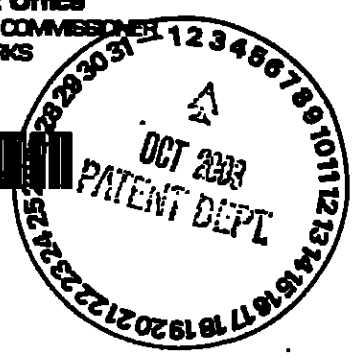
AVENTIS PHARMACEUTICALS INC.
GEORGE G. WANG
ROUTE 202-206 / P.O. BOX 6800
BRIDGEWATER, NJ 08807-0800

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RECORDATION DATE: 09/24/2003 REEL/FRAME: 013999/0825
NUMBER OF PAGES: 2
BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
LI, JIAYAO DOC DATE: 09/18/2003

ASSIGNEE:
AXYS PHARMACEUTICALS INC.
180 KIMBALL WAY
SOUTH SAN FRANCISCO, CALIFORNIA

94080

SERIAL NUMBER: 60332605 FILING DATE: 11/14/2001
PATENT NUMBER: ISSUE DATE:
SERIAL NUMBER: 10294526 FILING DATE: 11/14/2002
PATENT NUMBER: ISSUE DATE:

013999/0825 PAGE 2

VIOLET MCCOY, EXAMINER
ASSIGNMENT DIVISION
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SEP. 24. 2003 1:21PM
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 700645432
 RECORDATION FORM COVER SHEET
 PATENTS NLY

NO. 2416 P. 1/2

FORM PTO-1085
1-31-82
(modified)

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PATENT AND TRADEMARK OFFICE**

I hereby certify that this correspondence is being transmitted via facsimile to the Commissioner for Patents, Alexandria, VA 22313-1460, Patent and Trademark Assignment System, at (703) 305-5963, on
Date September 24, 2003

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To the Commissioner of Patents. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
1. Jixiao LI

2. Name and address of receiving party(ies):

Name: **Arys Pharmaceuticals Inc.**
Internal Address:
Street Address: **180 Kimball Way**
City: **South San Francisco** State: **CA** ZIP: **94080**

3. Nature of Conveyance:

☒	Assignment
☐	Security Agreement
☐	Other

Merge Change of Name

Additional name(s) and address(es) attached? ☐ YES ☒ NO

Exclusion Date: 1. 9/18/03

4. Application number(s) or patent number(s):
(If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s): **60/332,605**
10/294,516

B. Patent No.(s):

Additional numbers attached? ☐ YES ☒ NO

8. Name and address of party to whom correspondence concerning document should be mailed:

Name: George G. Wang, Reg. No. 41,419
Internal Address: Aventis Pharmaceuticals Inc.
Street Address: Route 202-206 / P.O. Box 6800
City: Bridgewater **State:** NJ **ZIP:** 08807-0800
FAX NUMBER: (908) 231-2826
Our Reference No.: USAV2001/0197 US NP

8. Total number of applications and patents involved: 2

7. Total (37 CFR 3.41): **500.00**

☐ Enclosed
☒ Authorized to be charged to deposit account

8. Deposit account number: 18-1982

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

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Name of Person Signing

Date: 9-24-03
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ASSIGNMENT AND AGREEMENT

For value received and intending to be legally bound, I/we, the undersigned joint inventor(s) (Assignor(s)), sell, assign and transfer to Axyx Pharmaceuticals Inc. (Assignee), 180 Kimball Way, South San Francisco, California 94080 and its successors, assigns and legal representatives, the entire right, title and interest in and to my/our invention and any improvements thereon for all countries of the world, relating in and to the applications for Letters Patent as identified and listed below and for all patent applications which claim priority to or are derived from said priority applications listed below and entitled:

NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN S INHIBITORS

US Priority Application No. 60/332,605
US Filing Date: November 14, 2001

1st US Non-Provisional Application No. 10/294,526
US Filing Date: November 14, 2002

International Application
PCT Application No. US02/36396
International Filing Date November 14, 2002

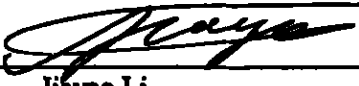
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I/we authorize and request competent authorities to grant and issue any and all patents on said invention to said assignee or its successor, assigns and legal representatives, or to such nominees as said assignee may designate.

I/we agree that, when requested, I/we will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining patents for said invention in any and all countries and for vesting title thereto in said assignee, its successors, assigns, legal representatives or nominees.

I/we covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have full right to convey the same as herein expressed.

Signed at So. San Francisco, CA 94080 – U.S.A. on this 18 day of September, 2003.
(City, State and Nation)

Signature: 
Inventor's Name: Jiayao Li
Residential Address: 888 Foster City Blvd., E5
Foster City CA 94404



UNITED STATES DEPARTMENT OF COMMERCE
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SEPTEMBER 26, 2003

PTAS

AVENTIS PHARMACEUTICALS INC.
GEORGE G. WANG
ROUTE 202-206/P.O. BOX 6800
BRIDGEWATER, NJ 08807-0800



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RECORDATION DATE: 09/24/2003

REEL/FRAME: 013999/0778
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ALDOUS, DAVID J.

DOC DATE: 09/16/2003

ASSIGNOR:
THURAIRATNAM, SUKANTHINI

DOC DATE: 09/22/2003

ASSIGNEE:
AVENTIS PHARMACEUTICALS INC.
300 SOMERSET CORPORATION BOULEVARD
BRIDGEWATER, NEW JERSEY 08807

SERIAL NUMBER: 60332605
PATENT NUMBER:

FILING DATE: 11/14/2001
ISSUE DATE:

SERIAL NUMBER: 10294526
PATENT NUMBER:

FILING DATE: 11/14/2002
ISSUE DATE:

013999/0778 PAGE 2

TARA WASHINGTON, EXAMINER
ASSIGNMENT DIVISION
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AVENTIS US PAT DEPT

NO. 2406 P. 1

TO: US USPTO AS-1

09/24/2003

90064542

FORM PTO-1536
1-31-02
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Date September 24, 2003

Signature 

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1. Name of conveying party(ies):

1. David J. ALDOUS

2. Subenthiel THURAIRATNAM

2. Name and address of receiving party(ies):

Name: Aventis Pharmaceuticals Inc.

Internal Address:

Street Address: 300 Somerset Corporate Boulevard

City: Bridgewater State: NJ ZIP: 08807

Additional name(s) of conveying party(ies) attached? ☐ YES ☒ NO

3. Nature of Conveyance:

☒ Assignment☐ Security Agreement☐ Other☐ Merger☐ Change of NameAdditional name(s) and address(es) attached? ☐ YES ☒ NO

Execution Date: 1. 9/16/03 2. 9/22/03

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s): 60/332,605

18/294,526

B. Patent No.(s):

Additional numbers attached? ☐ YES ☒ NO

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: George G. Wang, Reg. No. 41,419

Internal Address: Aventis Pharmaceuticals Inc.

Street Address: Route 202-206 / P.O. Box 6800

City: Bridgewater State: NJ ZIP: 08807-0000

** FAX NUMBER: (800) 231-2628 **

Our Reference No.: USAV2001/0197 US NP

6. Total number of applications and patents involved: 2

7. Total (\$7 CFR 3.49): \$80.00

☐ Enclosed☒ Authorized to be charged to deposit account

A. Deposit account number: 18-1982

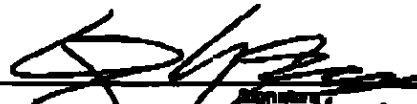
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B. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

George G. Wang, Reg. No. 41,419

Name of Person Signing


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Total number of pages comprising cover sheet: 3

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ASSIGNMENT AND AGREEMENT

For value received and intending to be legally bound, I/we, the undersigned joint inventor(s) (Assignor(s)), sell, assign and transfer to Aventis Pharmaceuticals Inc. (Assignee), 300 Somerset Corporate Boulevard, Bridgewater, New Jersey 08807-2854, and its successors, assigns and legal representatives, the entire right, title and interest in and to my/our invention and any improvements thereon for all countries of the world, relating in and to the applications for Letters Patent as identified and listed below and for all patent applications which claim priority to or are derived from said priority applications listed below and entitled:

NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN S INHIBITORS

US Priority Application No.	60/332,605
US Filing Date:	November 14, 2001
1 st US Non-Provisional Application No.	10/294,526
US Filing Date:	November 14, 2002
International Application	
PCT Application No.	US02/36396
International Filing Date	November 14, 2002

and all the rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, including the right to claim priority based on said United States application, and under any and all Letters Patent which may be granted therefor, and all right, title and interest in and to every patent application filed or to be filed on said invention in any other country or patent organization, including continuations, divisions, renewals, revivals, and any substitute applications of said United States application, and any and all patents which may issue thereon, and any reissues, pipelines and extensions, and governmental exclusivity rights of the same.

I/we authorize and request competent authorities to grant and issue any and all patents on said invention to said assignee or its successor, assigns and legal representatives, or to such nominees as said assignee may designate.

I/we agree that, when requested, I/we will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining patents for said invention in any and all countries and for vesting title thereto in said assignee, its successors, assigns, legal representatives or nominees.

I/we covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have full right to convey the same as herein expressed.

Signed at Bridgewater, NJ, USA on this 16 day of September, 2003.
(City, State and Nation)

Signature: 
Inventor's Name: David J. Aldous
Residential Address: 268 Gates Avenue
Gillette, NJ 07933

Signed at Bridgewater, NJ, USA on this 22nd day of September, 2003.
(City, State and Nation)

Signature: Sukanthini Thuraiatnam
Inventor's Name: Sukanthini THURAIRATNAM
Residential Address: 6 Smoke Rise Lane
Bedminster, NJ 07921

Signed at _____ on this _____ day of _____, 2003.
(City, State and Nation)

Signature: _____
Inventor's Name: _____
Residential Address: _____

Signed at _____ on this _____ day of _____, 2003.
(City, State and Nation)

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Inventor's Name: _____
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Signature: _____
Inventor's Name: _____
Residential Address: _____

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 May 2003 (22.05.2003)

PCT

(10) International Publication Number
WO 03/042197 A1

(51) International Patent Classification: C07D 271/06,
271/10, A61K 31/4245

(21) International Application Number: PCT/US02/36396

(22) International Filing Date:
14 November 2002 (14.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/332,605 14 November 2001 (14.11.2001) US

(71) Applicants (for all designated States except US): AVEN-
TIS PHARMACEUTICALS INC. [US/US]; 300 Som-
erset Corporate Boulevard, Bridgewater, NJ 08807-2854
(US). AXYS PHARMACEUTICALS, INC. [US/US];
180 Kimball Way, South San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LI, Jinyao [CN/US];
442 Milton Avenue, Apartment 3, San Bruno, CA 94066
(US). ALDOUS, David, J. [US/US]; 268 Gates Avenue,
Gillette, NJ 07933 (US). THURAIRATNAM, Sukanthini
[GB/US]; 6 Smoke Rise Lane, Bedminster, NJ 07921 (US).

(74) Agents: WANG, George, G. et al.; Aventis Pharmaceu-
ticals Inc., P.O. Box 6800, Route 202-206, Bridgewater, NJ
08807-0800 (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,
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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).

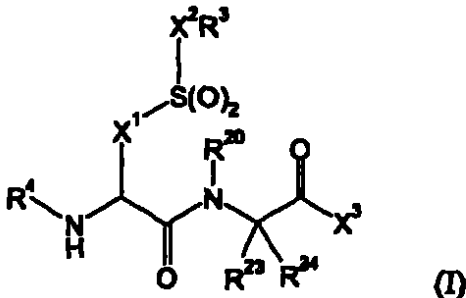
Declaration under Rule 4.17:
— of inventorship (Rule 4.17(iv)) for US only

Published:
— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

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

(54) Title: OLIGOPEPTIDES AND COMPOSITIONS CONTAINING THEM AS CATHEPSIN S INHIBITORS

(57) Abstract: The present invention relates to novel selective cathepsin S
inhibitors, the pharmaceutically acceptable salts and N-oxides thereof, their
uses as therapeutic agents and the methods of their making. Formula (I).



WO 03/042197 A1

OLIGOPEPTIDES AND COMPOSITIONS CONTAINING THEM AS CATHEPSIN S INHIBITORS

THE INVENTION

5 This Application is based on and claims priority from U.S. Provisional Application No. 60/332,605 filed on November 14, 2001, which is 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
10 cathepsin S.

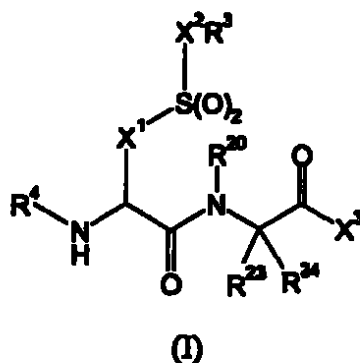
DESCRIPTION OF THE FIELD

 Cysteine proteases represent a class of peptidases characterized by the presence of
15 a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated 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,
20 tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic 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.

25

SUMMARY OF THE INVENTION

This Application relates to compounds of Formula (I):



wherein:

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

- 10 R^3 is $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$, $-CR^7=NR^8$, or (C_{3-12}) cycloalkyl, wherein R^5 and R^6 are independently 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}) cycloalkyl, hetero (C_{3-12}) cycloalkyl, (C_{6-12}) aryl, hetero (C_{5-12}) 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_{3-12}) cycloalkyl, 15 hetero (C_{5-12}) 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, $-X^4NR^9R^9$, $-X^4OR^9$, $-X^4SR^9$, $-X^4C(O)NR^9R^9$, $-X^4C(O)OR^9$, $-X^4S(O)R^{10}$, $-X^4S(O)_2R^{10}$ 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 20 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 -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,
 5 (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
 10 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
 15 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,
 20 -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,
 25 -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;

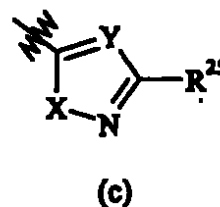
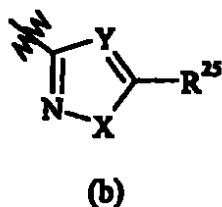
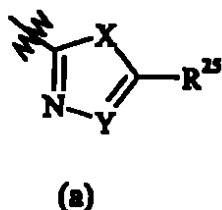
5 R²⁰ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

R²³ is selected from hydrogen, (C₁₋₆)alkyl, alkoxy(C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl
10 and hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵ wherein R¹⁵ is as described above; and

R²⁴ is selected from hydrogen or (C₁₋₆)alkyl; or

R²³ and R²⁴ taken together with the carbon atom to which both R²³ and R²⁴ are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene;

15 X³ is selected from group (a), (b) or (c);



wherein X is O and Y is N;

20 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;

wherein R²⁵ 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.

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 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 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.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as described herein. Exemplary alkoxy groups include methoxy and ethoxy.

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).

25

"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

30

(-CH₂CH=CHCH₂-), 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), 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.

"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.

"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, 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, 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, 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, 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)-.

"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 or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C₃₋₁₀)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 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.

"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.

"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, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

"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, 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, dibenzofuranyl, 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, pyrazinyl, 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.

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

"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.

"Heterocycloalkylene" means cycloalkylene, as defined in this Application, 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, (C₁₋₆)alkyl or a protecting group.

5 "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 (C₁₋₆)alkyl.

10 "Isomers" mean compounds of Formula (I) having identical molecular formulae but 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
15 "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical 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 either an
20 individual diastereomers or as a mixture of diastereomers, termed a "diastereomeric mixture". When 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*-
25 and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods 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
30 meant to be encompassed all possible stereoisomers. Thus, for example, the name

morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide is meant to include morpholine-4-carboxylic acid {S-2-phenylmethanesulfonyl-1-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide and morpholine-4-carboxylic acid {R-2-phenylmethanesulfonyl-1-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-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.

10 "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.

20 "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.

25 "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.

30 "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, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *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.

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 that 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, dialkylamino-methylbenzoates 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 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:

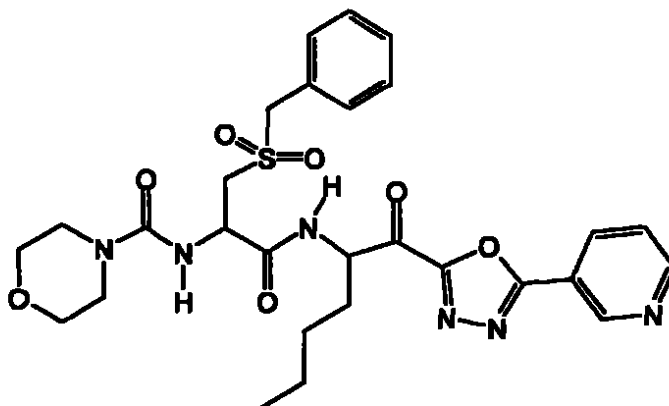
(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(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

(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:

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, R⁴ is morpholine-4-carbonyl, R²⁰ is hydrogen, R²³ is hydrogen, R²⁴ is n-butyl, X¹ is methylene, X² is methylene and X³ is 5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl; that is, a compound having the following structure:



10

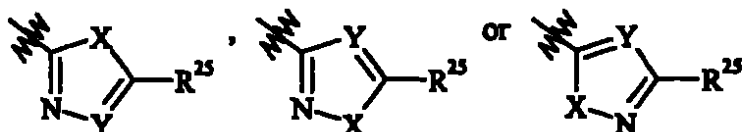
is named morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide.

With reference to formula (I) above, the following are particular and preferred groupings:

15

X¹ may particularly represent methylene when X² is methylene.

X¹ may also particularly represent ethylene when X² is a bond.

20 X³ may particularly represent

wherein X is O, Y is N and R²⁵ is selected from hydrogen, halo(C₁₋₃)alkyl, (C₁₋₆)alkyl,

(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₃)aryl(C₀₋₆)alkyl, wherein R²⁵ 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 or halo-substituted (C₁₋₃)alkyl.

5

R³ may particularly represent -CR⁵=CHR⁶, -CR⁵(CR⁶)₂, -CR⁷=NR⁸, or (C₃₋₁₂)cycloalkyl, wherein R⁵ and R⁶ is independently hydrogen or (C₁₋₄)alkyl or R⁵ and R⁶ together with the atoms to which R⁵ and R⁶ are attached form (C₃₋₁₂)cycloalkyl, (C₆₋₁₂)aryl, hetero(C₅₋₁₂)aryl or (C₉₋₁₂)bicycloaryl and R⁷ and R⁸ together with the
 10 atoms to which R⁷ and R⁸ are attached form hetero(C₅₋₁₂)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, in which X⁴ is a bond or (C₁₋₂)alkylene, R⁹ at each occurrence independently is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl.

15

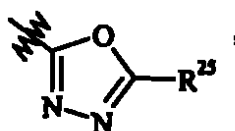
R⁴ may particularly represent -C(O)X⁵R¹¹ or -S(O)₂X⁵R¹¹, wherein X⁵ is a bond, -O- or -NR¹²-, wherein R¹² is hydrogen or (C₁₋₆)alkyl, and R¹¹ is (i) (C₁₋₆)alkyl or (ii) hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl or (iii)
 20 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
 25 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

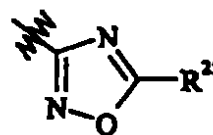
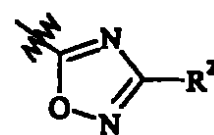
halo-substituted (C₁₋₃)alkyl and R¹⁸ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl.

R²⁰ may particularly represent hydrogen and (C₁₋₆)alkyl.

5 R²³ may particularly represent (C₁₋₆)alkyl or (C₆₋₁₂)aryl(C₀₋₆)alkyl.

R²⁴ may particularly represent hydrogen or (C₁₋₆)alkyl.

X³ more preferably is selected from the group consisting of 

10  or  wherein R²⁵ is selected from *tert*-butyl,

cyclopropyl, ethyl, phenyl, pyrazinyl, pyridazinyl, pyridinyl, thienyl or trifluoromethyl.

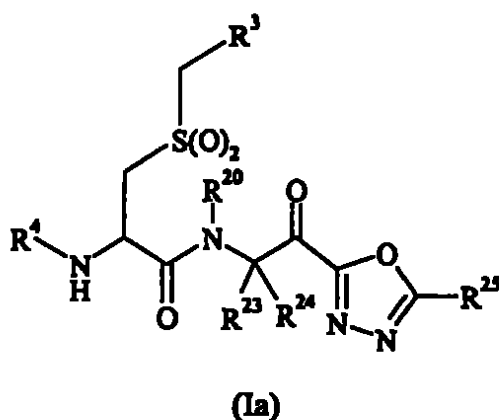
R³ more preferably is selected from the group consisting of phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, vinyl, 2-difluoromethoxyphenyl, 1-oxy-pyridin-2-yl, 15 4-methoxyphenyl, 4-methylphenyl, 2-methylphenyl, 4-chlorophenyl, 3,5-dimethylphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 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- 20 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, 25 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. Most preferred R³ groups include cyclopropyl, isopropyl and phenyl.

R⁴ 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-fluoro-4-methoxy-benzoyl, 4-methoxy-benzoyl, 4-trifluoromethoxy-benzoyl, 3,4-difluoro-benzoyl, 4-fluoro-benzoyl, 3,4-dimethoxy-benzoyl, 3-methyl-benzoyl, 4-bromo-benzoyl, 4-trifluoromethyl-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*-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-isindole-2-carbonyl. R⁴ is most preferably morpholine-4-carbonyl.

It is to be understood that this invention covers all appropriate combinations of the particular and preferred groupings referred to herein unless otherwise stated.

- 5 A particular preferred group of compounds of the invention are compounds of Formula (Ia):



10

- wherein R³, R⁴, R²⁰, R²³, R²⁴ and R²⁵ are as hereinbefore described, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ia) and their *N*-oxides and their
 15 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

- Compounds of Formula (Ia) in which R³ is -CR⁵=CHR⁶ wherein R⁵ and R⁶ together with the atoms to which R⁵ and R⁶ are attached form (C₆₋₁₂)aryl, optionally substituted by 1
 20 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, in which X⁴ is a bond or (C₁₋₂)alkylene, R⁹ at each occurrence independently is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl, are preferred. Compounds of Formula (Ia) in which R³ represents phenyl or 2-difluoromethoxyphenyl are especially preferred.

Compounds of Formula (Ia) in which R^3 is $-CR^5(CR^6_3)_2$ wherein R^5 is hydrogen and R^6 is (C_{1-4}) alkyl are also preferred. Compounds of Formula (Ia) in which R^3 represents $-CH(CH_3)_2$ are especially preferred.

5

Compounds of Formula (Ia) in which R^3 is (C_{3-12}) cycloalkyl are also preferred. Compounds of Formula (Ia) in which R^3 represents cyclopropyl are especially preferred.

10

Compounds of Formula (Ia) in which R^4 is $-C(O)X^5R^{11}$ wherein X^5 is a bond and R^{11} is hetero(C_{5-12})cycloalkyl(C_{0-3})alkyl, particularly hetero(C_{5-12})cycloalkyl, are preferred.

Compounds of Formula (Ia) in which R^4 represents $-C(O)-N$  O are especially preferred.

15

Compounds of Formula (Ia) in which R^{20} is hydrogen are preferred.

Compounds of Formula (Ia) in which R^{23} is (C_{1-6}) alkyl [e.g. ethyl or butyl] are preferred.

Compounds of Formula (Ia) in which R^{24} is hydrogen are preferred.

20

Compounds of Formula (Ia) in which R^{25} is *tert*-butyl, cyclopropyl, ethyl, phenyl, pyridin-3-yl, pyridin-4-yl, thien-3-yl or trifluoromethyl are preferred.

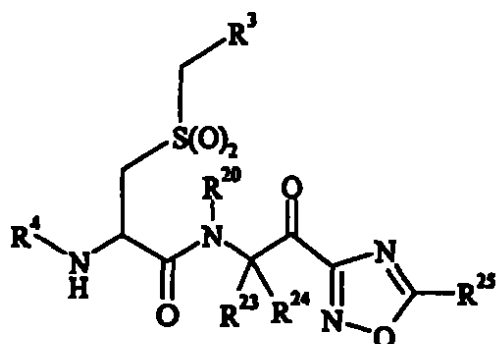
25

A preferred group of compounds of the invention are compounds of Formula (Ia) in which: R^3 is $-CR^5-CHR^6$ [e.g. phenyl or 2-difluoromethoxyphenyl], $-CR^5(CR^6_3)_2$ or (C_{3-12}) cycloalkyl [e.g. $-CH(CH_3)_2$ or cyclopropyl]; R^4 is $-C(O)X^5R^{11}$ [e.g.

$-\text{C}(\text{O})-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{ } \quad \text{ } \\ \diagdown \quad \diagup \\ \text{O} \end{array} \text{O}]$; R^{20} is hydrogen; R^{23} is (C_{1-6}) alkyl [e.g. ethyl or butyl]; R^{24} is

hydrogen; and R^{25} is *tert*-butyl, cyclopropyl, ethyl, phenyl, pyridin-3-yl, pyridin-4-yl, thien-3-yl or trifluoromethyl, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the
 5 pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ia) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

10 A further particular preferred group of compounds of the invention are compounds of Formula (Ib):



(Ib)

15 wherein R^3 , R^4 , R^{20} , R^{23} , R^{24} and R^{25} are as hereinbefore described, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ib) and their *N*-oxides and their
 20 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Compounds of Formula (Ib) in which R^3 is $-\text{CR}^5=\text{CHR}^6$ wherein R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{6-12}) aryl, optionally substituted by 1

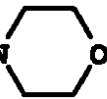
to 5 radicals independently selected from a group consisting of (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, -X⁴OR⁹ and -X⁴C(O)OR⁹, wherein X⁴ is a bond or (C₁₋₂)alkylene, R⁹ at each occurrence independently is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl, are preferred. Compounds of Formula (Ib) in which R³ represents phenyl or
 5 2-difluoromethoxyphenyl are especially preferred.

Compounds of Formula (Ib) in which R³ is -CR⁵(CR⁶)₂ wherein R⁵ is hydrogen and R⁶ is (C₁₋₄)alkyl are also preferred. Compounds of Formula (Ib) in which R³ represents -CH(CH₃)₂ are especially preferred.

10

Compounds of Formula (Ib) in which R³ is (C₃₋₁₂)cycloalkyl are also preferred. Compounds of Formula (Ib) in which R³ represents cyclopropyl are especially preferred.

Compounds of Formula (Ib) in which R⁴ is -C(O)X⁵R¹¹ wherein X⁵ is a bond and R¹¹ is hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, particularly hetero(C₅₋₁₂)cycloalkyl, are preferred.
 15

Compounds of Formula (Ib) in which R⁴ represents $-C(O)-N$  O are especially preferred.

Compounds of Formula (Ib) in which R²⁰ is hydrogen are preferred.

20

Compounds of Formula (Ib) in which R²³ is (C₁₋₆)alkyl [e.g. ethyl or butyl] are preferred.

Compounds of Formula (Ib) in which R²⁴ is hydrogen are preferred.

25 Compounds of Formula (Ib) in which R²⁵ is *tert*-butyl, cyclopropyl, ethyl, phenyl, pyridin-3-yl, pyridin-4-yl, thien-3-yl or trifluoromethyl are preferred.

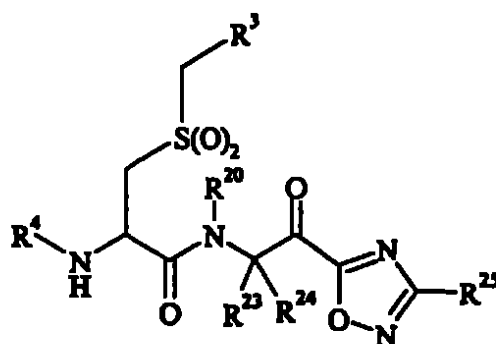
A preferred group of compounds of the invention are compounds of Formula (Ib) in which: R^3 is $-CR^5=CHR^6$ [e.g. phenyl or 2-difluoromethoxyphenyl], $-CR^5(CR^6_3)_2$ or (C_{3-12}) cycloalkyl [e.g. $-CH(CH_3)_2$ or cyclopropyl]; R^4 is $-C(O)X^5R^{11}$ [e.g.

5 $-C(O)-N$  O]; R^{20} is hydrogen; R^{23} is (C_{1-6}) alkyl [e.g. ethyl or butyl]; R^{24} is

hydrogen; and R^{25} is *tert*-butyl, cyclopropyl, ethyl, phenyl, pyridin-3-yl, pyridin-4-yl, thien-3-yl or trifluoromethyl, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of

10 Formula (Ib) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

A particular preferred group of compounds of the invention are compounds of Formula (Ic):



I(c)

wherein R^3 , R^4 , R^{20} , R^{23} , R^{24} and R^{25} are as hereinbefore described, and their

20 corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ic) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers

thereof.

Compounds of Formula (Ic) in which R^3 is $-CR^5=CHR^6$ wherein R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{6-12}) aryl, optionally 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, are preferred. Compounds of Formula (Ic) in which R^3 represents phenyl or 2-difluoromethoxyphenyl are especially preferred.

Compounds of Formula (Ic) in which R^3 is $-CR^5(CR^6_3)_2$ wherein R^5 is hydrogen and R^6 is (C_{1-4}) alkyl are also preferred. Compounds of Formula (Ic) in which R^3 represents $-CH(CH_3)_2$ are especially preferred.

Compounds of Formula (Ic) in which R^3 is $-CR^5(CR^6_3)_2$ wherein R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{3-12}) cycloalkyl are also preferred. Compounds of Formula (Ic) in which R^3 represents cyclopropyl are especially preferred.

Compounds of Formula (Ic) in which R^4 is $-C(O)X^5R^{11}$ wherein X^5 is a bond and R^{11} is hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, particularly hetero (C_{5-12}) cycloalkyl, are preferred.

Compounds of Formula (Ic) in which R^4 represents $-C(O)-N$  O are especially preferred.

Compounds of Formula (Ic) in which R^{20} is hydrogen are preferred.

Compounds of Formula (Ic) in which R^{23} is (C_{1-6}) alkyl [e.g. ethyl or butyl] are preferred.

Compounds of Formula (Ic) in which R²⁴ is hydrogen are preferred.

Compounds of Formula (Ic) in which R²⁵ is *tert*-butyl, cyclopropyl, ethyl, phenyl, pyridin-3-yl, pyridin-4-yl, thien-3-yl or trifluoromethyl are preferred.

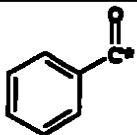
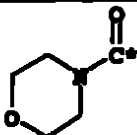
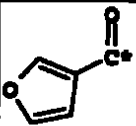
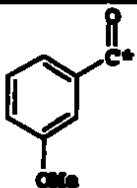
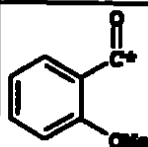
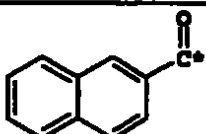
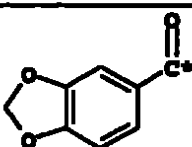
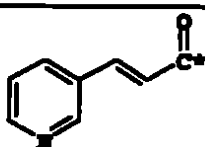
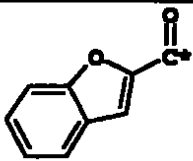
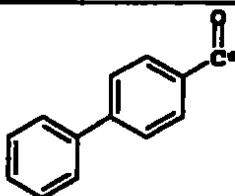
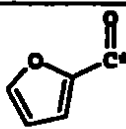
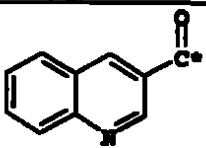
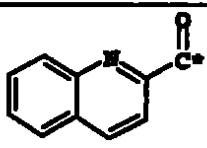
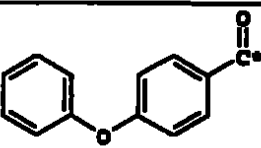
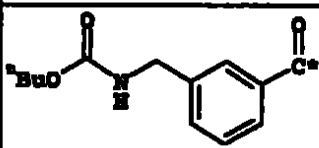
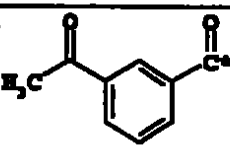
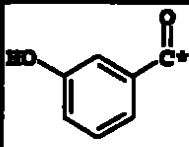
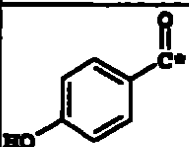
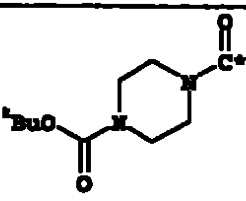
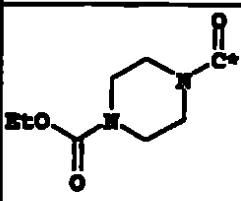
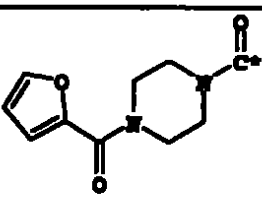
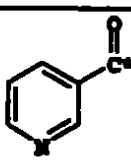
A preferred group of compounds of the invention are compounds of Formula (Ic) in which: R³ is -CR⁵=CHR⁶ [e.g. phenyl or 2-difluoromethoxyphenyl], -CR⁵(CR⁶)₂ or (C₃₋₁₂)cycloalkyl [e.g. -CH(CH₃)₂ or cyclopropyl]; R⁴ is -C(O)X⁵R¹¹ [e.g.

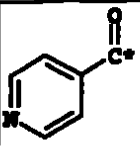
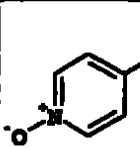
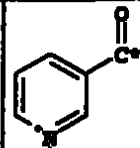
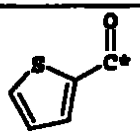
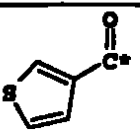
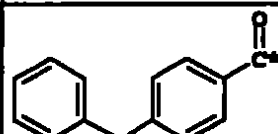
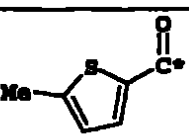
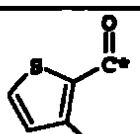
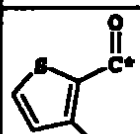
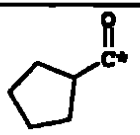
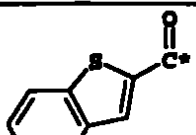
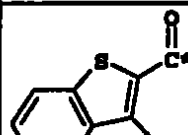
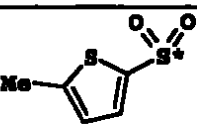
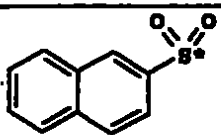
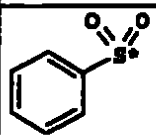
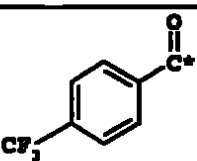
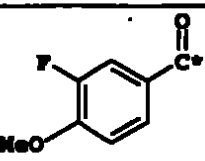
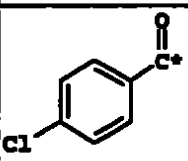
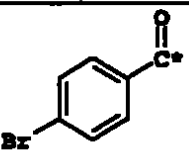
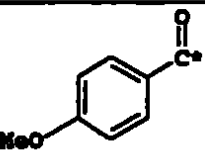
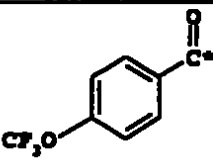
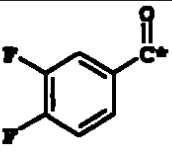
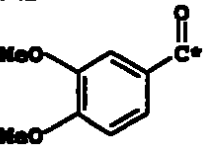
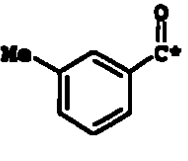
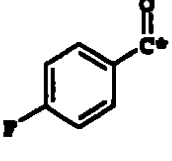
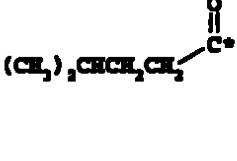
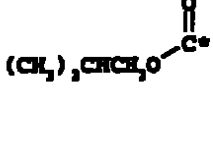
-C(O)-N₁O]; R²⁰ is hydrogen; R²³ is (C₁₋₆)alkyl [e.g. ethyl or butyl]; R²⁴ is

hydrogen; and R²⁵ is *tert*-butyl, cyclopropyl, ethyl, phenyl, pyridin-3-yl, pyridin-4-yl, thien-3-yl or trifluoromethyl, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ic) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Particular compounds of the invention may be prepared by joining carbon atom (C*) of one of the fragments (A1 to A36 or A40 to A71) or the sulfur atom (S*) of one of the fragments (A37 to A39 or A72) shown in Table 1 to the nitrogen atom (*N) of one of the fragments (B1 to B84) shown in Table 2, and joining the methine carbon atom (CH*) of one of the fragments (B1 to B84) shown in Table 2 to the acyl carbon atom (C*) of one of the fragments (C1 to C40) depicted in Table 3.

TABLE 1

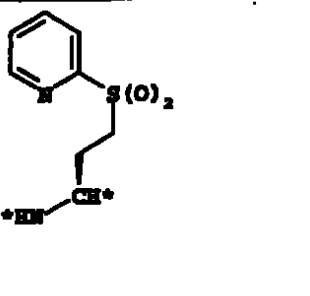
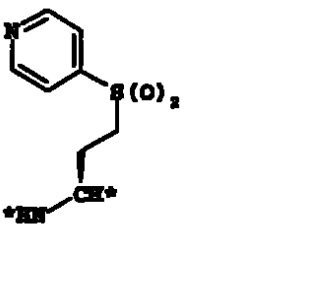
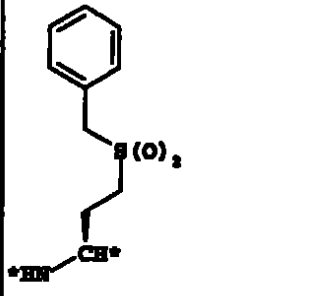
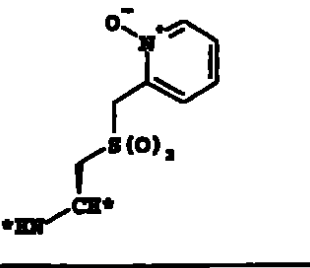
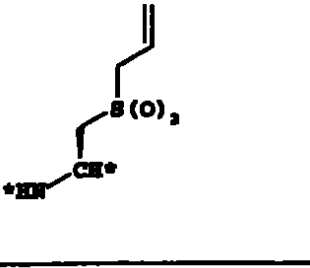
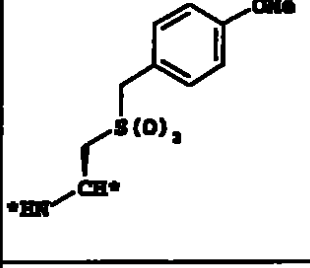
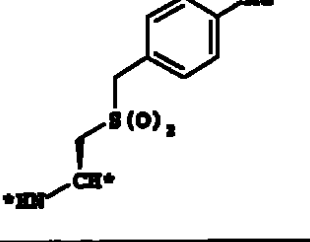
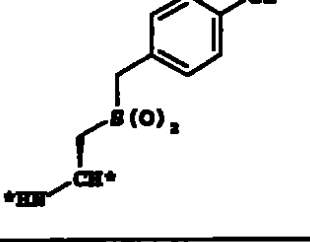
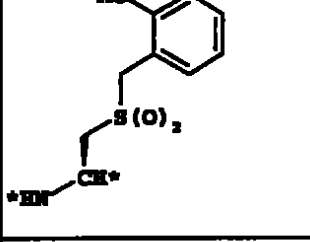
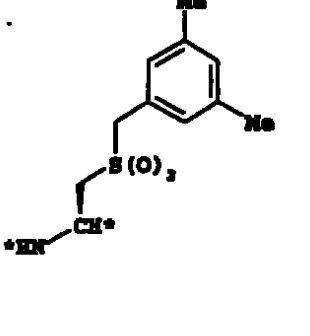
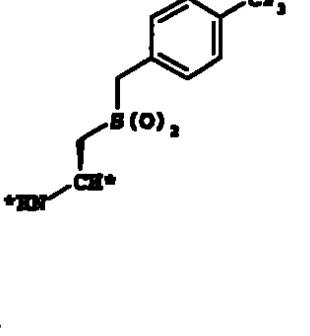
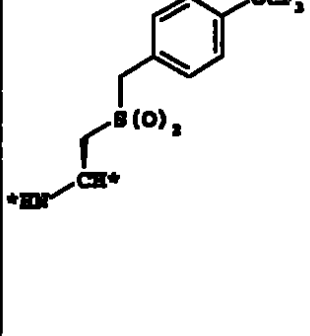
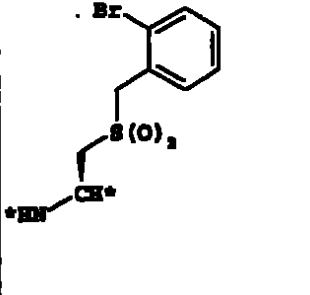
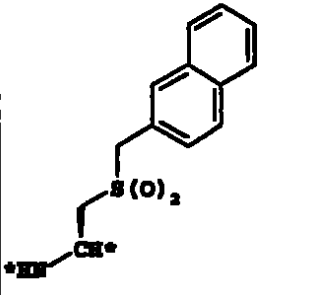
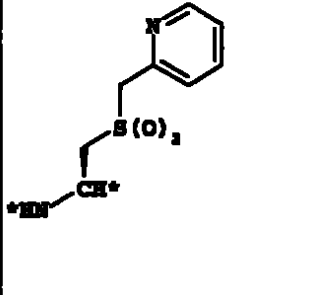
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A10		A11		A12	
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A16		A17		A18	
A19		A20		A21	
A22		A23		A24	

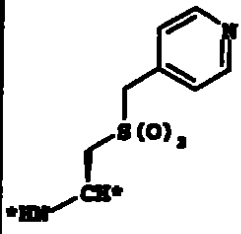
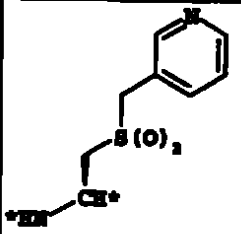
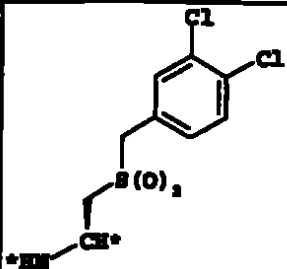
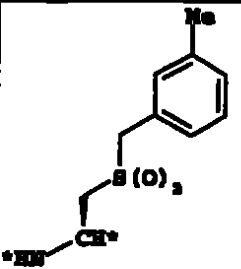
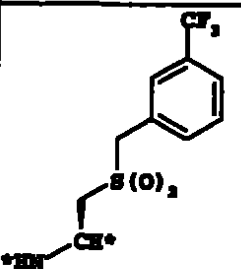
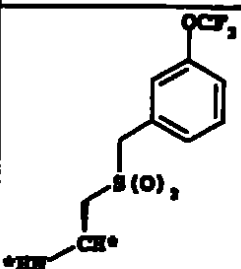
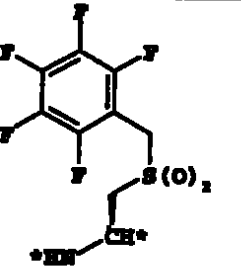
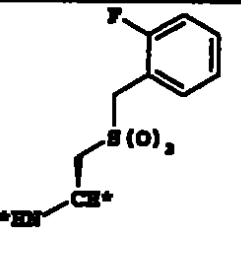
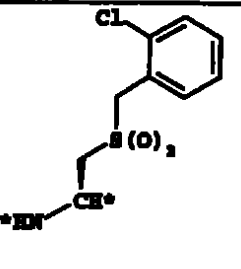
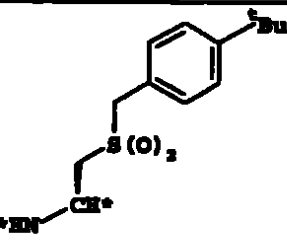
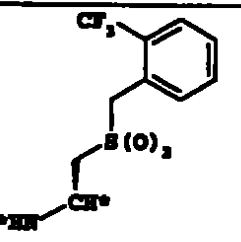
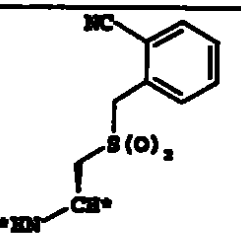
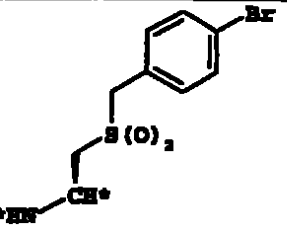
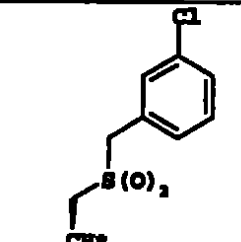
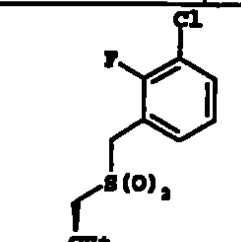
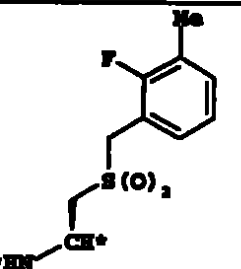
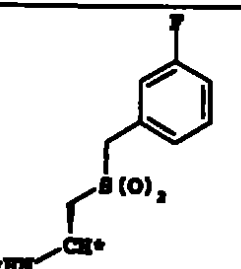
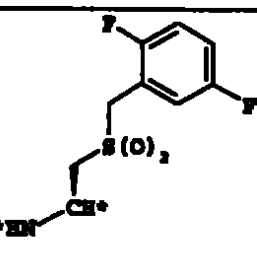
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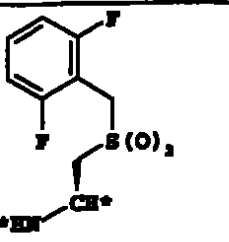
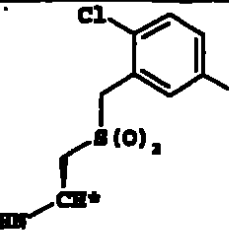
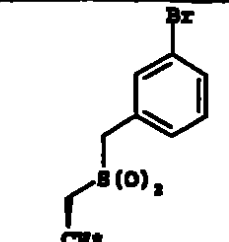
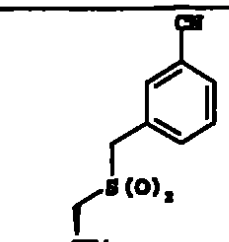
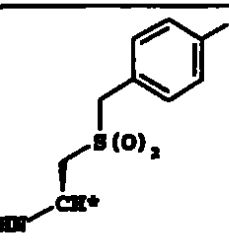
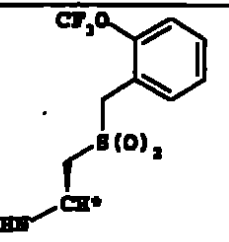
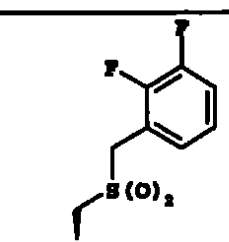
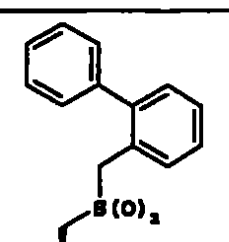
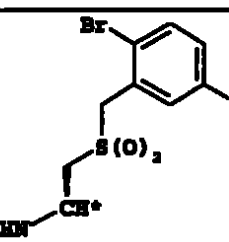
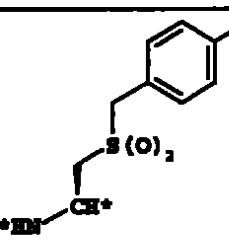
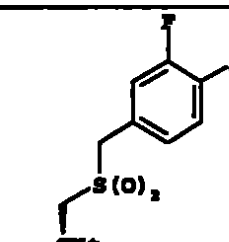
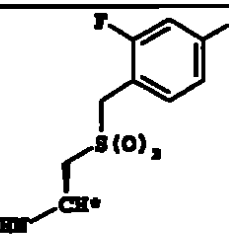
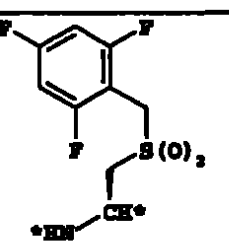
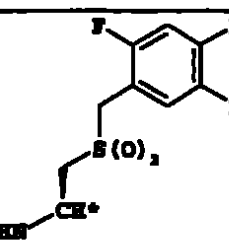
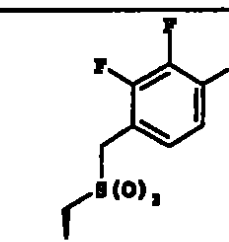
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A67		A68		A69	
A70		A71		A72	

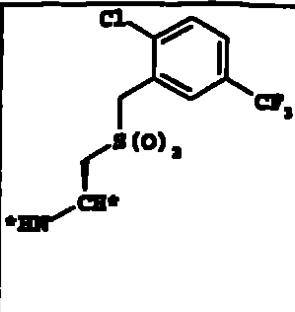
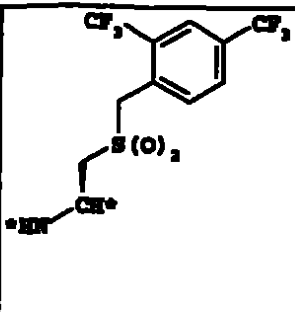
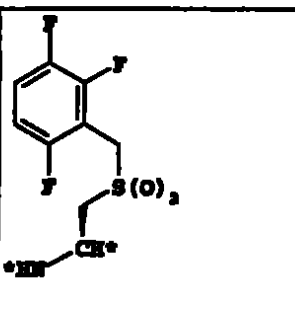
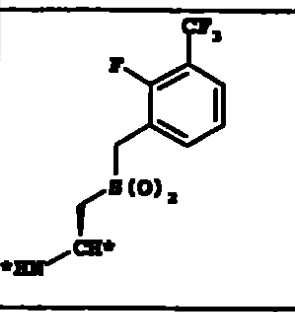
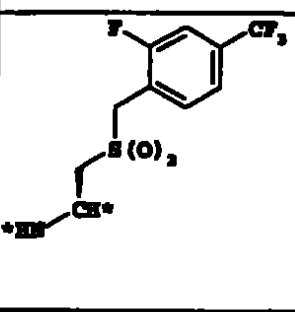
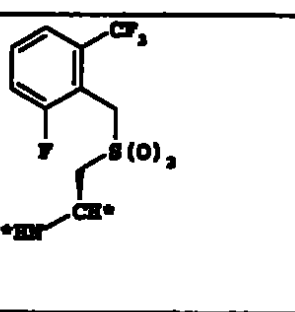
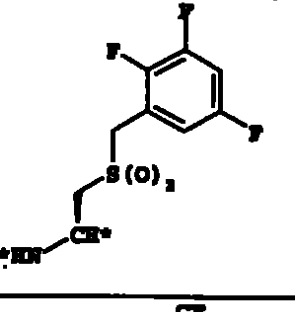
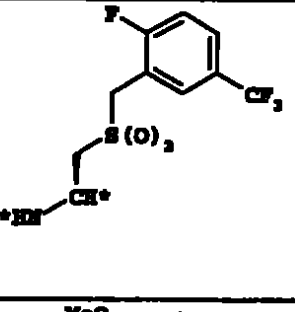
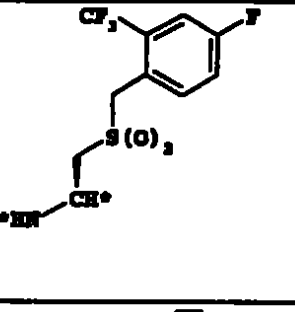
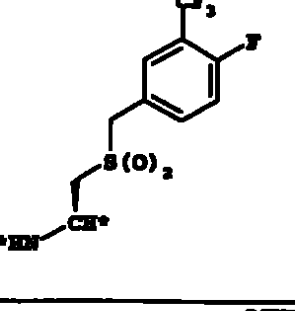
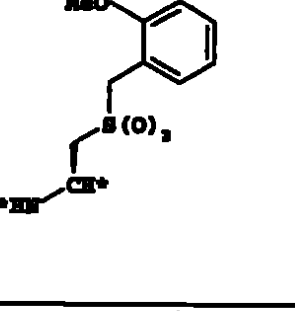
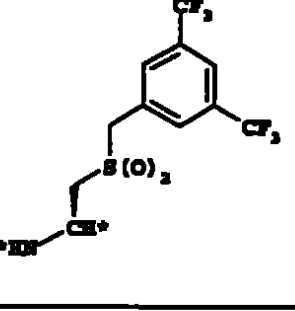
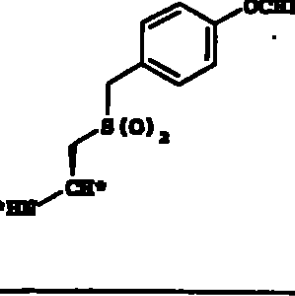
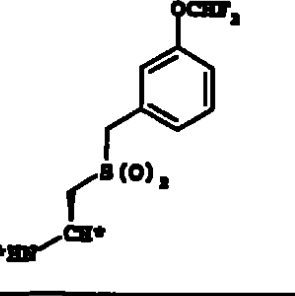
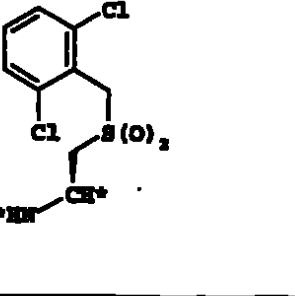
TABLE 2

B1		B2		B3	
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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	

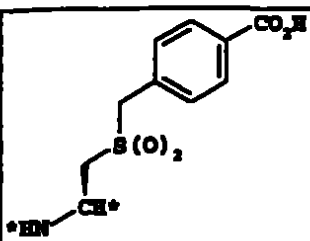
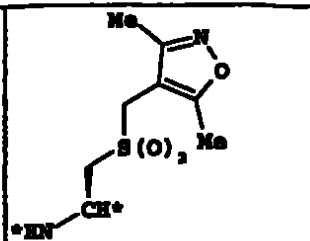
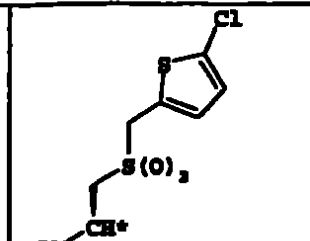
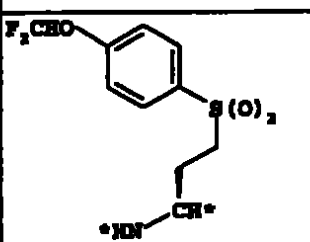
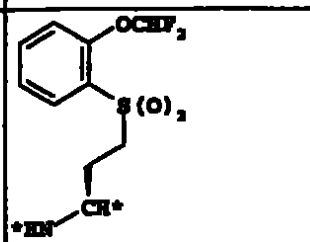
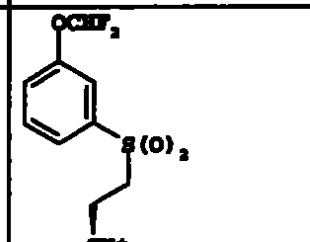
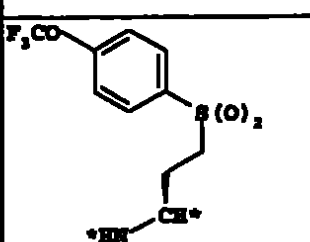
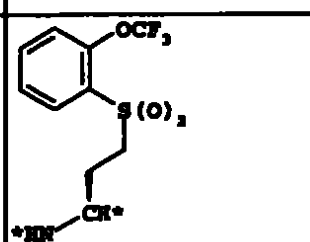
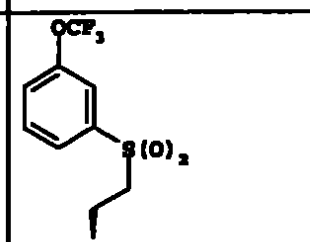
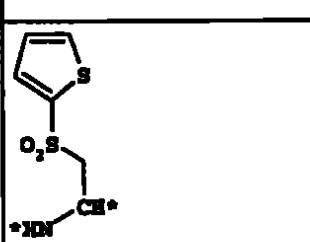
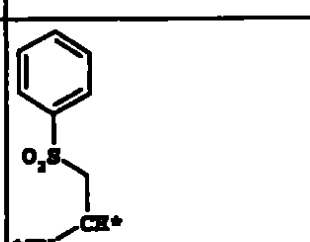
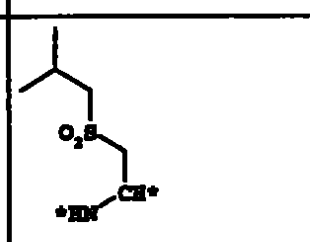
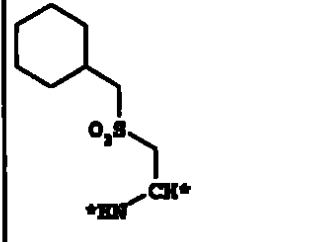
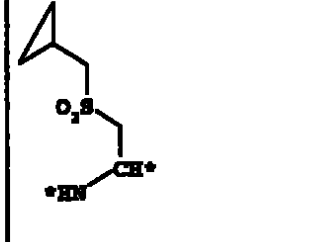
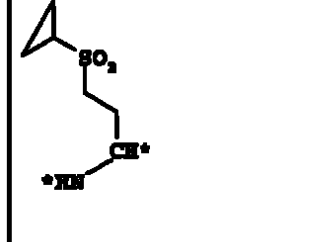
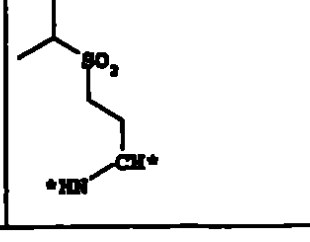
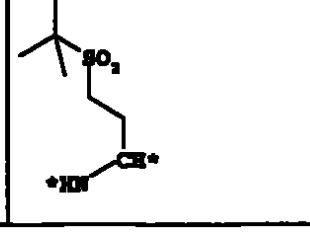
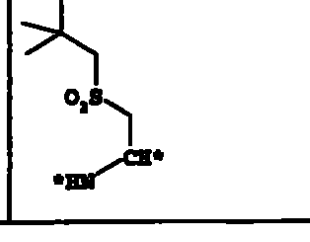
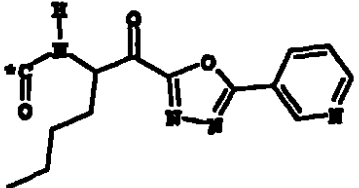
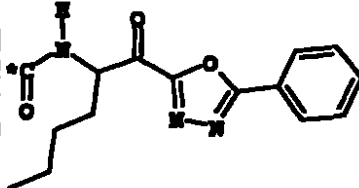
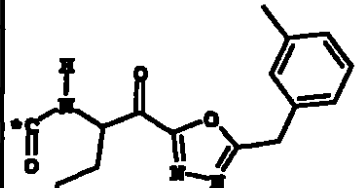
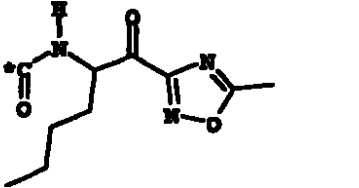
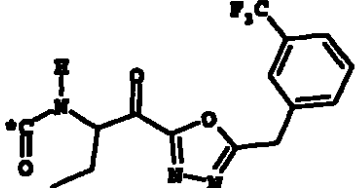
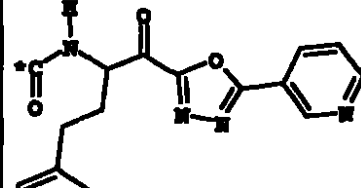
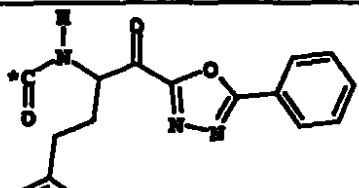
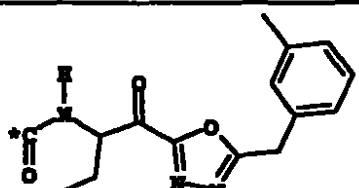
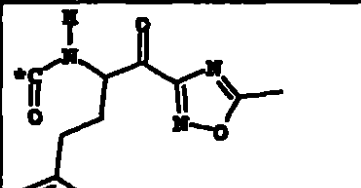
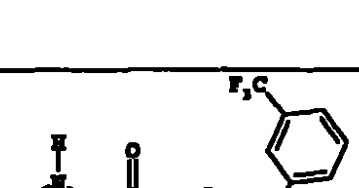
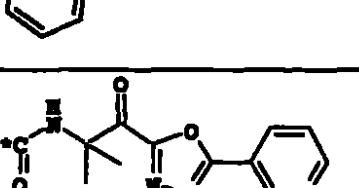
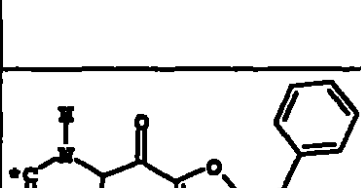
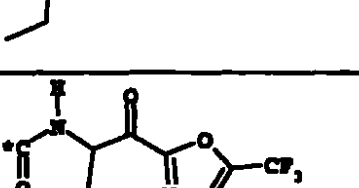
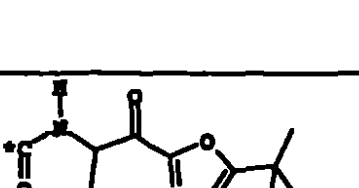
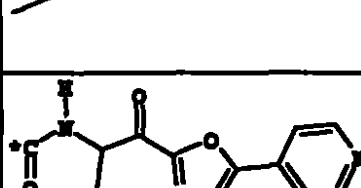
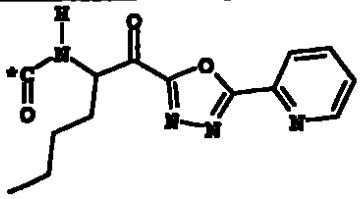
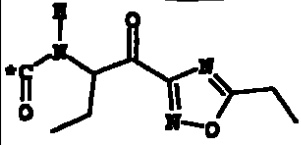
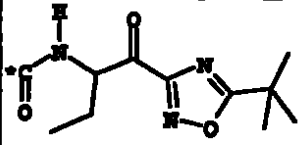
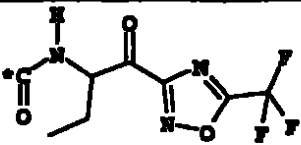
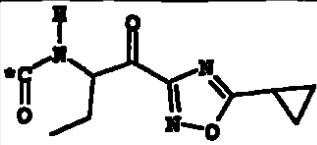
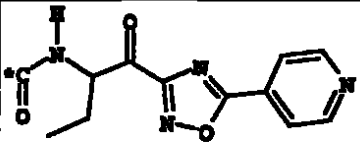
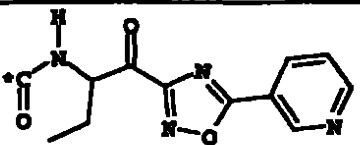
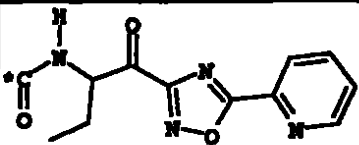
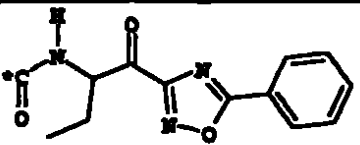
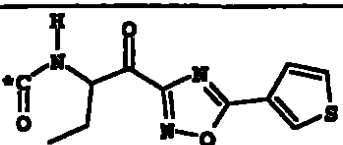
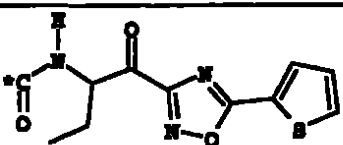
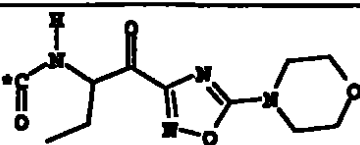
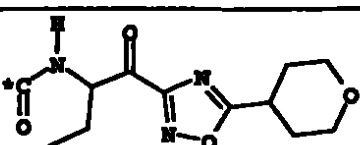
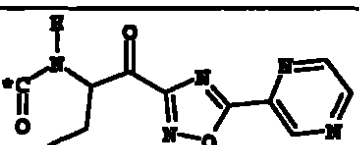
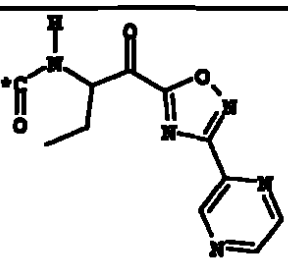
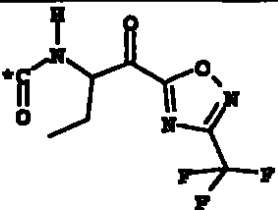
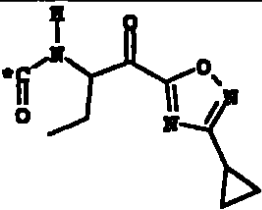
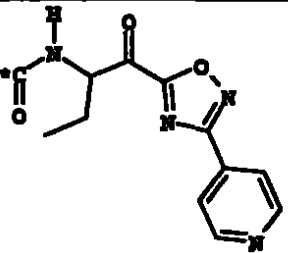
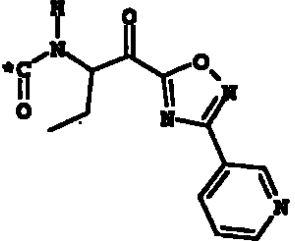
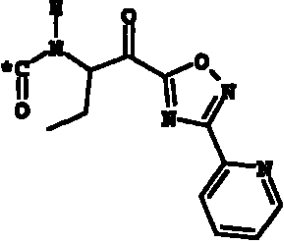
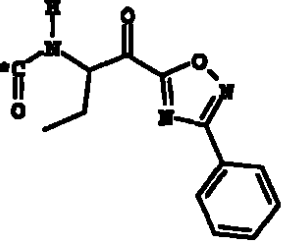
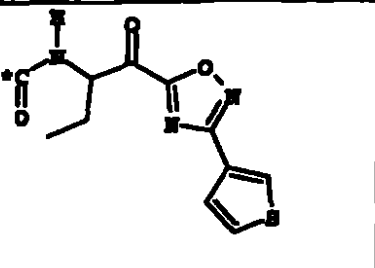
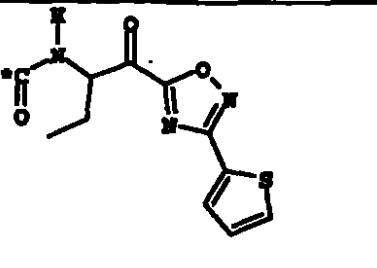
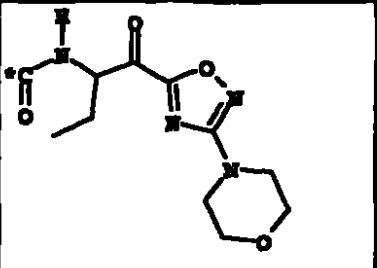
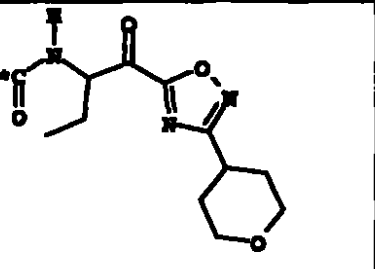
B67		B68		B69	
B70		B71		B72	
B73		B74		B75	
B76		B77		B78	
B79		B80		B81	
B82		B83		B84	

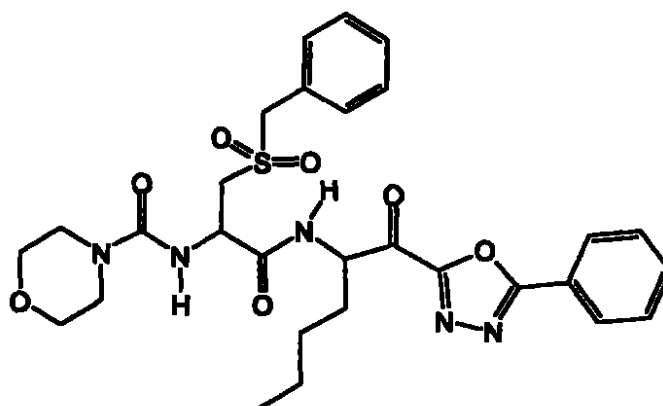
TABLE 3

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		C38		C39	
C40					

Thus, for example, the combination A2-B1-C2, that is, the combination of group A2 in Table 1 and B1 in Table 2 and C2 in Table 3, represents a compound of the invention, namely morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide:



Further particular compounds of the present invention include:

morpholine-4-carboxylic acid {2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-[1,1-dimethyl-2-oxo-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-ethylcarbamoyl]-ethyl}-amide;

10 morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide (Compound 1; A2, B1, C2);

morpholine-4-carboxylic acid {2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide (Compound

2; A2, B2, C1);

morpholine-4-carboxylic acid [1-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide;

morpholine-4-carboxylic acid {2-(2-methyl-propane-1-sulfonyl)-1-[1-(3-thiophen-2-yl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;

morpholine-4-carboxylic acid [1-[1-(3-tert-butyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide;

morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide;

morpholine-4-carboxylic acid {(R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-(5-trifluoromethyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide;

morpholine-4-carboxylic acid [(1-[(1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl)-amide;

{(R)-2-(2-methyl-propane-1-sulfonyl)-1-[(S)-1-(5-thiophen-3-yl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide;

morpholine-4-carboxylic acid {(R)-1-[(S)-1-(3-tert-butyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-amide;

morpholine-4-carboxylic acid {(R)-2-(2-methyl-propane-1-sulfonyl)-1-[(S)-1-(5-trifluoromethyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide;

morpholine-4-carboxylic acid {(R)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide;

morpholine-4-carboxylic acid {(R)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide;

morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;

morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-ethyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;

morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;

morpholine-4-carboxylic acid {2-(2-methyl-propane-1-sulfonyl)-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;

morpholine-4-carboxylic acid [1-[1-(3-ethyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide;

morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(3-phenyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;

5 morpholine-4-carboxylic acid {1-[1-(3-ethyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide;

morpholine-4-carboxylic acid {1-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide;

10 morpholine-4-carboxylic acid {1-[1-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide;

morpholine-4-carboxylic acid {2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-[1,1-dimethyl-2-oxo-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-ethylcarbamoyl]-ethyl}-amide;

and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable

15 salts and solvates (e.g. hydrates), and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Pharmacology and Utility:

The compounds of the invention are selective inhibitors of cathepsin S and, as
20 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
25 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
30 plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsin 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 25-28, *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 60 milligram per kilogram body weight (mg/kg) per day, typically from about 1 $\mu\text{g/kg/day}$ to about 20 mg/kg/day . Therefore, a therapeutically effective amount for an 80 kg human patient may range from about 80 $\mu\text{g/day}$ to about 4.8 g/day, typically from about 80 $\mu\text{g/day}$ to about 1.6 g/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). 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 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 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.,
5 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 depending upon the type of formulation, size of a unit dosage, kind of excipients and other
10 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
15 libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula (I) are described in Example 29, *infra*.

Chemistry:

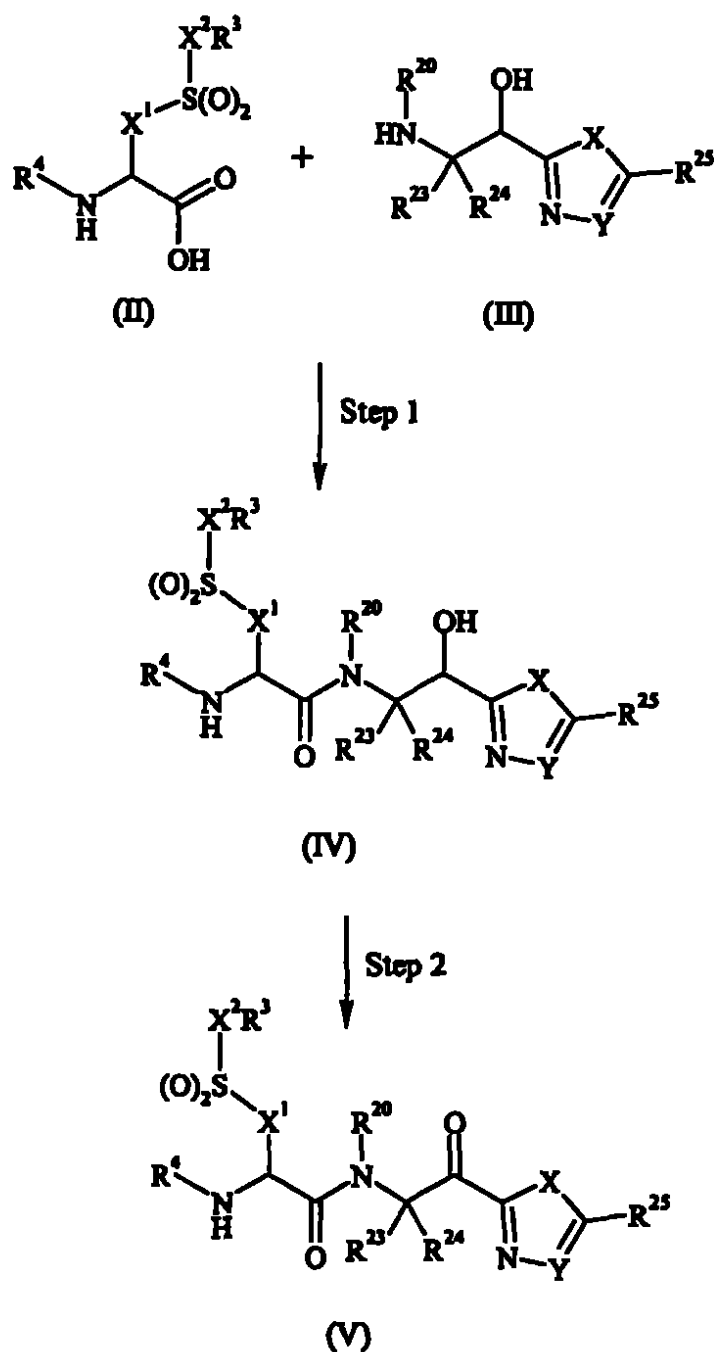
Processes for Making Compounds of Formula (I):

Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R.C. Larock in *Comprehensive Organic Transformations*,
25 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 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
30 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 group of formula (a) (as defined in the Summary of the Invention), i.e. compounds of Formula (V), can be prepared by proceeding as in the following Reaction Scheme 1:

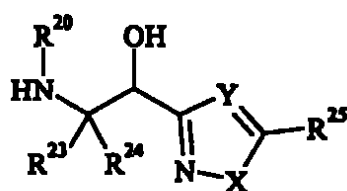
Reaction Scheme 1



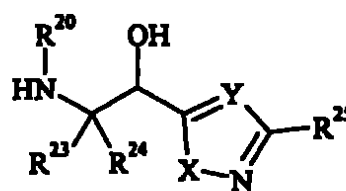
in which each X , X^1 , X^2 , Y , R^3 , R^4 , R^{20} , R^{23} , R^{24} and R^{25} are as defined for Formula
 5 (I) in the Summary of the Invention. Thus, in step 1, an acid of formula (II) may be condensed with an amino compound of formula (III) to give a β -hydroxy amide of formula (IV). The condensation 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),
 5 *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. The β -hydroxy amide of formula (IV) may then be oxidized, in step 2, to give
 a compound of formula (V). The oxidation reaction may conveniently be carried out using
 10 Dess-Martin periodinane in an inert solvent, such as dichloromethane, and at a temperature
 from about 0°C to about room temperature.

Compounds of Formula (I), where X^3 is a group of formula (b) (as defined in the
 Summary of the Invention), can be prepared by proceeding as in Reaction Scheme 2 but
 15 using an amino compound of formula (VI). Compounds of Formula (I), where X^3 is a
 compound of formula (c) (as defined in the Summary of the Invention), can be prepared
 by proceeding as in Reaction Scheme 2 but using an amino compound of formula (VII),



(VI)



(VII)

in which each X, Y, R^{20} , R^{23} , R^{24} and R^{25} are as defined for formula (I) in the Summary
 of the Invention.

25 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 20, *infra*.

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. 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).

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, 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 a 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).

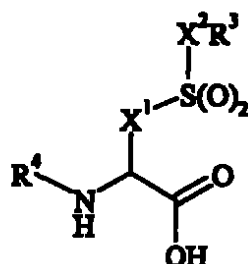
Protected derivatives of the compounds of Formula (I) can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

Compounds of the present invention may be conveniently prepared, or formed during the 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 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 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:

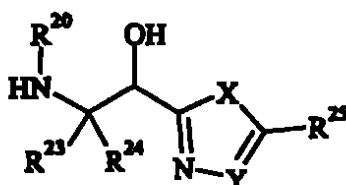
(A) reacting a compound of Formula (II):



5

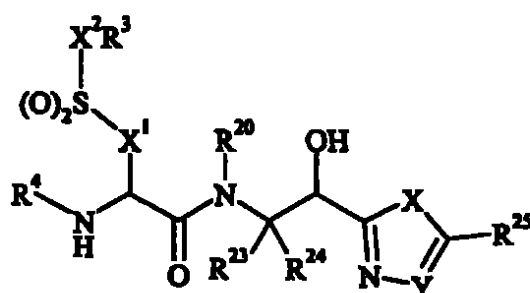
(II)

with a compound of the Formula (III):



(III)

followed by oxidation of the resulting β -hydroxy amide (IV):



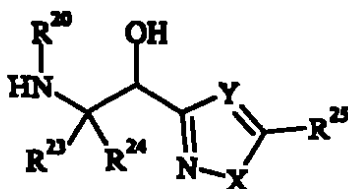
10

(IV)

in which X, Y, X¹, X², R³, R⁴, R²⁰, R²³, R²⁴ and R²⁵ are as defined in the Summary of the Invention for Formula (I); or

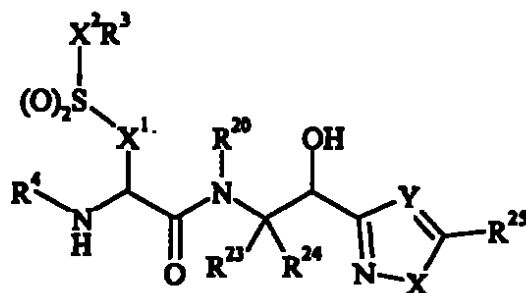
(B) reacting a compound of Formula (II) with a compound of the formula (VI):

15



(VI)

followed by oxidation of the resulting β -hydroxy amide (VIII):

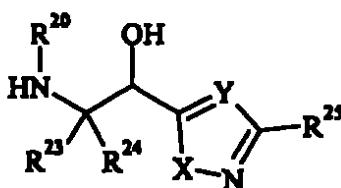


5

(VIII)

in which X, Y, R²⁰, R²³, R²⁴ and R²⁵ are as defined in the Summary of the Invention for Formula (I); or

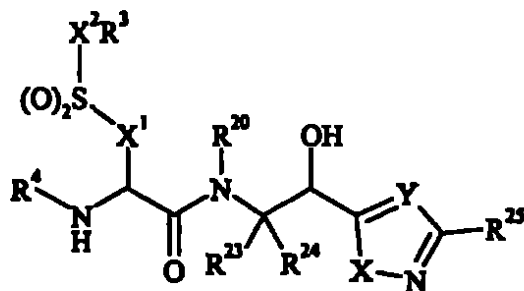
(C) reacting a compound of Formula (II) with a compound of the formula (VII):



10

(VII)

followed by oxidation of the resulting β -hydroxy amide (IX):



(IX)

15

in which X, Y, R²⁰, R²³, R²⁴ and R²⁵ 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;
- (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;
- 5 (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
- 10 non-derivatized form.

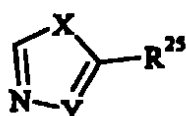
Intermediates of formula (II), wherein X^1 is methylene, X^2 is methylene and R^3 and R^4 are as hereinbefore defined, may be prepared by: (i) alkylation of cysteine with an alkyl bromide of formula R^3CH_2Br [the reaction may conveniently be carried out in the

15 presence of an alkali metal hydroxide, such sodium hydroxide, in ethanol and at a temperature up to about 40°C]; (ii) reaction with a compound of formula R^4-Cl (e.g. morpholine carbonyl chloride) in the presence of a suitable base, such as triethylamine, in an inert solvent, such as acetonitrile, and at room temperature; (iii) oxidation, for example with H_2WO_4 and hydrogen peroxide, in a suitable solvent, such as isopropyl alcohol, and

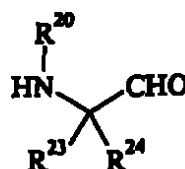
20 at a temperature at about 15-20°C.

Intermediates of formula (III), wherein X , Y , R^{20} , R^{23} , R^{24} and R^{25} are as hereinbefore defined, may be prepared by: (i) treatment of compounds of formula (X) [wherein X , Y and R^{25} are as hereinbefore defined] with butyl lithium in an inert solvent, such as

25 tetrahydrofuran, at a temperature at about -78°C; (ii) treatment of the resulting anion with magnesium bromide dietherate at a temperature at about -78°C; (iii) reaction of the resulting Grignard with an aldehyde of formula (XI) [wherein R^{20} , R^{23} and R^{24} are as hereinbefore defined at a temperature at about -45°C.



(X)

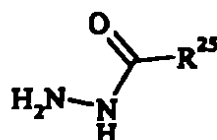


(XI)

The preparation of intermediates of formula (III) may be conveniently carried out with the NH of compounds of formula (XI) protected, with for example a Boc group.

5

Compounds of formula (X), wherein X, Y and R^{25} are as hereinbefore defined, may be prepared by reaction of hydrazones of formula (XII)



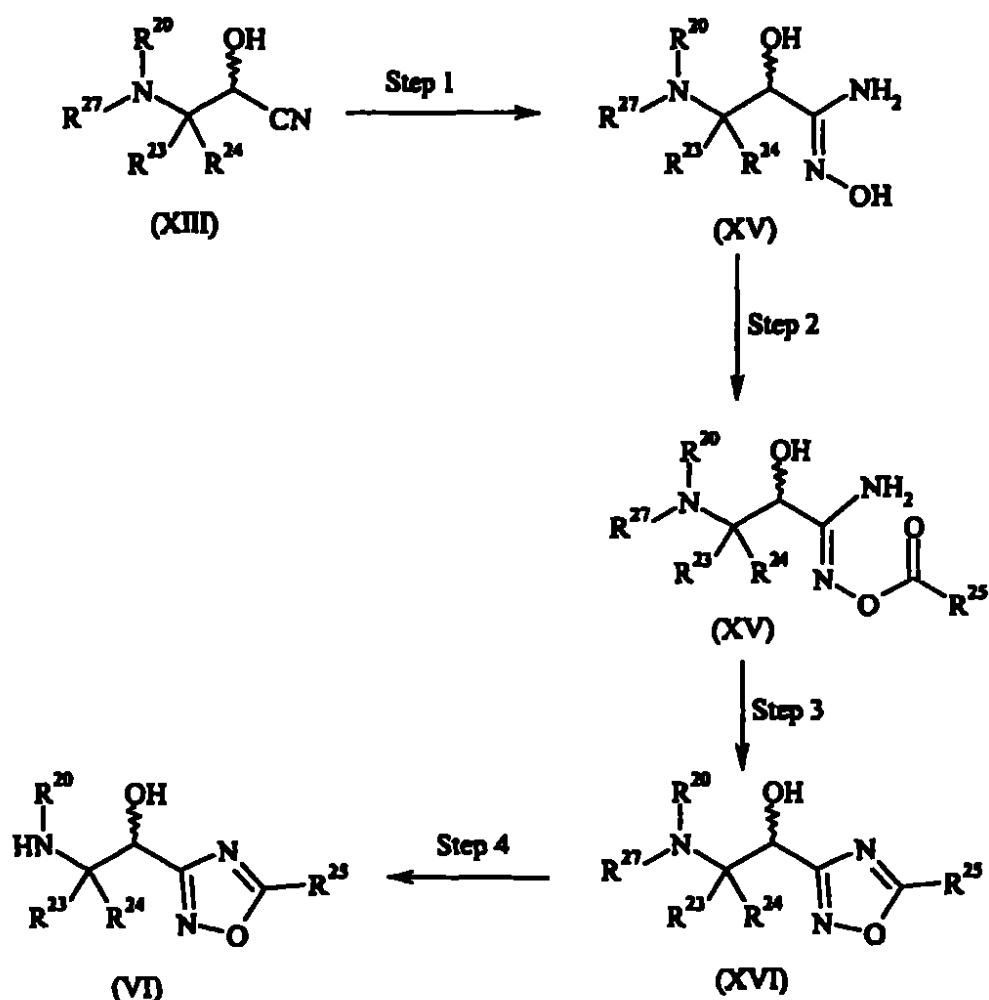
(XII)

- 10 wherein R^{25} is as hereinbefore defined, with triethylorthoformate, in the presence of an acid catalyst, such as para-toluenesulfonic acid, and at a temperature up to about 125°C.

Intermediates of formula (VI), wherein X, Y, R^{20} , R^{23} , R^{24} and R^{25} are as hereinbefore defined, may be prepared as in the following reaction scheme 2:

15

Reaction Scheme 2



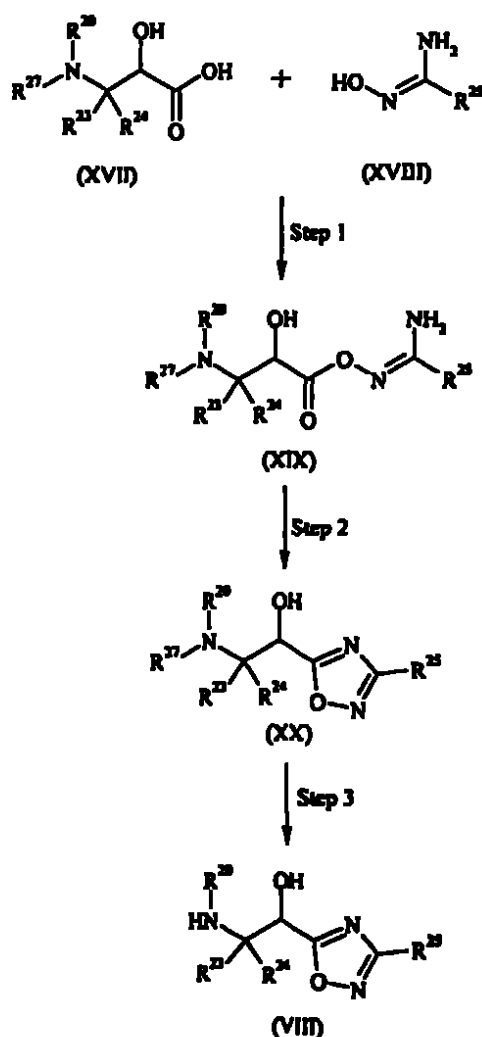
Thus, in step 1, α -hydroxy nitriles of formula (XIII) [wherein R^{20} , R^{23} , R^{24} and R^{25} are as hereinbefore defined and R^{27} is a suitable protecting group, such as *tert*-butyloxycarbonyl, may be reacted with hydroxylamine in the presence of an alkali metal alkoxide, such as sodium methoxide, in methanol and at 0°C . The resulting compounds of formula (XIV) [wherein R^{20} , R^{23} , R^{24} , R^{25} and R^{27} are as hereinbefore defined] may then be coupled, in step 2, with acids of formula $R^{25}-CO_2H$ [wherein R^{25} is as hereinbefore defined] in the presence of an appropriate coupling agent [e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI)] and optionally an appropriate catalyst [e.g. 1-hydroxybenzotriazole (HOBt)] and a non-nucleophilic base [e.g. triethylamine] at about room temperature. The resulting compounds of formula (XV) [wherein R^{20} , R^{23} , R^{24} , R^{25} and R^{27} are as hereinbefore defined] may

then be cyclised, in step 3, by heating in an inert solvent, such as diglyme, at a temperature from about 150°C to about 200°C in a microwave reactor. The cyclised compounds of formula (XVI) [wherein R²⁰, R²³, R²⁴, R²⁵ and R²⁷ are as hereinbefore defined] may then be deprotected, in step 4, to give intermediates of formula (VI) [for example when R²⁷ is *tert*-butoxycarbonyl the deprotection is conveniently carried out by treatment with trifluoroacetic acid at room temperature].

Intermediates of formula (VII), wherein X, Y, R²⁰, R²³, R²⁴ and R²⁵ are as hereinbefore defined, may be prepared as in the following reaction scheme 3:

10

Reaction Scheme 3



Thus, in step 1, α-hydroxy acids of formula (XVII) [wherein R²⁰, R²³, R²⁴ and R²⁷ are as hereinbefore defined] may be reacted with N-hydroxy-amidines of formula

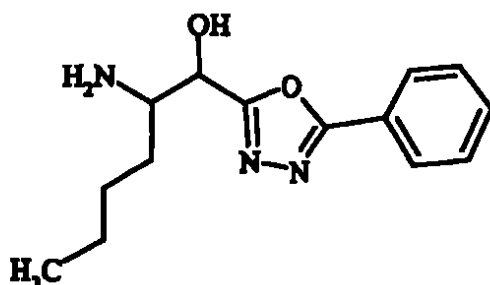
(XVIII) [wherein R^{25} is as hereinbefore defined] in the presence of a suitable coupling agent, such as N-cyclohexylcarbodiimide-N'-methyl polystyrene, in an inert solvent, such as dichloromethane and at a temperature at about 0°C. The resulting compounds of formula (XIX) [wherein R^{20} , R^{23} , R^{24} , R^{25} and R^{27} are as hereinbefore defined] are then cyclised, in step 2, by heating in a microwave reactor in an inert solvent, such as tetrahydrofuran, at a temperature at about 180°C. The resulting oxadiazoles of formula (XX) [wherein R^{20} , R^{23} , R^{24} , R^{25} and R^{27} are as hereinbefore defined] may then be deprotected, in step 4, to give intermediates of formula (VI) [for example when R^{27} is *tert*-butoxycarbonyl the deprotection is conveniently carried out by treatment with Silicycle triamine-3 in an inert solvent, such as dichloromethane, and at room temperature].

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

2-Amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-hexanol



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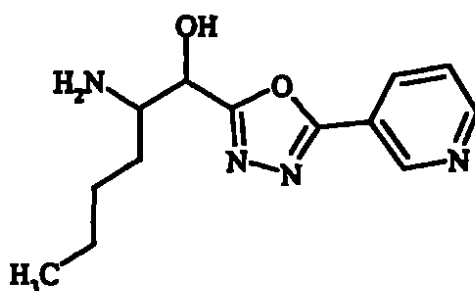
A mixture of the benzoylhydrazide (22.5g, 165mmol), triethylorthoformate (150ml) and p-toluenesulfonic acid (300mg) was heated at 120°C for 12 hours. Excess triethylorthoformate was removed under vacuum and the residue was subjected to silica gel column chromatography to produce 2-phenyl-[1,3,4]oxadiazole (14.5g); H^1 NMR $[(CD_3)_2SO]$: δ 9.34 (1H, s), 8.05-7.98 (2H, m), 7.68-7.55 (3H, m); MS: 147.4 (M+1)

25

To a stirred solution of 2-phenyl-[1,3,4]oxadiazole (1.46g, 10mmol) in THF (40ml) was added n-BuLi (1.6M solution in 6.2ml of hexane) drop-wise under N₂ at -78°C. After 1 hour, MgBr.Et₂O (1.29g, 5mmol) was added and the reaction mixture was allowed to warm to -45°C for 1 hour before being treated with 2-Boc-Nlu-aldehyde (1.07g, 5mmol) in THF (20ml). The reaction mixture was stirred for 1 hour, quenched with saturated NH₄Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO₄ and concentrated. The residue was subjected to silica gel column chromatography to yield 2-(2-Boc-amino-1-hydroxyhexyl)-5-phenyl-[1,3,4]oxadiazole (800mg); MS: 360.2 (M-1), 362.6 (M+1), 364.6 (M=23).

2-(2-Boc-amino-1-hydroxyhexyl)-5-phenyl-[1,3,4]oxadiazole (130mg, 0.36mmol) and MeCl₂ (5ml) were mixed and TFA (1ml) was added at room temperature. After stirring for 1 hour, the solvent and excess TFA were removed under vacuum to produce 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-hexanol.

REFERENCE 2

2-Amino-1-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-hexan-1-ol

To a stirred solution of 2-(3-pyridyl)-[1,3,4]oxadiazole (500mg, 3.4mmol), in THF (20ml) was added n-BuLi (1.6M solution in 2.1ml of hexane) drop-wise under N₂ at -78°C.

After 1 hour, MgBr.Et₂O (808.6g, 3.4mmol) was added and the reaction mixture was allowed to warm to -45°C for 1 hour before being treated with 2-Boc-Nlu-aldehyde (511g, 2.38mmol) in THF (10ml). The reaction mixture was stirred for 1 hour, quenched with saturated NH₄Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO₄ and concentrated. The residue was subjected to silica gel column chromatography to yield 2-(2-Boc-amino-1-hydroxyhexyl)-5-(3-pyridyl)-[1,3,4]oxadiazole

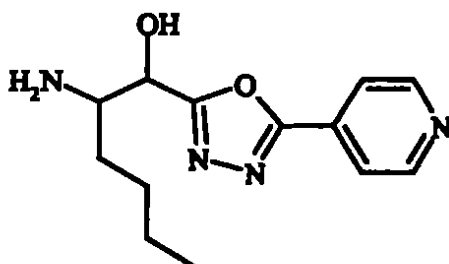
(200mg); MS: 361.4 (M-1), 363.2 (M+1).

2-(2-Boc-amino-1-hydroxyhexyl)-5-(3-pyridyl)-[1,3,4]oxadiazole (100mg, 0.27mmol) and MeCl₂ (5ml) were mixed and TFA (1ml) was added at room temperature.

After stirring for 1 hour, the solvent and excess TFA were removed under vacuum to produce 2-amino-1-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-hexan-1-ol.

REFERENCE 3

2-Amino-1-(5-(4-pyridyl)-[1,3,4]oxadiazol-2-yl)-1-hexanol



10 A mixture of the isonicotinic hydrazide (13.7g, 100mmol), triethylorthoformate (60ml) and p-toluenesulfonic acid (30mg) was heated at 130°C for 12 hours. Excess triethylorthoformate was removed under vacuum. The residue was crystallized from ethyl acetate to give 2-(4-pyridyl)-[1,3,4]oxadiazole (14.8g); ¹H NMR [(CD₃)₂SO]: δ 9.46 (1H, s), 8.8 (2H, dd), 7.9 (2H, dd).

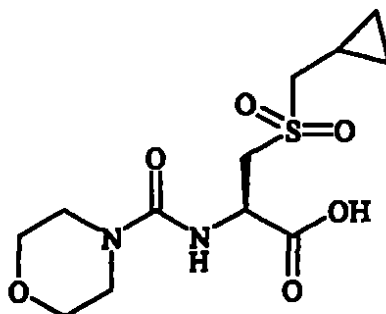
15 To a stirred solution of 2-(4-pyridyl)-[1,3,4]oxadiazole (2.94g, 20mmol) in THF (80ml) was added n-BuLi (1.6M solution in 12.5ml of hexane) drop-wise under N₂ at -78°C. After 1 hour, MgBr.Et₂O (5.16g, 20mmol) was added and the reaction mixture was allowed to warm to -45°C for 1 hour before being treated with 2-Boc-Nlu-aldehyde (2.58g, 12mmol) in THF (20ml). The reaction mixture was stirred for 1 hour, quenched with
20 saturated NH₄Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO₄ and concentrated. The residue was subjected to silica gel column chromatography to yield 2-(2-Boc-amino-1-hydroxyhexyl)-5-(4-pyridyl)-1,3,4-oxadiazole (950mg); MS: 361.4 (M-1), 363.4 (M+1).

25 2-(2-Boc-amino-1-hydroxyhexyl)-5-(4-pyridyl)-1,3,4-oxadiazole (950mg, 2.62mmol) and MeCl₂ (5ml) were mixed and TFA (1ml) was added at room temperature.

After stirring for 1 hour, the solvent and excess TFA were removed under vacuum to produce 2-amino-1-(5-(4-pyridyl)-[1,3,4]oxadiazol-2-yl)-1-hexanol TFA salt (1g); MS: 263.0 (M+1).

5

REFERENCE 4

3-Cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid

Step 1

To a suspension of L-cysteine (100 g) in ethanol (850 mL) under nitrogen was added over
10 40 min a solution of sodium hydroxide (2.0eq., 64.6 g) in ethanol (650mL) (the sodium hydroxide solution was maintained below 40°C during its preparation, 3 hours for complete dissolution). After the addition, cyclopropylmethyl bromide (1.1eq., 122.5g) was added over 20 minutes while maintaining the temperature at 25-30°C with a cold bath. The resulting white slurry was stirred for another 18 hours and then quenched by adding
15 2N HCl (0.73eq., 300mL) over 20 minutes. The thick suspension was concentrated (100mbars, 52°C bath) to about 400mL (1.5L ethanol/water distilled) and then water (750mL) was added. The pH (9.6) was adjusted to pH 6.5 with 2N HCl and the mixture was stirred at 4°C for 2 hours and then filtered. The cake was washed five times with water (100mL) and then dried in vacuum to afford S-cyclopropylmethyl-L-cysteine
20 (128.2g, 88.6% yield).

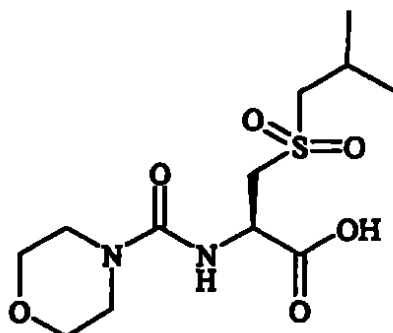
Step2

Triethylamine (2.2eq., 176mL) was added over 15 minutes to a suspension of S-cyclopropylmethyl-L-cysteine (100g) in acetonitrile (1.5L) and water (150mL) under nitrogen. Morpholine carbonyl chloride (1.15eq., 100g) was added to the suspension over
25 4hours at room temperature. The resulting solution was stirred for another 18hours at room

temperature and the mixture was concentrated to about 400mL (100mbars, 50°C bath). The mixture was diluted with water (250mL) and the pH (5.3) was adjusted to 12.5 by adding 2N sodium hydroxide (2.1eq., 616mL). The aqueous mixture was washed three times with dichloromethane (500mL). Additional dichloromethane (500mL) was added and the pH was adjusted to pH 2.0-2.5 by adding 2N HCl (1.0eq, 285mL). The aqueous layer was extracted twice with dichloromethane (100mL). The combined acidic extracts were washed with water (100mL) and concentrated to about 400mL. The mixture was then distilled under vacuum ($P \leq 300$ mbar, $temp \leq 50^\circ C$) while maintaining the volume constant by adding isopropyl alcohol (400mL). The mixture was then cooled to 15-20°C and H_2WO_4 (0.02eq., 2.9g) was added followed by 30% hydrogen peroxide solution (2.2eq., 130mL). The mixture was stirred overnight at room temperature then cooled to 0-5°C and a solution of $Na_2S_2O_3$ (0.2eq., 21.6g) in water (100mL) added. The mixture was extracted with ethyl acetate (1.6L), then twice with a mixture of ethyl acetate and isopropyl alcohol (500mL, 7/3, v/v). The combined organic layers were dried over Na_2SO_4 (300g) and then concentrated to about 250mL. Residual isopropyl alcohol was distilled under vacuum, keeping the volume constant by adding ethyl acetate (250mL). The resulting slurry was stirred at room temperature for another hour and then filtered. The solid was washed twice with ethyl acetate (50mL) and then dried in vacuum to afford the cyclopropyl sulfone (182.6 g, 64.8 % yield). The filtrate was concentrated in vacuum, more product was isolated from ethyl acetate (150mL), washed twice with ethyl acetate (50mL) and then dried to afford another 27.2g of acid (14.9%). ^1H NMR (DMSO- d_6): 12.9 (bs, 1H), 7.16 (d, 1H), 4.5 (m, 1H), 3.6-3.42 (m, 5H), 3.35-3.2 (m, 5H), 3.15-3.0 (m, 2H), 1.0 (m, 1H), 0.6 (m, 2H), 0.3 (m, 2H). MS: 321 (MH^+).

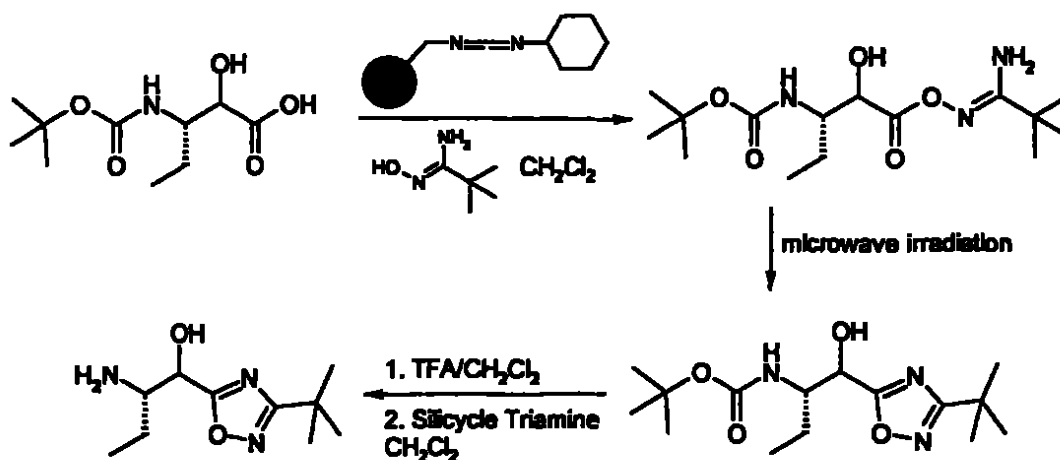
REFERENCE 5

3-(2-Methyl-propane-1-sulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid



By proceeding in a similar manner to Reference Example 4 above but using isobutyl bromide instead of cyclopropylmethyl bromide, and 10 N sodium hydroxide solution instead of ethanolic sodium hydroxide, in Step 1 there was prepared 3-(2-methyl-propane-1-sulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid. ¹H NMR (CDCl₃): 10.0 (bs, 1H), 6.1 (d, 1H), 4.8 (m, 1H), 3.75-3.6 (m, 6H), 3.5-3.3 (m, 4H), 3-2.85 (d, 2H), 2.35 (m, 1H), 1.1 (d, 6H). MS: 323 (MH⁺).

REFERENCE 6

(S)-2-Amino-1-(3-tert-butyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol

A solution of (S)-3-tert-butoxycarbonylamino-2-hydroxy-pentanoic acid (1.63g, 7mmol) and N-hydroxy-2,2-dimethyl-propionamidine (0.9g, 7.75mmol) in dichloromethane (40mL) was stirred at 0°C. N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.92mmol/g, 5.1g, 9.8mmol) was added in portions. The reaction mixture was stirred under nitrogen for one hour. The reaction mixture was filtered, the resin washed with dichloromethane and the filtrate evaporated under vacuum to dryness. The residue was dissolved in THF (20mL), the solution split into five equal parts, which were filled into microwave reactor

vials and heated in a microwave reactor at 180°C for three minutes. The reactors were cooled to room temperature, the solutions combined and the THF evaporated under vacuum. The residue was subjected to flash chromatography (eluting with a gradient from 5% to 65% ethyl acetate in heptane) to give a colorless oil [LC/MS $m/z=336$ ($M+Na^+$), 214 ($M+H^+-Boc$)].

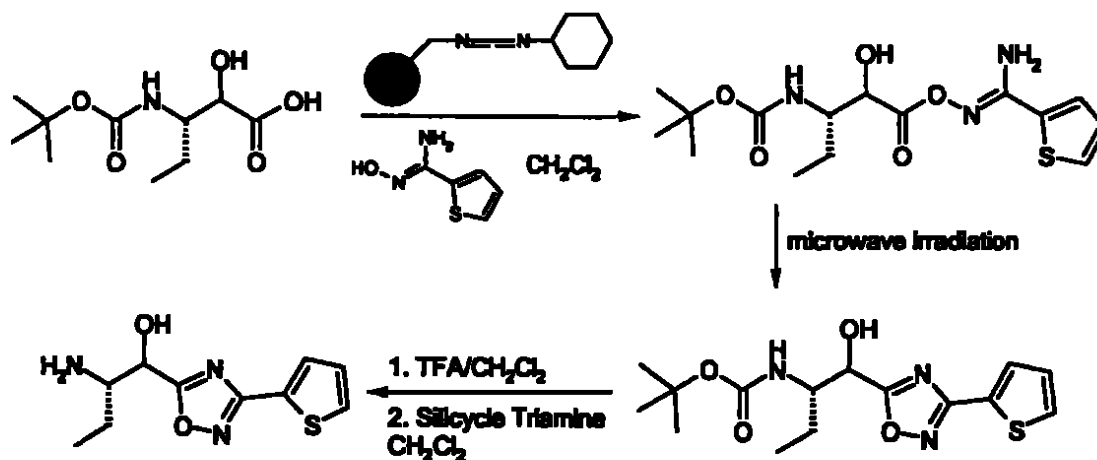
The colorless oil was dissolved in dichloromethane (45mL) and trifluoroacetic acid (5mL) was added. After two hours the reaction was evaporated under vacuum to dryness. The residue was re dissolved in 50mL of dichloromethane. Silicycle triamine-3 (4.19g, 16.45mmol) was added and the mixture stirred at room temperature overnight. The mixture was filtered and washed with dichloromethane. The filtrate was concentrated under vacuum to give (S)-2-amino-1-(3-tert-butyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol (675mg, 45% overall) as a white solid. Obtained as mixture of diastereomers.

^1H NMR ($CDCl_3$, 300MHz): [4.87 (d, $J=4.5Hz$) 4.69 (d, $J=3.5Hz$), 1H], [3.18 (ddd, $J=8Hz$, 5.5Hz, 4Hz) 3.09 (ddd, $J=9Hz$, 2x 4.5Hz), 1H], 1.71-1.21 (m, 2H), 1.40 (s, 9H), [1.04 (t, $J=7.5Hz$) 1.00 (t, $J=7.5Hz$), 3H].

[LC/MS $m/z=214$ ($M+H$)]

REFERENCE 7

(S)-2-Amino-1-(3-thiophen-2-yl-[1,2,4]oxadiazol-5-yl)-butan-1-ol



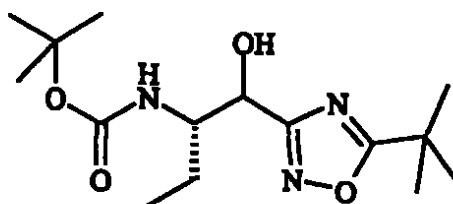
A solution of (S)-3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (2g, 8.6mmol) and N-Hydroxy-thiophene-2-carboxamidine (1.35g, 9.5mmol) in dichloromethane (40 mL)

was stirred at 0°C. N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.90mmol/g, 6.05g, 11.5mmol) was added in portions. The reaction mixture was stirred under nitrogen for four hours at 0°C and then for 15 hours at room temperature. The reaction mixture was filtered, the resin washed with dichloromethane and the filtrate evaporated under vacuum to dryness. The residue was dissolved in tetrahydrofuran (20mL), the solution split into five equal parts, which were filled into microwave reactor vials and heated in a microwave reactor at 180°C for four minutes. The reactors were cooled to room temperature, the solutions combined and the THF evaporated under vacuum. The residue was purified via flash chromatography (eluted with a gradient from 5% to 60% ethyl acetate in heptane) to give a colorless oil. [LC/MS m/z=362 (M+Na⁺), 240 (M+H⁺-Boc)].

The colorless oil was dissolved in dichloromethane (45 mL) and trifluoroacetic acid (5 mL) was added. After two hours the reaction mixture was evaporated under vacuum to dryness. The residue was re dissolved in 50 mL of dichloromethane. Silicycle triamine-3 (3.47g, 13.65mmol) was added and the mixture stirred at room temperature overnight. The mixture was filtered and washed with dichloromethane. The filtrate was concentrated under vacuum to give (S)-2-Amino-1-(3-thiophen-2-yl-[1,2,4]oxadiazol-5-yl)-butan-1-ol, a mixture of diastereomers, (560mg, 27% overall) as off- white solid. ¹H NMR (CDCl₃, 300MHz): [7.84 (d, J=1Hz) 7.82 (d, J=1Hz), 1H], [7.53 (dd, J=5Hz, 1Hz) 7.52 m, 1H], [7.18 (d, J=5Hz) 7.17 (d, J=5Hz), 1H], [4.94 (d, J=5Hz) 4.76 (d, J=4Hz), 1H], [3.26 (ddd, J=8Hz, 5.5Hz, 3.5Hz) 3.13 (ddd, J=9Hz, 2x4.5Hz), 1H], 1.79-1.21 (m, 2H), [1.07 (t, J=7.5Hz) 1.04 (t, J=7.5Hz), 3H]. LC/MS m/z=240 (M+H).

REFERENCE 8

{{(S)-1-[(S-tert-Butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert butyl ester

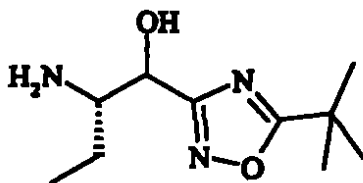


A suspension of {{(S)-1-[Hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic

acid tert-butyl ester (3.24g, 13.12mmol) in toluene (25ml) was treated with trimethyl acetic anhydride (2.93ml, 14.44mmol) and 1-ethyl-3-methyl-1H-imidazolium hexafluorophosphate (0.38g, 1.48mmol) and the mixture heated at 200°C in a microwave (Smith Creator, S00219) for 20 minutes. Solvent evaporated under reduced pressure. The residue was subjected to flash chromatography eluting with a mixture of ethyl acetate and heptane to give [(S)-1-[(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl]-carbamic acid tert butyl ester as a brown oil (2.73 g) (mixture of diastereoisomers).
¹H NMR (CDCl₃): 4.92-4.69 (m, 2H), 4.05-3.85 (m, 1H), 1.73-1.48 (m, 2H), 1.45 & 1.44 (2xs, 9H), 1.43 & 1.39 (2xs, 9H), 0.99 & 0.96 (2xt, J=7.5Hz, 3H). MS: 314 (MH⁺).

REFERENCE 9

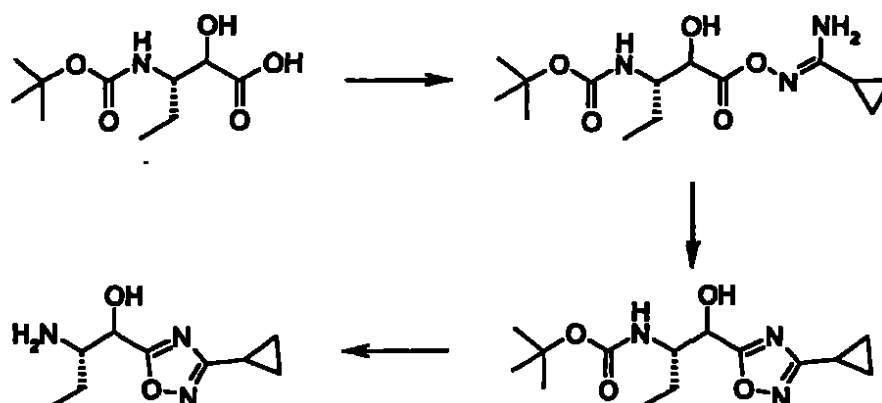
(S)-2-Amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol



A solution of [(S)-1-[(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl]-carbamic acid tert butyl ester (2.11g, 6.72mmol) in methylene chloride (20ml) was treated with trifluoroacetic acid (5.18ml, 67.25mmol) and stirred at room temperature for 3hours. The solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride (100ml) and treated with PS-trisamine from Argonaut Technologies (5.38g, 20.18mmol, 3.75mmol/g loading) and the reaction stirred at room temperature for 4h, filtered and the filtrate evaporated to give (S)-2-amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol as an orange oil (975 mg) (mixture of diastereoisomers). ¹H NMR (CDCl₃): 4.73 & 4.58 (2xd, J=5Hz, 1H), 3.12-3.00 (m, 1H), 2.64-2.31 (bs, 3H), 1.69-1.44 (m, 2H), 1.43 (s, 9H), 0.99 & 0.97 (2xt, J=7.5Hz, 3H). MS: 214 (MH⁺).

REFERENCE 10

(S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol

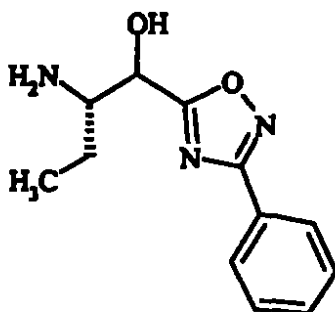


A solution of (S)-3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (2.00g, 8.57mmol) and N-hydroxy-cyclopropanecarboxamidine (1.03g, 10.29mmol) in dichloromethane (20mL) was stirred at 0°C and 1.25 equivalents of N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.70mmol/g, 6.30g, 10.72mmol) was added in portions. The reaction mixture stirred under nitrogen for three hours while warming to 15°C. The reaction mixture was filtered, the resin washed with dichloromethane and the filtrate evaporated under vacuum to dryness. [LC/MS m/z=338 (M+H+Na)].

The residue was dissolved in tetrahydrofuran (20mL) and heated in a microwave reactor (Smith Creator) at 160°C for three minutes, cooled to room temperature and evaporated under vacuum to dryness. [LC/MS m/z=320 (M+H+Na)]. The residue was dissolved in dichloromethane (50mL) and stirred at room temperature as a 50mL solution of 50% trifluoroacetic acid in dichloromethane was added dropwise. After three hours the reaction was evaporated under vacuum to dryness and dissolved in 50mL of dichloromethane again. Three equivalents of Silicycle triamine-3 was added and the mixture stirred at room temperature overnight. The mixture was filtered and washed with dichloromethane. Evaporate under vacuum to give 1.04g (61% overall). [LC/MS m/z=198 (M+H)]

REFERENCE 11

(S)-2-Amino-1-(3-phenyl-1,2,4-oxadiazol-5-yl)-butan-1-ol

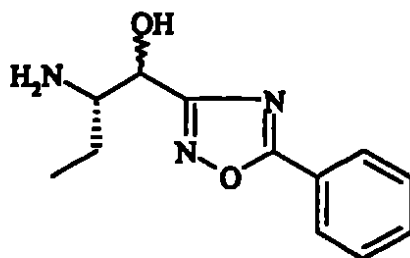


A solution of (S)-3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (2.00g, 8.57mmol) and N-hydroxy-benzamidine (1.3g, 9.5mmol) in dichloromethane (40mL) was stirred at 0°C. N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.90mmol/g, 6g, 11.4mmol) was added in portions. The reaction mixture was stirred under nitrogen for one hour. The reaction mixture was filtered, the resin washed with dichloromethane and the filtrate evaporated under vacuum to dryness. [LC/MS $m/z=352$ ($M+H^+$), 296($M+H^+$ -isobutene)]. The residue was dissolved in tetrahydrofuran (20mL) and heated in a microwave reactor (Smith Creator) at 180°C for three minutes, cooled to room temperature and evaporated under vacuum to dryness. The residue was purified via flash chromatography (eluted with a gradient from 5% to 65% ethyl acetate in heptane) to give the product as a white solid [LC/MS $m/z=356$ ($M+Na^+$), 234 ($M+H^+$ -Boc)].

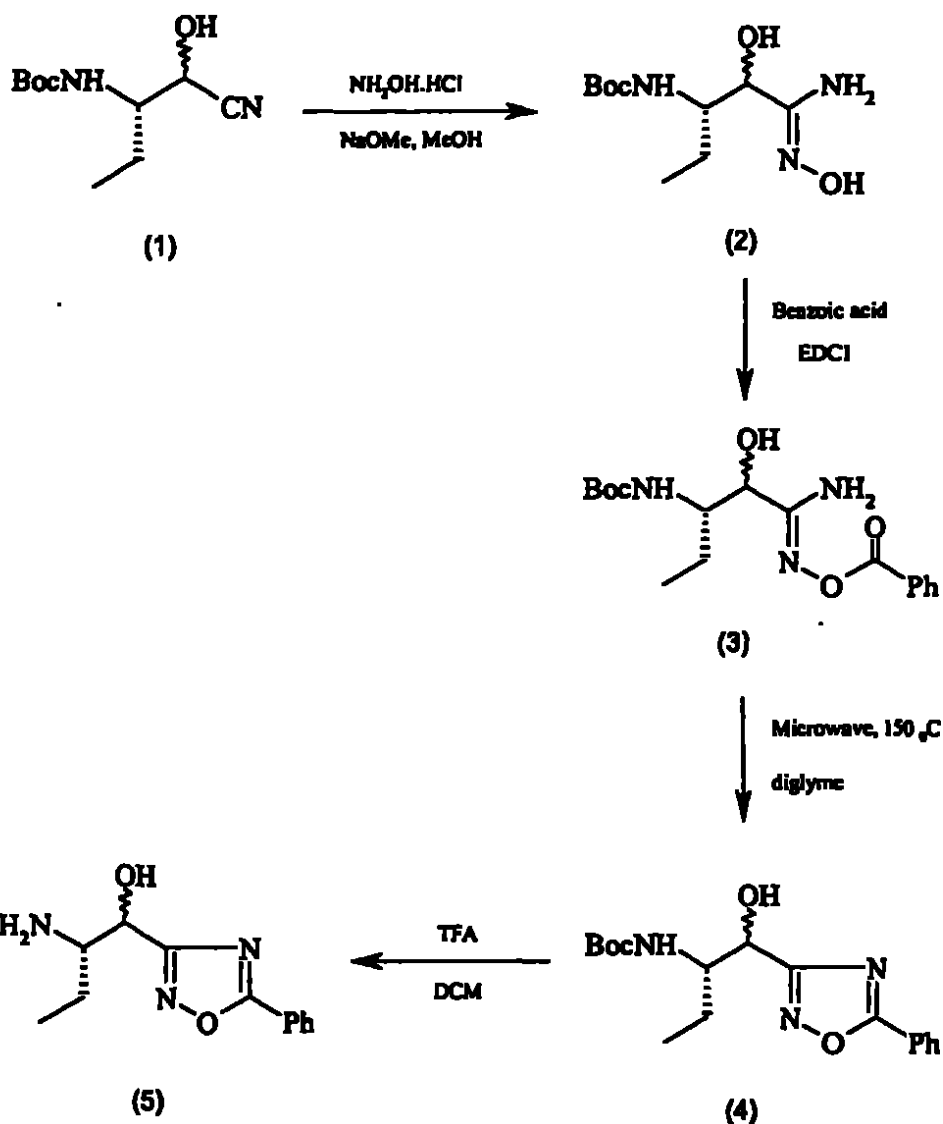
It was dissolved in dichloromethane (45mL) and trifluoroacetic acid (5mL) was added. After two hours the reaction was evaporated under vacuum to dryness. The residue was redissolved in 50mL of dichloromethane. Silicycle triamine-3 (9.9g, 39mmol) was added and the mixture stirred at room temperature overnight. The mixture was filtered and washed with dichloromethane. The filtrate was concentrated under vacuum to give 775mg (38% overall) product as a white solid. [LC/MS $m/z=234$ ($M+H$)]. ^1H NMR ($CDCl_3$) 8.12-8.06 (m, 2H), 7.54-7.45 (m, 3H), 4.93 & 4.75 (2xd, $J=5Hz$ & $3.5Hz$, 1H), 3.25 & 3.11 (2xm, 1H), 1.78-1.42 (2xm, 2H), 1.04 & 1.01 (2x t, $J=7.5Hz$, 3H).

REFERENCE 12

(S)-2-Amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol



Synthesized as described in the following reaction scheme:



5 **[(S)-1-[Hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl]-carbamic acid tert-butyl ester (2)**

A solution of (2-cyano-1-ethyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (9.53g, 44mmol) in methanol (80ml) was cooled to 0°C and treated successively with hydroxylamine hydrochloride (3.05g, 44mmol) in methanol (80ml) and 25% sodium

methoxide solution in methanol (10.2ml). After stirring at 0°C for 5 minutes the reaction mixture stirred at room temperature for 5 hours and then evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was separated, dried (MgSO₄) and then evaporated under reduced pressure. The residual yellow oil was subjected to mpic, eluting with a mixture of ethyl acetate and heptane to give {(S)-1-[hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (3.5g) as white solid. MS: M(H⁺) 248.

{1-[Hydroxy-(N-benzoyloxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (3)

A solution of {1-[hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (2) (2.5g, 10mmol) in dichloromethyl (125ml) was treated with benzoic acid (1.36g, 11mmol), EDCI (2.14 g, 11mmol), HOBT (1.37g, 10mmol) and triethylamine (1.35mL, 11mmol) and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate solution, then water, then dried over Na₂SO₄ and then evaporated under reduced pressure. The residue was subjected to mpic eluting with 1% triethylamine in 2:3 v/v ethyl acetate and heptane mixture to give {1-[hydroxy-(N-benzoyloxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (850mg) as a yellow solid. MS: MH⁺ 352.

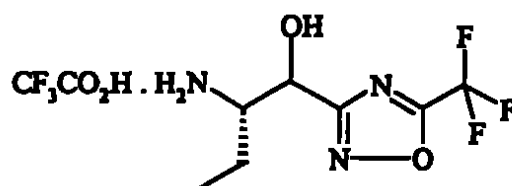
2-Amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol (5)

A solution of (3) (1.5g, 4.3mmol) in diglyme was heated at 150°C in a microwave reactor (Smith Creator, S00219) for 40 minutes. Solvent evaporated under vacuum in Genevac Evaporator at 80°C for 3hours to give a brown solid. This was taken in dichloromethane (40ml) and treated with trifluoroacetic acid at room temperature for 2 hours. Solvent evaporated to dryness under reduced pressure, crude taken in water, washed with DCM, aqueous layer basified with 1M NaOH solution and extracted with dichloromethane. Organic layer dried over Na₂SO₄ and evaporated under reduced pressure to give 2-amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol (300mg) as a pale brown solid. ¹HNMR (CDCl₃) 8.14-8.10 (m, 2H), 7.59-7.47 (m, 3H), 4.83 & 4.65 (d, J= 5Hz,

1H), 3.18-3.05 (2m, 1H), 1.71-1.20(m, 2H), 1.05-0.97 (2Xt, J= 7.2Hz, 3H).

REFERENCE 13

- 5 (S)-2-Amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol; compound with trifluoro-acetic acid



A solution of {(S)-1-[hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (452mg, 1.83mmol) in dioxane (5mL) was treated with trifluoroacetic anhydride (0.349ml, 2.47mmol) and heated at 100°C in a microwave reactor (Smith Creator, S00219) for 7 minutes. Solvent evaporated under reduced pressure and the crude was subjected to flash chromatography eluting with a mixture of ethyl acetate and heptane to give {(S)-1-[hydroxy-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-methyl]-propyl}-carbamic acid tert-butyl ester as a brown solid (476mg) (mixture of diastereoisomers).

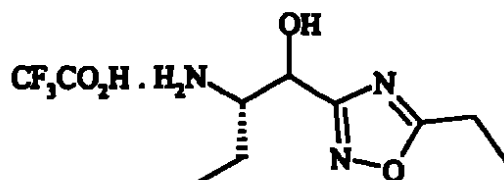
- 15 ¹H NMR (CDCl₃) : 5.00 (d, J=4Hz, 1H), 4.82, 4.65 (bd, J=7Hz, 1H), 4.00, 3.85 (broad m, 1H), 1.78-1.52 (m, 1H), 1.52-1.32 (m, 1H), 1.44, 1.37 (2xs, 9H), 1.02 (2xt, J=7Hz & 4Hz, 3H). MS: 348 (M+Na)

A solution of {(S)-1-[hydroxy-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-methyl]-propyl}-carbamic acid tert-butyl ester (3.6g, 0.011 mol) in methylene chloride (15mL) was treated with trifluoroacetic acid (8.53mL, 0.111 mol) and stirred at room temperature for 3hours. Solvent evaporated under reduced pressure to give (S)-2-amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol; compound with trifluoro-acetic acid as a brown oil (4.42 g) (mixture of diastereoisomers). ¹H NMR (CDCl₃): 8.22 (bs, 2H), 7.04 (bs, 1H), 5.14, 4.90 (d, J=4Hz & 7Hz, 1H), 3.40-3.28 (m, 1H), 1.64-1.37 (m, 2H), 0.80 (2xt, J=7Hz, 3H).

- 25 MS: 226 (MH⁺)

REFERENCE 14

(S)-2-Amino-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol; compound with trifluoroacetic acid



5

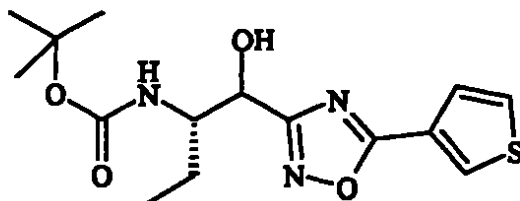
A solution of {(S)-1-[hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (525mg, 2.13mmol) in dioxane (5mL) was treated with propionic anhydride (0.300ml, 2.34mmol) and heated at 150°C in a microwave reactor (Smith Creator, S00219) for 35 minutes. Solvent evaporated under reduced pressure and the crude was subjected to flash chromatography eluting with a mixture of ethyl acetate and heptane to give {(S)-1-
10 [(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester as a yellow solid (406 mg) (mixture of diastereoisomers). ¹H NMR (CDCl₃): 4.98-4.72 (m, 2H), 4.00, 3.88 (m, 1H), 3.64, 3.45 (bs, 1H), 2.89 (2xq, J=7.6 Hz, 2H), 1.69 (m, 1H), 1.47 (m, 1H), 1.45, 1.39 (2xs, 9H), 1.44-1.36 (m, 3H), 0.98 (2xt, J=9Hz & 7Hz, 3H). MS: 308
15 (M+Na)

A solution of {(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester (214mg, 0.751mmol) in methylene chloride (5mL) was treated with trifluoroacetic acid (0.578mL, 7.504mmol) and stirred at room temperature for 3 hours. Solvent evaporated under reduced pressure to give (S)-2-amino-1-(5-ethyl-1,2,4-oxadiazol-
20 3-yl)-butan-1-ol trifluoroacetate, a mixture of diastereoisomers, (224mg) as a brown oil. MS: 186 (MH⁺). ¹H NMR (CDCl₃): 8.10-7.33 (2xbs, 3H), 5.24, 5.07 (d, J=3.5Hz & 5.5Hz, 1H), 3.77, 3.62 (bs, 1H), 2.91 (2xq, J=7 Hz, 2H), 1.78 (m, 1H), 1.76-1.40 (m, 1H), 1.39 (2xt, J=7Hz, 3H), 1.02 (2xt, J=7.5 Hz, 3H).

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REFERENCE 15

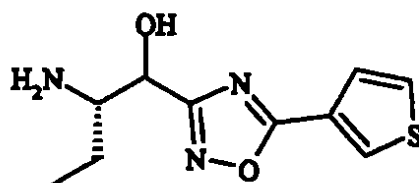
{(S)-1-[Hydroxy-(5-thiophen-3-yl)-1,2,4-oxadiazol-3-yl]-methyl}-propyl}-carbamic acid tert-butyl ester



A suspension of ((S)-1-[hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl)-carbamic acid tert-butyl ester (2.4g, 9.7mmol) in dioxane (15ml) was treated with thiophene carbonyl chloride (1.45g, 9.9mmol) and triethylamine (1.36ml, 9.8mmol) and the mixture heated at 150 °C in a microwave (Smith Creator, S00219) for 15 minutes. Solvent evaporated under reduced pressure. The residue was subjected to flash chromatography eluting with a mixture of ethyl acetate and heptane to give ((S)-1-[hydroxy-(5-thiophen-3-yl-1,2,4-oxadiazol-3-yl)-methyl]-propyl)-carbamic acid tert-butyl ester, a mixture of diastereoisomers, (144 mg) as a brown solid. ¹H NMR (CDCl₃): 8.21 (m, 1H), 7.66 (m, 1H), 7.45 (m, 1H), 4.92-4.69 (m, 2H), 5.02-4.80 (m, 2H), 4.10-3.85 (2xm, 1H), 1.80-1.45 (m, 2H), 1.46 & 1.38 (2xs, 9H), 1.01 & 0.99 (2xt, J=7.5Hz, 3H). MS : 340 (MH⁺).

REFERENCE 16

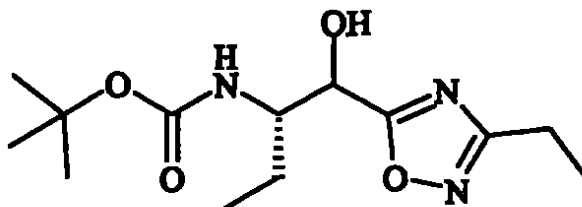
15 (S)-2-Amino-1-(5-thiophen-3-yl-1,2,4-oxadiazol-3-yl)-butan-1-ol



By proceeding in a similar manner to that described for Reference Example 9 above, but using there was prepared (S)-2-amino-1-(5-thiophen-3-yl-1,2,4-oxadiazol-3-yl)-butan-1-ol. ¹H NMR (CDCl₃): 8.24-8.18 (2xdd, J=1Hz & 3Hz, 1H), 7.69-7.62 (2xdd, J=1Hz & J=5Hz, 1H), 7.43 (dd, J=3.0Hz & J=5.0Hz), 4.88 & 4.70 (2xd, J=4.4Hz, 1H), 3.27-3.11 (m, 1H), 3.05-2.45 (bs, 3H), 1.74-1.21 (m, 2H), 1.02 & 0.99 (2xt, J=7.5Hz, 3H). MS: 240 (MH⁺).

REFERENCE 17

{{(S)-1-[(3-Ethyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester



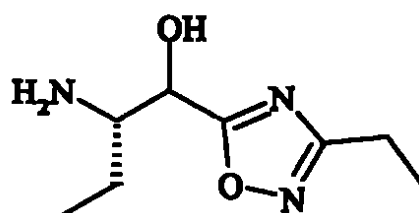
5

A solution of (S)-3-tert-butoxycarbonylamino-2-hydroxy-pentanoic acid (4.00g, 17.2mmol) and N-hydroxy-propionamidine (1.87g, 21.5mmol) in dichloromethane (50mL) was stirred at 0°C and N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.90mmol/g, 10g, 19mmol) was added in portions. The reaction mixture was stirred under nitrogen for three hours while warming to 15°C and stirred at room temperature for 48 hours. The reaction mixture was filtered, the resin washed three times with dichloromethane (50mL), the filtrate evaporated under vacuum to dryness and subjected to flash column chromatography eluting with 10% MeOH in dichloromethane to give a foam (3.51g). A portion (340mg) of this material was dissolved in tetrahydrofuran (1.5mL) and the solution was heated in a microwave reactor (Smith Creator) at 150°C for three minutes, cooled to room temperature then evaporated under vacuum to dryness. The residue was subjected to flash column chromatography eluting with 5% methanol in dichloromethane to give {{(S)-1-[(3-ethyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester as viscous oil (236mg). MS: 308 (M+Na⁺).

20

REFERENCE 18

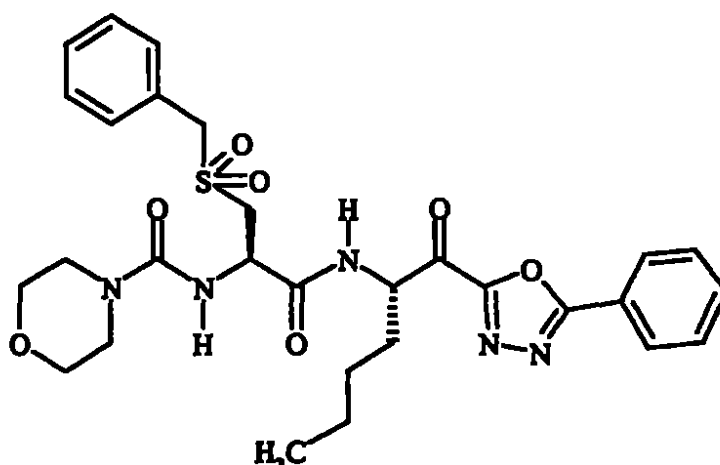
(S)-2-Amino-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-butan-1-ol



A solution of {(S)-1-[(3-ethyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester (3.67g, 12.87mmol) in dichloromethane (50mL) was treated with trifluoroacetic acid (10mL) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with toluene then evaporated under vacuum to dryness. The residue was dissolved in dichloromethane (75mL) and the solution was treated with MP-Carbonate (3.3mmol/g, 6.0 g). This mixture was stirred at room temperature overnight, then filtered, then washed with 10% dichloromethane methanol and evaporated under vacuum to give (S)-2-amino-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-butan-1-ol, a mixture of diastereomers, (2.26g). ¹H NMR [(CD₃)₂SO]: δ 4.61 and 4.54 (d, J = 5Hz, 1H), 2.86 (m, 1H), 2.71 (q, J=8Hz, 2H), 1.6-1.0 (2xm, 2H), 1.22 (t, J = 8Hz, 3H), 0.88 (m, 3H). MS m/z 186 (M+H) .

EXAMPLE 1

Morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide
(Compound 1)



To a stirred mixture of 2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (135mg, 0.37mmol), 2-amino-1-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1-hexanol TFA salt (135mg, 0.36mmol), prepared as in Reference 1, and HOBT (66mg, 0.43mmol) in MeCl₂ (5ml), was added EDC (103.6mg, 0.54mmol) and N-methylmorpholine (0.4ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated

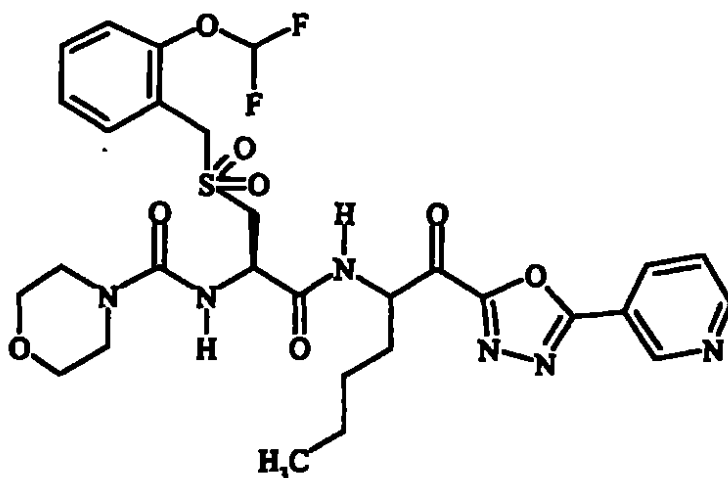
NaHCO₃, brine, dried with MgSO₄ and concentrated. The residue was subjected to silica gel column chromatography to yield morpholine-4-carboxylic acid (1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-2-phenylmethane-sulfonyl-ethyl)-amide (150mg); MS: 598.6 (M-1), 600.6 (M+1).

- 5 Morpholine-4-carboxylic acid (1-{1-[hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-2-phenylmethane-sulfonyl-ethyl)-amide (150mg, 0.25mmol), in MeCl₂ (5ml), was treated with Dess-Martin periodinane (183mg, 0.43mmol) at room temperature. After stirring for 1 hour, 5ml of saturated Na₂S₂O₃-NaHCO₃ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with MgSO₄ and concentrated. The residue was purified with silica gel column chromatography to yield morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide (84mg); H¹ NMR(DMSO-d): 8.71 (1H, d, J=6.6Hz, NH), 8.12-8.05 (2H, m), 7.75-7.59 (3H, m), 7.38-7.36 (5H, m), 7.04 (1H, d, J=8.1Hz, NH), 5.12-5.01 (1H, m), 4.8-4.65 (1H, m), 4.47 (2H, s), 3.58-3.46 (4H, m), 3.35-3.2 (6H, m), 2.05-1.85 (1H, m), 1.8-1.65 (1H, m), 1.5-1.2 (4H, m), 0.87 (3H, t, J=6.9Hz, CH₃); MS: 596.8 9M-1), 598.6 (M+1).

EXAMPLE 2

- 20 Morpholine-4-carboxylic acid {2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide

(Compound 2)



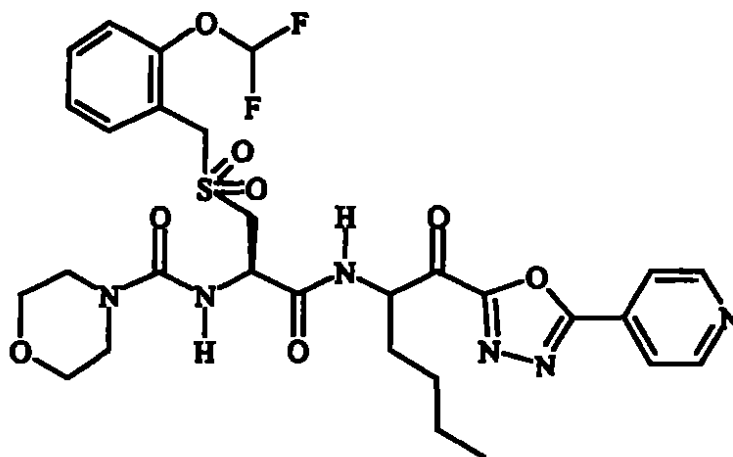
To a stirred mixture of 2-[(morpholine-4-carbonyl)-amino]-3-o-difluoromethoxyphenylmethane-sulfonyl-propionic acid (105.5mg, 0.25mmol), 2-amino-1-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-hexan-1-ol TFA salt (101.6mg, 0.27mmol), prepared
 5 as in Reference 2, and HOBt (46mg, 0.3mmol) in MeCl₂ (5ml), was added EDC (73mg, 0.38mmol) and N-methylmorpholine (0.2ml) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated NaHCO₃, brine, dried with MgSO₄ and concentrated. The residue was subjected to silica gel column chromatography to yield morpholine-4-carboxylic acid (1-
 10 {1-[hydroxy-(5-(3-pyridyl)-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-2-o-difluoromethoxyphenylmethane-sulfonyl-ethyl)-amide (56mg); MS: 665.4 (M-1), 667.0 (M+1).

Morpholine-4-carboxylic acid (1-{1-[hydroxy-(5-(3-pyridyl)-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-2-o-difluoromethoxyphenylmethane-sulfonyl-ethyl)-amide
 15 (56mg, 0.084mmol), in MeCl₂ (5ml), was treated with Dess-Martin periodinane (53.4mg, 0.12mmol) at room temperature. After stirring for 1 hour, 5ml of saturated Na₂S₂O₃-NaHCO₃ were added. After a further 0.5 hours, the reaction mixture was extracted with ethyl acetate, washed with brine, dried with MgSO₄ and concentrated. The residue was purified with silica gel column chromatography to yield morpholine-4-carboxylic acid {2-
 20 (2-difluoromethoxy-phenylmethanesulfonyl)-1-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide (45mg); H¹ NMR(DMSO-d): 9.247 (1H, d, J=2.2Hz, NH), 8.86 (1H, dd, J=1.7Hz, J=4.9Hz), 8.79 (1H, t, J=5.9Hz), 8.5-8.45(1H, m), 7.73-7.68(1H, m), 7.5-7.4(2H, m), 7.3-7.2(2H, m), 7.1(1H, t, J=73.9Hz), 7.05-6.9(1H, m), 5.12-5.02(1H, m), 4.78-4.66(1H, m), 4.53(2H, s), 3.55-3.45(5H, m), 3.32-3.26(5H, m),
 25 2.05-1.85(1H, m), 1.8-1.6(1H, m), 1.45-1.2(6H, m), 0.87 (3H, t, J=6.9Hz, CH₃); MS: 663.4M-1, 665.4(M+1).

EXAMPLE 3

Morpholine-4-carboxylic acid {2-o-difluoromethoxyphenylmethanesulfonyl-1-[1-(5-(4-
 30 pyridyl)-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide

(Compound 3)



To a stirred mixture of 2-[(morpholine-4-carbonyl)-amino]-3-o-
 difluoromethoxyphenylmethane-sulfonyl-propionic acid (278mg, 0.66mmol), 2-amino-1-
 5 (5-(4-pyridyl)-[1,3,4]oxadiazol-2-yl)-1-hexanol TFA salt (248mg, 0.66mmol), prepared
 as above, and HOBt (121mg, 0.79mmol) in MeCl₂ (5ml), was added EDC (190mg,
 0.99mmol) and N-methylmorpholine (0.4ml) at room temperature. After stirring for 14
 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed
 with saturated NaHCO₃, brine, dried with MgSO₄ and concentrated. The residue was
 10 subjected to silica gel column chromatography to yield morpholine-4-carboxylic acid (1-
 {1-[hydroxy-(5-(4-pyridyl)-[1,3,4]oxadiazol-2-yl)-methyl]-pentylcarbamoyl}-2-o-difluoro-
 methoxyphenylmethane-sulfonyl-ethyl)-amide (430mg); MS: 665.4 (M-1), 667.2 (M+1).
 Morpholine-4-carboxylic acid (1-{1-[hydroxy-(5-(4-pyridyl)-[1,3,4]oxadiazol-2-yl)-
 methyl]-pentylcarbamoyl}-2-o-difluoromethoxyphenylmethane-sulfonyl-ethyl)-amide
 15 (400mg, 0.6mmol), in MeCl₂ (5ml), was treated with Dess-Martin periodinane (330mg,
 0.78mmol) at room temperature. After stirring for 1 hour, 5ml of saturated Na₂S₂O₃-
 NaHCO₃ were added. After a further 0.5 hours, the reaction mixture was extracted with
 ethyl acetate, washed with brine, dried with MgSO₄ and concentrated. The residue was
 purified with silica gel column chromatography to yield morpholine-4-carboxylic acid (2-
 20 o-difluoromethoxyphenylmethanesulfonyl-1-[1-(5-(4-pyridyl)-[1,3,4]oxadiazole-2-
carbonyl)-pentylcarbamoyl]-ethyl)-amide (148mg); H¹ NMR(DMSO-d): 8.88-8.82
 (2H+1H, m), 8.02-7.97 (2H, m), 7.48-7.45 (2H, m), 7.27-7.24 (2H, m), 7.1 (1H, t,

J=73.9Hz), 7.2-6.97 (1H, m), 5.12-5.01 (1H, m), 4.8-4.65 (1H, m), 4.53 (2H, s), 3.58-3.46 (4H, m), 3.35-3.2 (6H, m), 2.05-1.85 (1H, m), 1.8-1.65 (1H, m), 1.5-1.2 (4H, m), 0.87 (3H, t, J=6.9Hz, CH₃); MS: 663.4 (M-1), 665.4 (M+1).

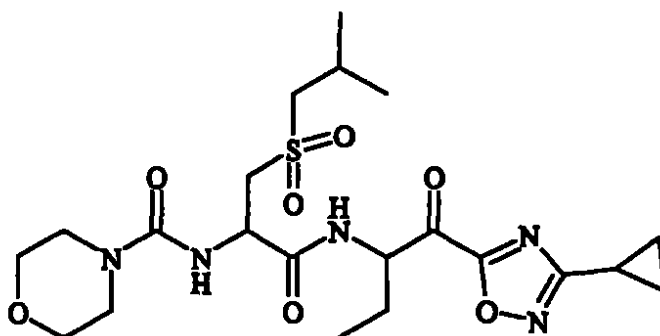
5 The following compounds were prepared by the methods described and exemplified above:

morpholine-4-carboxylic acid {2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-[1,1-dimethyl-2-oxo-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-ethylcarbamoyl]-ethyl}-amide.

10

EXAMPLE 4

Morpholine-4-carboxylic acid [1-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide



15 Step 1

A mixture of 3-(2-methylpropane-1-sulfonyl)-2-[(morpholin-4-carbonyl)amino]-propionic acid (163mg, 0.507mmol, Reference Example 5), 1-hydroxybenzotriazole hydrate (75mg, 0.558mmol), N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.93mmol/g, 289mg, 0.558mmol) and of dichloromethane (5.0 mL) was stirred under nitrogen at room temperature for 10 minutes. A solution of (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol (0.507mmol, Reference Example 10) in of dichloromethane (2mL) was added and the reaction mixture stirred at room temperature under nitrogen for four hours. Tris-(2-aminoethyl)amine polystyrene (3.40mmol/g, 447mg, 1.521mmol) and an additional 3.0mL of dichloromethane were added and the reaction mixture stirred at room temperature under nitrogen overnight. The reaction mixture was filtered and the resin washed with

20

25

dichloromethane. Evaporated under vacuum to dryness to yield morpholine-4-carboxylic acid (1-{1-[hydroxy-(3-cyclopropyl)-[1,2,4]oxadiazol-2-yl]-methyl}-propylcarbamoyl)-2-methyl-propane-1-sulfonyl-ethyl)-amide (240mg) as a pale yellow foam. [LC/MS $m/z=502$ (M+H)].

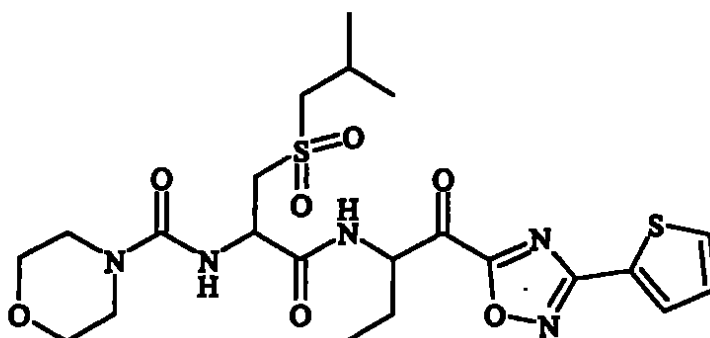
5 Step2

Morpholine-4-carboxylic acid (1-{1-[hydroxy-(3-cyclopropyl)-[1,2,4]oxadiazol-2-yl]-methyl}-propylcarbamoyl)-2-methyl-propane-1-sulfonyl-ethyl)-amide (240mg) was dissolved in of dichloromethane (7.5mL) and stirred at 0°C as 2.5 equivalents of Dess-Martin periodinane (2.63mL of a 15% solution in DCM) was added. Stirred under nitrogen
10 overnight as the reaction warms to room temperature. Evaporated most of the dichloromethane and dissolved the residue in ethyl acetate. Washed with $\text{Na}_2\text{S}_2\text{O}_3$ solution, NaHCO_3 solution, then brine. The organic phase was dried (Na_2SO_4), filtered and evaporated under vacuum to dryness. The residue was subjected to flash chromatography on silica eluting with a gradient from 5% ethyl acetate in dichloromethane to 95% ethyl
15 acetate in dichloromethane to give morpholine-4-carboxylic acid [1-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide, a mixture of diastereomers, (60mg, 24% overall) as a white solid. ^1H NMR (CDCl_3 , 300MHz): δ [7.87 (d, $J=6\text{Hz}$), 7.79 (d, $J=7\text{Hz}$), 1H], [6.10 (d, $J=6.5\text{Hz}$), 6.06 (d, $J=6.2\text{Hz}$), 1H], 5.27-5.23 (m, 1H), 4.91-4.85 (m, 1H), 3.72-3.66 (m, 5H), 3.48-3.34 (m, 5H), 3.17-
20 3.05 (m, 2H), 2.42-2.38 (m, 1H), 2.24-2.19 (m, 1H), 2.15-2.07 (m, 1H), 1.90-1.81 (m, 1H), 1.17-1.15 (m, 10H), 1.01 (t, $J=7\text{Hz}$, 3H). LC/MS $m/z=500$ (M+H)

EXAMPLE 5

Morpholine-4-carboxylic acid {2-(2-methyl-propane-1-sulfonyl)-1-[1-(3-thiophen-2-yl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide

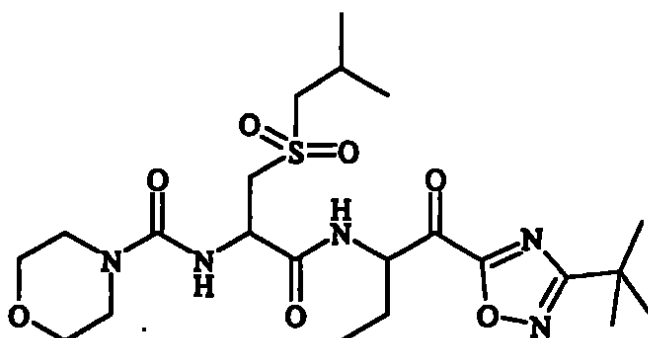
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By proceeding in a similar manner to that described in Example 4 above but using (S)-2-amino-1-(3-thiophen-2-yl-[1,2,4]oxadiazol-5-yl)-butan-1-ol (Reference Example 7) instead of (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol in Step 1 there was prepared morpholine-4-carboxylic acid {2-(2-methyl-propane-1-sulfonyl)-1-[1-(3-thiophen-2-yl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide, a mixture of diastereomers, (110mg, 40% overall yield) as a white solid. ¹H NMR (CDCl₃, 300MHz): [7.97 (d, J=6.5Hz), 7.87 (d, J=6.5Hz), 1H], 7.91 (d, J=3.8Hz), 1H, 7.59 (d, J=5Hz, 1H), 7.22-7.21 (m, 1H), 6.11-6.05 (m, 1H), 5.35-5.32 (m, 1H), 4.93-4.87 (m, 1H), 3.76-3.60 (m, 5H), 3.54-3.35 (m, 5H), 3.18-3.04 (m, 2H), 2.43-2.36 (m, 1H), 2.21-2.15 (m, 1H), 2.00-1.93 (m, 1H), 1.29-1.14 (m, 6H), 1.08 (t, J=7.5Hz, 3H). LC/MS m/z=542 (M+H)

EXAMPLE 6

Morpholine-4-carboxylic acid [1-[1-(3-tert-butyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide



Step 1

N-Cyclohexylcarbodiimide-N'-methylpolystyrene (0.526g, 1mmol, loading 1.9mmol/g) was suspended in dichloromethane (20mL). 3-(2-methyl-propane-1-sulfonyl)-2-

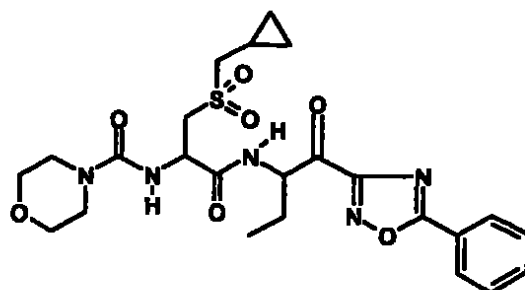
[(morpholine-4-carbonyl)-amino]-propionic acid (0.242g, 0.6mmol, reference Example 5) and HOBt (0.114g, 0.85mmol) were added and the reaction mixture was stirred for 20 minutes. (2S)-2-Amino-1-(3-tert-butyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol (0.107g, 0.5mmol, Reference Example 6) was added and stirring continued for 5 hours. Silicycle Triamine (1.27g, 5mmol) was added and the mixture stirred for 15 hours. The reaction mixture was filtered under suction and the filtrate concentrated to give morpholine-4-carboxylic acid [1-{1-[(3-tert-butyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide (0.271g), [LC/MS m/z= 518(M+H⁺)].

10 Step 2

Morpholine-4-carboxylic acid [1-{1-[(3-tert-butyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide (0.271g) was dissolved in dichloromethane (10mL) and the Dess-Martin periodinane (0.424g, 1mmol) was added. The reaction mixture was stirred for two hours and then poured into a mixture of saturated sodium bicarbonate and saturated sodium thiosulfate solution (1/1, 50mL). The phases were separated and the aqueous phase extracted with dichloromethane. The combined organic phases were washed with sodium bicarbonate solution and brine. The solution was dried with magnesium sulfate and then concentrated under vacuum. The residue was subjected to flash chromatography (gradient from 5% ethyl acetate in heptane to 75% ethyl acetate in heptane) to give morpholine-4-carboxylic acid [1-[1-(3-tert-butyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide, a mixture of diastereomers. ¹H NMR (CDCl₃, 300MHz): [7.87 (d, J=6.5Hz) 7.79 (d, J=7Hz), 1H], [6.11 (d, J=6.5Hz) 6.06 (d, J=6.5Hz), 1H], 5.38-5.30 (m, 1H), 4.92-4.13 (m, 1H), 3.78-3.68 (m, 5H), 3.49-3.33 (m, 5H), 3.24-3.04 (m, 2H), 2.47-2.37 (m, 1H), 2.20-2.07 (m, 1H), 1.95-1.85 (m, 1H), 1.45 (s, 9H), 1.17 (d, J=6.5Hz, 6H), [1.04 (t, J=7.5Hz) 1.03 (t, J=7.5Hz), 3H]. [LC/MS m/z= 516(M+H⁺)]

EXAMPLE 7

Morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide



Step 1

A suspension of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid (110mg, 0.344mmol, Reference Example 4) in methylene chloride (10mL) was treated with PS-bound N-cyclohexylcarbodiimide (HL 200-400 mesh cross linked with 2% DVB) from Novabiochem (320mg, 0.618mmol, 1.93mmol/g loading) and stirred at room temperature for 10 minutes. HOBt (43 mg, 0.319mmol) was added followed by (S)-2-amino-1-(5-phenyl-1,2,4-oxadiazol-3-yl)-butan-1-ol (73mg, 0.313mmol, Reference Example 12) and the reaction mixture was stirred at room temperature overnight. PS-trisamine from Argonaut Technologies (413mg, 1.549mmol, 3.75mmol/g loading) was added and the reaction was stirred for another 3hours. The mixture was filtered and the filtrate was evaporated under reduced pressure to give morpholine-4-carboxylic acid (2-cyclopropylmethanesulfonyl-1-[1-[hydroxy-(5-phenyl-1,2,4-oxadiazol-3-yl)-methyl]-propylcarbamoyl]-ethyl)-amide as an orange solid (183mg). MS: 536 (MH⁺)

Step 2

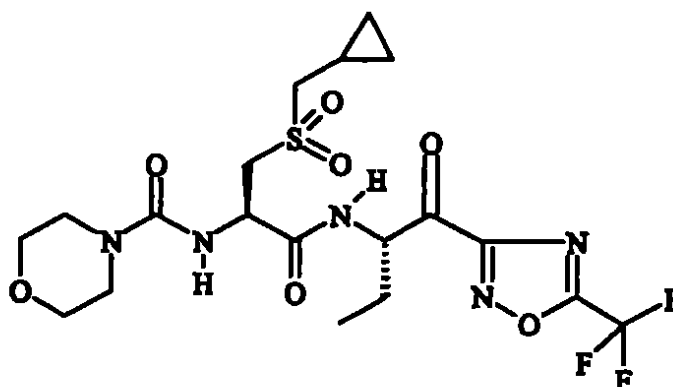
To a solution of morpholine-4-carboxylic acid (2-cyclopropylmethanesulfonyl-1-[1-[hydroxy-(5-phenyl-1,2,4-oxadiazol-3-yl)-methyl]-propylcarbamoyl]-ethyl)-amide (183mg, 0.34mmol) in methylene chloride (10mL), Dess-Martin Periodinane (200mg, 0.47mmol) was added and stirred at room temperature for 2hours. The reaction mixture was washed with a solution of Na₂S₂O₃ in water (0.26M), saturated bicarbonate, and water, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to flash chromatography eluting with a mixture of ethyl acetate and heptane to give morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide, a mixture of diastereomers, (45mg) as an off white solid. ¹H NMR (CDCl₃): 8.22 (d, J = 7Hz, 2H), 7.83, 7.75 (2xd, J = 7Hz, 1H), 7.65 (m, 1H), 7.60-7.51 (m, 2H), 6.10-6.07 (2xd, J = 7Hz, 1H), 5.36 (m, 1H), 5.00-4.86 (m,

1H), 3.79 (m, 1H), 3.74-3.66 (m, 4H), 3.48 (m, 1H), 3.47-3.37 (m, 4H), 3.20-3.07 (m, 2H), 2.24-2.06 (m, 1H), 2.00-1.82 (m, 1H), 1.22 (m, 1H), 1.01 (t, J = 7Hz, 3H), 0.80-0.68 (m, 2H), 0.56-0.38 (m, 2H). MS : 534 (MH⁺).

5

EXAMPLE 8

Morpholine-4-carboxylic acid {(R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-carbonyl)-propylcarbamoyl]-ethyl}-amide

**Step 1**

- 10 A solution of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid (266mg, 0.83mmol, Reference Example 4) in dimethylformamide (10mL) was treated successively with (S)-2-amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoroacetate (282mg, 0.83mmol, Reference Example 13), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (316mg, 0.83mmol) and diisopropylethylamine (0.289mL, 1.66mmol). Reaction stirred at room temperature overnight. Solvent evaporated under reduced pressure. Residue taken up in ethyl acetate and washed with 1N hydrochloric acid, saturated aqueous bicarbonate solution and water, dried over Na₂SO₄ and solvent evaporated under reduced pressure to give morpholine-4-carboxylic acid {(R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[hydroxy-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-methyl]-propylcarbamoyl]-ethyl}-amide as a brown oil (370 mg). MS : 528 (MH⁺).

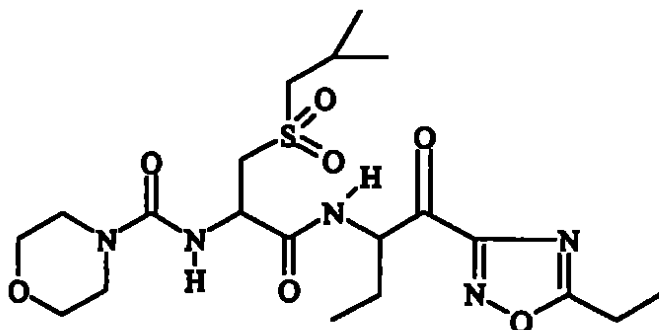
Step 2

A solution of morpholine-4-carboxylic acid {(R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[hydroxy-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-methyl]-propylcarbamoyl]-ethyl}-amide

(370mg, 0.70mmol) in methylene chloride (10 mL) was treated with Dess Martin periodinane (298mg, 0.70mmol) and stirred at room temperature for 3 hours. The reaction mixture was washed with an aqueous solution of Na₂S₂O₃ (0.26M), saturated aqueous bicarbonate solution and water, dried over Na₂SO₄ and the solvent evaporated under reduced pressure. The crude was subjected to flash chromatography eluting with a mixture of ethyl acetate and heptane. It was then further subjected to preparative HPLC (using Gilson 215 liquid handler, and MonoChrom 10microns C18 column – PN0504 – 100x212 from MetaChem), eluting with a mixture of acetonitrile and water, going from 10% to 100% acetonitrile in water to give morpholine-4-carboxylic acid [(R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-(5-trifluoromethyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl]-amide as a white solid (9mg). ¹H NMR (CDCl₃) : 7.87 (d, J = 6Hz, 1H), 5.99 (d, J = 6Hz, 1H), 5.16 (m, 1H), 4.87 (m, 1H), 3.74-3.66 (m, 5H), 3.44-3.36 (m, 5H), 3.14 (d, J = 7Hz, 2H), 2.20-2.02 (m, 1H), 1.98-1.78 (m, 1H), 1.21 (m, 1H), 1.02 (t, J = 7Hz, 3H), 0.82-0.70 (m, 2H), 0.57-0.40 (m, 2H). MS : 526 (MH⁺)

EXAMPLE 9

Morpholine-4-carboxylic acid [(1-[(1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide

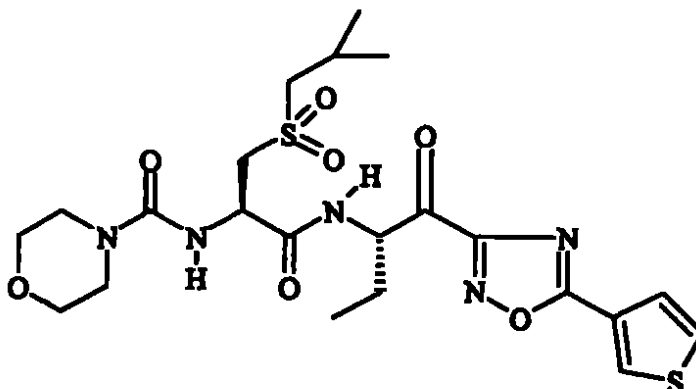


By proceeding in a similar manner to Example 8 above but using (R)-3-(2-methyl-propane-1-sulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid (Reference Example 5) instead of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid and (S)-2-amino-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol (Reference Example 14) instead of (S)-2-amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoroacetate, in Step 1, there was prepared morpholine-4-carboxylic acid [1-[(1-(5-ethyl-

1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-
 amide, a mixture of diastereomers. ¹H NMR (CDCl₃): 7.81, 7.72 (2xd, J = 6.5Hz, 1H),
 6.14-6.01 (2xd, J = 6.5Hz, 1H), 5.28 (m, 1H), 4.95-4.81 (m, 1H), 3.75-3.65 (m, 5H), 3.54-
 3.32 (m, 5H), 3.12(m, 2H), 3.01 (q, J = 7.5Hz, 2H), 2.45-2.30 (m, 1H), 2.17-2.04 (m, 1H),
 5 1.93-1.78 (m, 1H), 1.44 (t, J = 7.5Hz, 3H), 1.13 (d, J = 6.5Hz, 6H), 0.98 (t, J = 7.5Hz, 3H).
 MS: 488 (MH⁺).

EXAMPLE 10

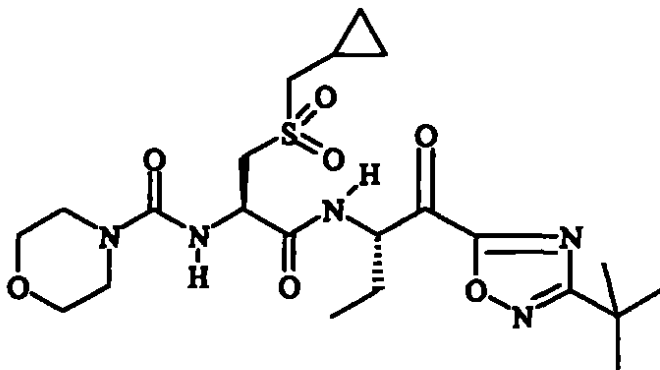
{(R)-2-(2-Methyl-propane-1-sulfonyl)-1-[(S)-1-(5-thiophen-3-yl)-1,2,4-oxadiazole-3-
carbonyl)-propylcarbamoyl]-ethyl}-amide



By proceeding in a similar manner to Example 8 above but using (R)-3-(2-methyl-propane-
 1-sulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid (Reference Example 5)
 instead of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-
 15 propionic acid and (S)-2-amino-1-(5-thiophen-3-yl)-1,2,4-oxadiazol-3-yl)-butan-1-ol
 (Reference Example 16) instead of (S)-2-amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-
 butan-1-ol trifluoroacetate, there was prepared morpholine-4-carboxylic acid {(R)-2-(2-
methyl-propane-1-sulfonyl)-1-[(S)-1-(5-thiophen-3-yl)-1,2,4-oxadiazole-3-carbonyl)-
propylcarbamoyl]-ethyl}-amide. ¹H NMR (CDCl₃): 8.33 (dd, J= 3 and 1.1 Hz, 1H), 7.83
 20 (d, J = 6.5Hz, 1H), 7.73 (dd, J=5.1 and 1.1 Hz, 1H), 7.48 (dd, J=5.0 and 3.0 Hz, 1H), 6.04
 (d, J = 6.5Hz, 1H), 5.33 (m, 1H), 4.86 (m, 1H), 3.78-3.66 (m, 5H), 3.49-3.35 (m, 5H),
 3.22-3.05 (m, 2H), 2.46-2.32 (m, 1H), 2.22-2.07 (m, 1H), 1.98-1.82 (m, 1H), 1.14 (d, J =
 7Hz, 6H), 1.01 (t, J = 7.5Hz, 3 H). MS : 542 (MH⁺).

EXAMPLE 11

Morpholine-4-carboxylic acid {(R)-1-[(S)-1-(3-tert-butyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-amide



5

By proceeding in a similar manner to Example 8 above but using (S)-2-amino-1-(3-tert-butyl-1,2,4-oxadiazol-5-yl)-butan-1-ol (Reference Example 6) instead of (S)-2-amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoroacetate there was prepared

10 **morpholine-4-carboxylic acid {(R)-1-[(S)-1-(3-tert-butyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-amide.** ¹H NMR (CDCl₃) : 7.80

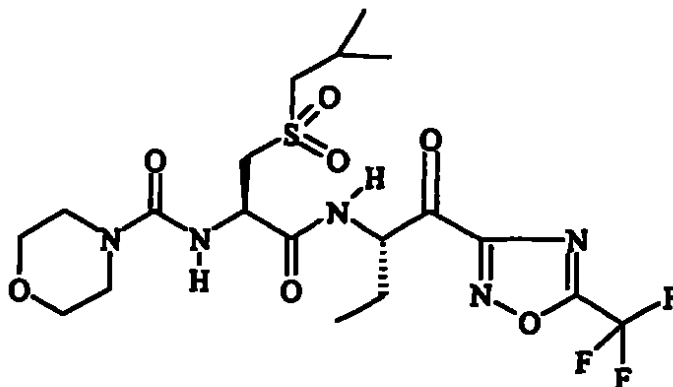
(d, J=6.5Hz, 1H), 6.02 (d, J=6.5Hz, 1H), 5.31 (m, 1H), 4.88 (m, 1H), 3.82-3.66 (m, 5H), 3.50-3.36 (m, 5H), 3.15 (d, J = 7Hz, 2H), 2.20-2.04 (m, 1H), 1.95-1.80 (m, 1H), 1.42 (s, 9H), 1.26-1.15 (m, 1H), 1.00 (t, J=7.5Hz, 3H), 0.79-0.72 (m, 2H), 0.56-0.41 (m, 2H).

MS : 514 (MH⁺).

15

EXAMPLE 12

Morpholine-4-carboxylic acid {(R)-2-(2-methyl-propane-1-sulfonyl)-1-[(S)-1-(5-trifluoromethyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide

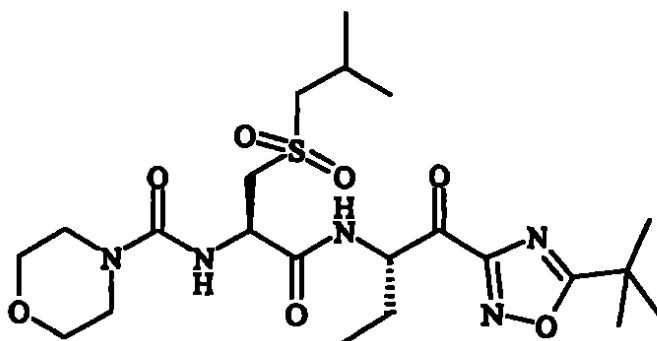


By proceeding in a similar manner to Example 8 above but using (R)-3-(2-methyl-propane-1-sulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid (Reference Example 5) instead of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid there was prepared morpholine-4-carboxylic acid {(R)-2-(2-methyl-propane-1-sulfonyl)-1-[(S)-1-(5-trifluoromethyl)-1,2,4-oxadiazole-3-carbonyl]-

propylcarbamoyl]-ethyl}-amide. ¹H NMR (CDCl₃) : 7.90 (d, J=6Hz, 1H), 6.00 (d, J=6Hz, 1H), 5.17(m, 1H), 4.83 (m, 1H), 3.73-3.62 (m, 5H), 3.45-3.36 (m, 5H), 3.13 (m, 2H), 2.45-2.32 (m, 1H), 2.18-2.04 (m, 1H), 1.96-1.80 (m, 1H), 1.14 (d, J=7Hz, 6H), 1.03 (t, J=7.5Hz, 3H). MS: 528 (MH⁺).

EXAMPLE 13

Morpholine-4-carboxylic acid {(R)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide



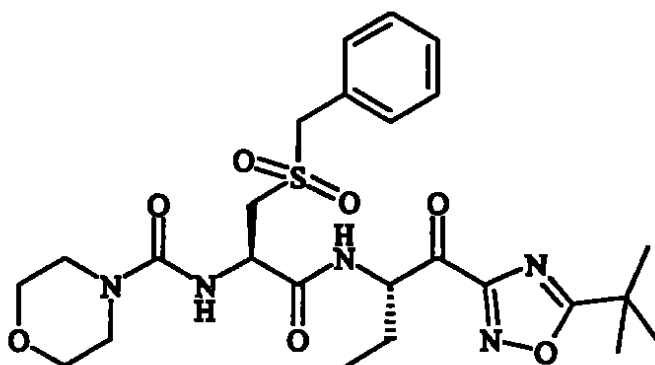
By proceeding in a similar manner to Example 8 above but using (R)-3-(2-methyl-propane-1-sulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid (Reference Example 5) instead of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-

propionic acid and (S)-2-amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol (Reference Example 9) instead of (S)-2-amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoroacetate there was prepared morpholine-4-carboxylic acid {(R)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
 5 amide. ¹H NMR (CDCl₃): 7.78 (d, J=7Hz, 1H), 6.04 (d, J=6.5Hz, 1H), 5.30 (m, 1H), 4.85 (m, 1H), 3.76-3.64 (m, 5H), 3.48-3.34 (m, 5H), 3.13 (m, 2H), 2.47-2.31 (m, 1H), 2.19-2.02 (m, 1H), 1.95-1.80 (m, 1H), 1.48 (s, 9H), 1.14 (d, J=6.5Hz, 6H), 0.99 (t, J=7.5Hz, 3H). MS : 516 (MH⁺).

10

EXAMPLE 14

Morpholine-4-carboxylic acid {(R)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-
propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide

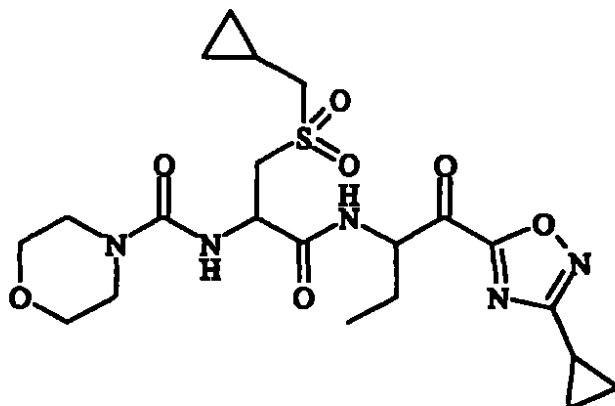


15

By proceeding in a similar manner to Example 8 above but using (R)-2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid instead of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid and (S)-2-amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol (Reference Example 9) instead of (S)-2-amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoroacetate there was prepared morpholine-4-carboxylic acid {(R)-1-[(S)-1-(5-tert-
 20 butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
amide. ¹H NMR (CDCl₃): 7.67 (d, J=7Hz, 1H), 7.50-7.34 (m, 5H), 6.01 (d, J=7Hz, 1H), 5.31 (m, 1H), 4.93 (m, 1H), 4.52 & 4.40 (2xd, J=14Hz, 2H), 3.76-3.64 (m, 5H), 3.46-3.26 (m, 5H), 2.20-2.06 (m, 1H), 1.94-1.78 (m, 1H), 1.48 (s, 9H), 0.98 (t, J=7.5Hz, 3H). MS : 550 (MH⁺).

EXAMPLE 15

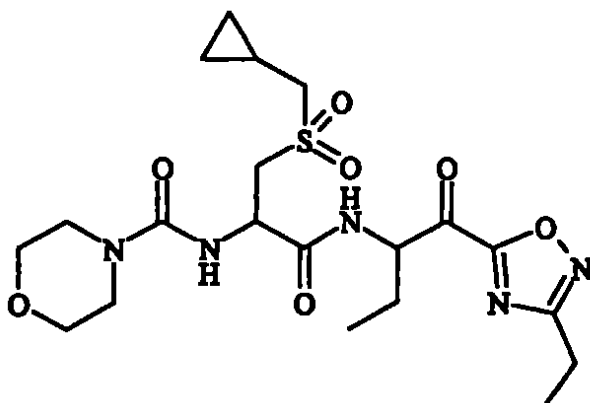
Morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide



By proceeding in a similar manner to Example 8 above but using (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol (Reference Example 10) instead of (S)-2-amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoroacetate there was prepared morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide, a mixture of diastereomers, as a white solid. ¹H NMR (CDCl₃) δ 7.83, 7.74 (d, J = 7Hz, 1H), 6.02 (d, J = 7Hz, 1H), 5.22 (m, 1H), 4.87 (m, 1H), 3.72 (m, 5H), 3.41 (m, 5H), 3.16 (d, 2H), 2.21 (m, 1H), 2.15 (m, 1H), 1.86 (m, 1H), 1.03-1.24 (m, 5H), 0.99 (t, J = 7Hz, 3H), 0.76 (m, 2H), 0.48 (m, 2H). MS (M/Z) = 498 (M+H). LC Kromasil KR 100-10 Sil, 250 4.6mm ID (90% (heptane / THF / ACN)/(220/60/14,v/v/v) retention time = 24.1 minutes, flow rate 1.5mL / min.

EXAMPLE 16

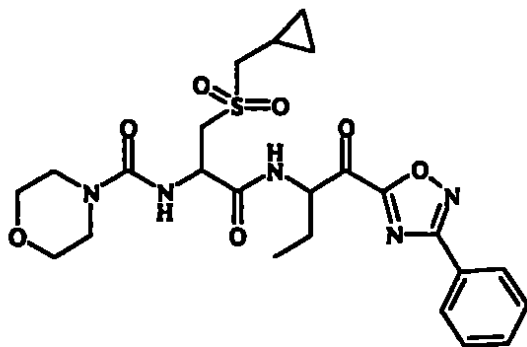
Morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-ethyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide



By proceeding in a similar manner to Example 8 above but using (S)-2-amino-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-butan-1-ol trifluoroacetate (Reference Example 14) instead of (S)-2-amino-1-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoroacetate there was prepared morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-ethyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide, as a 1:1 mixture of diastereomers. ¹HNMR (CDCl₃) δ 7.85 and 7.75 (2xd, J = 6Hz, 1H), 6.07 (m, 1H), 5.28 (m, 1H), 4.92 (m, 1H), 3.8-3.6 (m, 5H), 3.42 (m, 5H), 3.2-3.1 (m, 2H), 2.88 (q, J = 7Hz, 2H), 2.13 (m, 1H), 1.87 (m, 1H), 1.39 (t, J = 7Hz, 3H), 1.22 (m, 1H), 1.02 (t, J = 7Hz, 3H), 0.75 (m, 2H), 0.48 (m, 2H). MS m/z 486 (M+H)

EXAMPLE 17

Morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide



Step 1

To a solution of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid (130.5mg, 0.41mmol) and di-isopropylethylamine (0.41mmol, 53.0mg,

0.0714mL) in dry dichloromethane (6mL) was added polystyrene-bound cyclohexyl carbodiimide (2.0eq., 0.82mmol, 432mg) followed by HOBt monohydrate (1.7eq., 0.70mmol, 94.2mg). The mixture was stirred at room temperature for 15 minutes then the (2S)-2-amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol (0.41mmol, 95mg) was added.

- 5 The mixture was stirred for another 64 hours then silica-bound trisamine (5.0eq., 2.05mmol, 569.4mg) was added. The mixture was stirred for another 2 hours then filtered. The filtrate was concentrated in vacuum and purified over 12g silica gel, eluted with a mixture of ethyl acetate and heptane (2:1 then 1:0) to afford 182 mg (83%) of the desired alcohol. (LC/MS 100% M+1 536).

10 Step 2

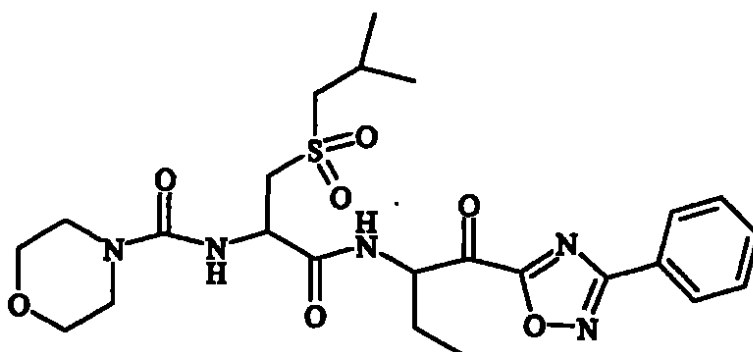
To a solution of alcohol (170mg, 0.32mmol) in 5 mL of dry dichloromethane was added a solution of Dess-Martin reagent (15%wt. Sol., 2eq., 0.63mmol, 1.80g). The mixture was stirred at room temperature for 2 hours then quenched by adding a solution of Na₂S₂O₃ (4.0eq., 1.28mmol, 202.4mg) in saturated sodium bicarbonate (30 mL). The aqueous layer
15 was extracted twice with dichloromethane (20mL). The organic layers were dried (MgSO₄) and concentrated in vacuum. The residue was purified over 12g silica gel, eluting with a mixture of ethyl acetate and heptane (1.5:1 then 2:1) to afford morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide, a 3:1 mixture of diastereomers, (139mg, 82%).

- 20 ¹H NMR (CDCl₃) : 8.15 (d, J = 7.6 Hz, 2H), 8.0 (d, J = 6.6 Hz, 1H, major), 7.9 (d, J = 7 Hz, 1H minor), 7.6 (m, 3H), 6.08 (2xd, J = 6.5 Hz, 1H), 5.4 (m, 1H), 4.95 (m, 1H), 3.8-3.69 (m, 5H), 3.53-3.35 (m, 5H), 3.15 (m, 2H), 2.2 (m, 1H), 1.95 (m, 1H), 1.2 (m, 1H), 1.06 (t, J = 7.5 Hz, 3H), 0.8 (m, 2H), 0.5 (m, 2H). LC/MS shows 35% M+1 534 as well as 65% hydrate M+18 552.

25

EXAMPLE 18

Morpholine-4-carboxylic acid {2-(2-methyl-propane-1-sulfonyl)-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide



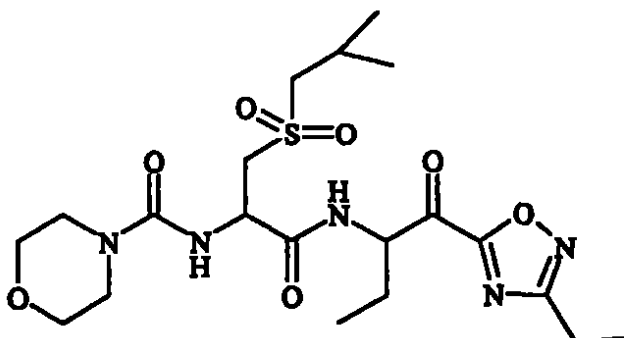
By proceeding in a similar manner to Example 17 above but using (R)-3-(2-methyl-propane-1-sulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid (Reference Example 5) instead of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid, in Step 1, there was prepared morpholine-4-carboxylic acid {2-(2-methyl-propane-1-sulfonyl)-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-

propylcarbamoyl]-ethyl}-amide. ¹H NMR (CDCl₃): 8.15 (dd, 2H), 7.95-7.85 (2xd, 1H), 7.45 (m, 3H), 6.14-6.0 (2xd, 1H), 5.35 (m, 1H), 4.90 (m, 1H), 3.70 (m, 5H), 3.40 (m, 5H), 3.2-3.0 (m, 2H), 2.50-2.30 (m, 1H), 2.30-2.10 (m, 1H), 2.05-1.90 (m, 1H), 1.10 (t, 6H),

1.05 (t, 3H). MS: 536 (MH⁺).

EXAMPLE 19

Morpholine-4-carboxylic acid [1-[1-(3-ethyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide



To a suspension of the (R)-3-(2-methyl-propane-1-sulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid (113mg, 0.35mmol, Reference Example 5), (S)-2-amino-1-(3-ethyl-1,2,4-oxadiazol-5-yl)-butan-1-ol (0.35mmol, 65mg) and di-isopropylethylamine (1.2eq., 0.073mL) in dry dichloromethane (7mL) was added PyBOP (1.1eq., 200mg). The mixture

was stirred at room temperature overnight then quenched with NaHCO_3 solution. The volatiles were removed in vacuum, and the aqueous mixture was extracted in ethyl acetate.

The organic layers were dried (Na_2SO_4) and then concentrated in vacuum. The residue

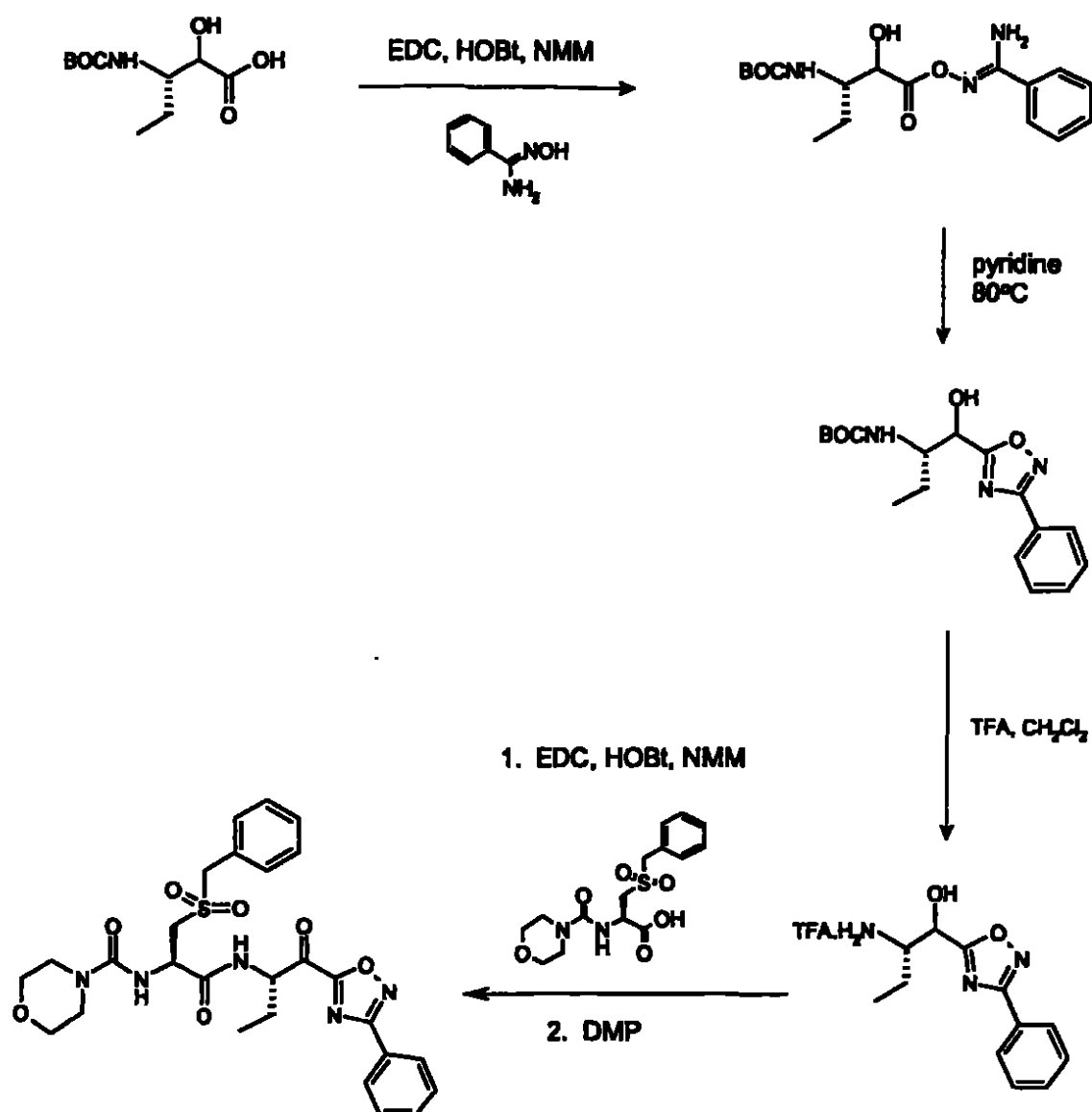
5 was purified over silica gel, eluting with ethyl acetate: dichloromethane to afford the desired alcohol. To a solution of the alcohol in dry dichloromethane was added a solution of Dess-Martin reagent (15%wt. Sol., 2eq.). The mixture was stirred at room temperature for 2 hours then quenched by adding a solution of $\text{Na}_2\text{S}_2\text{O}_3$ (4.0eq.) in saturated sodium bicarbonate. The aqueous layer was extracted with dichloromethane. The organic layers

10 were dried (MgSO_4) and concentrated in vacuo. The residue was purified over silica gel, eluted with a mixture of ethyl acetate and dichloromethane to afford morpholine-4-carboxylic acid [1-[1-(3-ethyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methylpropane-1-sulfonyl)-ethyl]-amide (98mg, 57%).

^1H NMR (CDCl_3) 4:1 mixture of isomers 7.9 (d, $J = 6.4$ Hz, 1H, major), 7.8 (d, $J = 6$ Hz, 1H, minor), 6.1 (d, $J = 6.1$ Hz, 1H, minor), 6.0 (d, $J = 6.1$ Hz, 1H, major), 5.25 (m, 1H),
15 4.95 (m, 1H), 3.74-3.67 (m, 5H), 3.4 (m, 5H), 3.2 (m, 2H), 2.2 (m, 1H), 2.9 (q, $J = 7.5$ Hz, 2H), 2.4 (m, 1H), 2.2 (m, 1H), 1.9 (m, 1H), 1.4 (t, $J = 7.6$ Hz, 3H), 1.2 (d, $J = 6.6$ Hz, 6H), 1.0 (t, $J = 7.4$ Hz, 3H). LC/MS shows 52% $M+1$ 588 as well as 37% hydrate $M+18$ 506.

EXAMPLE 20

20 Morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide



Step 1

3-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid (500mg, 2.14mmol) was combined
 5 with EDC (600mg, 3.14mmol), HOBt (600mg, 3.92mmol), and N-hydroxy-benzamidine
 (292mg, 2.14mmol). Dichloromethane (10mL) was added and then 4-methylmorpholine
 (1mL). The mixture was stirred at ambient temperature for 16hours. After dilution with
 ethyl acetate (200mL), the solution was washed with water (30mL), saturated aqueous
 NaHCO₃ solution and brine, then dried with MgSO₄ and then evaporated under vacuum.

10

Step 2

The product from step 1 was dissolved in pyridine (10mL) and the solution was heated at 80°C for 15hours. The pyridine was evaporated under vacuum and the residue was subjected to flash chromatography on silica gel (eluent: ethyl acetate) to give {1-[hydroxy-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methyl]-propyl}-carbamic acid tert-butyl ester (290mg (0.83mmol).

Step 3

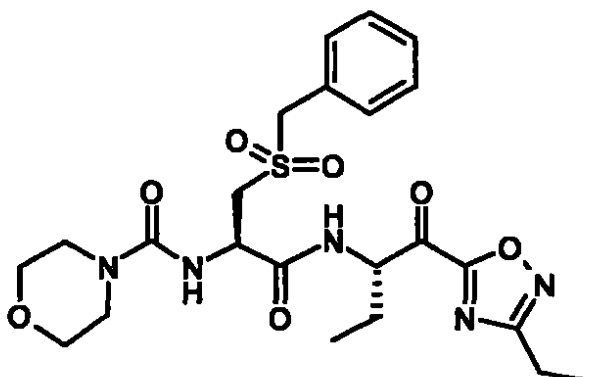
{1-[Hydroxy-(3-phenyl-[1,2,4]oxadiazol-5-yl)-methyl]-propyl}-carbamic acid tert-butyl ester (145mg, 0.41mmol) was dissolved in CH₂Cl₂ (4mL) and TFA (4mL) was added. After stirring for 1hour, the mixture was evaporated to dryness.

Step 4

2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (200mg, 0.56mmol), EDC (200mg, 1.05mmol), HOBt (200mg, 1.30mmol) and CH₂Cl₂ (4mL) were added to the product from step 3 above. 4-Methylmorpholine (0.5mL) was added and the mixture was stirred at ambient temperature for 2hours. After dilution with ethyl acetate (150mL), the solution was washed with water (30mL), saturated aqueous NaHCO₃ solution and brine, then dried with MgSO₄ and then evaporated under vacuum. The residue was dissolved in dry dichloromethane (10mL) and Dess-Martin periodinane (500mg, 1.2mmol) was added. After stirring at ambient temperature for 1hour the mixture was diluted with ethyl acetate (150mL) and the mixture was treated with 0.26M Na₂S₂O₃ solution in saturated aqueous NaHCO₃. The organic phase was washed with saturated aqueous NaHCO₃ and brine, then dried with MgSO₄ and then evaporated. The residue was subjected to flash chromatography on silica gel (hexane/ ethyl acetate 1:2 to ethyl acetate) to give morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(3-phenyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide (40mg, 0.07mmol). ¹H NMR (DMSO): 8.79 (d, J=6 Hz, 1H), 8.04 (d, J=8Hz, 2H), 7.65-7.53 (m, 3H), 7.41-7.32 (m, 5H), 7.02 (d, J=8Hz, 1H), 4.96-4.90 (m, 1H), 4.73-4.66 (m, 1H), 4.45 (s, 2H), 3.57-3.19 (m, 10H), 2.04-1.95 (m, 1H), 1.80-1.71 (m, 1H), 0.95 (t, J=7.6 Hz, 3H). MS: (M⁺+1) 570.

EXAMPLE 21

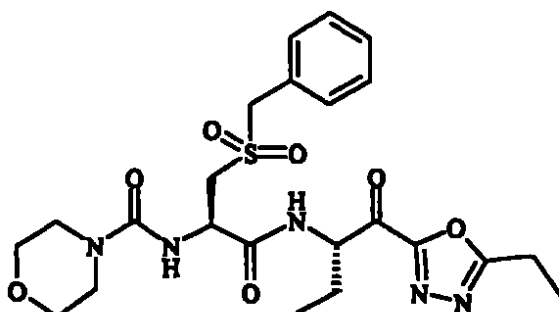
Morpholine-4-carboxylic acid {1-[1-(3-ethyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide



By proceeding in a similar manner to that described in Example 20 above but using
 5 N-hydroxy-propionamidine instead of N-hydroxy-benzamidine in step 1, there was
 prepared morpholine-4-carboxylic acid {1-[1-(3-ethyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide. ¹H NMR (DMSO): 8.73 (d,
 J=6.4Hz, 1H), 7.40-7.33 (m, 5H), 7.01 (d, J=8Hz, 1H), 4.88-4.82 (m, 1H), 4.71-4.65 (m,
 1H), 4.47 (s, 2H), 3.57-3.24 (m, 10H), 2.81 (q, J=7.6Hz, 2H), 1.99-1.88 (m, 1H), 1.75-1.64
 10 (m, 1H), 1.26 (t, J=7.6Hz, 3H), 0.92 (t, J=7.6 Hz, 3H). MS: (M++1) 522.

EXAMPLE 22

Morpholine-4-carboxylic acid {1-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide



15

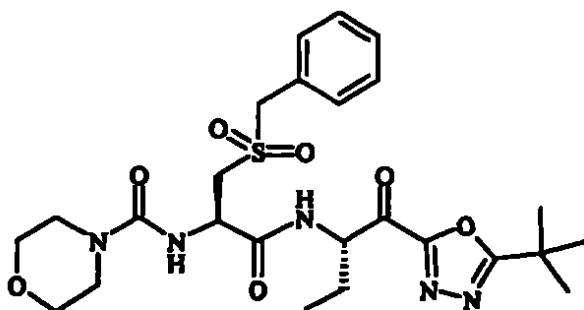
By proceeding in a similar manner to that described in Example 1 there was prepared
morpholine-4-carboxylic acid {1-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide. ¹H NMR (DMSO): 8.64 (d,
 J=6.8Hz, 1H), 7.42-7.32 (m, 5H), 7.02 (d, J=8.8 Hz, 1H), 5.04-4.96 (m, 1H), 4.62-4.72 (m,

1H), 4.47 (s, 2H), 3.64-3.24 (m, 10H), 2.96 (q, J=7.6Hz, 2H), 1.89-1.79 (m, 1H), 1.72-1.60 (m, 1H), 1.38-1.16 (m, 2H), 1.29 (t, J=7.6Hz, 3H), 0.89 (t, J=7.2 Hz, 3H). MS: (M⁺+1) 536.

5

EXAMPLE 23

Morpholine-4-carboxylic acid {1-[1-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide

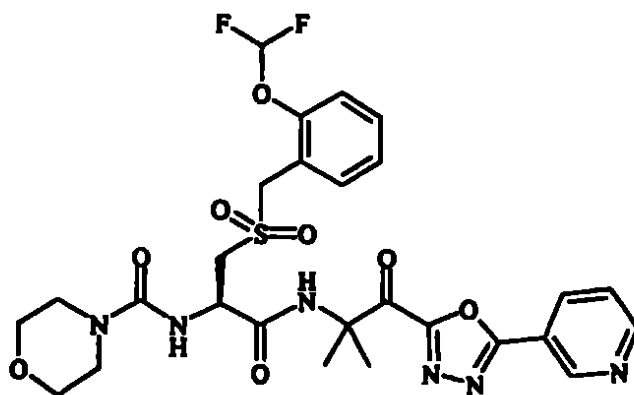


By proceeding in a similar manner to that described in Example 1 there was prepared
 10 morpholine-4-carboxylic acid {1-[1-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide. ¹H NMR (DMSO): 8.63 (d, J=5.2Hz, 1H), 7.26-7.46 (m, 5H), 7.02 (d, J=8.8 Hz, 1H), 4.98-5.08 (m, 1H), 4.62-4.72 (m, 1H), 4.48 (s, 2H), 3.24-3.64 (m, 10H), 1.76-1.92 (m, 1H), 1.58-1.74 (m, 1H), 1.39 (s, 9H), 1.16-1.38 (m, 2H), 0.89 (t, J=7.6 Hz, 3H). MS: (M⁺+1) 564.

15

EXAMPLE 24

Morpholine-4-carboxylic acid {2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-[1,1-dimethyl-2-oxo-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-ethylcarbamoyl]-ethyl}-amide



By proceeding in a similar manner to that described in Example 2 there was prepared

¹H NMR (DMSO-d): 9.33(1H, s, NH), 9.22(1H, dd, J=1.74Hz), 8.84(1H, dd),
8.43(1H, d,t)7.68(1H, dd, J=1.75Hz, J=6.7Hz), 7.42(2H, m), 7.3-7.2(2H, m), 7.07(1H,
t, J=74.1Hz), 6.76(1H, d, J=8.6Hz, NH), 4.7-4.6(1H, m), 4.45(2H, s), 3.5-3.4(4H, m),
5 3.38-3.2(2H, m), 3.2-3.1(4H, m), 1.52(6H, s). MS: 635.6(M-1), 637.4(M+1).

EXAMPLE 25

Cathepsin S 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 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 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.

EXAMPLE 26

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 27

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 28

Cathepsin L 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 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 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.

Compounds of the invention were tested according to the above-described assays for protease inhibition and observed to exhibit selective cathepsin S inhibitory activity. For example, the compounds of the invention were found to inhibit cathepsin S protease activity at concentrations that are least 50 fold less than those concentrations required to produce an equiactive inhibition of cathepsin K protease 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 $10^{-7}M$.

5

EXAMPLE 29

Representative Pharmaceutical Formulations Containing a Compound of Formula I

ORAL FORMULATION

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

15

INTRAVENOUS FORMULATION

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

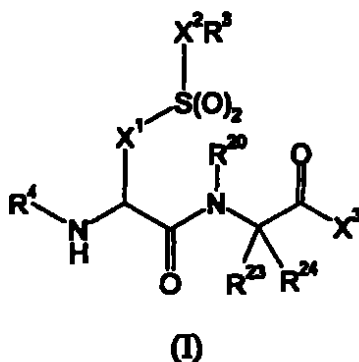
TABLET FORMULATION

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

WE CLAIM:

1. A compound of Formula (I):

5



wherein:

- 10 X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is methylene or a bond;
 R^3 is $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$, $-CR^7=NR^8$, or (C_{3-12}) cycloalkyl, wherein R^5
and R^6 are independently 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}) cycloalkyl, hetero (C_{3-12}) cycloalkyl,
 (C_{6-12}) aryl, hetero (C_{5-12}) aryl, (C_{9-12}) bicycloaryl or hetero (C_{8-12}) bicycloaryl and R^7 and
15 R^8 together with the atoms to which R^7 and R^8 are attached form hetero (C_{3-12}) cycloalkyl,
hetero (C_{5-12}) 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, $-X^4NR^9R^9$, $-X^4OR^9$, $-X^4SR^9$, $-X^4C(O)NR^9R^9$,
 $-X^4C(O)OR^9$, $-X^4S(O)R^{10}$, $-X^4S(O)_2R^{10}$ and $-X^4C(O)R^{10}$, wherein X^4 is a bond or
20 (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 (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 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 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, $-X^6NR^{17}R^{17}$, $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$, $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$, $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$, $-X^6P(O)(OR^{18})OR^{17}$, $-X^6OP(O)(OR^{18})OR^{17}$, $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$, $-X^6S(O)_2R^{18}$ 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, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$, $-NR^{17}C(NR^{17})NR^{17}R^{17}$, $-OR^{17}$, $-SR^{17}$,

-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
 5 (C₁₋₃)alkyl;

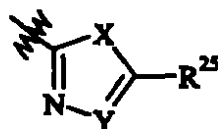
R²⁰ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl,
 (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl
 or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

R²³ is selected from hydrogen, (C₁₋₆)alkyl, alkoxy(C₁₋₃)alkyl, halo(C₁₋₃)alkyl,
 10 (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 optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵
 wherein R¹⁵ is as described above; and

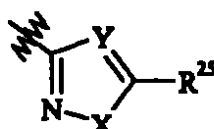
R²⁴ is selected from hydrogen or (C₁₋₆)alkyl; or

R²³ and R²⁴ taken together with the carbon atom to which both R²³ and R²⁴
 15 are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene;

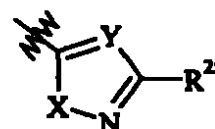
X³ is selected from group (a), (b) or (c);



(a)



(b)



(c)

20 wherein X is O and Y is N;

R²⁵ is selected from hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₂)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;

5 wherein R²⁵ 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,
 10 -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,
 15 -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

a derivative of said compound selected from the group consisting of *N*-oxide derivatives, prodrug derivatives, protected derivatives, isomers, and mixtures of isomers
 20 of said compound; or a pharmaceutically acceptable salt or solvate of said compound or said derivative.

2. A compound of claim 1 wherein:

X¹ and X² are both methylene or X¹ is ethylene and X² is a bond;

25 R³ is -CR⁵=CHR⁶, -CR⁵(CR⁶)₂, -CR⁷=NR⁸, or (C₃₋₁₂)cycloalkyl, wherein R⁵ and R⁶ are independently hydrogen or (C₁₋₄)alkyl or R⁵ and R⁶ together with the atoms to which R⁵ and R⁶ are attached form (C₃₋₁₂)cycloalkyl, (C₆₋₁₂)aryl, hetero(C₅₋₁₂)aryl

or (C₉₋₁₂)bicycloaryl and R⁷ and R⁸ together with the atoms to which R⁷ and R⁸ are attached form hetero(C₅₋₁₂)aryl;

wherein within R³ any cycloalkyl, aryl, heteroaryl or bicycloaryl group may be substituted with 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 and R⁹ at each occurrence independently is (C₁₋₃)alkyl and halo-substituted (C₁₋₃)alkyl;

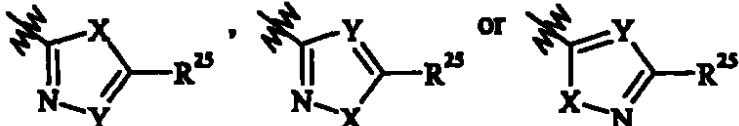
R⁴ is -C(O)X⁵R¹¹ or -S(O)₂X⁵R¹¹, wherein X⁵ is a bond, -O- or -NR¹²-, wherein R¹² is hydrogen or (C₁₋₆)alkyl, and R¹¹ is (i) (C₁₋₆)alkyl or (ii) hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl 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 within R⁴ any alicyclic or aromatic ring system may be substituted with 1 to 5 radicals independently selected from a group consisting of (C₁₋₆)alkyl, halo, -X⁶NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)OR¹⁷, -X⁶NC(O)R¹⁶ and -X⁶C(O)R¹⁸, wherein 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;

R²⁰ is hydrogen or (C₁₋₆)alkyl;

R²³ is (C₁₋₆)alkyl or (C₆₋₁₂)aryl(C₀₋₆)alkyl;

R²⁴ is hydrogen or (C₁₋₆)alkyl;

X³ is  wherein X is O,

Y is N and R²⁵ is selected from hydrogen, halo(C₁₋₃)alkyl, (C₁₋₆)alkyl,

(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₃)aryl(C₀₋₆)alkyl, wherein within R²⁵ any alicyclic or aromatic ring system may be substituted with 1 to 5 radicals independently selected from (C₁₋₆)alkyl and halo-substituted (C₁₋₃)alkyl; or

a derivative of said compound selected from the group comprising *N*-oxide derivatives, prodrug derivatives, protected derivatives, isomers, and mixtures of isomers of said compound; or a pharmaceutically acceptable salt or solvate of said compound or said derivative.

3. A compound of claim 2 wherein R³ 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; or

a derivative of said compound selected from the group consisting of *N*-oxide derivatives, prodrug derivatives, protected derivatives, isomers, and mixtures of isomers of said compound; or a pharmaceutically acceptable salt or solvate of said compound or said derivative.

4. A compound of claim 3 wherein 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-flouro-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-methyl-thiophene-2-sulfonyl, thiophene-2-sulfonyl, formamyl-methyl ester, 4-methyl-pentanoyl, formamyl-isobutyl ester, formamyl-monoallyl ester, formamyl-isopropyl ester, *N,N*-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; or

a derivative of said compound selected from the group consisting of *N*-oxide derivatives, prodrug derivatives, protected derivatives, isomers, and mixtures of isomers of said compound; or a pharmaceutically acceptable salt or solvate of said compound or said derivative.

5. A compound of claim 4 wherein R²⁵ is *tert*-butyl, cyclopropyl, ethyl, phenyl,

pyrazinyl, pyridazinyl, pyridinyl, thienyl or trifluoromethyl; or

a derivative of said compound selected from the group consisting of *N*-oxide derivatives, prodrug derivatives, protected derivatives, isomers, and mixtures of isomers of said compound; or a pharmaceutically acceptable salt or solvate of said compound or said derivative.

6. A compound of claim 2, wherein R^3 is $-CR^5-CHR^6$ wherein R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{6-12}) aryl, optionally 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.

7. A compound of claim 6 wherein R^3 is phenyl or 2-difluoromethoxyphenyl.

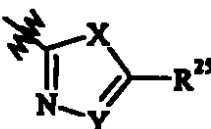
8. A compound of claim 2 wherein R^3 is $-CR^5(CR^6)_2$ wherein R^5 is hydrogen and R^6 is (C_{1-4}) alkyl.

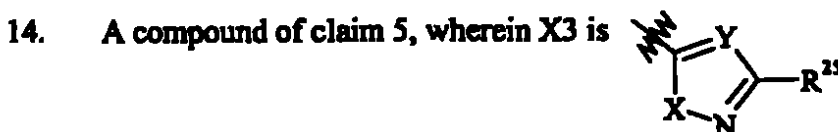
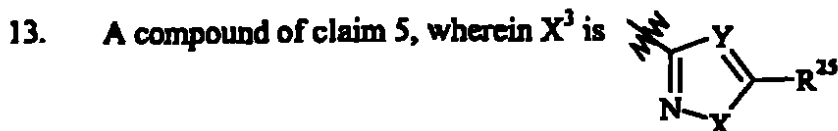
9. A compound of claim 8 wherein R^3 is $-CH(CH_3)_2$.

10. A compound of claim 2 wherein R^3 is (C_{3-12}) cycloalkyl.

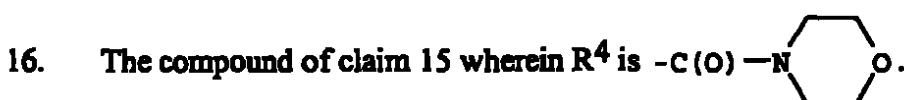
11. A compound of claim 10 wherein R^3 is cyclopropyl.

12. A compound of claim 5, wherein X^3 is





15. The compound of claim 2 wherein R^4 is $-C(O)X^5R^{11}$ wherein X^5 is a bond and R^{11} is hetero(C_{5-12})cycloalkyl(C_{0-3})alkyl.



17. The compound of claim 2 wherein R^{20} is hydrogen, R^{23} is (C_{1-6})alkyl, R^{24} is hydrogen, R^{25} is *tert*-butyl, cyclopropyl, ethyl, phenyl, pyridin-3-yl, pyridin-4-yl, thien-3-yl or trifluoromethyl.

18. The compound of claim 1 selected from the group consisting of:

- 15 morpholine-4-carboxylic acid {2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-[1,1-dimethyl-2-oxo-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-ethylcarbamoyl]-ethyl}-amide;
morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide;
morpholine-4-carboxylic acid {2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)-pentylcarbamoyl]-ethyl}-amide;
20 morpholine-4-carboxylic acid [1-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide;
morpholine-4-carboxylic acid {2-(2-methyl-propane-1-sulfonyl)-1-[1-(3-thiophen-2-yl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;
25 morpholine-4-carboxylic acid [1-[1-(3-*tert*-butyl-1,2,4-oxadiazole-5-carbonyl)-

- propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide;
morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide;
morpholine-4-carboxylic acid {(R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-(5-trifluoromethyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide;
5 morpholine-4-carboxylic acid [(1-[(1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide;
{(R)-2-(2-methyl-propane-1-sulfonyl)-1-[(S)-1-(5-thiophen-3-yl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide;
10 morpholine-4-carboxylic acid {(R)-1-[(S)-1-(3-tert-butyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-amide;
morpholine-4-carboxylic acid {(R)-2-(2-methyl-propane-1-sulfonyl)-1-[(S)-1-(5-trifluoromethyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-ethyl}-amide;
morpholine-4-carboxylic acid {(R)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide;
15 morpholine-4-carboxylic acid {(R)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide;
morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;
20 morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-ethyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;
morpholine-4-carboxylic acid {2-cyclopropylmethanesulfonyl-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;
morpholine-4-carboxylic acid {2-(2-methyl-propane-1-sulfonyl)-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;
25 morpholine-4-carboxylic acid [1-[1-(3-ethyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-(2-methyl-propane-1-sulfonyl)-ethyl]-amide;
morpholine-4-carboxylic acid {2-phenylmethanesulfonyl-1-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-ethyl}-amide;
30 morpholine-4-carboxylic acid {1-[1-(3-ethyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide;

morpholine-4-carboxylic acid {1-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide;

morpholine-4-carboxylic acid {1-[1-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide; and

- 5 morpholine-4-carboxylic acid {2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-[1,1-dimethyl-2-oxo-2-(5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl)-ethylcarbamoyl]-ethyl}-amide.

19. A derivative selected from the group consisting of *N*-oxide derivatives, prodrug derivatives, protected derivatives, isomers, and mixtures of isomers, of a compound of
10 claim 18; or a pharmaceutically acceptable salt or solvate of a compound of claim 18 or said derivative.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

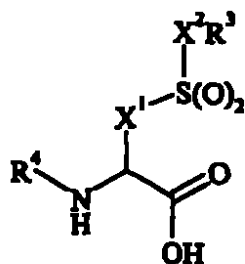
15

21. 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
20 thereof; or a pharmaceutically acceptable salt or solvate of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

22. A method of manufacturing a pharmaceutical composition using a compound of
25 Claim 1 for treating a disease in an animal in which Cathepsin S activity contributes to the pathology and/or symptomology of the disease.

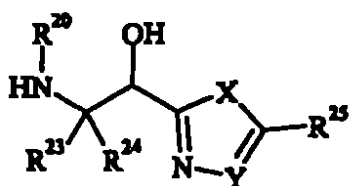
23. A process for preparing a compound of claim 1 by:

(A) reacting a compound of Formula (II):



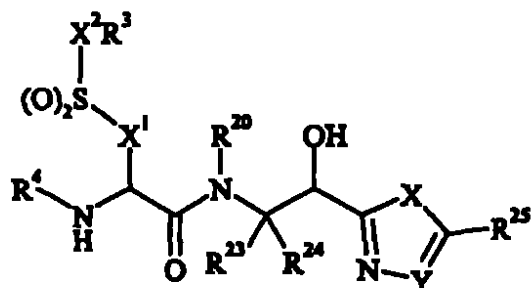
(II)

with a compound of the Formula (III):



(III)

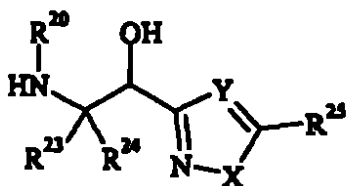
to afford a β -hydroxy amide (IV):



(IV)

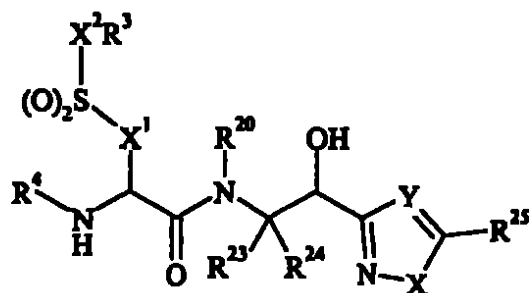
and then oxidizing said β -hydroxy amide to afford a compound of claim 1; or

(B) reacting a compound of Formula (II) with a compound of the formula (VI):



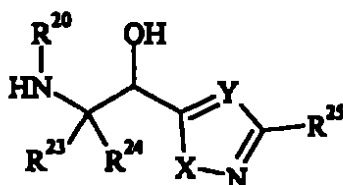
(VI)

to afford a β -hydroxy amide (VIII):



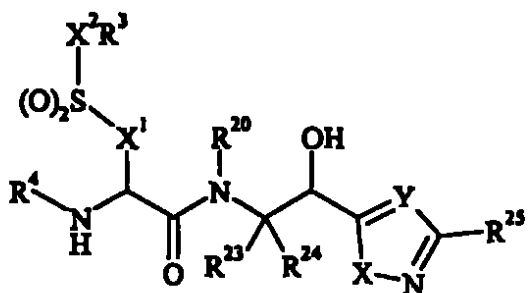
(VIII)

and then oxidizing said β -hydroxy amide to afford a compound of claim 1; or
(C) reacting a compound of Formula (II) with a compound of the formula (VII):



(VII)

to afford a β -hydroxy amide (IX):



(IX)

and then oxidizing said β -hydroxy amide to afford a compound of claim 1;
wherein X , Y , X^1 , X^2 , R^3 , R^4 , R^{20} , R^{23} , R^{24} and R^{25} are the same as in Formula
(I) defined in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 02/36396

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D271/06 C07D271/10 A61K31/4245

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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 used, where practical, search terms used)

CHEM ABS Data, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 19808 A (LINK JOHN O ; ZIPFEL SHEILA (US); AXYS PHARM INC (US); GRAUPE MICHA) 22 March 2001 (2001-03-22) page 1, line 5 - line 21 page 2, formula I examples 1-4 claims 1,9	1-23
Y	US 6 255 453 B1 (KAWABATA KAZUHITO ET AL) 3 July 2001 (2001-07-03) page 1, line 15 - line 55 column 2, formula (I) column 3, line 49 - line 61 claim 1	1-23

☐ 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

6 March 2003

Date of mailing of the international search report

13/03/2003

Name and mailing address of the ISA

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Authorized officer

Hoepfner, W

INTERNATIONAL SEARCH REPORT

Intern: ication No.
PCT/US 02/36396

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 21 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.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 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

 International Application No
 PCT/US 02/36396

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0119808 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
		US 6492362 B1	10-12-2002
US 6255453 B1	03-07-2001	US 6001813 A	14-12-1999
		US 6001814 A	14-12-1999
		US 2002010315 A1	24-01-2002
		AU 4330899 A	19-06-2000
		AU 4415899 A	20-12-1999
		EP 1089752 A1	11-04-2001
		EP 1135151 A1	26-09-2001
		WO 0032216 A1	08-06-2000
		WO 9962538 A1	09-12-1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference US20010197W0	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/ 36396	International filing date (day/month/year) 14/11/2002	(Earliest) Priority Date (day/month/year) 14/11/2001
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 4 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

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

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

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, 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:

OLIGOPEPTIDES AND COMPOSITIONS CONTAINING THEM AS CATHEPSIN S INHIBITORS

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

national application No.
PCT/US 02/36396

84

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 21 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.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependant 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

Info. Serial Application No.
PCT/US 02/36396

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D271/06 C07D271/10 A61K31/4245

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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)

CHEM ABS Data, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 19808 A (LINK JOHN O ;ZIPFEL SHEILA (US); AXYS PHARM INC (US); GRAUPE MICHA) 22 March 2001 (2001-03-22) page 1, line 5 - line 21 page 2, formula I examples 1-4 claims 1,9	1-23
Y	US 6 255 453 B1 (KAWABATA KAZUHIITO ET AL) 3 July 2001 (2001-07-03) page 1, line 15 - line 55 column 2, formula (I) column 3, line 49 - line 61 claim 1	1-23



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 claims 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
- "&" document member of the same patent family

Date of the actual completion of the international search

6 March 2003

Date of mailing of the international search report

13/03/2003

Name and mailing address of the ISA

European Patent Office, P.B. 6816 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Hoepfner, W

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/36396

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0119808	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
			US 6492362 B1	10-12-2002
US 6255453	B1	03-07-2001	US 6001813 A	14-12-1999
			US 6001814 A	14-12-1999
			US 2002010315 A1	24-01-2002
			AU 4330899 A	19-06-2000
			AU 4415899 A	20-12-1999
			EP 1089752 A1	11-04-2001
			EP 1135151 A1	26-09-2001
			WO 0032216 A1	08-06-2000
			WO 9962538 A1	09-12-1999

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

(19) Organización Mundial de la Propiedad Intelectual
Oficina Internacional
OMPI

(43) Fecha de Publicación Internacional
22 Mayo 2003 (22.05.2003)

PCT

(10) Número de Publicación Internacional
WO 03/042167 A1

(51) Clasificación Internacional de Patentes: C07D 271/06, 271/10, A61K
31/4245

(21) Número de Solicitud Internacional: PCT/US02/36396

(22) Fecha de Presentación Internacional: 14 Noviembre 2002 (14.11.2002)

(25) Idioma de Presentación: Inglés

(26) Idioma de Publicación: Inglés

(30) Datos de Prioridad:
60/332,605 14 Noviembre 2001 (14.11.2001) US

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(81) Estados Designados (nacional): 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, UZ, VN, YU, ZA, ZM, ZW

(84) Estados Designados (regional): ARIPO patente (GH, GM, KE, LS, MW, MZ,
SD, SL, SZ, TZ, UG, ZM, ZW), Patente Euroasiática (AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR,
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:

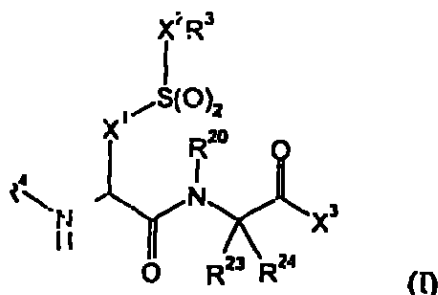
de relación de inventores (Regla 4.17(iv)) solo para US.

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: OLIGOPÉPTIDOS Y COMPOSICIONES QUE LOS CONTIENEN
COMO INHIBIDORES DE CATEPSINA S



(57) Extracto: La presente invención se relaciona con novedosos inhibidores selectivos de catepsina S, sus sales farmacéuticamente aceptables y sus N-óxidos sus usos como agentes terapéuticos y los métodos para su elaboración.

**NUEVOS COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES
DE CATEPSINA S**

LA INVENCION

5 Esta solicitud se basa en y reivindica la prioridad de la Solicitud Provisional de EE.UU. N° 60/332.605 presentada el 14 de Noviembre de 2001, que se incorpora aquí mediante referencia.

10 Esta solicitud se refiere a compuestos y composiciones para tratar enfermedades asociadas con la actividad de proteasas cisteínicas, particularmente enfermedades asociadas con la actividad de catepsina S.

DESCRIPCIÓN DE LA ESPECIALIDAD

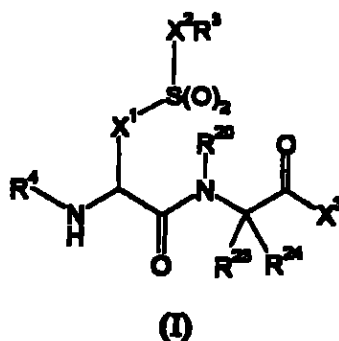
15 Las proteasas cisteínicas representan una clase de peptidasas caracterizadas por la presencia de un residuo de cisteína en el sitio catalítico de la enzima. Las proteasas cisteínicas están asociadas con la degradación y el procesamiento normal de proteínas. Sin embargo, la actividad aberrante de las proteasas cisteínicas, por ejemplo, como resultado de una expresión incrementada o una activación aumentada, puede tener consecuencias patológicas. A este respecto, ciertas proteasas cisteínicas están asociadas con un número de estados de enfermedad, incluyendo la artritis, la distrofia muscular, la inflamación, la invasión tumoral, la glomerulonefritis, la malaria, la enfermedad periodontal, la leucodistrofia metacromática y otros. Un incremento en la actividad de catepsina S contribuye a la patología y/o la sintomatología de un número de enfermedades. De acuerdo con esto, las moléculas que inhiben la actividad de la proteasa catepsina S son útiles como agentes terapéuticos en el tratamiento de tales enfermedades.

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SUMARIO DE LA INVENCION

Esta solicitud se refiere a compuestos de Fórmula (I):



5 en la que:

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

R^3 es $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$, $-CR^7=NR^8$ o cicloalquilo(C_{3-12}), en donde R^5 y R^6 son independientemente hidrógeno o 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 cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), arilo(C_{6-12}), hetero-arilo(C_{5-12}), bicicloarilo(C_{9-12}) o hetero-bicicloarilo(C_{8-12}) y R^7 y R^8 junto con los átomos a los que R^7 y R^8 están unidos forman hetero-cicloalquilo(C_{3-12}), hetero-arilo(C_{5-12}) o hetero-bicicloarilo(C_{8-12}), en donde R^3 opcionalmente está sustituido por 1 a 5 radicales seleccionados independientemente de un grupo que consiste en alquilo(C_{1-4}), ciano, halo, alquilo(C_{1-4}) sustituido por halo, 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 donde X^4 es un enlace o alquilen(C_{1-2}), R^9 en cada presencia es independientemente hidrógeno, alquilo(C_{1-3}) o alquilo(C_{1-3}) sustituido por halo y R^{10} es alquilo(C_{1-3}) o alquilo(C_{1-3}) sustituido por halo; y

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

alquilo(C₀₋₃), bicicloaril(C₈₋₁₂)-alquilo(C₀₋₃) o hetero-
 bicicloaril(C₈₋₁₂)-alquilo(C₀₋₃) y R¹⁴ en cada presencia es
 independientemente hidrógeno o alquilo(C₁₋₆), o (ii) ci-
 cloalquil(C₃₋₁₂)-alquilo(C₀₋₃), hetero-cicloalquil(C₅₋₁₂)-
 5 alquilo(C₀₋₃), aril(C₆₋₁₂)-alquilo(C₀₋₃), hetero-aril(C₅₋₁₂)-
 alquilo(C₀₋₃), bicicloaril(C₈₋₁₂)-alquilo(C₀₋₃) o hetero-
 bicicloaril(C₈₋₁₂)-alquilo(C₀₋₃) o (iii) cicloalquil(C₃₋₆)-
 alquilo(C₀₋₃), hetero-cicloalquil(C₅₋₆)-alquilo(C₀₋₃), fe-
 nil-alquilo(C₀₋₃) o hetero-aril(C₅₋₆)-alquilo(C₀₋₃) susti-
 10 tuido por -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 donde X⁶ es un enla-
 ce o metileno,
 15 R¹⁵ es cicloalquil(C₃₋₆)-alquilo(C₀₋₃), hetero-
 cicloalquil(C₅₋₆)-alquilo(C₀₋₃), fenil-alquilo(C₀₋₃) o hete-
 ro-aril(C₅₋₆)-alquilo(C₀₋₃) y R¹⁶ es hidrógeno o alquilo(C₁₋₆);
 en donde R⁴ contiene además opcionalmente 1 a 5 susti-
 tuyentes que cuando están presentes dentro de un sistema
 20 anular alicíclico o aromático son radicales seleccionados
 independientemente de un grupo que consiste en alquilo(C₁₋₆),
 alquilideno(C₁₋₆), ciano, halo, nitro, alquilo(C₁₋₃)
 sustituido por halo, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -
 X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -
 25 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 cuando
 están presentes dentro de un resto alifático son radica-
 les seleccionados independientemente del grupo que con-
 30 siste en ciano, 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 y -C(O)R¹⁸, en donde X⁶ es un enlace o alquile-
 35 no(C₁₋₆), R¹⁷ en cada presencia es independientemente hi-
 drógeno, alquilo(C₁₋₆) o alquilo(C₁₋₃) sustituido por halo
 y R¹⁸ es alquilo(C₁₋₆) o alquilo(C₁₋₃) sustituido por halo;

R²⁰ se selecciona del grupo que consiste en hidróge-
 40 no, alquilo(C₁₋₆), cicloalquil(C₃₋₁₂)-alquilo(C₀₋₆), hetero-

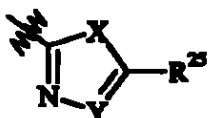
cicloalquil(C₃₋₁₂)-alquilo(C₀₋₆), aril(C₆₋₁₂)-alquilo(C₀₋₆) o hetero-aril(C₅₋₁₂)-alquilo(C₀₋₆);

R²³ se selecciona de hidrógeno, alquilo(C₁₋₆), alcoxi-
alquilo(C₁₋₃), halo-alquilo(C₁₋₃), cicloalquil(C₃₋₁₂)-
5 alquilo(C₀₋₆), hetero-cicloalquil(C₅₋₁₂)-alquilo(C₀₋₆),
aril(C₆₋₁₂)-alquilo(C₀₋₆) y hetero-aril(C₅₋₁₂)-alquilo(C₀₋₆)
opcionalmente sustituido con amino, -NHC(O)R¹⁵ o -R¹⁵ en
donde R¹⁵ es como se describe anteriormente; y

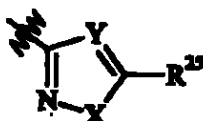
R²⁴ se selecciona de hidrógeno o alquilo(C₁₋₆); o

10 R²³ y R²⁴ tomados junto con el átomo de carbono al
que tanto R²³ como R²⁴ están unidos forman cicloalquile-
no(C₃₋₈) o heterocicloalquilenos(C₃₋₈);

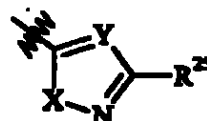
X³ se selecciona del grupo (a), (b) o (c);



(a)



(b)



(c)

15 en donde X es O e Y es N;

R²⁵ se selecciona de hidrógeno, alquilo(C₁₋₆), ci-
cloalquil(C₃₋₁₂)-alquilo(C₀₋₆), hetero-cicloalquil(C₅₋₁₂)-
alquilo(C₀₋₆), aril(C₆₋₁₂)-alquilo(C₀₋₆), hetero-aril(C₅₋₁₂)-
alquilo(C₀₋₆), -X⁴NHR¹⁵, -X⁴S(O)₂R²⁶ o -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷
20 en donde R¹⁵, R¹⁷ y X⁴ son como se describen anteriormente;

R²⁶ se selecciona del grupo que consiste en hidróge-
no, alquilo(C₁₋₆), cicloalquil(C₃₋₁₂)-alquilo(C₀₋₆), hetero-
cicloalquil(C₅₋₁₂)-alquilo(C₀₋₆), aril(C₆₋₁₂)-alquilo(C₀₋₆),
hetero-aril(C₅₋₁₂)-alquilo(C₀₋₆), bicicloaril(C₉₋₁₂)-
25 alquilo(C₀₋₃) y hetero-bicicloaril(C₈₋₁₂)-alquilo(C₀₋₃);

en la que R²⁵ contiene además opcionalmente 1 a 5
sustituyentes que cuando están presentes dentro de un
sistema anular alicíclico o aromático son radicales se-
leccionados independientemente de un grupo que consiste
30 en alquilo(C₁₋₆), alquilideno(C₁₋₆), ciano, halo, nitro,
alquilo(C₁₋₃) sustituido por halo, -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,
35 -X⁶OP(O)(OR⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ y
-X⁶C(O)R¹⁸ y cuando están presentes dentro de un resto

alifático son radicales seleccionados independientemente de un grupo que consiste en ciano, halo, nitro, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$, $-NR^{17}C(NR^{17})NR^{17}R^{17}$, $-OR^{17}$, $-SR^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-P(O)(OR^{17})OR^{17}$, $-OP(O)(OR^{17})OR^{17}$, $-NR^{17}C(O)R^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$ y $-C(O)R^{18}$, en donde R^{15} , R^{17} , R^{18} y X^6 son como se describen anteriormente.

Un segundo aspecto de la invención es una composición farmacéutica que contiene un compuesto de Fórmula (I) o sus derivados de N-óxido, isómeros individuales o una mezcla de sus isómeros, o sus sales farmacéuticamente aceptables, 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 que la inhibición de catepsina S puede prevenir, inhibir o mejorar la patología y/o la sintomatología de la enfermedad, método que comprende administrar al animal una cantidad terapéuticamente eficaz de compuesto de Fórmula (I) o uno de sus derivados de N-óxido, isómeros individuales o mezclas de isómeros; o una de sus sales farmacéuticamente aceptables.

Un cuarto aspecto de la invención es el procedimiento para preparar compuestos de Fórmula (I) y sus derivados de N-óxido, derivados de profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros; y sus sales farmacéuticamente aceptables.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Definiciones:

A no ser que se indique otra cosa, los siguientes términos usados en la memoria descriptiva y en las reivindicaciones se definen para los propósitos de esta Solicitud y tienen los siguientes significados.

"Alicíclico" significa un resto caracterizado por la disposición de los átomos de carbono en estructuras anulares no aromáticas cerradas que tienen propiedades que se asemejan a las de los compuestos alifáticos y pueden estar saturadas o parcialmente saturadas con dos o más dobles o triples enlaces.

91

"Alifático" significa un resto caracterizado por una disposición de cadena lineal o ramificada de los átomos de carbono constituyentes y puede estar saturado o parcialmente insaturado con dos o más dobles o triples enlaces.

"Alcoxi" significa un grupo alquil-O- en el que el grupo alquilo es como se describe aquí. Grupos alcoxi ejemplares incluyen metoxi y etoxi.

"Alquilo" representado por sí mismo significa un radical alifático lineal o ramificado, saturado o insaturado, que tiene el número de átomos de carbono indicado (por ejemplo, alquilo(C₁₋₆) incluye 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). El alquilo representado junto con otro radical (por ejemplo, como en arilalquilo) significa un radical divalente alifático lineal o ramificado, saturado o insaturado, que tiene el número de átomos indicado o cuando no están indicados átomos significa un enlace (por ejemplo, aril(C₆₋₁₀)-alquilo(C₀₋₃) incluye fenilo, bencilo, fenetilo, 1-feniletilo, 3-fenilpropilo y similares).

"Alquileno", a no ser que se indique otra cosa, significa un radical divalente alifático, lineal o ramificado, saturado o insaturado, que tiene el número de átomos de carbono indicado (por ejemplo, alquileno(C₁₋₆) incluye 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 insaturado, que tiene el número de átomos de carbono indicado (por ejemplo, alquilideno(C₁₋₆) incluye metilideno (=CH₂), etilideno (=CHCH₃), isopropilideno (=C(CH₃)₂), propilideno (=CHCH₂CH₃), alilideno (=CH-CH=CH₂), y similares).

"Amino" significa el radical -NH₂. A no ser que se indique otra cosa, los compuestos de la invención que contienen restos amino incluyen sus derivados protegidos.

Grupos protectores adecuados para restos amino incluyen acetilo, terc-butoxicarbonilo, benciloxicarbonilo y similares.

"Animal" incluye seres humanos, mamíferos no humanos (por ejemplo, perros, gatos, conejos, vacas, caballos, ovejas, cabras, cerdos, ciervos y similares) y no mamíferos (por ejemplo, aves y similares).

"Aromático" significa un resto en el que los átomos constituyentes forman un sistema anular insaturado, todos los átomos en el sistema anular están hibridados sp^2 y el número total de electrones π es igual a $4n+2$.

"Arilo" significa una disposición anular monocíclica o bicíclica condensada que contiene el número total de átomos de carbono de anillo indicado, en donde cada anillo está comprendido por 6 átomos de carbono de anillo y es aromático o cuando está condensado con un segundo anillo forma una disposición anular aromática. Por ejemplo, arilo(C_{6-10}) opcionalmente sustituido, según se usa en esta Solicitud, incluye, pero no se limita 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-etoxicarbonilfenilo, 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. Arilo(C_{6-10}) opcionalmente sustituido, según se usa en esta Solicitud, incluye 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 sistema anular bicíclico que contiene el número de átomos de carbono de anillo indicado, en el que los anillos están conectados por un enlace sencillo o condensados y al menos uno de los anillos que comprende el sistema es aromático, y cualquiera de sus derivados de cetona carbocíclica, tiocetona o imino-cetona (por ejemplo, bicicloarilo(C₉₋₁₀) incluye ciclo-
10 hexilfenilo, 1,2-dihidronaftilo, 2,4-dioxo-1,2,3,4-tetrahidronaftilo, indanilo, indenilo, 1,2,3,4-tetrahidronaftilo, y similares).

"Carbamóilo" significa el radical -C(O)NH₂. A no ser que se indique otra cosa, los compuestos de la invención
15 que contienen restos carbamóilo incluyen sus derivados protegidos. Grupos protectores adecuados para restos carbamóilo incluyen acetilo, terc-butoxicarbonilo, benciloxicarbonilo y similares, y tanto los derivados desprotegidos como los protegidos están dentro del alcance de
20 la invención.

"Derivado de cetona carbocíclica" significa un derivado que contiene el resto -C(O)-.

"Carboxi" significa el radical -C(O)OH. A no ser que se indique otra cosa, los compuestos de la invención que
25 contienen restos carboxi incluyen sus derivados protegidos. Grupos protectores adecuados para restos carboxi incluyen bencilo, terc-butilo y similares.

"Cicloalquilo" significa un sistema anular monocíclico, bicíclico condensado o policíclico con puentes, saturado o parcialmente insaturado, que contiene el número de átomos de carbono de anillo indicado, y cualquiera de sus derivados de cetona carbocíclica, tiocetona o iminocetona (por ejemplo, cicloalquilo(C₃₋₁₀) incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclo-
30 hexenilo, 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 sistema anular monocíclico o anular policíclico con puentes, saturado o par-
40

cialmente insaturado, divalente, que contiene el número de átomos de carbono de anillo indicado, y cualquiera de sus derivados de cetona carbocíclica, tiocetona o imino-cetona.

5 "Enfermedad" incluye específicamente cualquier estado no sano de un animal o una de sus partes e incluye un estado no sano que puede estar provocado por, o ser inherente a, una terapia médica o veterinaria aplicada a ese animal, es decir, los "efectos secundarios" de tal
10 terapia.

"Halo" significa fluoro, cloro, bromo o yodo.

"Alquilo sustituido por halo", como un grupo aislado o parte de un grupo mayor, significa "alquilo" sustituido por uno o más átomos de "halo", según se definen tales
15 términos en esta Solicitud. Alquilo sustituido por halo incluye haloalquilo, dihaloalquilo, trihaloalquilo, perhaloalquilo y similares (por ejemplo, alquilo(C₁₋₃) sustituido por halo incluye clorometilo, diclorometilo, difluorometilo, trifluorometilo, 2,2,2-trifluoroetilo, perfluoroetilo, 2,2,2-trifluoro-1,1-dicloroetilo y simila-
20 res).

"Heteroarilo" significa arilo, según se define en esta Solicitud, con tal de que uno o más de los átomos de carbono de anillo indicados se reemplacen por un resto de
25 heteroátomo seleccionado de -N=, -NR-, -N⁺(O⁻)=, -O- o -S-, en donde R es hidrógeno, alquilo(C₁₋₆), un grupo protector o representa la valencia libre que sirve como el punto de unión a un nitrógeno del anillo, y cada anillo está comprendido por 5 6 6 átomos de anillo. Por ejemplo,
30 hetero-arilo(C₅₋₁₃) opcionalmente sustituido, según se usa en esta Solicitud, incluye, pero no se limita a, 4-amino-2-hidroxipirimidin-5-ilo, benzotiazol-2-ilo, 1H-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, dibenzofuranilo, 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-
40 hidroxi-6-metilpirid-2-ilo, 3-hidroxipirid-2-ilo, 1H-

imidazol-2-ilo, 1H-imidazol-4-ilo, 1H-indol-3-ilo, isoxazol-4-ilo, isoxazol-4-ilo, 2-metilfur-3-ilo, 5-metilfur-2-ilo, 1-metil-1H-imidazol-2-ilo, 5-metil-3H-imidazol-4-ilo, 5-metilisoxazol-3-ilo, piracinilo, 5-metil-2H-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, 2H-pirazol-3-ilo, 3H-pirazol-4-ilo, piridacin-3-ilo, pirid-2-ilo, pirid-3-ilo, pirid-4-ilo, 5-pirid-3-il-2H-[1,2,4]triazol-3-ilo, pirimidin-4-ilo, pirimidin-5-ilo, 1H-pirrol-3-ilo, quinolin-2-ilo, 1H-tetrazol-5-ilo, tiazol-2-ilo, tiazol-5-ilo, tien-2-ilo, tien-3-ilo, 2H-[1,2,4]triazol-3-ilo, 3H-[1,2,3]triazol-4-ilo, 5-trifluorometilpirid-2-ilo, y similares. Grupos protectores adecuados incluyen terc-butoxicarbonilo, benciloxycarbonilo, bencilo, 4-metoxibencilo, 2-nitrobencilo y similares. Hetero-arilo(C₅₋₁₀) opcionalmente sustituido, según se usa en esta Solicitud para definir 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.

"Resto de heteroátomo" incluye -N=, -NR-, -N⁺(O⁻)=, -O-, -S- o -S(O)₂-, en donde R es hidrógeno, alquilo(C₁₋₆) o un grupo protector.

"Heterodibiccloarilo" significa bicicloarilo, según se define en esta Solicitud, con tal de que uno o más de los átomos de carbono de anillo indicados se reemplacen por un resto de heteroátomo seleccionado de -N=, -NR-, -O- o -S-, en donde R es hidrógeno, alquilo(C₁₋₆), un grupo protector o representa la valencia libre que sirve como el punto de unión a un nitrógeno del anillo, y cualquiera de sus derivados de cetona carbocíclica, tiocetona o iminocetona. Por ejemplo, hetero-bicicloarilo(C₈₋₁₀) opcionalmente sustituido, según se usa en esta Solicitud, incluye, pero no se limita a, 2-amino-4-oxo-3,4-dihidropteridin-6-ilo y similares. En general, el término heterobicicloarilo, según se usa en esta Solicitud, incluye, por ejemplo, benzo[1,3]dioxol-5-ilo, 3,4-dihidro-2H-[1,8]naftiridinilo, 3,4-dihidro-2H-quinolinilo, 2,4-dioxo-3,4-dihidro-2H-quinazolinilo, 1,2,3,4,5,6-

hexahidro[2,2']bipiridinililo, 3-oxo-2,3-
dihidrobenczo[1,4]oxacinilo, 5,6,7,8-
tetrahydroquinolinilo, y similares.

"Heterocicloalquilo" significa cicloalquilo, según
5 se define en esta Solicitud, con tal de que uno o más de
los átomos de carbono de anillo indicados se reemplacen
por un resto de heteroátomo seleccionado de -N=, -NR-, -
O- o -S-, en donde R es hidrógeno, alquilo(C₁₋₆), un grupo
protector o representa la valencia libre que sirve como
10 el punto de unión a un nitrógeno de anillo, y cualquiera
de sus derivados de cetona carbocíclica, tiocetona o imi-
nocetona (por ejemplo, el término hetero-cicloalquilo(C<sub>5-
10</sub>) incluye imidazolinilo, morfolinilo, piperacinilo, pi-
peridilo, pirrolidinilo, pirrolinilo, quinuclidinilo y
15 similares). Grupos protectores adecuados incluyen terc-
butoxicarbonilo, benciloxicarbonilo, bencilo, 4-
metoxibencilo, 2-nitrobencilo y similares. Tanto los de-
rivados desprotegidos como los protegidos están dentro
del alcance de la invención.

20 "Heterocicloalquilenos" significa cicloalquilenos, se-
gún se define en esta Solicitud, con tal de que uno o más
de los átomos de carbono que son miembros de anillo indi-
cados se reemplace por un resto de heteroátomo seleccio-
nado de -N=, -NR-, -O-, -S- o -S(O)₂-, en donde R es
25 hidrógeno, alquilo(C₁₋₆) o un grupo protector.

"Hidroxilo" significa el radical -OH. A no ser que se
indique otra cosa, los compuestos de la invención que
contienen radicales hidroxilo incluyen sus derivados prote-
gidos. Grupos protectores adecuados para restos hidroxilo
30 incluyen bencilo y similares.

"Derivado de iminocetona" significa un derivado que
contiene el resto -C(NR)-, en el que R es hidrógeno o al-
quilo(C₁₋₆).

"Isómeros" significa compuestos de fórmula I que
35 tienen fórmulas moleculares idénticas pero difieren en la
naturaleza o la secuencia de unión 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
denominan "estereoisómeros". Los estereoisómeros que no
40 son imágenes especulares entre sí se denominan "diaste-

reoisómeros" y los estereoisómeros que son imágenes espe-
culares no superponibles se denominan "enantiómeros" o a
veces "isómeros ópticos". Un átomo de carbono unido a
cuatro sustituyentes no idénticos se denomina un "centro
5 quiral". Un compuesto con un centro quiral que tiene dos
formas enantiómeras de quiralidad opuesta se denomina una
"mezcla racémica". Un compuesto que tiene más de un cen-
tro quiral tiene 2^{n-1} pares enantiómeros, donde n es el
número de centros quirales. Los compuestos con más de un
10 centro quiral pueden existir como diastereoisómeros indi-
viduales o como una mezcla de diastereoisómeros, denomi-
nada una "mezcla diastereoisómera". Cuando está presente
un centro quiral, un estereoisómero puede caracterizarse
por la configuración absoluta de ese centro quiral. La
15 configuración absoluta se refiere a la disposición en el
espacio de los sustituyentes unidos al centro quiral. Los
enantiómeros se caracterizan por la configuración absolu-
ta de sus centros quirales y son descritos por las reglas
de secuenciación R y S de Cahn, Ingold y Prelog. Las con-
20 venciones para la nomenclatura estereoquímica, los méto-
dos para la determinación de la estereoquímica y la sepa-
ración de los estereoisómeros son bien conocidos en la
técnica (por ejemplo, véase "Advanced Organic Chemistry",
4ª edición, Marzo, Jerry, John Wiley & Sons, Nueva York,
25 1992). Se entiende que los nombres y la ilustración usa-
dos en esta Solicitud para describir los compuestos de
Fórmula I pretenden abarcar todos los posibles estereoisó-
meros. Así, por ejemplo, el nombre {2-
fenilmetanosulfonil-1-[1-(5-fenil-[1,3,4]oxadiazol-2-
30 carbonil)pentilcarbamoil]etil}-amida de ácido morfolino-
4-carboxílico incluye {S-2-fenilmetanosulfonil-1-[1-(5-
fenil-[1,3,4]oxadiazol-2-carbonil)pentilcarbamoil]-etil}-
amida de ácido morfolino-4-carboxílico y {R-2-
fenilmetanosulfonil-1-[1-(5-fenil-[1,3,4]oxadiazol-2-
35 carbonil)pentilcarbamoil]-etil}-amida de ácido morfolino-
4-carboxílico y cualquiera de sus mezclas, racémica u
otra.

"Derivado de cetona" significa un derivado que
contiene el resto -C(O)-. Por ejemplo, para 2-
40 acetoxiacetidin-3-ilo, el "derivado de cetona carbocíclico

ca" sería 2-acetoxi-4-oxoacetidin-3-ilo.

"Nitro" significa el radical -NO_2 .

"Opcional" u "opcionalmente" significa que el suceso o la circunstancia descrito posteriormente puede producirse o no, y que la descripción incluye casos en los que el suceso o la circunstancia se produce y casos en los que no. Por ejemplo, la expresión "en donde dentro de R^3 y R^4 cualquier anillo alicíclico o aromático puede estar sustituido adicionalmente por 1-5 radicales..." significa que R^3 y R^4 pueden estar sustituidos o no para estar dentro del alcance de la invención.

"Oxoalquilo" significa alquilo, según se define anteriormente, en el que uno del número de átomos de carbono indicado está reemplazado por un grupo oxígeno (-O-), por ejemplo, oxo-alquilo(C_{2-6}) incluye metoximetilo, etc.

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

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

"Farmacéuticamente aceptable" significa aquello que es útil al preparar una composición farmacéutica que es generalmente segura, atóxica y ni biológicamente ni de otro modo no deseable e incluye aquello que es aceptable para uso veterinario así como uso farmacéutico humano.

"Sales farmacéuticamente aceptables" significa sales de compuestos de Fórmula (I) que son farmacéuticamente aceptables, según se define anteriormente, y que poseen la actividad farmacológica deseada. Tales sales incluyen sales por adición de ácidos formadas con ácidos inorgánicos, tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares; o con ácidos orgánicos tales como ácido acético, ácido propiónico, ácido hexanoico, ácido heptanoico, ácido ciclopentanopropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido malónico, ácido succínico, ácido málico, ácido maleico, ácido fumárico, ácido tartárico,

ácido cítrico, ácido benzoico, ácido o-(4-hidroxibenzoil)benzoico, ácido cinámico, ácido mandélico, ácido metanosulfónico, ácido etanosulfónico, ácido 1,2-etanodisulfónico, ácido 2-hidroxietanosulfónico, ácido bencenosulfónico, ácido p-clorobencenosulfónico, ácido 2-naftalenosulfónico, ácido p-toluenosulfónico, ácido canforsulfónico, ácido 4-metilbiciclo[2.2.2]oct-2-eno-1-carboxílico, ácido glucoheptónico, 4,4'-metilenbis(ácido 3-hidroxi-2-eno-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido terc-butilacético, ácido laurilsulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico y similares.

Las sales farmacéuticamente aceptables también incluyen sales por adición de bases que pueden formarse con protones ácidos presentes que son capaces de reaccionar con bases inorgánicas u orgánicas. Bases inorgánicas aceptables incluyen hidróxido sódico, carbonato sódico, hidróxido potásico, hidróxido de aluminio e hidróxido cálcico. Bases orgánicas aceptables incluyen etanolamina, dietanolamina, trietanolamina, trometamina, N-metilglucamina y similares.

"Profármaco" significa un compuesto que puede convertirse in vivo por medios metabólicos (por ejemplo, mediante hidrólisis) en un compuesto de Fórmula (I). Por ejemplo, un éster de un compuesto de Fórmula (I) que contiene un grupo hidroxilo puede convertirse mediante hidrólisis in vivo en la molécula original. Alternativamente, un éster de un compuesto de Fórmula (I) que contiene un grupo carboxi puede convertirse mediante hidrólisis in vivo en la molécula original. Ésteres adecuados de compuestos de Fórmula (I) que contienen un grupo hidroxilo son, por ejemplo, acetatos, citratos, lactatos, tartratos, malonatos, oxalatos, salicilatos, propionatos, succinatos, fumaratos, maleatos, metilen-bis-b-hidroxinaftoatos, gentisatos, isetionatos, di-p-toluoiltartratos, metanosulfonatos, etanosulfonatos, bencenosulfonatos, p-toluenosulfonatos, ciclohexilsulfamatos y quinatos. Ésteres adecuados de compuestos de Fórmula (I) que contienen un grupo carboxi son, por ejemplo, los

descritos por F.J. Leinweber, Drug. Metab. Res., 1987, 18, página 379. Una clase especialmente útil de ésteres de compuestos de Fórmula (I) que contienen un grupo hidroxilo puede formarse a partir de restos ácidos seleccionados de los descritos por Bundgaard y otros, J. Med. Chem., 1989, 32, página 2503-2507, e incluyen (aminometil)-benzoatos sustituidos, por ejemplo, dialquilaminometilbenzoatos en los que los dos grupos alquilo pueden estar unidos entre sí y/o interrumpidos por un átomo de oxígeno o por un átomo de nitrógeno opcionalmente sustituido, por ejemplo un átomo de nitrógeno alquilado, más especialmente (morfolinometil)benzoatos, por ejemplo 3- 6 4-(morfolinometil)benzoatos y (4-alkilpiperacín-1-il)benzoatos, por ejemplo 3- 6 4-(4-alkilpiperacín-1-il)benzoatos.

"Derivados protegidos" significa derivados de compuestos de Fórmula (I) en los que un sitio o sitios reactivos están bloqueados con grupos protectores. Derivados protegidos de compuestos de Fórmula (I) son útiles en la preparación de compuestos de Fórmula (I) o por sí mismos pueden ser inhibidores activos de catepsina S. Una vista exhaustiva de grupos protectores adecuados puede encontrarse en T.W. Greene, *Protecting Groups in Organic Synthesis*, 3ª edición, John Wiley & Sons, Inc. 1999.

"Cantidad terapéuticamente eficaz" significa la cantidad que, cuando se administra a un animal para tratar una enfermedad, es suficiente para efectuar tal tratamiento para la enfermedad.

"Derivado de tiocetona" significa un derivado que contiene el resto -C(S)-.

"Tratamiento" o "tratar" significa cualquier administración de un compuesto de la presente invención e incluye:

(1) prevenir que la enfermedad se produzca en un animal que puede estar predispuesto a la enfermedad pero no experimenta o presenta todavía la patología o la sintomatología de la enfermedad,

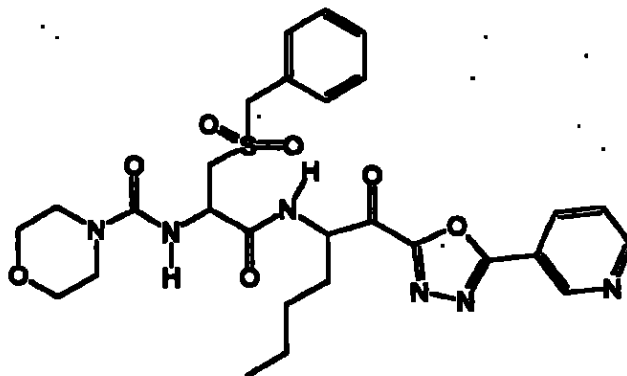
(2) inhibir la enfermedad en un animal que está experimentando o presentando la patología o la sintomatología de la enfermedad (es decir, que sufre un desarrollo adi-

cional de la patología y/o la sintomatología), o

(3) mejorar la enfermedad en un animal que está experimentando o presentando la patología o la sintomatología de la enfermedad (es decir, invertir la patología y/o la sintomatología).

Nomenclatura:

Los compuestos de Fórmula (I) y los productos intermedios y los materiales de partida usados en su preparación se nombran de acuerdo con las reglas de la IUPAC de nomenclatura en las que los grupos característicos tienen una prioridad descendente para la mención como el grupo principal como sigue: ácidos, éteres, amidas, etc. Alternativamente, los compuestos se nombran mediante AutoNom 4.0 (Beilstein Information Systems, Inc.). Por ejemplo, un compuesto de Fórmula (I) en la que R³ es fenilo, R⁴ es morfolino-4-carbonilo, R²⁰ es hidrógeno, R²³ es hidrógeno, R²⁴ es n-butilo, X¹ es metileno, X² es metileno y X³ es 5-piridin-3-il-[1,3,4]oxadiazol-2-ilo; que es un compuesto que tiene la siguiente estructura:



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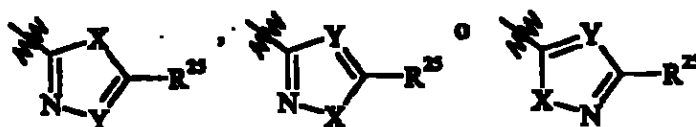
se denomina {2-fenilmetanosulfonil-1-[1-(5-piridin-3-il-[1,3,4]oxadiazol-2-carbonil)pentilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico.

Con referencia a la Fórmula (I) previa, los siguientes son agrupamientos particulares y preferidos:

X¹ puede representar particularmente metileno cuando X² es metileno.

X¹ también puede representar particularmente etileno cuando X² es un enlace.

30 X³ puede representar particularmente



en donde X es O, Y es N y R^{25} se selecciona de hidrógeno, halo-alquilo(C_{1-3}), alquilo(C_{1-6}), cicloalquil(C_{3-12})-alquilo(C_{0-6}), aril(C_{6-12})-alquilo(C_{0-6}) o hetero-aril(C_{5-13})-alquilo(C_{0-6}), en donde R^{25} contiene además opcionalmente 1 a 5 sustituyentes que cuando están presentes dentro de un sistema anular alicíclico o aromático son radicales seleccionados independientemente de un grupo que consiste en alquilo(C_{1-6}) o alquilo(C_{1-3}) sustituido por halo.

R^3 puede representar particularmente $-CR^5=CHR^6$, $-CR^5(CR^6)_2$, $-CR^7=NR^8$ o cicloalquilo(C_{3-12}), en donde R^5 y R^6 es independientemente hidrógeno o 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 cicloalquilo(C_{3-12}), arilo(C_{6-12}), hetero-arilo(C_{5-12}) o bicicloarilo(C_{9-12}), R^7 y R^8 junto con los átomos a los que R^7 y R^8 están unidos forman hetero-arilo(C_{5-12}), en donde R^3 opcionalmente está sustituido por 1 a 5 radicales seleccionados independientemente de un grupo que consiste en alquilo(C_{1-4}), ciano, halo, alquilo(C_{1-4}) sustituido con halo, $-X^4OR^9$ y $-X^4C(O)OR^9$, en el que X^4 es un enlace o alquilenos(C_{1-2}), R^9 en cada presencia es independientemente alquilo(C_{1-3}) o alquilo(C_{1-3}) sustituido por halo.

R^4 puede representar particularmente $-C(O)X^5R^{11}$ o $-S(O)_2X^5R^{11}$, en donde X^5 es un enlace, $-O-$ o $-NR^{12}-$, en donde R^{12} es hidrógeno o alquilo(C_{1-6}) y R^{11} es (i) alquilo(C_{1-6}) o (ii) hetero-cicloalquil(C_{5-12})-alquilo(C_{0-3}), aril(C_{6-12})-alquilo(C_{0-3}), hetero-aril(C_{5-12})-alquilo(C_{0-3}), bicicloaril(C_{9-12})-alquilo(C_{0-3}) o hetero-bicicloaril(C_{8-12})-alquilo(C_{0-3}) o (iii) hetero-cicloalquil(C_{5-6})-alquilo(C_{0-3}) o fenil-alquilo(C_{0-3}) sustituido por $-X^6OR^{15}$, $-X^6C(O)R^{15}$ o $-X^6NR^{16}C(O)OR^{16}$, en donde X^6 es un enlace o metileno, R^{15} es fenil-alquilo(C_{0-3}) o hetero-aril(C_{5-6})-alquilo(C_{0-3}) y R^{16} es hidrógeno o alquilo(C_{1-6}); en donde R^4 contiene opcionalmente además 1 a 5 sustituyentes que cuando están presentes dentro de un sistema anular alicíclico o aromático son radicales seleccionados independientemente de un grupo que consiste en alquilo(C_{1-6}), halo, $-X^6NR^{17}R^{17}$,

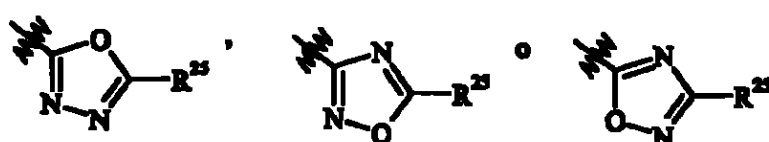
$-X^6OR^{17}$, $-X^6C(O)OR^{17}$, $-X^6NC(O)R^{16}$ y $-X^6C(O)R^{18}$, R^{17} en cada presencia es independientemente hidrógeno, alquilo(C_{1-6}) o alquilo(C_{1-3}) sustituido por halo y R^{18} es alquilo(C_{1-6}) o alquilo(C_{1-3}) sustituido por halo.

5 R^{20} puede representar particularmente hidrógeno y alquilo(C_{1-6}).

R^{23} puede representar particularmente alquilo(C_{1-6}) o aril(C_{6-12})-alquilo(C_{0-6}).

10 R^{24} puede representar particularmente hidrógeno o alquilo(C_{1-6}).

X^3 se selecciona más preferiblemente del grupo que

15 consiste  en

20

en donde R^{25} se selecciona de terc-butilo, ciclopropilo, etilo, fenilo, piracinilo, piridacinilo, piridinilo, tienilo o trifluorometilo.

R^3 se selecciona más preferiblemente del grupo que
 25 consiste en fenilo, piridin-2-ilo, piridin-3-ilo, piridin-4-ilo, vinilo, 2-difluorometoxifenilo, 1-oxipiridin-2-ilo, 4-metoxifenilo, 4-metilfenilo, 2-metilfenilo, 4-clorofenilo, 3,5-dimetilfenilo, 4-trifluorometilfenilo, 4-trifluorometoxifenilo, 2-bromofenilo, naftalen-2-ilo,
 30 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-fluoro-3-clorofenilo, 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,
 40 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-trifluorometilfenilo, 2-fluoro-4-trifluorometilfenilo, 2-fluoro-5-trifluorometilfenilo, 2,3,5-trifluorofenilo, 2-

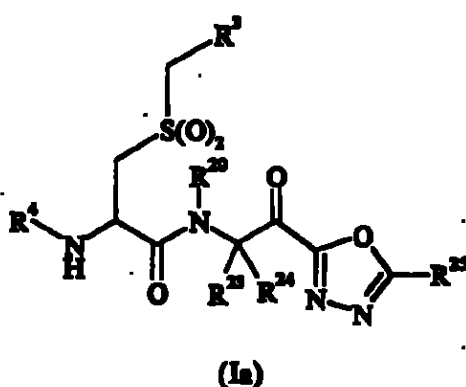
fluoro-5-trifluorometilfenilo, 5-fluoro-2-trifluorometilfenilo, 4-fluoro-3-trifluorometilfenilo, 2-metoxifenilo, 3,5-bis-trifluorometilfenilo, 4-difluorometoxifenilo, 3-difluorometoxifenilo, 2,6-diclorofenilo, 4-carboxifenilo, ciclohexilo, ciclopropilo, isopropilo, tiofen-2-ilo, 5-clorotiofen-2-ilo y 3,5-dimetilisoxazol-4-ilo. Los grupos R³ más preferidos incluyen ciclopropilo, isopropilo y fenilo.

R⁴ se selecciona más preferiblemente del grupo que
 10 consiste en benzofilo, morfolino-4-carbonilo, acetilo, furano-3-carbonilo, 2-metoxibenzofilo, 3-metoxibenzofilo, naftaleno-2-carbonilo, benzo[1,3]dioxol-5-carbonilo, 3-piridin-3-il-acrilofilo, benzofurano-2-carbonilo, furano-2-carbonilo, terc-butoxicarbonilo, bifenil-4-carbonilo,
 15 quinolino-2-carbonilo, quinolino-3-carbonilo, 3-acetilbenzofilo, 4-fenoxibenzofilo, 3-hidroxibenzofilo, 4-hidroxibenzofilo, piridino-3-carbonilo, 3-(terc-butoxicarbonilaminometil)-benzofilo, éster terc-butílico de ácido 4-carbonilpiperacino-1-carboxílico, éster etílico
 20 co de ácido 4-carbonilpiperacino-1-carboxílico, 4-(furano-2-carbonil)-piperacino-1-carbonilo, piridino-4-carbonilo, 1-oxipiridino-4-carbonilo, 1-oxipiridino-3-carbonilo, tiofeno-2-carbonilo, tiofeno-3-carbonilo, 4-benzoilbenzofilo, 5-metiltiofeno-2-carbonilo, 3-clorotiofeno-2-carbonilo, 3-bromotiofeno-2-carbonilo, 4-clorobenzofilo, 3-fluoro-4-metoxi-benzofilo, 4-metoxibenzofilo, 4-trifluorometoxibenzofilo, 3,4-difluorobenzofilo, 4-fluorobenzofilo, 3,4-dimetoxibenzofilo, 3-metilbenzofilo, 4-bromobenzofilo, 4-trifluorometilbenzofilo, 3-benzoilbenzofilo, ciclopentano-carbonilo, benzo[b]tiofeno-2-carbonilo, 3-clorobenzo[b]tiofeno-2-carbonilo, bencenosulfonilo, naftaleno-2-sulfonilo, 5-metiltiofeno-2-sulfonilo, tiofeno-2-sulfonilo, éster formamilmetílico, 4-metilpentanofilo, 35 éster formamilisobutílico, éster formamilmonoalílico, éster formamilisopropílico, N,N-dimetilformamilo, N-isopropilformamilo, N-piridin-4-ilformamilo, N-piridin-3-il-formamilo, 3-fenilacrilofilo, 1H-indol-5-carbonilo, piridino-2-carbonilo, piracino-2-carbonilo, 3-hidroxipiridino-2-carbonilo, 2-aminopiridino-3-carbonilo,
 40

2-hidroxipiridino-3-carbonilo, 6-aminopiridino-3-carbonilo, 6-hidroxipiridino-3-carbonilo, piridacino-4-carbonilo, 3-fenoxibenzoilo y 1-oxo-1,3-dihidroisoindol-2-carbonilo. Lo más preferiblemente R⁴ es morfolino-4-carbonilo.

Ha de entenderse que esta invención cubre todas las combinaciones apropiadas de los agrupamientos particulares y preferidos mencionados aquí, a no ser que se indique otra cosa.

Un grupo preferido particular de compuestos de la invención son compuestos de Fórmula (Ia):



en la que R³, R⁴, R²⁰, R²³, R²⁴ y R²⁵ son como se describen anteriormente aquí, y sus N-óxidos correspondientes, y sus profármacos, y sus derivados protegidos, sus isómeros individuales y mezclas de isómeros; y las sales y los solvatos (por ejemplo, hidratos) farmacéuticamente aceptables de tales compuestos de Fórmula (Ia) y sus N-óxidos y sus profármacos, y sus derivados protegidos, sus isómeros individuales y mezclas de isómeros.

Se prefieren compuestos de Fórmula (Ia) en la que R³ es -CR⁵=CHR⁶ en donde R⁵ y R⁶ junto con los átomos a los que R⁵ y R⁶ están unidos forman arilo(C₆₋₁₂), opcionalmente sustituido por 1 a 5 radicales seleccionados independientemente de un grupo que consiste en alquilo(C₁₋₄), ciano, halo, alquilo(C₁₋₄) sustituido por halo, -X⁴OR⁹ y -X⁴C(O)OR⁹, en los que X⁴ es un enlace o alquileno(C₁₋₂), R⁹ en cada presencia es independientemente alquilo(C₁₋₃) o alquilo(C₁₋₃) sustituido por halo. Se prefieren especialmente compuestos de Fórmula (Ia) en la que R³ representa fenilo o 2-difluorometoxifenilo.

Se prefieren especialmente compuestos de Fórmula

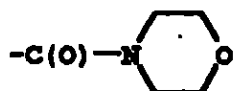
(Ia) en los que R^3 es $-CR^5(CR^6)_2$ en donde R^5 es hidrógeno y R^6 es alquilo (C_{1-4}). Se prefieren especialmente compuestos de Fórmula (Ia) en los que R^3 representa $-CH(CH_3)_2$.

También se prefieren compuestos de Fórmula (Ia) en los que R^3 es cicloalquilo (C_{3-12}).

Se prefieren especialmente compuestos de Fórmula (Ia) en los que R^3 representa ciclopropilo.

Se prefieren compuestos de Fórmula (Ia) en los que R^4 es $-C(O)X^5R^{11}$ en donde X^5 es un enlace y R^{11} es heterocicloalquil (C_{5-12})-alquilo (C_{0-3}), particularmente heterocicloalquilo (C_{5-12}).

Se prefieren especialmente compuestos de Fórmula (Ia) en



los que R^4 representa.

Se prefieren compuestos de Fórmula (Ia) en los que R^{20} es hidrógeno.

Se prefieren compuestos de Fórmula (Ia) en los que R^{23} es alquilo (C_{1-6}) [por ejemplo, etilo o butilo].

Se prefieren compuestos de Fórmula (Ia) en los que R^{24} es hidrógeno.

Se prefieren compuestos de Fórmula (Ia) en los que R^{25} es terc-butilo, ciclopropilo, etilo, fenilo, piridin-3-ilo, piridin-4-ilo, tien-3-ilo o trifluorometilo.

Un grupo preferido de compuestos de la invención son compuestos de Fórmula (Ia) en los que:

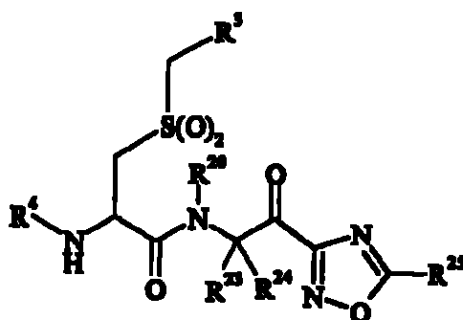
R^3 es $-CR^5=CHR^6$ [por ejemplo fenilo o 2-difluorometoxifenilo], $-CR^5(CR^6)_2$ o cicloalquilo (C_{3-12}) [por ejemplo, $-CH(CH_3)_2$ o

ciclopropilo]; R^4 es $-C(O)X^{5R^{11}}$ [por $-C(O)-N \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} O$ ejemplo];

R^{20} es hidrógeno; R^{23} es alquilo (C_{1-6}) [por ejemplo, etilo o butilo]; R^{24} es hidrógeno; y R^{25} es terc-butilo, ciclopropilo, etilo, fenilo, piridin-3-ilo, piridin-4-ilo, tien-3-ilo o trifluorometilo, y sus N-óxidos correspondientes, y sus profármacos, y sus derivados protegidos, sus isómeros individuales y mezclas de isómeros; y las

sales y los solvatos (por ejemplo, hidratos) farmacéuticamente aceptables de tales compuestos de Fórmula (Ia) y sus N-óxidos y sus profármacos, y sus derivados protegidos, sus isómeros individuales y mezclas de isómeros.

- 5 Un grupo preferido particular adicional de compuestos de la invención son compuestos de Fórmula (Ib):



(Ib)

- en la que R³, R⁴, R²⁰, R²³, R²⁴ y R²⁵ son como se describen anteriormente aquí, y sus N-óxidos correspondientes, y sus profármacos, y sus derivados protegidos, sus isómeros individuales y mezclas de isómeros; y las sales y los solvatos (por ejemplo, hidratos) farmacéuticamente aceptables de tales compuestos de Fórmula (Ib) y sus N-óxidos y sus profármacos, y sus derivados protegidos, sus isómeros individuales y mezclas de isómeros.

- Se prefieren compuestos de Fórmula (Ib) en la que R³ es -CR⁵=CHR⁶ en donde R⁵ y R⁶ junto con los átomos a los que R⁵ y R⁶ están unidos forman arilo (C₆₋₁₂), opcionalmente sustituido por 1 a 5 radicales seleccionados independientemente de un grupo que consiste en alquilo (C₁₋₄), ciano, halo, alquilo (C₁₋₄) sustituido por halo, -X⁴OR⁹ y -X⁴C(O)OR⁹, en donde R⁴ es un enlace o alquilen (C₁₋₂), R⁹ en cada presencia es independientemente alquilo (C₁₋₃) o alquilo (C₁₋₃) sustituido por halo. Se prefieren especialmente compuestos de Fórmula (Ib) en la que R³ representa fenilo o 2-difluorometoxifenilo.

- También se prefieren compuestos de Fórmula (Ib) en la que R³ es -CR⁵(CR⁶)₂ en donde R⁵ es hidrógeno y R⁶ es alquilo (C₁₋₄). Se prefieren especialmente compuestos de Fórmula (Ib) en la que R³ representa -CH(CH₃)₂.

También se prefieren compuestos de Fórmula (Ib) en la que R³ es cicloalquilo (C₃₋₁₂).

Se prefieren especialmente compuestos de Fórmula (Ib) en la que R^3 representa ciclopropilo.

Se prefieren compuestos de Fórmula (Ib) en la que R^4 es $-C(O)X^5R^{11}$ en donde X^5 es un enlace y R^{11} es hetero-
5 cicloalquil(C_{5-12})-alquilo(C_{0-3}), particularmente hetero-
cicloalquilo(C_{5-12}).

Se prefieren especialmente compuestos de Fórmula (Ib) en

10

la que R^4 representa $-C(O)-N$  .

15

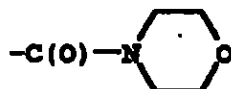
Se prefieren compuestos de Fórmula (Ib) en la que R^{20} es hidrógeno.

Se prefieren compuestos de Fórmula (Ib) en la que R^{23} es alquilo(C_{1-6}) [por ejemplo, etilo o butilo].

Se prefieren compuestos de Fórmula (Ib) en la que R^{24}
20 es hidrógeno.

Se prefieren compuestos de Fórmula (Ib) en la que R^{25} es terc-butilo, ciclopropilo, etilo, fenilo, piridin-3-ilo, piridin-4-ilo, tien-3-ilo o trifluorometilo.

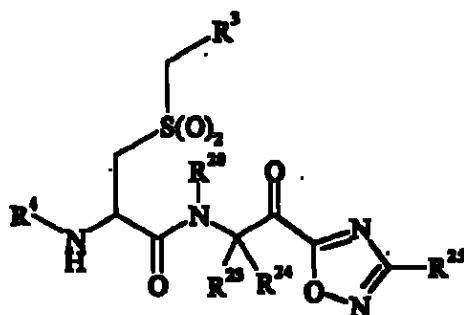
Un grupo preferido de compuestos de la invención son
25 compuestos de Fórmula (Ib) en la que: R^3 es $-CR^5=CHR^6$ [por ejemplo fenilo o 2-difluorometoxifenilo], $-CR^5(CR^6_3)_2$ o cicloalquilo(C_{3-12}) [por ejemplo, $-CH(CH_3)_2$ o ciclopropi-
30 lo]; R^4 es



$-C(O)X^{5R^{11}}$ [por ejemplo,]; R^{20} es hidrógeno;

35 R^{23} es alquilo(C_{1-6}) [por ejemplo, etilo o butilo]; R^{24} es hidrógeno; y R^{25} es terc-butilo, ciclopropilo, etilo, fenilo, piridin-3-ilo, piridin-4-ilo, tien-3-ilo o trifluorometilo, y sus N-óxidos correspondientes, y sus profármacos, y sus derivados protegidos, sus isómeros indivi-
40 duales y mezclas de isómeros; y las sales y los solvatos (por ejemplo, hidratos) farmacéuticamente aceptables de tales compuestos de Fórmula (Ib) y sus N-óxidos y sus profármacos, sus derivados protegidos, sus isómeros individuales y mezclas de isómeros.

45 Un grupo preferido particular de compuestos de la invención son compuestos de Fórmula (Ic):



I(c)

en la que R³, R⁴, R²⁰, R²³, R²⁴ y R²⁵ son como se describen
 anteriormente aquí, y sus N-óxidos correspondientes, y
 5 sus profármacos, y sus derivados protegidos, sus isómeros
 individuales y mezclas de isómeros; y las sales y los
 solvatos (por ejemplo, hidratos) farmacéuticamente acep-
 tables de tales compuestos de Fórmula (Ic) y sus N-óxidos
 y sus profármacos, y sus derivados protegidos, sus isóme-
 10 ros individuales y mezclas de isómeros.

Se prefieren compuestos de Fórmula (Ic) en la que R³
 es -CR⁵=CHR⁶ en donde R⁵ y R⁶ junto con los átomos a los
 que R⁵ y R⁶ están unidos forman arilo (C₆₋₁₂), opcionalmen-
 te sustituido por 1 a 5 radicales seleccionados indepen-
 15 dientemente de un grupo que consiste en alquilo(C₁₋₄),
 ciano, halo, alquilo(C₁₋₄) sustituido por halo, -X⁴OR⁹ y -
 X⁴C(O)OR⁹, en donde R⁴ es un enlace o alquilen(C₁₋₂), R⁹
 en cada presencia es independientemente alquilo(C₁₋₃) o
 alquilo(C₁₋₃) sustituido por halo. Se prefieren especial-
 20 mente compuestos de Fórmula (Ic) en la que R³ representa
 fenilo o 2-difluorometoxifenilo.

También se prefieren compuestos de Fórmula (Ic) en
 la que R³ es -CR⁵(CR⁶)₂ en donde R⁵ es hidrógeno y R⁶ es
 alquilo(C₁₋₄). Se prefieren especialmente compuestos de
 25 Fórmula (Ic) en la que R³ representa -CH(CH₃)₂.

También se prefieren compuestos de Fórmula (Ic) en
 la que R³ es cicloalquilo(C₃₋₁₂).

Se prefieren especialmente compuestos de Fórmula
 (Ic) en la que R³ representa ciclopropilo.

30 También se prefieren compuestos de Fórmula (Ic) en
 la que R³ es -CR⁵(CR⁶)₂ en donde R⁵ y R⁶ junto con los
 átomos a los que R⁵ y R⁶ están unidos forman cicloalqui-

lo(C₃₋₁₂). Se prefieren especialmente compuestos de Fórmula (Ic) en la que R³ representa ciclopropilo.

Se prefieren compuestos de Fórmula (Ic) en la que R⁴ es -C(O)X⁵R¹¹ en donde X⁵ es un enlace y R¹¹ es hetero-
5 cicloalquil(C₅₋₁₂)-alquilo(C₀₋₃), particularmente hetero-
cicloalquilo(C₅₋₁₂).

Se prefieren especialmente compuestos de Fórmula (Ic) en

10

la que R⁴ representa  .

15

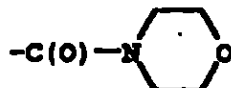
Se prefieren compuestos de Fórmula (Ic) en la que R²⁰ es hidrógeno.

Se prefieren compuestos de Fórmula (Ic) en la que R²³ es alquilo(C₁₋₆) [por ejemplo, etilo o butilo].

Se prefieren compuestos de Fórmula (Ic) en la que R²⁴
20 es hidrógeno.

Se prefieren compuestos de Fórmula (Ic) en la que R²⁵ es terc-butilo, ciclopropilo, etilo, fenilo, piridin-3-ilo, piridin-4-ilo, tien-3-ilo o trifluorometilo.

Un grupo preferido de compuestos de la invención son
25 compuestos de Fórmula (Ic) en la que: R³ es -CR⁵=CHR⁶ [por ejemplo fenilo o 2-difluorometoxifenilo], -CR⁵(CR⁶)₂ o cicloalquilo(C₃₋₁₂) [por ejemplo, -CH(CH₃)₂ o ciclopropi-
30 lo]; R⁴ es



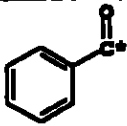
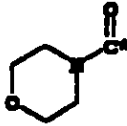
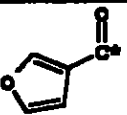
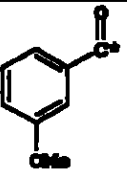
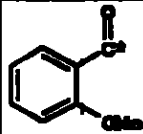
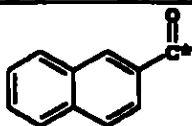
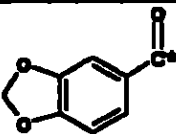
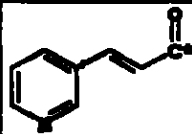
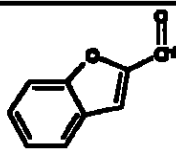
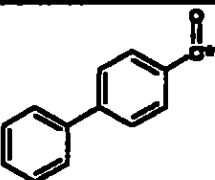
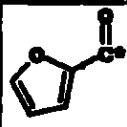
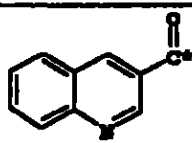
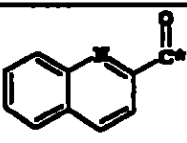
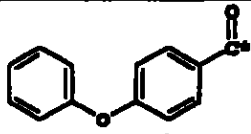
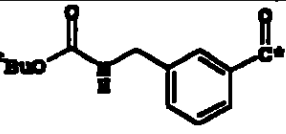
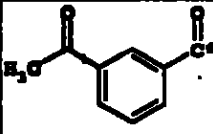
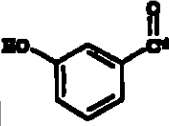
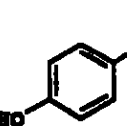
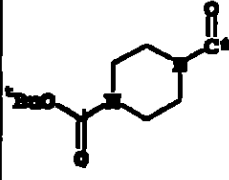
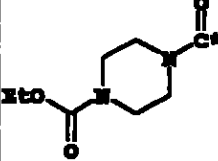
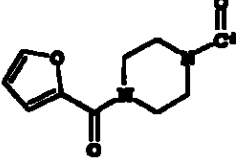
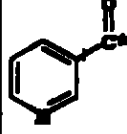
-C(O)X⁵R¹¹ [por ejemplo,]; R²⁰ es hidrógeno;

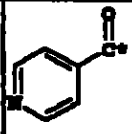
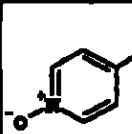
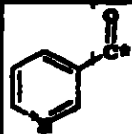
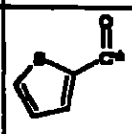
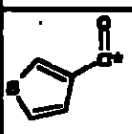
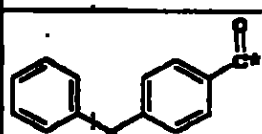
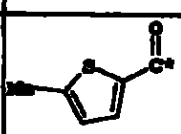
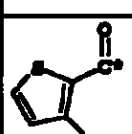
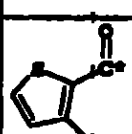
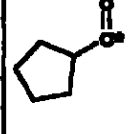
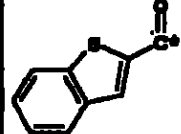
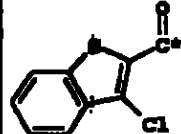
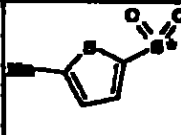
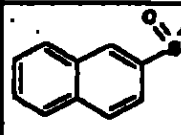
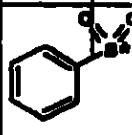
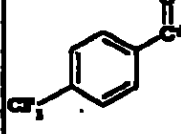
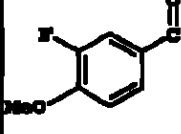
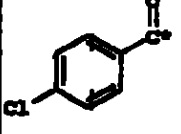
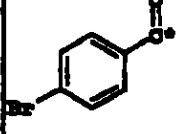
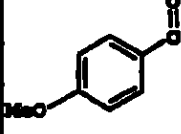
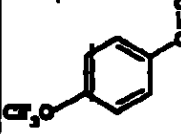
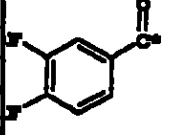
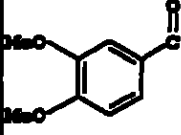
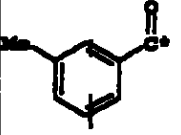
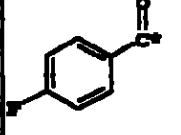
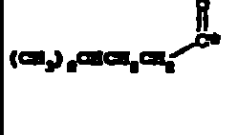
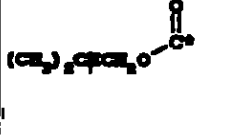
35 R²³ es alquilo(C₁₋₆) [por ejemplo, etilo o butilo]; R²⁴ es hidrógeno; y R²⁵ es terc-butilo, ciclopropilo, etilo, fenilo, piridin-3-ilo, piridin-4-ilo, tien-3-ilo o trifluorometilo, y sus N-óxidos correspondientes, y sus profármacos, y sus derivados protegidos, sus isómeros individuales y mezclas de isómeros; y las sales y los solvatos (por ejemplo, hidratos) farmacéuticamente aceptables de tales compuestos de Fórmula (Ib) y sus N-óxidos y sus profármacos, sus derivados protegidos, sus isómeros individuales y mezclas de isómeros.

45 Compuestos particulares de la invención pueden prepararse enlazando el átomo de carbono (C*) de uno de los fragmentos (A1 a A36 o A40 a A71) o el átomo de

fragmentos (A1 a A36 o A40 a A71) o el átomo de azufre (S*) de uno de los fragmentos (A37 a A39 o A72) mostrados en la Tabla 1 al átomo de nitrógeno (*N) de uno de los fragmentos (B1 a B84) mostrados en la Tabla 2, y enlazando el átomo de carbono del metino (CH*) de uno de los fragmentos (B1 a B84) mostrados en la Tabla 2 al átomo de carbono de acilo (C*) de uno de los fragmentos (C1 a C40) representados en la Tabla 3.

TABLE 1

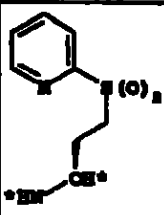
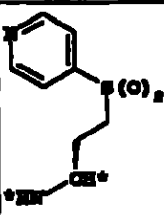
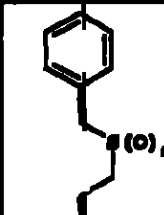
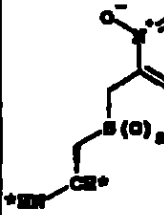
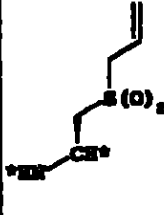
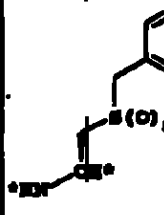
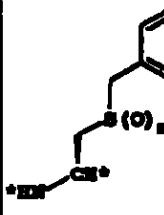
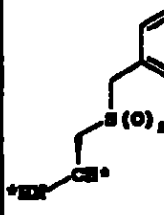
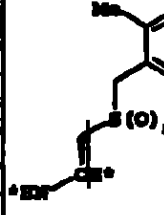
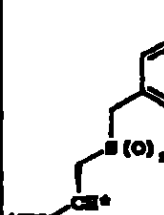
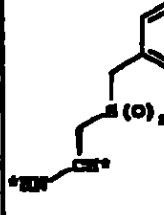
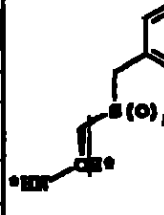
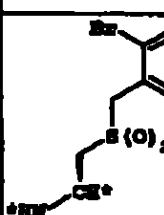
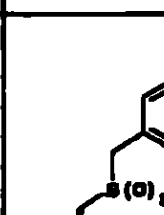
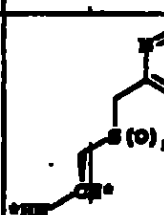
A1		A2		A3	
A4		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	
A16		A17		A18	
A19		A20		A21	
A22		A23		A24	

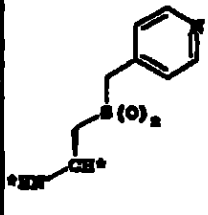
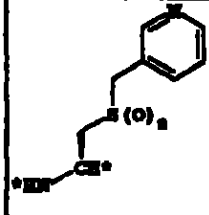
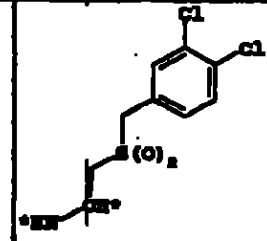
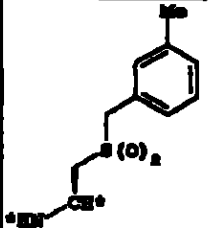
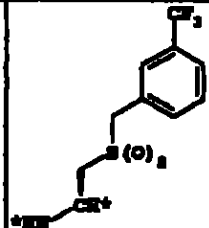
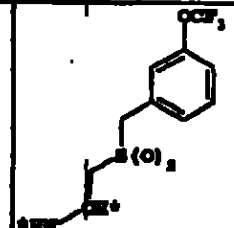
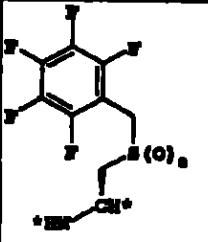
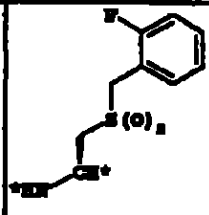
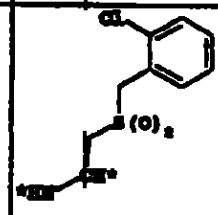
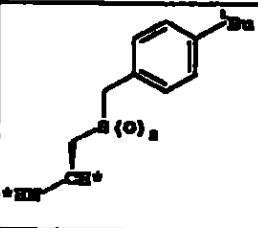
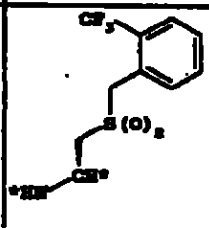
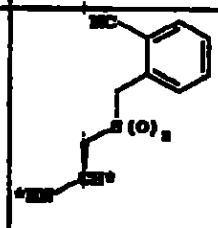
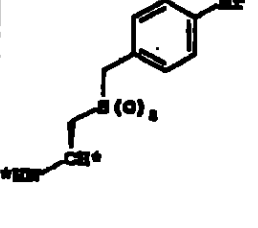
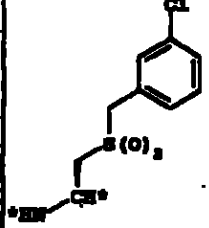
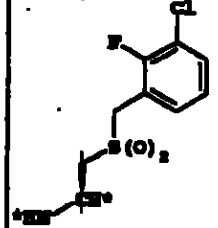
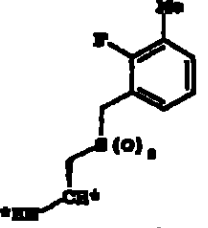
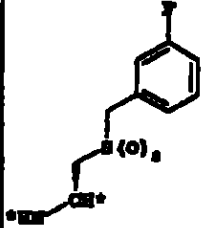
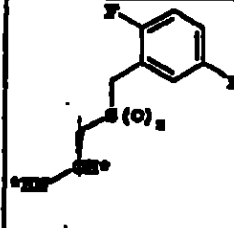
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A37		A38		A39	
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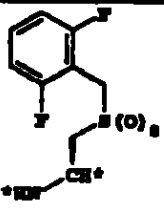
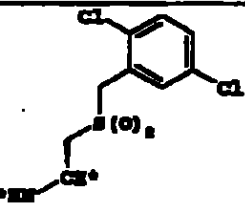
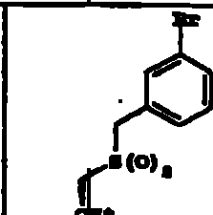
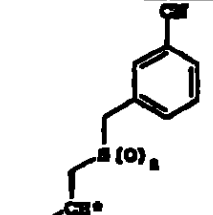
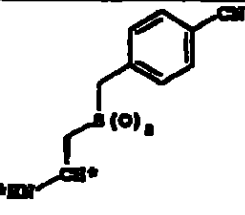
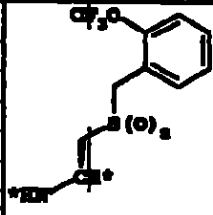
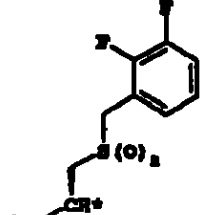
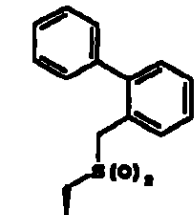
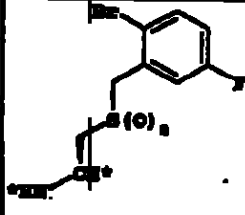
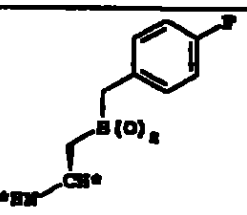
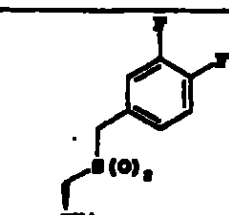
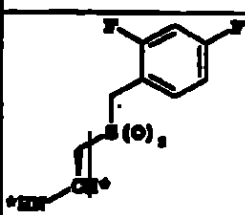
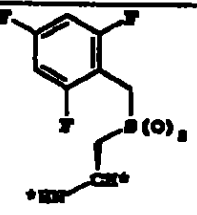
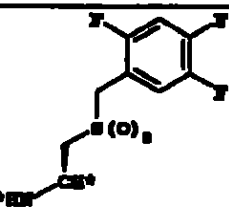
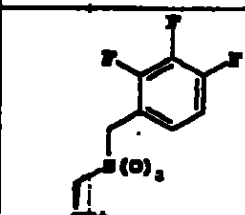
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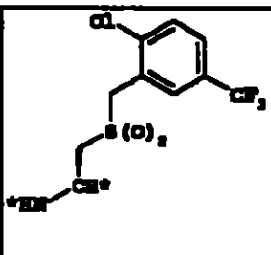
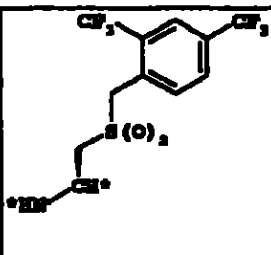
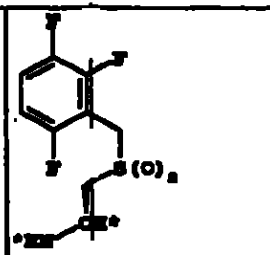
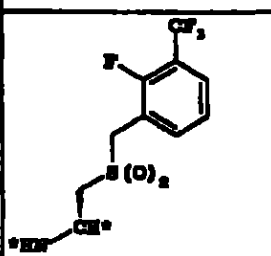
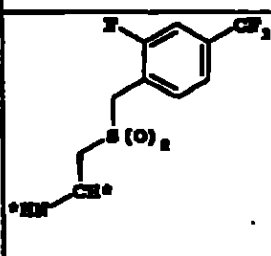
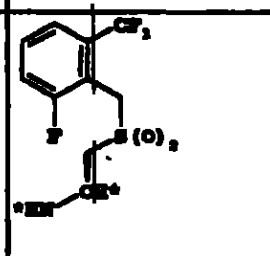
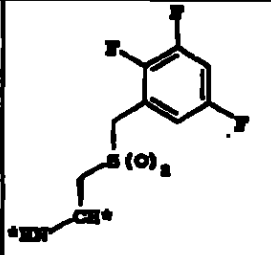
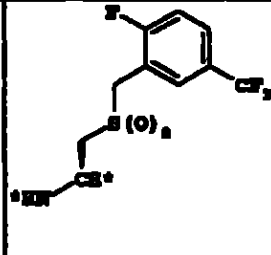
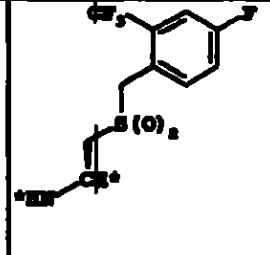
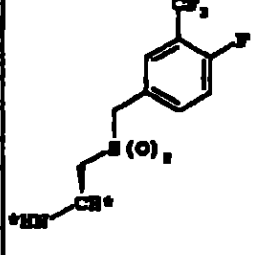
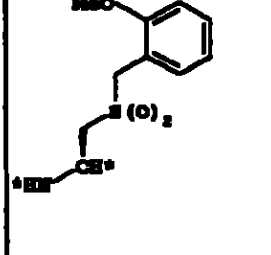
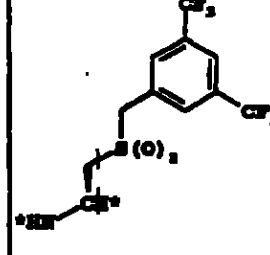
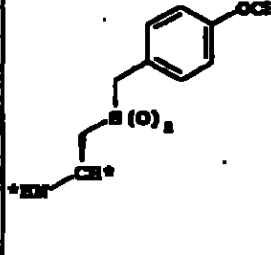
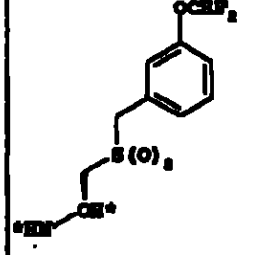
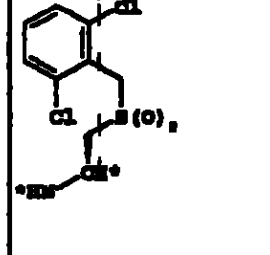
TABLA 2

B1		B2		B3	
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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	
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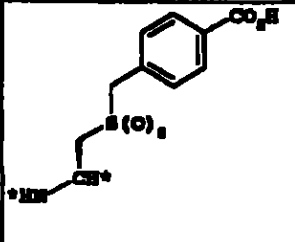
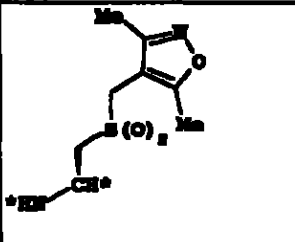
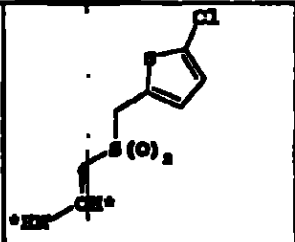
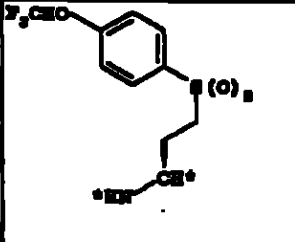
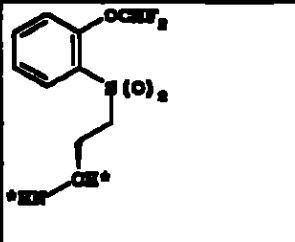
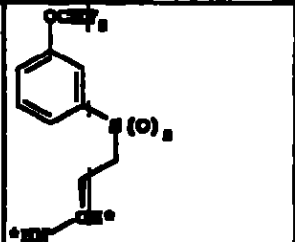
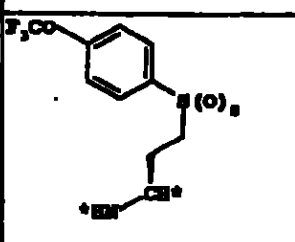
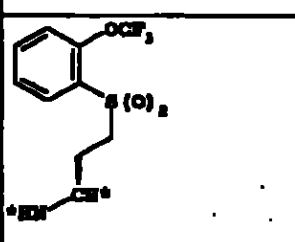
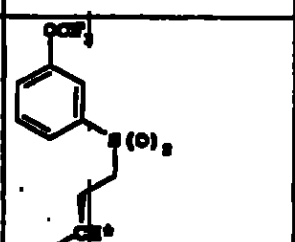
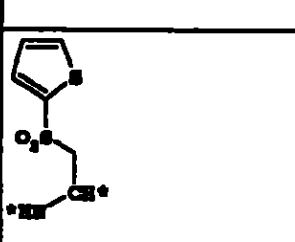
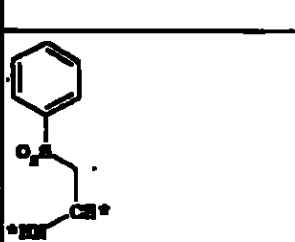
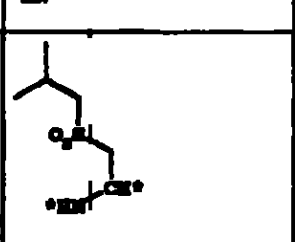
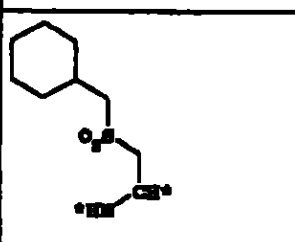
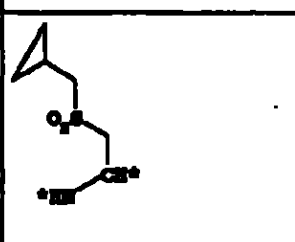
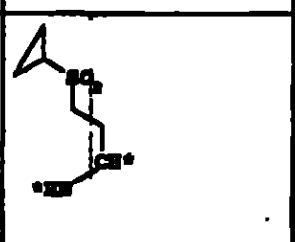
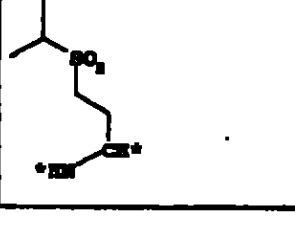
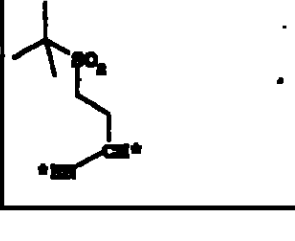
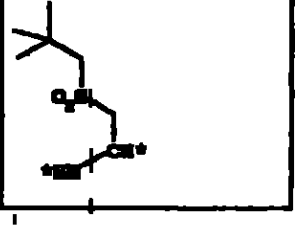
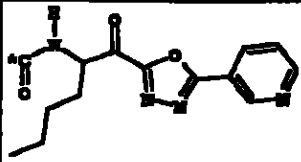
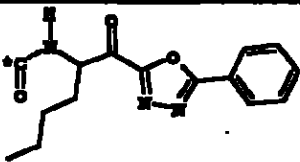
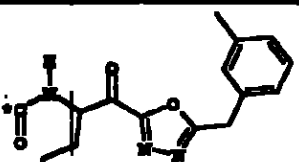
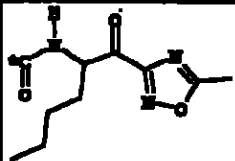
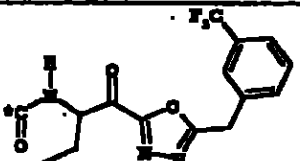
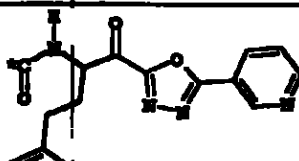
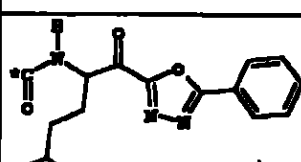
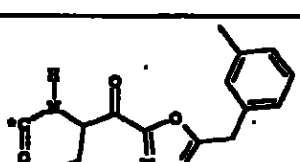
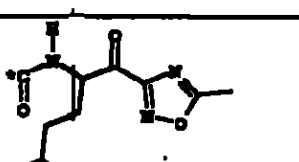
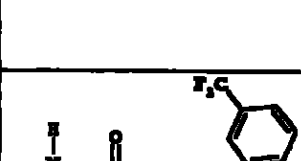
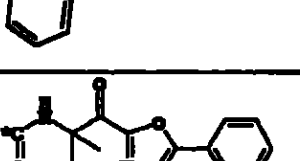
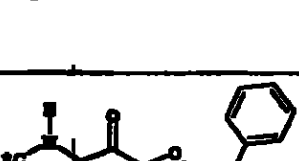
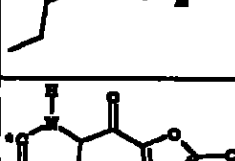
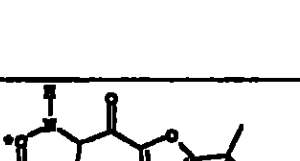
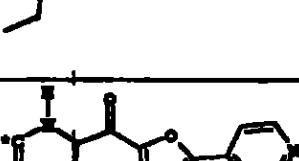
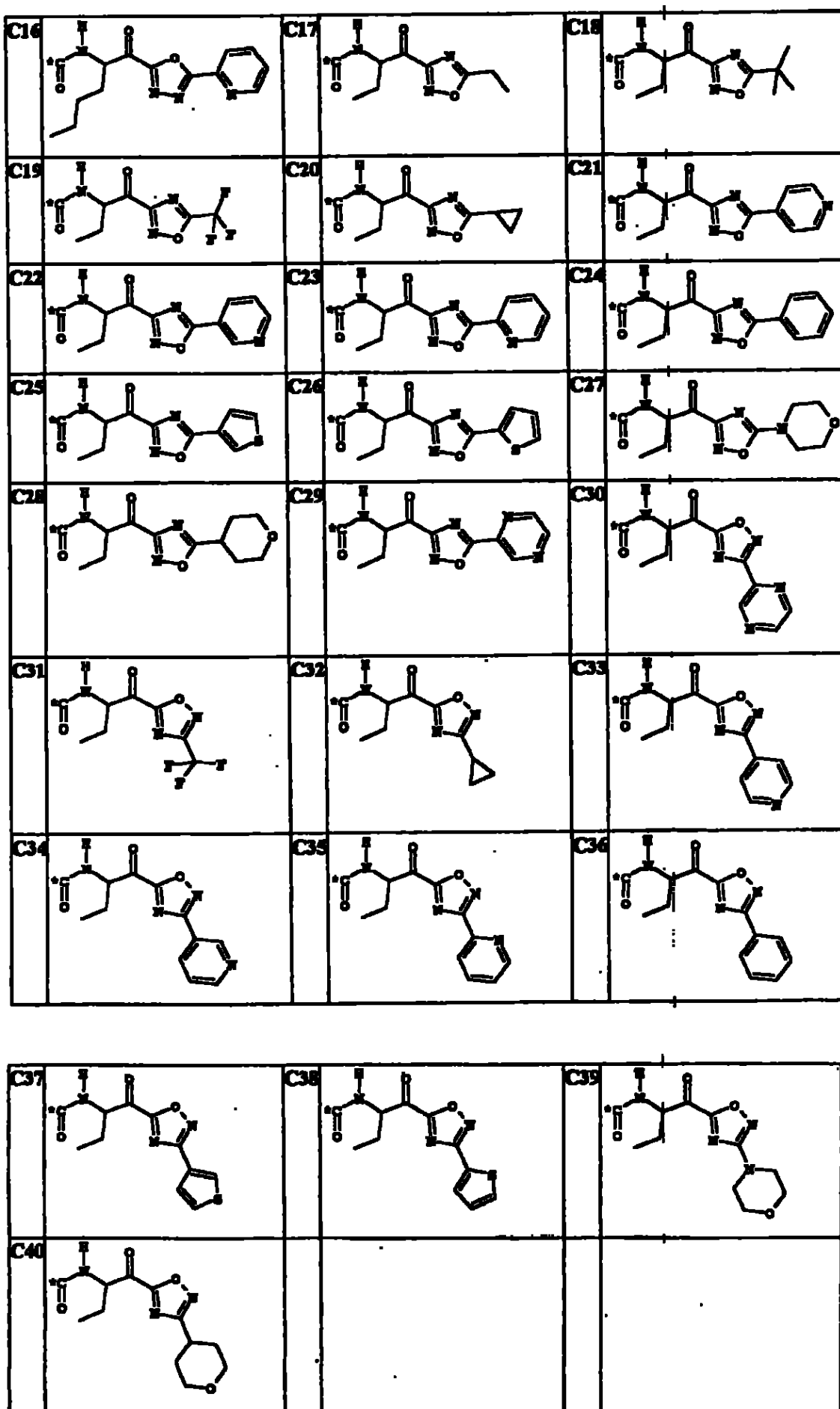
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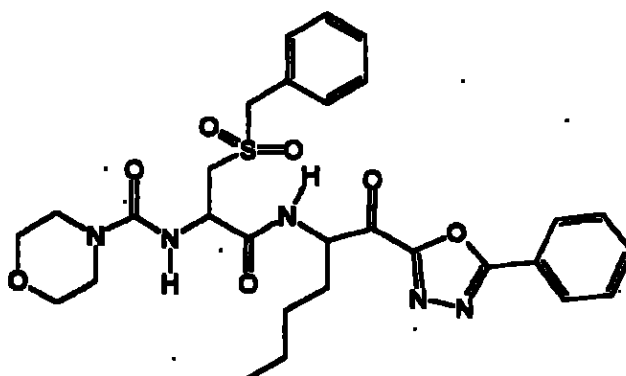
TABLA 3

C1		C2		C3	
C4		C5		C6	
C7		C8		C9	
C10		C11		C12	
C13		C14		C15	



Así, por ejemplo, la combinación A2-B1-C2, esto es,

la combinación del grupo A2 de la Tabla 1 y B1 de la Tabla 2 y C2 de la Tabla 3, representa un compuesto de la invención, a saber {2-fenilmetanosulfonil-1-[1-(5-fenil-[1,3,4]oxadiazol-2-carbonil)pentilcarbamoil]etil}amida de
 5 ácido morfolino-4-carboxílico:



Compuestos particulares adicionales de la presente invención incluyen:

- {2-(2-difluorometoxi-fenilmetanosulfonil-1-[1,1-dimetil-
 10 2-oxo-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-il)-
 etilcarbamoil]etil}-amida de ácido morfolino-4-carboxílico;
 {2-fenilmetanosulfonil-1-[1-(5-fenil-[1,3,4]oxadiazol-2-carbonil)pentilcarbamoil]etil}amida de ácido morfolino-4-
 15 carboxílico (Compuesto 1; A2, B1, C2);
 {2-(2-difluorometoxi-fenilmetanosulfonil-1-[1-(5-piridin-3-il-[1,3,4]oxadiazol-2-carbonil)pentilcarbamoil]etil}amida de ácido morfolino-4-carboxílico (Compuesto 2; A2, B2, C1);
 20 [1-[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]-2-(2-metilpropano-1-sulfonil)etil]amida de ácido morfolino-4-carboxílico;
 {2-(2-metilpropano-1-sulfonil)-1-[1-(3-tiofen-2-il-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido
 25 morfolino-4-carboxílico;
 [1-[1-(3-terc-butil-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]-2-(2-metilpropano-1-sulfonil)etil]amida de ácido morfolino-4-carboxílico;
 {2-ciclopropilmetanosulfonil-1-[1-(5-fenil-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido
 30 morfolino-4-carboxílico;
 {(R)-2-ciclopropilmetanosulfonil-1-[(S)-1-(5-trifluorometil-1,2,4-oxadiazol-3-

- carbonil)propilcarbamoil]etil}amida de ácido morfolino-4-carboxílico;
- [(1)-[(1-(5-etil-1,2,4-oxadiazol-3-carbonil)propilcarbamoil]-2-(2-metilpropano-1-sulfonil)etil]amida de ácido morfolino-4-carboxílico;
- 5 { (R)-2-(2-metilpropano-1-sulfonil)-1-[(S)-1-(5-tiofen-3-il-1,2,4-oxadiazol-3-carbonil)propilcarbamoil]etil}amida;
- { (R)-1-[(S)-1-(3-terc-butil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-2-ciclopropilmetanosulfoniletil}amida de
- 10 ácido morfolino-4-carboxílico;
- { (R)-2-(2-metilpropano-1-sulfonil)-1-[(S)-1-(5-trifluorometil-1,2,4-oxadiazol-3-carbonil)propilcarbamoil]etil}amida de ácido morfolino-4-carboxílico;
- 15 { (R)-1-[(S)-1-(5-terc-butil-1,2,4-oxadiazol-3-carbonil)propilcarbamoil]-2-fenilmetanosulfoniletil}amida de ácido morfolino-4-carboxílico;
- { (R)-1-[(S)-1-(5-terc-butil-1,2,4-oxadiazol-3-carbonil)propilcarbamoil]-2-fenilmetanosulfoniletil}amida
- 20 de ácido morfolino-4-carboxílico;
- {2-ciclopropilmetanosulfonil-1-[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido morfolino-4-carboxílico;
- {2-ciclopropilmetanosulfonil-1-[1-(3-etil-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido
- 25 morfolino-4-carboxílico;
- {2-ciclopropilmetanosulfonil-1-[1-(3-fenil-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido morfolino-4-carboxílico;
- 30 {2-(2-metilpropano-1-sulfonil)-1-[1-(3-fenil-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido morfolino-4-carboxílico;
- [1-[1-(3-etil-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]-2-(2-metilpropano-1-sulfonil)etil}amida de ácido morfolino-4-carboxílico;
- 35 {2-fenilmetanosulfonil-1-[1-(3-fenil-[1,2,4]-oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido morfolino-4-carboxílico;
- {1-[1-(3-etil-[1,2,4]-oxadiazol-5-carbonil)propilcarbamoil]-2-fenilmetanosulfoniletil}amida
- 40

de ácido morfolino-4-carboxílico;

{1-[1-(5-etil-[1,3,4]-oxadiazol-2-

carbonil)propilcarbamoil]-2-fenilmetanosulfoniletil}amida

de ácido morfolino-4-carboxílico;

5 {1-[1-(5-terc-butil[1,3,4]-oxadiazol-2-

carbonil)propilcarbamoil]-2-fenilmetanosulfoniletil}amida

de ácido morfolino-4-carboxílico;

{2-(2-difluorometoxifenilmetanosulfonil)-1-[1,1-dimetil-

2-oxo-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-

10 il)etilcarbamoil]etil}amida de ácido morfolino-4-carboxílico;

y sus correspondientes N-óxidos, y sus profármacos, y sus

derivados protegidos, sus isómeros individuales y mezclas

de isómeros; y las sales y los solvatos (por ejemplo,

15 hidratos) farmacéuticamente aceptables, y sus N-óxidos y

sus profármacos, y sus derivados protegidos, sus isómeros

individuales y mezclas de isómeros.

Farmacología y Utilidad:

20 Los compuestos de la invención son inhibidores selectivos de catepsina S y, como tales, son útiles para tratar enfermedades en las que la actividad de catepsina S contribuye a la patología y/o la sintomatología de la enfermedad. Por ejemplo, los compuestos de la invención

25 son útiles para tratar trastornos autoinmunes, incluyendo, pero no limitados a, diabetes de inicio juvenil, esclerosis múltiple, pénfigo vulgar, enfermedad de Graves, miastenia grave, lupus eritematoso sistémico, artritis reumatoide y toroiditis de Hashimoto, trastornos alérgicos,

30 cos, incluyendo, pero no limitados a, asma, y respuestas inmunes alogeneicas, incluyendo, pero no limitadas a, trasplantes de órganos o injertos de tejido.

La catepsina S también está implicada en trastornos que implican elastolisis excesiva, tales como enfermedad

35 pulmonar obstructiva crónica (por ejemplo, enfisema), bronquiolitis, elastolisis excesiva de las vías respiratorias en el asma y la bronquitis, neumonitis y enfermedad cardiovascular tal como ruptura de la placa y aterosclerosis. La catepsina S está implicada en la formación de fibrillas y, por lo tanto, los inhibidores de catepsina S

40

se usan en el tratamiento de la amiloidosis sistémica.

Las actividades inhibitoras de proteasas cisteínicas de los compuestos de la invención pueden determinarse mediante métodos conocidos por los expertos normales en la técnica. Se conocen ensayos in vitro adecuados para medir la actividad de proteasas y su inhibición por los compuestos de prueba. Típicamente, el ensayo mide la hidrólisis inducida por proteasa de un sustrato basado en péptidos. Detalles de ensayos para medir la actividad inhibitora de proteasas se indican en los Ejemplos 25-28, posteriormente.

Administración y Composiciones Farmacéuticas:

En general, los compuestos de Fórmula (I) se administrarán en cantidades terapéuticamente eficaces a través de cualquiera de los modos habituales y aceptables conocidos en la técnica, solos o en combinación con uno o más agentes terapéuticos. Una cantidad terapéuticamente eficaz puede variar ampliamente dependiendo de la gravedad de la enfermedad, la edad y la salud relativa del sujeto, la potencia del compuesto usado y otros factores. Por ejemplo, cantidades terapéuticamente eficaces de un compuesto de Fórmula (I) pueden variar de aproximadamente 1 microgramo por kilogramo de peso corporal ($\mu\text{g/kg}$) al día a aproximadamente 60 miligramos por kilogramo de peso corporal (mg/kg) al día, típicamente de aproximadamente 1 $\mu\text{g/kg/día}$ a aproximadamente 20 mg/kg/día . Por lo tanto, una cantidad terapéuticamente eficaz para un paciente humano de 80 kg puede variar de aproximadamente 80 $\mu\text{g/día}$ a aproximadamente 4,8 g/día, típicamente de aproximadamente 80 $\mu\text{g/día}$ a aproximadamente 1,6 g/día. En general, un experto normal en la técnica, actuando dependiendo del conocimiento personal y la descripción de esta Solicitud, podrá determinar una cantidad terapéuticamente eficaz de un compuesto de Fórmula (I) para tratar una enfermedad dada.

Los compuestos de Fórmula (I) pueden administrarse como composiciones farmacéuticas mediante una de las siguientes rutas: oral, sistémica (por ejemplo, transdérmica, intranasal o mediante supositorios) o parenteral (por

ejemplo, intramuscular, intravenosa o subcutánea). Las composiciones pueden tomar la forma de tabletas, píldoras, cápsulas, semisólidos, polvos, formulaciones de liberación sostenida, soluciones, suspensiones, elixires, aerosoles o cualquier otra composición apropiada, y están comprendidas por, en general, un compuesto de Fórmula (I) en combinación con al menos un excipiente farmacéuticamente aceptable. Los excipientes aceptables son atóxicos, ayudan a la administración y no afectan adversamente al beneficio terapéutico del ingrediente activo. Tal excipiente puede ser cualquier excipiente sólido, líquido, semisólido o, en el caso de una composición de aerosol, gaseoso que esté disponible generalmente para un experto en la técnica.

Excipientes farmacéuticos sólidos incluyen almidón, celulosa, talco, glucosa, lactosa, sacarosa, gelatina, malta, arroz, harina, creta, gel de sílice, estearato magnésico, estearato sódico, monoestearato de glicerol, cloruro sódico, leche desnatada deshidratada y similares. Los excipientes líquidos y semisólidos pueden seleccionarse de agua, etanol, glicerol, propilenglicol y diversos aceites, incluyendo los de origen petrolífero, animal, vegetal o sintético (por ejemplo, aceite de cacahuate, aceite de soja, aceite mineral, aceite de sésamo y similares). Portadores líquidos preferidos, particularmente para soluciones inyectables, incluyen agua, solución salina, dextrosa acuosa y glicoles.

La cantidad de un compuesto de Fórmula (I) en la composición puede variar ampliamente dependiendo del tipo de formulación, el tamaño de una dosificación unitaria, el tipo de excipiente y otros factores conocidos por los expertos en la técnica de la ciencia farmacéutica. En general, una composición de un compuesto de Fórmula (I) para tratar una enfermedad dada comprenderá de 0,01% en peso a 10% en peso, preferiblemente de 0,3% en peso a 1% en peso, de ingrediente activo, siendo el resto el excipiente o los excipientes. Preferiblemente, la composición farmacéutica se administra en una sola forma de dosificación unitaria para el tratamiento continuo o en una sola forma de dosificación unitaria a voluntad cuando se re-

quiere específicamente el alivio de los síntomas. Formu-
laciones farmacéuticas representativas que contienen un
compuesto de Fórmula (I) se describen en el Ejemplo 29,
más adelante.

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Química:

Procedimientos para Elaborar Compuestos de Fórmula (I):

Los compuestos de la invención pueden prepararse me-
diante la aplicación o la adaptación de métodos conoci-
dos, por lo que se entiende métodos usados hasta ahora
descritos en la literatura, por ejemplo los descritos por
R.C. Larock en Comprehensive Organic Transformations, VCH
publishers, 1989.

En las reacciones descritas más adelante aquí, puede
ser necesario proteger grupos funcionales reactivos, por
ejemplo grupos hidroxilo, amino, imino, tio o carboxi,
cuando estos se deseen en el producto final, para evitar
su participación no deseada en las reacciones. Pueden
usarse grupos protectores convencionales de acuerdo con
la práctica estándar, por ejemplo, véase T.W. Greene y
P.G.M. Wuts en "Protective Groups in Organic Chemistry"
John Wiley and Sons, 1991.

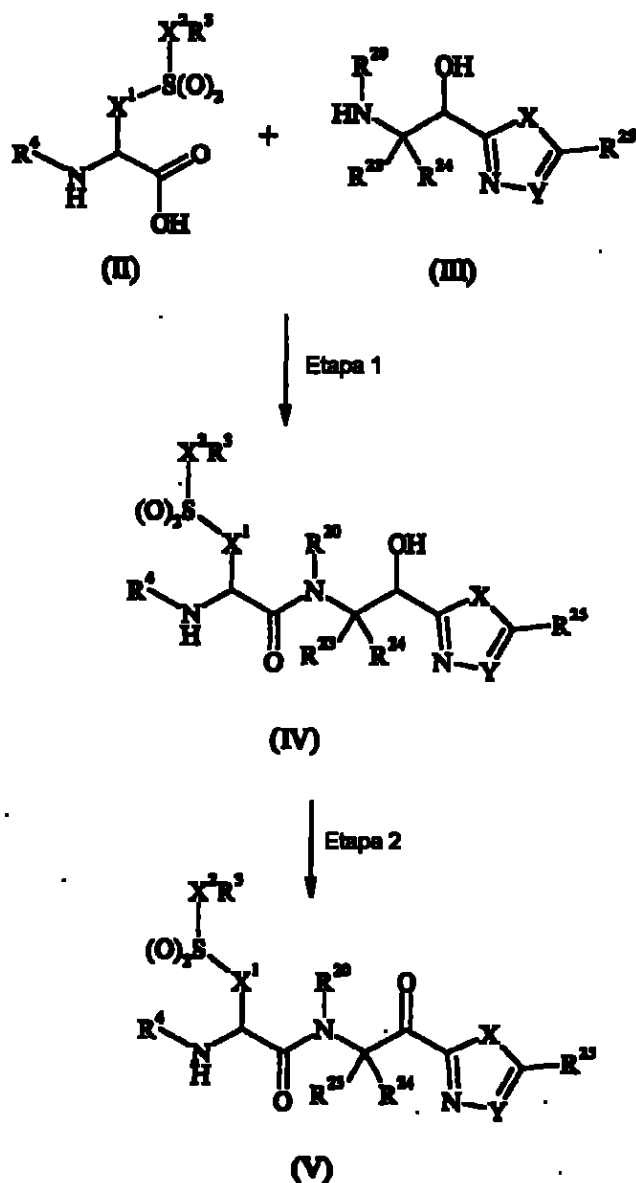
Compuestos de Fórmula (I), en la que X^3 es un grupo
de fórmula (a) (según se define en el Sumario de la In-
vención), es decir compuestos de Fórmula (V), pueden pre-
pararse procediendo como en el siguiente Esquema de Reac-
ción 1:

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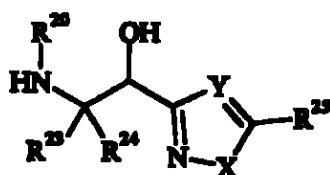
Esquema de Reacción 1



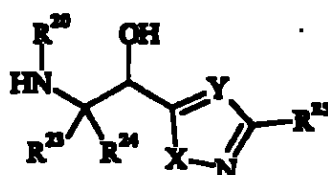
en el que cada uno de X, X^1 , X^2 , Y, R^3 , R^4 , R^{20} , R^{23} , R^{24} y
 5 R^{25} es como se define para la Fórmula (I) en el Sumario de
 la Invención. Así, en la etapa 1, un ácido de fórmula
 (II) puede condensarse con un compuesto amínico de fórmu-
 la (III) para dar una β -hidroxiamida de fórmula (IV). La
 reacción de condensación puede efectuarse con un agente
 10 de acoplamiento apropiado (por ejemplo, hexafluorofosfato
 de benzotriazol-1-iloxitrispirrolidinofosfonio (PyBOP[®]),
 hidrocioruro de 1-(3-dimetilaminopropil)-3-
 etilcarbodiimida (EDCI), hexafluorofosfato de O-
 benzotriazol-1-il-N,N,N',N'-tetrametiluronio (HBTU), 1,3-
 15 diciclohexilcarbodiimida (DCC) o similares) y opcional-
 mente un catalizador apropiado (por ejemplo, 1-

hidroxibenzotriazol (HOBt), 1-hidroxi-7-azabenzotriazol (HOAt), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio (HATU) o similares) y una base no nucleófila (por ejemplo, trietilamina, N-metilmorfolina y similares, o cualquiera de sus combinaciones adecuadas) a temperatura ambiente, y requiere 5 a 10 horas para completarse. La β -hidroxiamida de fórmula (IV) puede hidrolizarse a continuación, en la etapa 2, para dar un compuesto de fórmula (V). La reacción de oxidación puede llevarse a cabo convenientemente usando per-yodinano de Dess-Martin en un disolvente inerte, tal como diclorometano, y a una temperatura de aproximadamente 0°C a aproximadamente temperatura ambiente.

Los compuestos de Fórmula (I), donde X^3 es un grupo de fórmula (b) (según se define en el Sumario de la Invención), puede prepararse procediendo como en el Esquema de Reacción 2, pero usando un compuesto amínico de fórmula (VI). Los compuestos de Fórmula (I), donde X^3 es un compuesto de fórmula (C) (según se define en el Sumario de la Invención), pueden prepararse procediendo como en el Esquema de Reacción 2, pero usando un compuesto amínico de fórmula (VII),



(VI)



(VII)

en las que cada uno de X, Y, R^{20} , R^{23} , R^{24} y R^{25} es como se define para la Fórmula (I) en el Sumario de la Invención.

Descripciones detalladas para la síntesis de un compuesto de Fórmula (I) mediante los procedimientos del Esquema de Reacción 1 se indican en los Ejemplos 1 a 20, más adelante.

Procedimientos Adicionales para Preparar Compuestos de Fórmula (I):

Un compuesto de Fórmula (I) puede prepararse como una sal por adición de ácidos farmacéuticamente aceptable al hacer reaccionar la forma de base libre del compuesto

con un ácido inorgánico u orgánico farmacéuticamente aceptable. Alternativamente, una sal por adición de bases farmacéuticamente aceptable de un compuesto de Fórmula (I) puede prepararse al hacer reaccionar la forma de ácido libre del compuesto con una base inorgánica u orgánica farmacéuticamente aceptable. Ácidos y bases inorgánicos y orgánicos adecuados para la preparación de las sales farmacéuticamente aceptables de compuesto de Fórmula (I) se indican en la sección de definiciones de esta Solicitud.

10 Alternativamente, las formas de sal de los compuestos de Fórmula (I) pueden prepararse usando sales de los materiales de partida o productos intermedios.

Las formas de ácido libre o base libre de los compuestos de Fórmula (I) pueden prepararse a partir de la forma de sal por adición de bases o sal por adición de ácidos correspondiente. Por ejemplo, un compuesto de Fórmula (I) en una forma de sal por adición de ácidos puede convertirse en la correspondiente base libre al tratar con una base adecuada (por ejemplo, solución de hidróxido amónico, hidróxido sódico y similares). Un compuesto de Fórmula (I) en una forma de sal por adición de bases puede convertirse en el ácido libre correspondiente al tratar con un ácido adecuado (por ejemplo, ácido clorhídrico, etc).

15

20

Los N-óxidos de compuestos de Fórmula (I) pueden prepararse mediante métodos conocidos por los expertos normales en la técnica. Por ejemplo, los N-óxidos pueden prepararse tratando una forma no oxidada del compuesto de Fórmula (I) con un agente oxidante (por ejemplo, ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido meta-cloroperoxibenzoico o similares) en un disolvente orgánico inerte adecuado (por ejemplo, un hidrocarburo halogenado tal como diclorometano) a aproximadamente 0°C. Alternativamente, los N-óxidos de los compuestos de Fórmula (I) pueden prepararse a partir del N-óxido de un material de partida apropiado.

25

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Los compuestos de Fórmula (I) en forma no oxidada pueden prepararse a partir de N-óxidos de compuestos de Fórmula (I) tratando con un agente reductor (por ejemplo, azufre, dióxido de azufre, trifenilfosfina, borohidruro

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de litio, borohidruro sódico, tricloruro de fósforo, tribromuro o similares) en un disolvente orgánico inerte adecuado (por ejemplo, acetonitrilo, etanol, dioxano acuoso o similares) a de 0 a 80°C.

5 Los derivados de profármaco de los compuestos de Fórmula (I) pueden prepararse mediante métodos conocidos por los expertos normales en la técnica (por ejemplo, para detalles adicionales, véase Saulnier y otros (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 10 1985). Por ejemplo, pueden prepararse profármacos apropiados al hacer reaccionar un compuesto no derivado de Fórmula (I) con un agente de carbamilación adecuado (por ejemplo, carbonocloridato de 1,1-aciloxialquilo, carbonato de para-nitrofenilo o similares).

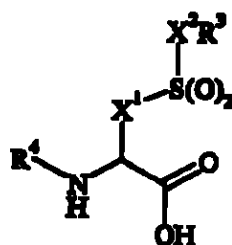
15 Derivados protegidos de los compuestos de Fórmula (I) pueden elaborarse por medios conocidos por los expertos en la técnica. Una descripción detallada de las técnicas aplicables a la creación de grupos protectores y su retirada puede encontrarse en T.W. Greene, *Protecting* 20 *Groups in Organic Synthesis*, 3ª edición, John Wiley & Sons, Inc. 1999.

Los compuestos de la presente invención pueden prepararse convenientemente, o formarse durante el procedimiento de la invención, como solvatos (por ejemplo, 25 hidratos). Los hidratos de los compuestos de la presente invención pueden prepararse convenientemente mediante recristalización en una mezcla de disolventes acuosos/orgánicos, usando disolventes orgánicos tales como dioxina, tetrahidrofurano o metanol. Los compuesto de 30 Fórmula (I) pueden prepararse como sus estereoisómeros individuales al hacer reaccionar una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diastereoisómeros, separar los diastereoisómeros y recuperar el enantiómero ópticamente puro. Aunque la resolución de los enantiómeros 35 puede llevarse a cabo usando derivados diastereoisómeros covalentes de los compuestos de Fórmula (I), se prefieren complejos disociables (por ejemplo, sales diastereoisómeras cristalinas). Los diastereoisómeros tienen propiedades físicas distintas (por ejemplo, puntos de fusión, 40

puntos de ebullición, solubilidades, reactividad, etc.) y pueden separarse fácilmente aprovechándose de estas diferencias. Los diastereoisómeros pueden separarse mediante cromatografía o, preferiblemente, mediante técnicas de
 5 separación/resolución basadas en diferencias de solubilidad. El enantiómero ópticamente puro se recupera a continuación, junto con el agente de resolución, mediante cualquier medio práctico que no dé como resultado la racemización. Una descripción más detallada de las técnicas
 10 aplicables a la resolución de estereoisómeros de compuestos a partir de su mezcla racémica puede encontrarse en Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

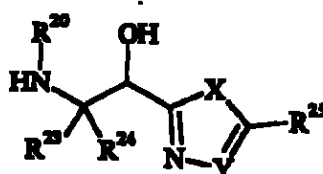
15 En resumen, los compuestos de Fórmula (I) se elaboran mediante un procedimiento que comprende:

(A) hacer reaccionar un compuesto de Fórmula (II):



(II)

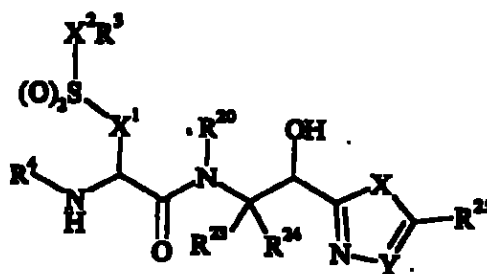
con un compuesto de la Fórmula (III):



(III)

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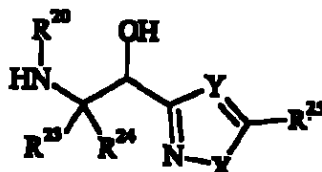
seguido por la oxidación de la β-hidroxiamida (IV) resultante:



(IV)

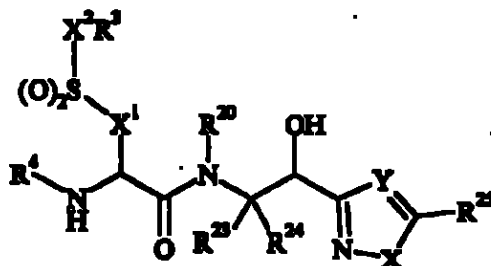
en la que X, Y, X¹, X², R³, R⁴, R²⁰, R²³, R²⁴ y R²⁵ son como se definen en el Sumario de la Invención para la Fórmula (I); o

- (B) hacer reaccionar un compuesto de Fórmula (II) con un
5 compuesto de la Fórmula (VI):



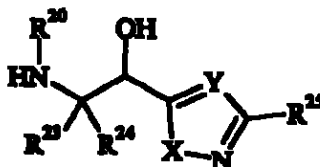
(VI)

seguido por la oxidación de β-hidroxiamida (VIII) resultante:



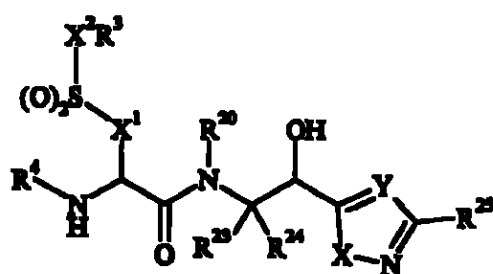
(VIII)

- 10 en la que X, Y, R²⁰, R²³, R²⁴ y R²⁵ son como se definen en el Sumario de la Invención para la Fórmula (I); o
(C) hacer reaccionar un compuesto de Fórmula (II) con un
compuesto de la Fórmula (VII):



(VII)

- 15 seguido por la oxidación de la β-hidroxiamida (IX) resultante:



(IX)

- en la que X, Y, R²⁰, R²³, R²⁴ y R²⁵ son como se definen en el Sumario de la Invención para la Fórmula (I); y
- (D) opcionalmente convertir un compuesto de Fórmula (I)
- 5 en una sal farmacéuticamente aceptable;
- (E) opcionalmente convertir una forma salina de un compuesto de Fórmula (I) en una forma no salina;
- (F) opcionalmente convertir una forma no oxidada de un compuesto de Fórmula (I) en un N-óxido farmacéuticamente aceptable;
- 10 (G) opcionalmente convertir una forma de N-óxido de un compuesto de Fórmula (I) en su forma no oxidada;
- (H) opcionalmente resolver un isómero individual de un compuesto de Fórmula (I) a partir de una mezcla de isómeros;
- 15 (I) opcionalmente convertir un compuesto no derivado de Fórmula (I) en un derivado de profármaco farmacéuticamente aceptable; y
- (J) opcionalmente convertir un derivado de profármaco de un compuesto de Fórmula (I) en su forma no derivada.
- 20

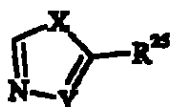
Los productos intermedios de Fórmula (II), en la que X¹ es metileno, X² es metileno y R³ y R⁴ son como se definen anteriormente aquí, pueden prepararse mediante: (i) la alquilación de cisteína con un bromuro de alquilo de fórmula R³CH₂Br [la reacción puede llevarse a cabo convenientemente en presencia de un hidróxido de metal alcalino, tal como hidróxido sódico, en etanol y a una temperatura de hasta aproximadamente 40°C]; (ii) la reacción con un compuesto de fórmula R⁴-Cl (por ejemplo cloruro de morfolinocarbonilo) en presencia de una base adecuada, tal como trietilamina, en un disolvente inerte, tal como acetonitrilo, y a temperatura ambiente; (iii) la oxidación, por ejemplo con H₂WO₄ y peróxido de hidrógeno, en un disolvente adecuado, tal como alcohol isopropílico, y a

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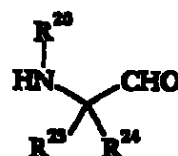
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una temperatura de aproximadamente 15-20°C.

Los productos intermedios de Fórmula (III), en la que X, Y, R²⁰, R²³, R²⁴ y R²⁵ son como se definen anteriormente aquí, pueden prepararse mediante: (i) el tratamiento de compuestos de fórmula (X) [en la que X, Y y R²⁵ son como se definen anteriormente aquí] con butil-litio en un disolvente inerte, tal como tetrahidrofurano, a una temperatura de aproximadamente -78°C; (ii) el tratamiento del anión resultante con dieterato de bromuro de magnesio a una temperatura de aproximadamente -78°C; (iii) la reacción del compuesto de Grignard resultante con un aldehído de fórmula (XI) [en la que R²⁰, R²³ y R²⁴ son como se definen previamente aquí] a una temperatura de aproximadamente -45°C.



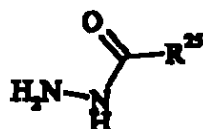
(X)



(XI)

La preparación de los productos intermedios de fórmula (III) puede llevarse a cabo convenientemente con el NH de compuestos de fórmula (XI) protegido, con, por ejemplo, un grupo Boc.

Los compuestos de fórmula (X), en la que X, Y y R²⁵ son como se definen anteriormente aquí, pueden prepararse mediante la reacción de hidrazonas de fórmula (XII)

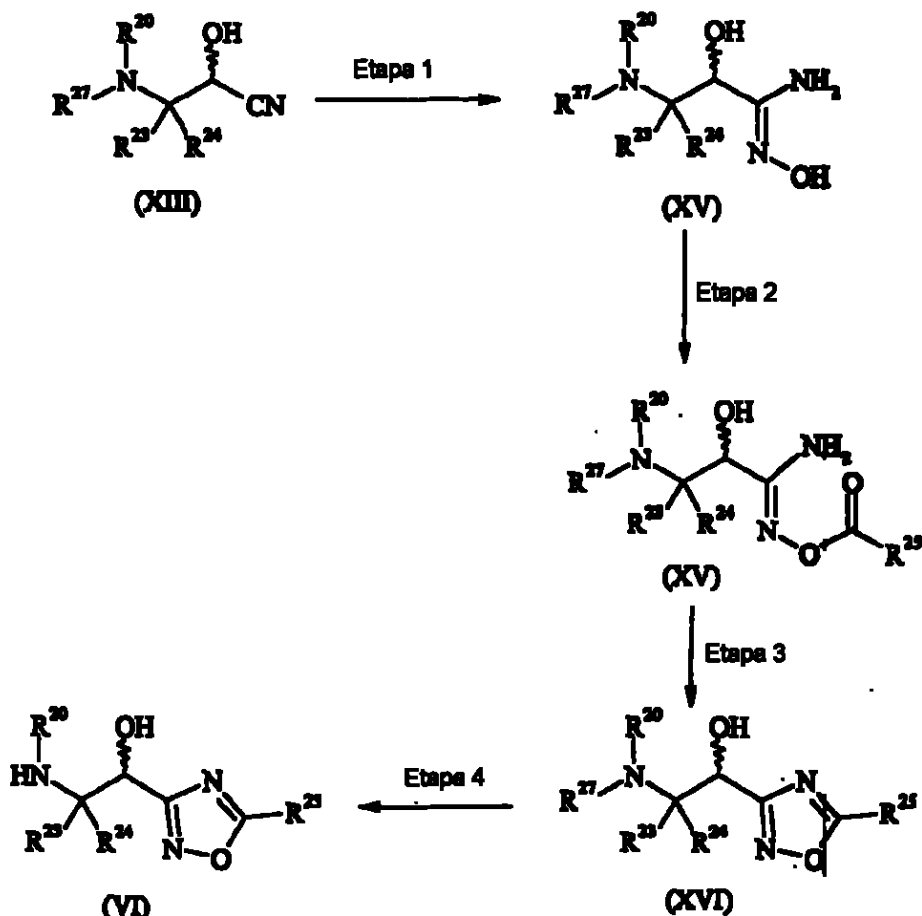


(XII)

en la que R²⁵ es como se define anteriormente aquí, con ortoformiato de trietilo, en presencia de un catalizador ácido, tal como ácido para-toluenosulfónico, y a una temperatura de hasta aproximadamente 125°C.

Los productos intermedios de fórmula (VI) en la que X, Y, R²⁰, R²³, R²⁴ y R²⁵ son como se definen anteriormente aquí, pueden prepararse en el esquema de reacción 2 siguiente:

Esquema de Reacción 2



Así, en la etapa 1, α -hidroxinitrilos de fórmula (XIII) [en la que R^{20} , R^{23} , R^{24} y R^{25} son como se definen
 5 anteriormente aquí y R^{27} es un grupo protector adecuado, tal como terc-butoxicarbonilo, pueden hacerse reaccionar con hidroxilamina en presencia de un alcóxido de metal alcalino, tal como metóxido sódico, en metanol y a $0^\circ C$. Los compuestos resultantes de fórmula (XIV) [en la que
 10 R^{20} , R^{23} , R^{24} , R^{25} y R^{27} son como se definen anteriormente aquí] pueden emplearse a continuación, en la etapa 2, con ácidos de fórmula $R^{25}-CO_2H$ [en la que R^{25} es como se define anteriormente aquí] en presencia de un agente de acoplamiento apropiado [por ejemplo, hidrocloreuro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI)] y opcio-
 15 nalmente un catalizador apropiado [por ejemplo, 1-hidroxibenzotriazol (HOBt)] y una base no nucleófila [por ejemplo, trietilamina] aproximadamente a temperatura ambiente. Los compuestos resultantes de fórmula (XV) [en la
 20 que R^{20} , R^{23} , R^{24} , R^{25} y R^{27} son como se definen anterior-

mente aquí] pueden ciclarse a continuación, en la etapa 3, calentando en un disolvente inerte, tal como diglime, a una temperatura de aproximadamente 150°C a aproximadamente 200°C en un reactor de microondas. Los compuestos
5 ciclados de fórmula (XVI) [en la que R^{20} , R^{23} , R^{24} , R^{25} y R^{27} son como se definen anteriormente aquí] pueden desprotegerse, en la etapa 4, para dar productos intermedios de fórmula (VI) [por ejemplo, cuando R^{27} es terc-butiloxicarbonilo, la desprotección se lleva a cabo convenientemente mediante tratamiento con ácido trifluoroacético a temperatura ambiente].
10

Los productos intermedios de fórmula (VII), en la que X, Y, R^{20} , R^{23} , R^{24} y R^{25} son como se definen anteriormente aquí, pueden prepararse como el siguiente esquema
15 de reacción 3:

20

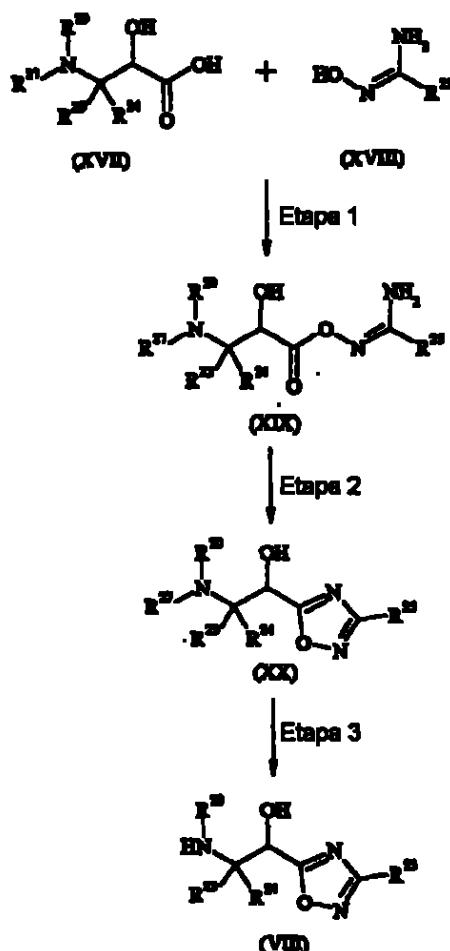
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Esquema de Reacción 3



Así, en la etapa 1, α -hidroxiácidos de fórmula 5 (XVII) [en la que R^{20} , R^{23} , R^{24} y R^{27} son como se definen anteriormente aquí] pueden hacerse reaccionar con N-hidroxiamidinas de fórmula (XVIII) [en la que R^{25} es como se define anteriormente aquí] en presencia de un agente de acoplamiento adecuado, tal como N-ciclohexilcarbodiimida-N'-metilpoliestireno, en un disolvente inerte, tal como diclorometano, y a una temperatura de aproximadamente 0°C. El compuesto resultante de fórmula (XIX) [en la que R^{20} , R^{23} , R^{24} , R^{25} y R^{27} son como se definen anteriormente aquí] se ciclan a continuación, en la 15 etapa 2, calentando en un reactor de microondas en un disolvente inerte, tal como tetrahidrofurano, a una temperatura de aproximadamente 180°C. Los oxadiazoles resultantes de fórmula (XX) [en la que R^{20} , R^{23} , R^{24} , R^{25} y R^{27} son como se definen anteriormente aquí] pueden desprotegerse a continuación, en la etapa 4, para dar productos 20

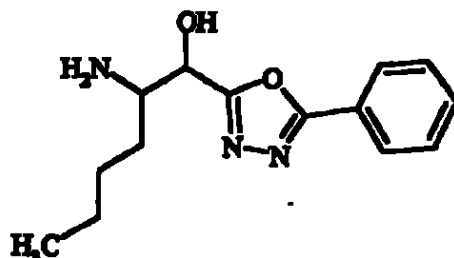
intermedios de fórmula (VI) [por ejemplo, cuando R²⁷ es terc-butoxicarbonilo, la desprotección se lleva a cabo convenientemente mediante tratamiento con triamina-3 Silicycle en un disolvente inerte, tal como diclorometano, y a temperatura ambiente].

Ejemplos:

La presente invención se ejemplifica adicionalmente, pero no se limita por, los siguientes ejemplos que ilustran la preparación de compuestos de Fórmula (I) (Ejemplos) y productos intermedios (Referencias) de acuerdo con la invención.

REFERENCIA 1

2-Amino-1-(5-fenil-[1,3,4]oxadiazol-2-il)-1-hexanol



Una mezcla de la benzoilhidracida (22,5 g, 165 milimoles), ortoformiato de trietilo (150 ml) y ácido p-toluenosulfónico (300 mg) se calentó a 120°C durante 12 horas. El ortoformiato de trietilo en exceso se retiró bajo vacío y el residuo se sometió a cromatografía en columna de gel de sílice para producir 2-fenil-[1,3,4]oxadiazol (14,5 g); ¹H NMR [(CD₃)₂SO]: δ 9,34 (1H, s), 8,05-7,98 (2H, m), 7,68-7,55 (3H, m); MS: 147,4 (M+1).

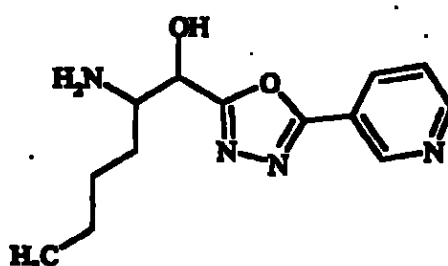
Se añadió n-BuLi (solución 1,6 M en 6,2 ml de hexano) gota a gota bajo N₂ a -78°C a una solución agitada de 2-fenil-[1,3,4]oxadiazol (1,46 g, 10 milimoles) en THF (40 ml). Después de 1 hora, se añadió MgBr.Et₂O (1,29 g, 5 milimoles) y la mezcla de reacción se dejó calentar hasta -45°C durante 1 hora antes de tratarse con 2-Boc-Nlu-aldehído (1,07 g, 5 milimoles) en THF (20 ml). La mezcla de reacción se agitó durante 1 hora, se extinguió con NH₄Cl saturado y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó con MgSO₄ y

se concentró. El residuo se sometió a cromatografía en columna de gel de sílice para dar 2-(2-Boc-amino-1-hidroxihexil)-5-fenil-[1,3,4]oxadiazol (800 mg); MS: 360,2 (M-1), 362,6 (M+1), 364,6 (M=23).

5 Se mezclaron 2-(2-Boc-amino-1-hidroxihexil)-5-fenil-[1,3,4]oxadiazol (130 mg, 0,36 milimoles) y MeCl₂ (5 ml) y se añadió TFA (1 ml) a temperatura ambiente. Después de agitar durante 1 hora, el disolvente y el TFA en exceso se retiraron bajo vacío para producir 2-amino-1-(5-fenil-
10 [1,3,4]oxadiazol-2-il)-1-hexanol.

REFERENCIA 2

2-Amino-1-(5-piridin-3-il-[1,3,4]oxadiazol-2-il)hexan-1-ol



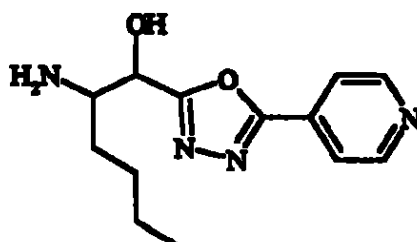
15

Se añadió n-BuLi (solución 1,6 M en 2,1 ml de hexano) gota a gota bajo N₂ a -78°C a una solución agitada de 2-(3-piridil)-[1,3,4]oxadiazol (500 mg, 2,4 milimoles) en THF (20 ml). Después de 1 hora, se añadió MgBr.Et₂O
20 (808,6 g, 3,4 milimoles) y la mezcla de reacción se dejó calentar hasta -45°C durante 1 hora antes de tratarse con 2-Boc-Nlu-aldehído (511 g, 2,38 milimoles) en THF (10 ml). La mezcla de reacción se agitó durante 1 hora, se extinguió con NH₄Cl saturado y se extrajo con acetato de
25 etilo. La capa orgánica se lavó con salmuera, se secó con MgSO₄ y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice para dar 2-(2-(2-Boc-amino-1-hidroxihexil)-5-(3-piridil)-[1,3,4]oxadiazol (200 mg); MS: 361,4 (M-1), 363,2 (M+1).

30 Se mezclaron 2-(2-Boc-amino-1-hidroxihexil)-5-(3-piridil)-[1,3,4]oxadiazol (100 mg, 0,27 milimoles) y MeCl₂ (5 ml) y se añadió TFA (1 ml) a temperatura ambiente. Después de agitar durante 1 hora, el disolvente y TFA en exceso se retiraron bajo vacío para producir 2-amino-
35 1-(5-piridin-3-il-[1,3,4]oxadiazol-2-il)-1-hexan-1-ol.

REFERENCIA 3

2-Amino-1-(5-(4-piridil)-[1,3,4]oxadiazol-2-il)-1-hexanol



Una mezcla de la hidracida isonicotínica (13,7 g, 5 100 milimoles), ortoformiato de trietilo (60 ml) y ácido p-toluenosulfónico (30 mg) se calentó a 130°C durante 12 horas. El ortoformiato de trietilo en exceso se retiró bajo vacío. El residuo se cristalizó en acetato de etilo para dar 2-(4-piridil)-[1,3,4]oxadiazol (14,8 g); H^1 NMR 10 $[(CD_3)_2SO]$: δ 9,46 (1H, s), 8,8 (2H, dd), 7,9 (2H, dd)

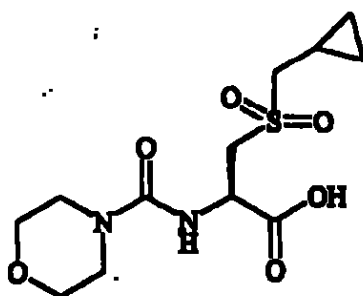
Se añadió n-BuLi (solución 1,6 M en 12,5 ml de hexa- no) gota a gota bajo N_2 a -78°C a una solución agitada de 2-(4-piridil)-[1,3,4]oxadiazol (2,94 g, 20 milimoles) en THF (80 ml). Después de 1 hora, se añadió MgBr.Et₂O (5,16 15 g, 20 milimoles) y la mezcla de reacción se dejó calentar hasta -45°C durante 1 hora antes de tratarse con 2-Boc-Nlu-aldehído (2,58 g, 12 milimoles) en THF (20 ml). La mezcla de reacción se agitó durante 1 hora, se apagó con NH₄Cl saturado y se extrajo con acetato de etilo. La capa 20 orgánica se lavó con salmuera, se secó con MgSO₄ y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice para dar 2-(2-Boc-amino-1-hidroxi-hexil)-5-(4-piridil)-1,3,4-oxadiazol (950 mg); MS: 361,4 (M-1), 363,4 (M+1).

Se mezclaron 2-(2-Boc-amino-1-hidroxi-hexil)-5-(4- 25 piridil)-1,3,4-oxadiazol (950 mg, 2,62 milimoles) y MeCl₂ (5 ml) y se añadió TFA (1 ml) a temperatura ambiente. Después de agitar durante 1 hora, el disolvente y el TFA en exceso se retiraron bajo vacío para producir sal de 30 TFA de 2-amino-1-(5-(4-piridil)-[1,3,4]oxadiazol-2-il)-1-hexanol (1 g); MS: 263,0 (M+1).

REFERENCIA 4

Ácido 3-ciclopropilmetanosulfonil-2-[(morfolino-4-carbonil)amino]propiónico

35



Etapas 1

Se añadió durante 40 minutos una solución de hidróxido sódico (2,0 eq., 64,6 g) en etanol (650 ml) (la
5 solución de hidróxido sódico se mantuvo por debajo de 40°C durante su preparación, 3 horas para la disolución completa) a una suspensión de L-cisteína (100 g) en etanol (850 ml) bajo nitrógeno. Después de la adición, se
añadió durante 20 minutos bromuro de ciclopropilmetilo
10 (1,1 eq., 122,5 g) mientras se mantenía la temperatura a 25-30°C con un baño frío. La suspensión blanca resultante se agitó durante otras 18 horas y a continuación se extinguió al añadir HCl 2N (0,73 eq., 300 ml) durante 20 minutos. La suspensión espesa se concentró (100 milibares, baño a 52°C) hasta aproximadamente 400 ml (1,5 l de
15 etanol/agua destilada) y a continuación se añadió agua (750 ml). El pH (9,6) se ajustó hasta pH 6,5 con HCl 2N y la mezcla se agitó a 4°C durante 2 horas y a continuación se filtró. La torta se lavó cinco veces con agua (100 ml)
20 y a continuación se secó a vacío para proporcionar S-ciclopropilmetil-L-cisteína (128,2 g, 88,6% de rendimiento).

Etapas 2

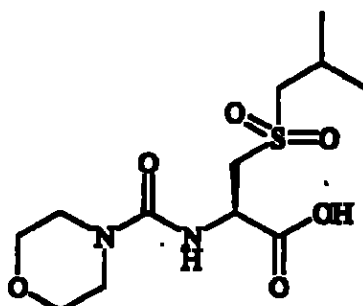
Se añadió trietilamina (2,2 eq., 176 ml) durante 15
25 minutos a una suspensión de S-ciclopropilmetil-L-cisteína (100 g) en acetonitrilo (1,5 l) y agua (150 ml) bajo nitrógeno. Se añadió cloruro de morfolinocarbonilo (1,15 eq., 100 g) a la suspensión durante 4 horas a temperatura ambiente. La solución resultante se agitó durante otras
30 18 horas a temperatura ambiente y la mezcla se concentró hasta aproximadamente 400 ml (100 milibares, baño a 50°C). La mezcla se diluyó con agua (250 ml) y el pH (5,3) se ajustó hasta 12,5 al añadir hidróxido sódico 2N (2,1 eq., 616 ml). La mezcla acuosa se lavó tres veces

con diclorometano (500 ml). Se añadió diclorometano adicional (500 ml) y el pH se ajustó hasta pH 2,0-2,5 añadiendo HCl 2N (1,0 eq., 285 ml). La capa acuosa se extrajo dos veces con diclorometano (100 ml). Los extractos
5 ácidos combinados se lavaron con agua (100 ml) y se concentraron hasta aproximadamente 400 ml. La mezcla se destiló a continuación bajo vacío ($P \leq 300$ milibares, temperatura $\leq 50^\circ\text{C}$) mientras se mantenía el volumen constante al añadir alcohol isopropílico (400 ml). La mezcla se en-
10 frió a continuación hasta $15-20^\circ\text{C}$ y se añadió H_2WO_4 (0,02 eq., 2,9 g) seguido por solución de peróxido de hidrógeno al 30% (2,2 eq., 130 ml). La mezcla se agitó durante la noche a temperatura ambiente y a continuación se enfrió hasta $0-5^\circ\text{C}$ y se añadió una solución de $\text{Na}_2\text{S}_2\text{O}_3$ (0,2 eq.,
15 21,6 g) en agua (100 ml). La mezcla se extrajo con acetato de etilo (1,6 l) y a continuación dos veces con una mezcla de acetato de etilo y alcohol isopropílico (500 ml, 7/3, v/v). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 (300 g) y a continuación se concentraron hasta
20 aproximadamente 250 ml. El alcohol isopropílico residual se destiló bajo vacío, manteniendo el volumen constante al añadir acetato de etilo (250 ml). La suspensión resultante se agitó a temperatura ambiente durante otra hora y a continuación se filtró. El sólido se lavó dos
25 veces con acetato de etilo (50 ml) y a continuación se secó a vacío para proporcionar la ciclopropilsulfona (182,6 g, 64,8% de rendimiento). El filtrado se concentró a vacío, se aisló más producto en acetato de etilo (150 ml), se lavó dos veces con acetato de etilo (50 ml) y a
30 continuación se secó para proporcionar otros 27,2 g de ácido (14,9%). $^1\text{H-NMR}$ (DMSO-d_6): 12,9 (s ancho, 1H), 7,16 (d, 1H), 4,5 (m, 1H), 3,6-3,42 (m, 5H), 3,35-3,2 (m, 5H), 3,15-3,0 (m, 2H), 1,0 (m, 1H), 0,6 (m, 2H), 0,3 (m, 2H).
MS: 321 (MH^+).

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REFERENCIA 5

Ácido 3-(2-metil-propano-1-sulfonil)-2-[(morfolino-4-carbonil)amino]propiónico

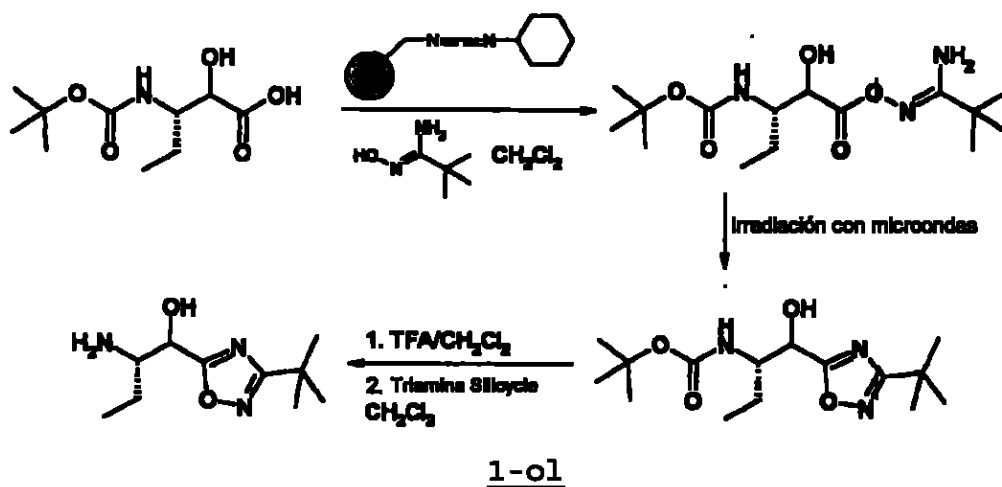


Al proceder de una manera similar al Ejemplo de Referencia 4 anterior pero usando bromuro de isobutilo en lugar de bromuro de ciclopropilmetilo y solución de 5 hidróxido sódico 10N en lugar de hidróxido sódico etanólico, en la Etapa 1 se preparó ácido 3-(2-metilpropano-1-sulfonyl)-2-[(morfolino-4-carbonil)-amino]-propiónico.

$^1\text{H-NMR}$ (CDCl_3): 10,0 (s ancho, 1H), 6,1 (d, 1H), 4,8 (m, 1H), 3,75-3,6 (m, 6H), 3,5-3,3 (m, 4H), 3-2,85 (d, 2H), 10 2,35 (m, 1H), 1,1 (d, 6H). MS: 323 (MH^+).

REFERENCIA 6

(S)-2-Amino-1-(3-terc-butil-[1,2,4]oxadiazol-5-il)-butan-



15

Una solución de ácido (S)-3-terc-butoxicarbonilamino-2-hidroxipentanoico (1,63 g, 7 milimoles) y N-hidroxi-2,2-dimetilpropionamidina (0,9 g, 7,75 milimoles) en diclorometano (40 ml) se agitó a 0°C. Se 20 añadió en porciones N-ciclohexilcarbodiimida-N'-metilpoliestireno (1,92 milimoles/g, 5,1 g, 9,8 milimoles). La mezcla de reacción se agitó bajo nitrógeno durante 1 hora. La mezcla de reacción se filtró, la resina se lavó con diclorometano y el filtrado se evaporó bajo

vacío hasta sequedad. El residuo se disolvió en THF (20 ml), la solución se dividió en cinco partes iguales, que se cargaron en viales de reactor de microondas y se calentaron en un reactor de microondas a 180°C durante 3 minutos. Los reactores se enfriaron hasta temperatura ambiente, las soluciones se combinaron y el THF se evaporó bajo vacío. El residuo se sometió a cromatografía de desarrollo rápido (eluyendo con un gradiente de 5% a 65% de acetato de etilo en heptano) para dar un aceite incoloro [LC/MS m/z=336 (M+Na⁺), 214 (M+H⁺-Boc)]. El aceite incoloro se disolvió en diclorometano (45 ml) y se añadió ácido trifluoroacético (5 ml). Después de 2 horas la reacción se evaporó bajo vacío hasta sequedad. El residuo se redisolvió en 50 ml de diclorometano. Se añadió triamina-3 Silicycle(4,19 g, 16,45 milimoles) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla se filtró y se lavó con diclorometano. El filtrado se concentró bajo vacío para dar (S)-2-amino-1-(3-terc-butyl-[1,2,4]oxadiazol-5-il)-butan-1-ol (675 mg, 45% global) como un sólido blanco. Se obtuvo como una mezcla de diastereoisómeros.

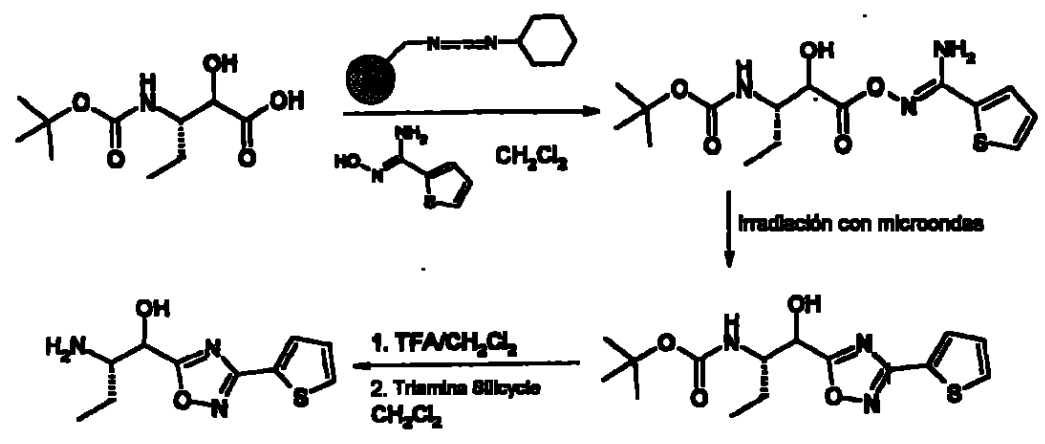
¹H NMR (CDCl₃, 300 MHz): [4,87 (d, J=4,5Hz) 4,69 (d, J=3,5Hz), 1H], [3,18 (ddd, J=8Hz, 5,5Hz, 4Hz) 3,09 (ddd, J=9Hz, 2x 4,5Hz), 1H], 1,71-1,21 (m, 2H), 1,40 (s, 9H), [1,04 (t, J=7,5Hz) 1,00 (t, J=7,5Hz), 3H].

[LC/MS m/z=214 (M+H)].

REFERENCIA 7

(S)-2-Amino-1-(3-tiofen-2-il-[1,2,4]oxadiazol-5-il)-butan-1-ol

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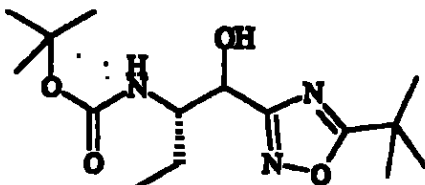


Una solución de ácido (S)-3-terc-butoxicarbonilamino-2-hidroxipentanoico (2 g, 8,6 milimoles) y N-hidroxitiofeno-2-carboxamidina (1,35 g, 9,5 milimoles) en diclorometano (40 ml) se agitó a 0°C. Se añadió en porciones N-ciclohexilcarbodiimida-N'-metilpoliestireno (1,90 milimoles/g, 6,05 g, 11,5 milimoles). La mezcla de reacción se agitó bajo nitrógeno durante 4 horas a 0°C y a continuación durante 15 horas a temperatura ambiente. La mezcla de reacción se filtró, la resina se lavó con diclorometano y el filtrado se evaporó bajo vacío hasta sequedad. El residuo se disolvió en tetrahidrofurano (20 ml), la solución se dividió en cinco partes iguales, que se cargaron en viales para reactor de microondas y se calentaron en un reactor de microondas a 180°C durante 4 minutos. Las reacciones se enfriaron hasta temperatura ambiente, las soluciones se combinaron y el THF se evaporó bajo vacío. El residuo se purificó a través de cromatografía de desarrollo rápido (eluida con un gradiente de 5% a 60% de acetato de etilo en heptano) para dar un aceite incoloro [LC/MS m/z=362 (M+Na⁺), 240 (M+H⁺-Boc)].

El aceite incoloro se disolvió en diclorometano (45 ml) y se añadió ácido trifluoroacético (5 ml). Después de 2 horas la reacción se evaporó bajo vacío hasta sequedad. El residuo se redisolvió en 50 ml de diclorometano. Se añadió triamina-3 Silicycle (3,47 g, 13,65 milimoles) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla se filtró y se lavó con diclorometano. El filtrado se concentró bajo vacío para dar (S)-2-amino-1-(3-tiofen-2-il-[1,2,4]oxadiazol-5-il)-butan-1-ol, una mezcla de diastereoisómeros, (560 mg, 27% global) como un sólido blanquecino. ¹H NMR (CDCl₃, 300 MHz): [7,84 (d, J=1Hz) 7,82 (d, J=1Hz), 1H], [7,53 (dd, J=5Hz, 1Hz) 7,52 m, 1H], [7,18 (d, J=5Hz) 7,17 (d, J=5Hz), 1H], [4,94 (d, J=5Hz) 4,76 (d, J=4Hz), 1H], [3,26 (ddd, J=8Hz, 5,5Hz, 3,5Hz) 3,13 (ddd, J=9Hz, 2x4,5Hz), 1H], 1,79-1,21 (m, 2H), [1,07 (t, J=7,5Hz) 1,04 (t, J=7,5Hz), 3H]. LC/MS m/z=240 (M+H).

REFERENCIA 8

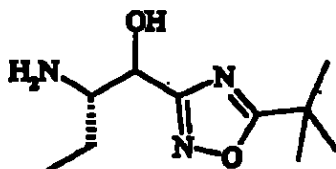
Éster ter-butílico de ácido {(S)-1-[(5-terc-butil-1,2,4-oxdiazol-3-il)-hidroxi-metil]propil}carbámico



- 5 Una suspensión de éster ter-butílico de ácido {(S)-1-[hidroxi-(N-hidroxicarbamimidoil)metil]propil}carbámico (3,24 g, 13,12 milimoles) en tolueno (25 ml) se trató con anhídrido trimetilacético (2,93 ml, 14,44 milimoles) y hexafluorofosfato de 1-etil-3-metil-1H-imidazolio (0,38
- 10 g, 1,48 milimoles) y la mezcla se calentó a 200°C en un microondas (Smith Creator, S00219) durante 20 minutos. El disolvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía de desarrollo rápido eluyendo con una mezcla de acetato de etilo y heptano para dar éster
- 15 ter terc-butílico de ácido {(S)-1-[(5-terc-butil-1,2,4-oxdiazol-3-il)-hidroximetil]propil}carbámico como un aceite marrón (2,73 g) (mezcla de diastereoisómeros).
- ¹H NMR (CDCl₃): 4,92-4,69 (m, 2H), 4,05-3,85 (m, 1H), 1,73-1,48 (m, 2H), 1,45 y 1,44 (2xs, 9H), 1,43 y 1,39
- 20 (2xs, 9H), 0,99 y 0,96 (2xt, J=7,5Hz, 3H). MS: 314 (MH⁺).

REFERENCIA 9

(S)-2-Amino-1-(5-terc-butil-1,2,4-oxadiazol-3-il)-butan-1-ol



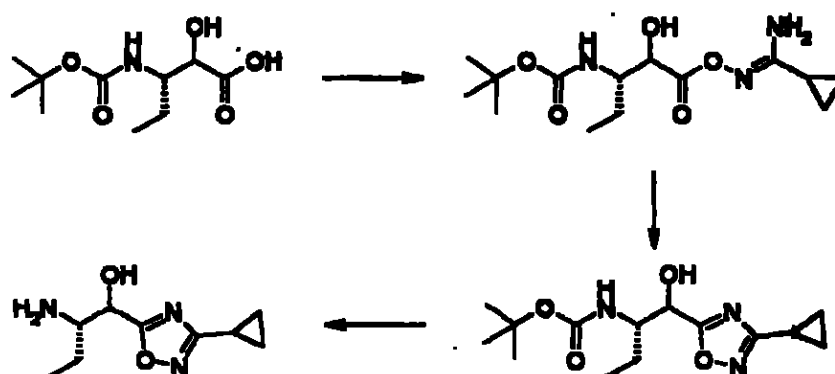
- 25 Una solución de éster terc-butílico de ácido {(S)-1-[(5-terc-butil-1,2,4-oxadiazol-3-il)hidroximetil]propil}carbámico (2,11 g, 6,72 milimoles) en cloruro de metileno (20 ml) se trató con ácido trifluoroacético (5,18 ml, 67,25 milimoles) y se agitó a
- 30 temperatura ambiente durante 3 horas. El disolvente se evaporó bajo presión reducida. El residuo se disolvió en cloruro de metileno (100 ml) y se trató con PS-trisamina

de Argonaut Technologies (5,38 g, 20,18 milimoles, 3,75 milimoles/g de carga) y la reacción se agitó a temperatura ambiente durante 4 h, se filtró y el filtrado se evaporó para dar (S)-2-amino-1-(5-terc-butil-1,2,4-oxadiazol-3-il)-butan-1-ol como un aceite naranja (975 mg) (mezcla de diastereoisómeros). ^1H NMR (CDCl_3): 4,73 y 4,58 (2xd, $J=5\text{Hz}$, 1H), 3,12-3,00 (m, 1H), 2,64-2,31 (s ancho, 3H), 1,69-1,44 (m, 2H), 1,43 (s, 9H), 0,99 y 0,97 (2xt, $J=7,5\text{Hz}$, 3H). MS: 214 (MH^+).

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REFERENCIA 10

(S)-2-Amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol



15 Una solución de ácido (S)-3-terc-butoxicarbonilamino-2-hidroxi-pentanoico (2,00 g, 8,57 milimoles) y N-hidroxiciclopropanocarboxamidina (1,03 g, 10,29 milimoles) en diclorometano (20 ml) se agitó a 0°C y se añadieron en porciones 1,25 equivalentes de N-ciclohexilcarbodiimida-N'-metilpoliestireno (1,70 milimoles/g, 6,30 g, 10,72 milimoles). La mezcla de reacción se agitó bajo nitrógeno durante 3 horas mientras se calentaba hasta 15°C . La mezcla de reacción se filtró, la resina se lavó con diclorometano y el filtrado se evaporó bajo vacío hasta sequedad. [LC/MS $m/z=338$ ($\text{M}+\text{H}+\text{Na}$)].

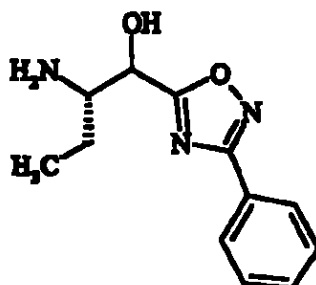
El residuo se disolvió en tetrahidrofurano (20 ml) y se calentó en un reactor de microondas (Smith Creator) a 160°C durante tres minutos, se enfrió hasta temperatura ambiente y se evaporó bajo vacío hasta sequedad. [LC/MS $m/z=320$ ($\text{M}+\text{H}+\text{Na}$)]. El residuo se disolvió en diclorometano (50 ml) y se agitó a temperatura ambiente a medida que se añadía gota a gota una solución de 50 ml de ácido tri-

30

fluoroacético al 50% en diclorometano. Después de 3 horas la reacción se evaporó bajo vacío hasta sequedad y se disolvió de nuevo en 50 ml de diclorometano. Se añadieron tres equivalentes de triamina-3 Silicycle y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla se filtró y se lavó con diclorometano. Se evaporó bajo vacío para dar 1,04 g (61% global). [LC/MS $m/z=198$ (M+H)].

REFERENCIA 11

10 (S)-2-Amino-1-(3-fenil-1,2,4-oxadiazol-5-il)-butan-1-ol

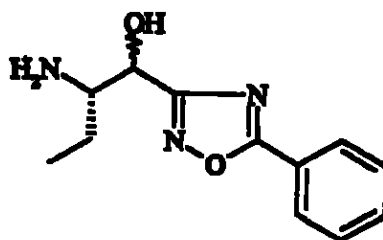


Una solución de ácido (S)-3-terc-butoxicarbonilamino-2-hidroxi-pentanoico (2,00 g, 8,57 milimoles) y N-hidroxibenzamidina (1,3 g, 9,5 milimoles) en diclorometano (40 ml) se agitó a 0°C. Se añadió en porciones N-ciclohexilcarbodiimida-N'-metilpoiestireno (1,90 milimoles/g, 6 g, 11,4 milimoles). La mezcla de reacción se agitó bajo nitrógeno durante 1 hora. La mezcla de reacción se filtró, la resina se lavó con diclorometano y el filtrado se evaporó bajo vacío hasta sequedad. [LC/MS $m/z=352$ (M+H⁺), 296 (M+H⁺-isobuteno)]. El residuo se disolvió en tetrahidrofurano (20 ml) y se calentó en un reactor de microondas (Smith Creator) a 180°C durante tres minutos, se enfrió hasta temperatura ambiente y se evaporó bajo vacío hasta sequedad. El residuo se purificó a través de cromatografía de desarrollo rápido (eluida con un gradiente de 5% a 65% de acetato de etilo en heptano) para dar el producto como un sólido blanco [LC/MS $m/z=356$ (M+Na⁺), 234 (M+H⁺-Boc)].

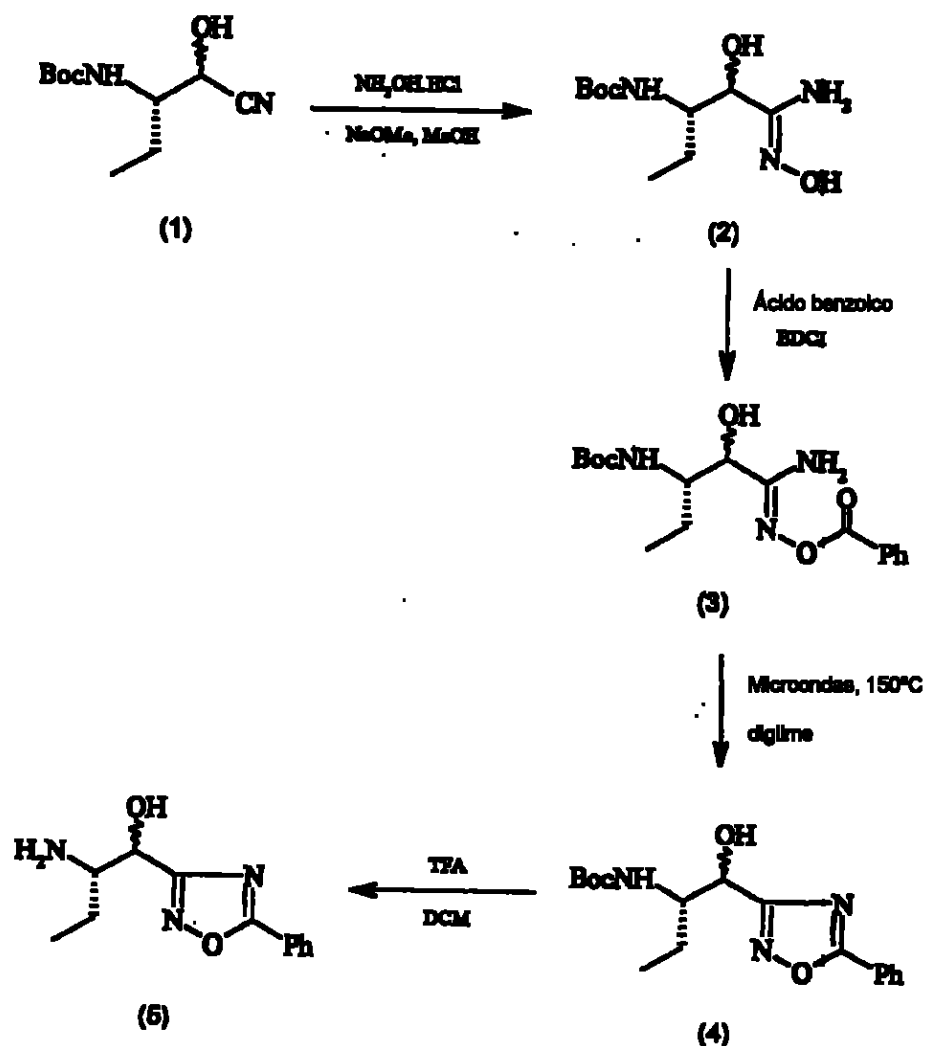
30 Se disolvió en diclorometano (45 ml) y se añadió ácido trifluoroacético (5 ml). Después de 2 horas la reacción se evaporó bajo vacío hasta sequedad. El residuo se redisolvió en 50 ml de diclorometano. Se añadió triamina-3 Silicycle (9,9 g, 39 milimoles) y la mezcla se

agitó a temperatura ambiente durante la noche. La mezcla se filtró y se lavó con diclorometano. El filtrado se concentró bajo vacío para dar 775 mg (38% global) de producto como un sólido blanco. [LC/MS $m/z=234$ (M+H)]. ^1H NMR (CDCl_3) 8,12-8,06 (m, 2H), 7,54-7,45 (m, 3H), 4,93 y 4,75 (2xd, $J=5\text{Hz}$ y $3,5\text{Hz}$, 1H), 3,25 y 3,11 (2xm, 1H), 1,78-1,42 (2xm, 2H), 1,04 y 1,01 (2x t, $J=7,5\text{Hz}$, 3H).

REFERENCIA 12

10 (S)-2-Amino-1-(5-fenil-[1,2,4]oxadiazol-3-il)-butan-1-ol

Se sintetizó como se describe en el siguiente esquema de reacción:



Éster terc-butílico de ácido {(S)-1-[hidroxi-(N-hidroxicarbamimidoil)-metil]-propil}-carbámico

Una solución de éster terc-butílico de ácido (2-ciano-1-etil-2-hidroxietil)carbámico (9,53 g, 44 milimoles) en metanol (80 ml) se enfrió hasta 0°C y se trató sucesivamente con hidrocloreuro de hidroxilamina (3,05 g, 44 milimoles) en metanol (80 ml) y solución de metóxido sódico al 25% en metanol (10,2 ml). Después de agitar a 0°C durante 5 minutos, la mezcla de reacción se agitó a temperatura ambiente durante 5 horas y a continuación se evaporó. El residuo se sometió a reparto entre acetato de etilo y agua. La capa orgánica se separó, se secó (MgSO₄) y a continuación se evaporó bajo presión reducida. El aceite amarillo residual se sometió a mplc, eluyendo con una mezcla de acetato de etilo y heptano para dar éster terc-butílico de ácido {(S)-1-[hidroxi-(N-hidroxicarbamimidoil)-metil]-propil}-carbámico (3,5 g) como un sólido blanco. MS: M(H⁺) 248.

20 Éster terc-butílico de ácido {1-[hidroxi-(N-benzoilcarbamimidoil)-metil]-propil}-carbámico

Una solución de éster terc-butílico de ácido {1-[hidroxi-(N-hidroxicarbamimidoil)-metil]-propil}-carbámico (2) (2,5 g, 10 milimoles) en diclorometilo (125 ml) se trató con ácido benzoico (1,36 g, 11 milimoles), EDCI (2,14 g, 11 milimoles), HOBT (1,37 g, 10 milimoles) y trietilamina (1,35 ml, 11 milimoles) y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se lavó con solución saturada de bicarbonato sódico, a continuación agua, a continuación se secó sobre Na₂SO₄ y a continuación se evaporó bajo presión reducida. El residuo se sometió a mplc eluyendo con trietilamina al 1% en mezcla de acetato de etilo y heptano 2:3 v/v para dar éster terc-butílico de ácido {1-[hidroxi-(N-benzoilcarbamimidoil)-metil]-propil}-carbámico (850 mg) como un sólido amarillo. MS: MH⁺ 352.

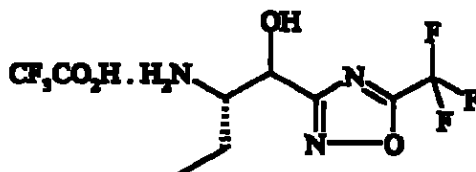
2-Amino-1-(5-fenil-[1,2,4]oxadiazol-3-il)-butan-1-ol (5)

40 Una solución de (3) (1,5 g, 4,3 milimoles) en digli-

me se calentó a 150°C en un reactor de microondas (Smith Creator, S00219) durante 40 minutos. El disolvente se evaporó bajo vacío en un Genevac Evaporator a 80°C durante 3 horas para dar un sólido marrón. Este se recogió en diclorometano (40 ml) y se trató con ácido trifluoroacético a temperatura ambiente durante 2 horas. El disolvente se evaporó hasta sequedad bajo presión reducida, el material en bruto se recogió en agua, se lavó con DCM, la capa acuosa se basificó con solución de NaOH 1M y se extrajo con diclorometano. La capa orgánica se secó sobre Na₂SO₄ y se evaporó bajo presión reducida para dar 2-amino-1-(5-fenil-[1,2,4]oxadiazol-3-il)-butan-1-ol (300 mg) como un sólido marrón claro. ¹H NMR (CDCl₃) 8,14-8,10 (m, 2H), 7,59-7,47 (m, 3H), 4,83 y 4,65 (d, J=5Hz, 1H), 3,18-3,05 (2m, 1H), 1,71-1,20 (m, 2H), 1,05-0,97 (2xt, J=7,2Hz, 3H).

REFERENCIA 13

(S)-2-Amino-1-(5-trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol; compuesto con ácido trifluoroacético



Una solución de éster terc-butílico de ácido {(S)-1-[hidroxi-(N-hidroxycarbamimidoil)-metil]-propil}-carbámico (452 mg, 1,83 milimoles) en dioxano (5 ml) se trató con anhídrido trifluoroacético (0,349 ml, 2,47 milimoles) y se calentó a 100°C en un reactor de microondas (Smith Creator, S00219) durante 7 minutos. El disolvente se evaporó bajo presión reducida y el material en bruto se sometió a cromatografía de desarrollo rápido eluyendo con una mezcla de acetato de etilo y heptano para dar éster terc-butílico de ácido {(S)-1-[hidroxi-(5-trifluorometil-1,2,4-oxadiazol-3-il)-metil]-propil}-carbámico como un sólido marrón (476 mg) (mezcla de diastereoisómeros).

¹H NMR (CDCl₃): 5,00 (d, J=4Hz, 1H), 4,82, 4,65 (d ancho, J=7Hz, 1H), 4,00, 3,85 (m ancho, 1H), 1,78-1,52 (m, 1H), 1,52-1,32 (m, 1H), 1,44, 1,37 (2xs, 9H), 1,02 (2xt, J=7Hz

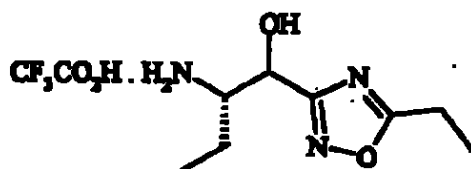
y 4Hz, 3H). MS: 348 (M+Na).

Una solución de éster terc-butílico de ácido {(S)-1-[hidroxi-(5-trifluorometil-1,2,4-oxadiazol-3-il)-metil]-propil}-carbámico (3,6 g, 0,011 moles) en cloruro de metileno (15 ml) se trató con ácido trifluoroacético (8,53 ml, 0,111 moles) y se agitó a temperatura ambiente durante 3 horas. El disolvente se evaporó bajo presión reducida para dar (S)-2-amino-1-(5-trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol; compuesto con ácido trifluoroacético como un aceite marrón (4,42 g) (mezcla de diastereoisómeros). ^1H NMR (CDCl_3): 8,22 (s ancho, 2H), 7,04 (s ancho, 1H), 5,14, 4,90 (d, $J=4\text{Hz}$ y 7Hz , 1H), 3,40-3,28 (m, 1H), 1,64-1,37 (m, 2H), 0,80 (2xt, $J=7\text{Hz}$, 3H). MS: 226 (MH^+)

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REFERENCIA 14

(S)-2-Amino-1-(5-etil-1,2,4-oxadiazol-3-il)-butan-1-ol;
compuesto con ácido trifluoroacético



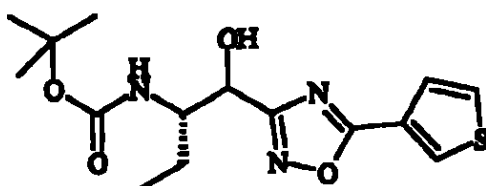
20 Una solución de éster terc-butílico de ácido {(S)-1-[hidroxi-(N-hidroxicarbamimidoil)-metil]-propil}-carbámico (525 mg, 2,13 milimoles) en dioxano (5 ml) se trató con anhídrido propiónico (0,300 ml, 2,34 milimoles) y se calentó a 150°C en un reactor de microondas (Smith Creator, S00219) durante 35 minutos. El disolvente se evaporó bajo presión reducida y el material en bruto se sometió a cromatografía de desarrollo rápido eluyendo con una mezcla de acetato de etilo y heptano para dar éster terc-butílico de ácido {(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroximetil]-propil}-carbámico como un sólido amarillo (406 mg) (mezcla de diastereoisómeros). ^1H NMR (CDCl_3): 4,98-4,72 (m, 2H), 4,00, 3,88 (m, 1H), 3,64, 3,45 (s ancho, 1H), 2,89 (2xq, $J=7,6\text{ Hz}$, 2H), 1,69 (m, 1H), 1,47 (m, 1H), 1,45, 1,39 (2xs, 9H), 1,44-1,36 (m, 3H), 0,98 (2xt, $J=9\text{Hz}$ y 7Hz , 3H). MS: 308 (M+Na).

35 Una solución de éster terc-butílico de ácido {(S)-1-

[(5-etil-1,2,4-oxadiazol-3-il)-hidroximetil]-propil}-carbámico (214 mg, 0,751 milimoles) en cloruro de metileno (5 ml) se trató con ácido trifluoroacético (0,578 ml, 7,504 milimoles) y se agitó a temperatura ambiente durante 3 horas. El disolvente se evaporó bajo presión reducida para dar trifluoroacetato de (S)-2-amino-1-(5-etil-1,2,4-oxadiazol-3-il)-butan-1-ol, una mezcla de diastereoisómeros, (224 mg) como un aceite marrón. MS: 186 (MH⁺). ¹H NMR (CDCl₃): 8,10-7,33 (2xs ancho, 3H), 5,24, 5,07 (, J=3,5Hz y 5,5Hz, 1H), 3,77, 3,62 (s ancho, 1H), 2,91 (2xq, J=7 Hz, 2H), 1,78 (m, 1H), 1,76-1,40 (m, 1H), 1,39 (2xt, J=7Hz, 3H), 1,02 (2xt, J=7,5 Hz, 3H).

REFERENCIA 15

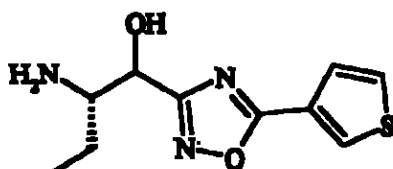
15 Éster terc-butílico de ácido {(S)-1-[hidroxi-(5-tiofen-3-il-1,2,4-oxadiazol-3-il)-metil]-propil}-carbámico



Una suspensión de éster terc-butílico de ácido {(S)-1-[hidroxi-(N-hidroxycarbamimidoil)-metil]-propil}-carbámico (2,4 g, 9,7 milimoles) en dioxano (15 ml) se trató con cloruro de tiofenocarbonilo (1,45 g, 9,9 milimoles) y trietilamina (1,36 ml, 9,8 milimoles) y la mezcla se calentó a 150°C en un microondas (Smith Creator, S00219) durante 15 minutos. El disolvente se evaporó bajo presión reducida. El residuo se sometió a cromatografía de desarrollo rápido eluyendo con una mezcla de acetato de etilo y heptano para dar éster terc-butílico de ácido {(S)-1-[hidroxi-(5-tiofen-3-il-1,2,4-oxadiazol-3-il)-metil]-propil}-carbámico, una mezcla de diastereoisómeros (144 mg), como un sólido marrón. ¹H NMR (CDCl₃): 8,21 (m, 1H), 7,66 (m, 1H), 7,45 (m, 1H), 4,92-4,69 (m, 2H), 5,02-4,80 (m, 2H), 4,10-3,85 (2xm, 1H), 1,80-1,45 (m, 2H), 1,46 y 1,38 (2xs, 9H), 1,01 y 0,99 (2xt, J=7,5Hz 3H). MS : 340 (MH⁺).

REFERENCIA 16

(S)-2-Amino-1-(5-tiofen-3-il-1,2,4-oxadiazol-3-il)-butan-1-ol



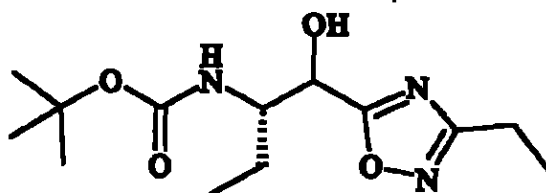
5 Al proceder de una manera similar a la descrita para el Ejemplo de Referencia 9 anteriormente, se preparó (S)-2-amino-1-(5-tiofen-3-il-1,2,4-oxadiazol-3-il)-butan-1-ol.

¹H NMR (CDCl₃): 8,24-8,18 (2xdd, J=1Hz y 3Hz, 1H), 7,69-7,62 (2xdd, J=1Hz y J=5Hz, 1H), 7,43 (dd, J=3,0Hz y J=5,0Hz), 4,88 y 4,70 (2xd, J=4,4Hz, 1H), 3,27-3,11 (m, 1H), 3,05-2,45 (s ancho, 3H), 1,74-1,21 (m, 2H), 1,02 y 0,99 (2xt, J=7,5Hz, 3H). MS: 240 (MH⁺).

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REFERENCIA 17

Éster terc-butílico de ácido {(S)-1-[(3-etil-1,2,4-oxadiazol-5-il)-hidroxi-metil]-propil}-carbámico

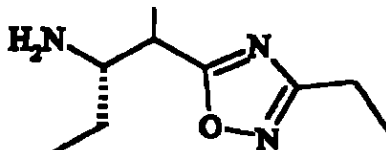


Una solución de ácido (S)-3-terc-butoxicarbonilamino-2-hidroxipentanoico (4,00 g, 17,2 milimoles) y N-hidroxipropionamidina (1,87 g, 21,5 milimoles) en diclorometano (50 ml) se agitó a 0°C y se añadió en porciones N-ciclohexilcarbodiimida-N'-metilpoliestireno (1,90 milimoles/g, 10 g, 19 milimoles). La mezcla de reacción se agitó bajo nitrógeno durante 3 horas mientras se calentaba hasta 15°C y se agitaba a temperatura ambiente durante 48 horas. La mezcla de reacción se filtró, la resina se lavó tres veces con diclorometano (50 ml), el filtrado se evaporó bajo vacío hasta sequedad y se sometió a cromatografía en columna de desarrollo rápido eluyendo con MeOH al 10% en diclorometano para dar una espuma (3,51 g). Una porción (340 mg) de es-

te material se disolvió en tetrahidrofurano (1,5 ml) y la solución se calentó en un reactor de microondas (Smith Creator) a 150°C durante tres minutos, se enfrió hasta temperatura ambiente y a continuación se evaporó bajo vacío hasta sequedad. El residuo se sometió a cromatografía en columna de desarrollo rápido eluyendo con metanol al 5% en diclorometano para dar éster terc-butílico de ácido {(S)-1-[(3-etil-1,2,4-oxadiazol-5-il)-hidroximetil]-propil}-carbámico como un aceite viscoso (236 mg). MS: 308 (M+Na⁺).

REFERENCIA 18

(S)-2-Amino-1-(3-etil-1,2,4-oxdiazol-5-il)-butan-1-ol

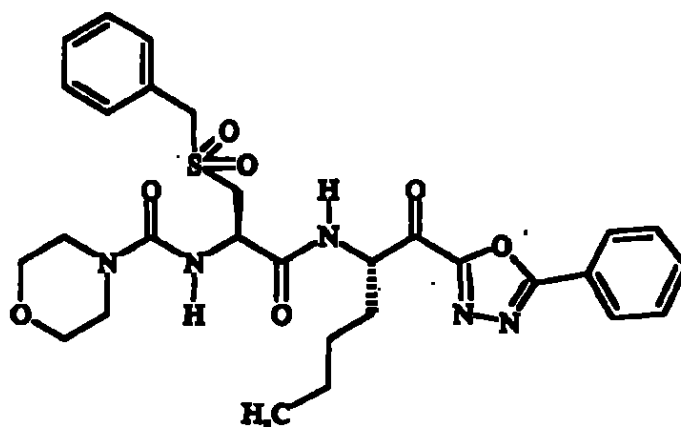


Una solución de éster terc-butílico de ácido {(S)-1-[(3-etil-1,2,4-oxadiazol-5-il)-hidroximetil]-propil}-carbámico (3,67 g, 12,87 milimoles) en diclorometano (50 ml) se trató con ácido trifluoroacético (10 ml) y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con tolueno y a continuación se evaporó bajo vacío hasta sequedad. El residuo se disolvió en diclorometano (75 ml) y la solución se trató con MP-Carbonate (3,3 milimoles/g, 6,0 g). Esta mezcla se agitó a temperatura ambiente durante la noche, a continuación se filtró, a continuación se lavó con diclorometano al 10% en metanol y se evaporó bajo vacío para dar (S)-2-amino-1-(3-etil-1,2,4-oxadiazol-5-il)-butan-1-ol, una mezcla de diaestereoisómeros, (2,26 g). ¹H NMR [(CD₃)₂SO]: δ 4,61 y 4,54 (d, J= 5Hz, 1H), 2,86 (m, 1H), 2,71 (q, J=8Hz, 2H), 1,6-1,0 (2xm, 2H), 1,22 (t, J = 8Hz, 3H), 0,88 (m, 3H). MS m/z 186 (M+H).

EJEMPLO 1

{2-Fenilmetanosulfonil-1-[1-(5-fenil-[1,3,4]oxadiazol-2-carbonil)-pentilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico

(Compuesto 1)



Se añadió EDC (103,6 mg, 0,54 milimoles) y N-metilmorfolina (0,4 ml) a temperatura ambiente a una mezcla agitada de ácido 2-[(morfolino-4-carbonil)-amino]-3-fenilmetanosulfonilpropiónico (135 mg, 0,37 milimoles), sal de TFA de 2-amino-1-(5-fenil-[1,3,4]oxadiazol-2-il)-1-hexanol (135 mg, 0,36 milimoles), preparada como en la Referencia 1, y HOBT (66 mg, 0,43 milimoles) en MeCl₂ (5 ml). Después de agitar durante 14 horas, la mezcla de reacción se extrajo con acetato de etilo. La capa orgánica se lavó con NaHCO₃ saturado, salmuera, se secó con MgSO₄ y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice para dar (1-{1-[hidroxi-(5-fenil-[1,3,4]oxadiazol-2-il)-metil]-pentilcarbamoil}-2-fenilmetanosulfoniletil)-amida de ácido morfolino-4-carboxílico (150 mg); MS: 598,6 (M-1), 600,6 (M+1).

Se trató (1-{1-[hidroxi-(5-fenil-[1,3,4]oxadiazol-2-il)-metil]-pentilcarbamoil}-2-fenilmetanosulfoniletil)-amida de ácido morfolino-4-carboxílico (150 mg, 0,25 milimoles), en MeCl₂ (5 ml), con peryodinano de Dess-Martin (183 mg, 0,43 milimoles) a temperatura ambiente. Después de agitar durante 1 hora, se añadieron 5 ml de Na₂S₂O₃-NaHCO₃ saturado. Después de 0,5 horas más, la mezcla de reacción se extrajo con acetato de etilo, se lavó con salmuera, se secó con MgSO₄ y se concentró. El residuo se purificó con cromatografía en columna de gel de sílice para dar {2-fenilmetanosulfonil-1-[1-(5-fenil-[1,3,4]oxadiazol-2-carbonil)-pentilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico (84 mg); ¹H NMR (DMSO-d): 8,71 (1H, d, J=6,6Hz, NH), 8,12-8,05 (2H, m), 7,75-

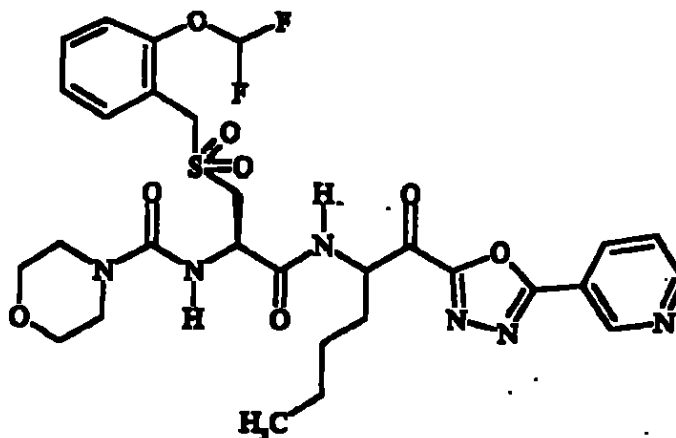
7,59 (3H, m), 7,38-7,36 (5H, m), 7,04 (1H, d, J=8,1Hz, NH), 5,12-5,01 (1H, m), 4,8-4,65 (1H, m), 4,47 (2H, s), 3,58-3,46 (4H, m), 3,35-3,2 (6H, m), 2,05-1,85 (1H, m), 1,8-1,65 (1H, m), 1,5-1,2 (4H, m), 0,87 (3H, t, J=6,9Hz, 5 CH₃); MS: 596,8 9M-1), 598,6 (M+1).

EJEMPLO 2

{2-(2-Difluorometoxifenilmetanosulfonil)-1-[1-(5-piridin-3-il-[1,3,4]oxadiazol-2-carbonil)-pentilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico

10

(Compuesto 2)



Se añadió EDC (73 mg, 0,38 milimoles) y N-metilmorfolina (0,2 ml) a temperatura ambiente a una mezcla agitada de ácido 2-[(morfolino-4-carbonil)-amino]-3-o-
 15 difluorometoxifenilmetanosulfonilpropiónico (105,5 mg, 0,25 milimoles), sal de TFA de 2-amino-1-(5-piridin-3-il-[1,3,4]oxadiazol-2-il)-hexan-1-ol (101,6 mg, 0,27 milimoles), preparada como en la Referencia 2, y HOBT (46 mg, 0,3 milimoles) en MeCl₂ (5 ml). Después de agitar durante
 20 14 horas, la mezcla de reacción se extrajo con acetato de etilo. La capa orgánica se lavó con NaHCO₃ saturado, salmuera, se secó con MgSO₄ y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice para dar (1-{1-{hidroxi-(5-(3-piridil)-[1,3,4]oxadiazol-2-il)-
 25 metil]-pentilcarbamoil}-2-o-difluorometoxifenilmetanosulfoniletil)-amida de ácido morfolino-4-carboxílico (56 mg); MS: 665,4 (M-1), 667,0 (M+1).

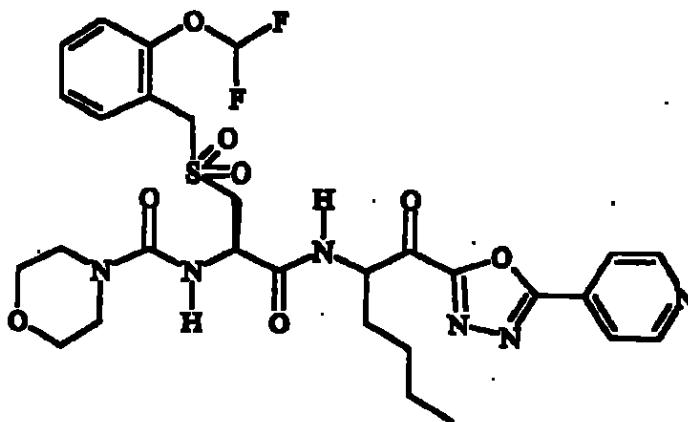
Se trató (1-{1-{hidroxi-(5-(3-piridil)-
 30 [1,3,4]oxadiazol-2-il)-metil]-pentilcarbamoil}-2-o-difluorometoxifenilmetanosulfoniletil)-amida de ácido

morfolino-4-carboxílico (56 mg, 0,084 milimoles), en MeCl₂ (5 ml) con peryodinano de Dess-Martin (53,4 mg, 0,12 milimoles) a temperatura ambiente. Después de agitar durante 1 hora, se añadieron 5 ml de Na₂S₂O₃-NaHCO₃ saturado. Después de 0,5 horas más, la mezcla de reacción se extrajo con acetato de etilo, se lavó con salmuera, se secó con MgSO₄ y se concentró. El residuo se purificó con cromatografía en columna de gel de sílice para dar {2-(2-difluorometoxi-fenilmetanosulfonil)-1-[1-(5-piridin-3-il-[1,3,4]oxadiazol-2-carbonil)-pentilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico (45 mg); H¹ NMR (DMSO-d): 9,247 (1H, d, J=2,2Hz, NH), 8,86 (1H, dd, J=1,7Hz, J=4,9Hz), 8,79 (1H, t, J=5,9Hz), 8,5-8,45 (1H, m), 7,73-7,68 (1H, m), 7,5-7,4 (2H, m), 7,3-7,2 (2H, m), 7,1 (1H, t, J=73,9Hz), 7,05-6,9 (1H, m), 5,12-5,02 (1H, m), 4,78-4,66 (1H, m), 4,53 (2H, s), 3,55-3,45 (5H, m), 3,32-3,26 (5H, m), 2,05-1,85 (1H, m), 1,8-1,6 (1H, m), 1,45-1,2 (6H, m), 0,87 (3H, t, J=6,9Hz, CH₃); MS: 663,4 (M-1), 665,4 (M+1).

20

EJEMPLO 3

{2-o-Difluorometoxifenilmetanosufonil-1-[1-(5-(4-piridil)-[1,3,4]oxadiazol-2-carbonil)-pentilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico



Se añadió EDC (190 mg, 0,99 milimoles) y N-metilmorfolina (0,4 ml) a temperatura ambiente a una mezcla agitada de ácido 2-[(morfolino-4-carbonil)-amino]-3-

30

o-difluorometoxifenilmetanosulfonilpropiónico (278 mg, 0,66 milimoles), sal de TFA 2-amino-1-(5-(4-piridil)-[1,3,4]oxadiazol-2-il)-1-hexanol (248 mg, 0,66 milimoles), preparada como anteriormente, y HOBt (121 mg, 0,79 milimoles) en MeCl₂ (5 ml). Después de agitar durante 14 horas, la mezcla de reacción se extrajo con acetato de etilo. La capa orgánica se lavó con NaHCO₃ saturado, salmuera, se secó con MgSO₄ y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice para dar (1-{1-[hidroxi-(5-(4-piridil)-[1,3,4]oxadiazol-2-il)-pentilcarbamoil]-2-o-difluorometoxifenilmetanosulfoniletil)-amida de ácido morfolino-4-carboxílico (430 mg); MS: 665,4 (M-1), 667,2 (M+1).

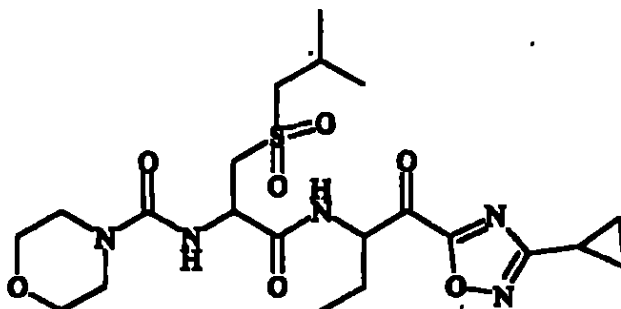
La (1-{1-[hidroxi-(5-(4-piridil)-[1,3,4]oxadiazol-2-il)-pentilcarbamoil]-2-o-difluorometoxifenilmetanosulfoniletil)-amida de ácido morfolino-4-carboxílico (400 mg, 0,6 milimoles), en MeCl₂ (5 ml), se trató con peryodinano de Dess-Martin (330 mg, 0,78 milimoles) a temperatura ambiente. Después de agitar durante 1 hora, se añadieron 5 ml de Na₂S₂O₃-NaHCO₃ saturado. Después de 0,5 horas más, la mezcla de reacción se extrajo con acetato de etilo, se lavó con salmuera, se secó con MgSO₄ y se concentró. El residuo se purificó con cromatografía en columna en gel de sílice para dar {2-o-difluorometoxifenilmetanosulfonil-1-[1-(5-(4-piridil)-[1,3,4]oxadiazol-2-carbonil)-pentilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico (148 mg); H¹ NMR (DMSO-d): 8,88-8,82 (2H+1H, m), 8,02-7,97 (2H, m), 7,48-7,45 (2H, m), 7,27-7,24 (2H, m), 7,1(1H, t, J=73,9Hz), 7,2-6,97 (1H, m), 5,12-5,01 (1H, m), 4,8-4,65 (1H, m), 4,53 (2H, s), 3,58-3,46 (4H, m), 3,35-3,2 (6H, m), 2,05-1,85 (1H, m), 1,8-1,65 (1H, m), 1,5-1,2 (4H, m), 0,87 (3H, t, J=6,9Hz, CH₃); MS: 663,4 (M-1), 665,4 (M+1).

Los siguientes compuestos se prepararon mediante los métodos descritos y ejemplificados anteriormente:

{2-(2-difluorometoxifenilmetanosulfonil)-1-[1,1-dimetil-2-oxo-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-il)-etilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico

EJEMPLO 4

{ [1- [1- (3-ciclopropil-1,2,4-oxadiazol-5-carbonil) -
propilcarbamoil] -2- (2-metilpropano-1-sulfonil) -
etil] -amida de ácido morfolino-4-carboxílico



5

Etapa 1

Una mezcla de ácido 3- (2-metilpropano-1-sulfonil) -2-
 [(morfolino-4-carbamoil) amino] -propiónico (163 mg, 0,507
 milimoles, Ejemplo de Referencia 5), hidrato de 1-
 10 hidroxibenzotriazol (75 mg, 0,558 milimoles), N-
 ciclohexilcarbodiimida-N'-metilpoliestireno (1,93 milimo-
 les/g, 289 mg, 0,558 milimoles) y de diclorometano (5,0
 ml) se agitó bajo nitrógeno a temperatura ambiente duran-
 te 10 minutos. Se añadió una solución de (S)-2-amino-1-
 15 (3-ciclopropil-1,2,4-oxadiazol-5-il) -butan-1-ol (0,507
 milimoles, Ejemplo de Referencia 10) en diclorometano (2
 ml) y la mezcla de reacción se agitó a temperatura am-
 biente bajo nitrógeno durante 4 horas. Se añadieron tris-
 (2-aminoetil) aminopoliestireno (3,40 milimoles/g, 447 mg,
 20 1,521 milimoles) y 3,0 ml adicionales de diclorometano y
 la mezcla de reacción se agitó a temperatura ambiente ba-
 jo nitrógeno durante la noche. La mezcla de reacción se
 filtró y la resina se lavó con diclorometano. Se evaporó
 hasta sequedad para dar (1-{1-[hidroxi-(3-ciclopropil)-
 25 [1,2,4]oxadiazol-2-il) -metil] -propilcarbamoil} -2-
 metilpropano-1-sulfoniletil) -amida ácido morfolino-4-
 carboxílico (240 mg) como una espuma de color amarillo
 claro. [LC/MS m/z=502 (M+H)].

Etapa 2

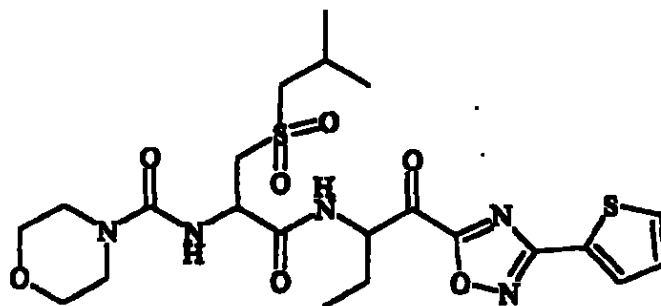
30 Se disolvió (1-{1-[hidroxi-(3-ciclopropil)-
 [1,2,4]oxadiazol-2-il) -metil] -propilcarbamoil} -2-
 metilpropano-1-sulfoniletil) -amida ácido morfolino-4-
 carboxílico (240 mg) en diclorometano (7,5 ml) y se agitó

a 0°C a medida que se añadían 2,5 equivalentes de peryo-
dinano de Dess-Martin (2,63 ml de una solución al 15% en
DCM). Se agitó bajo nitrógeno durante la noche a medida
que la reacción se calentaba hasta temperatura ambiente.
5 Se evaporó la mayoría del diclorometano y se disolvió el
residuo en acetato de etilo. Se lavó con solución de
NaS₂O₃, solución de NaHCO₃ y a continuación salmuera. La
fase orgánica se secó (Na₂SO₄), se filtró y se evaporó ba-
jo vacío hasta sequedad. El residuo se sometió a cromato-
10 grafía de desarrollo rápido sobre sílice eluyendo con un
gradiente de acetato de etilo al 5% en diclorometano has-
ta acetato de etilo al 95% en diclorometano para dar { [1-
[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-
propilcarbamoil]-2-(2-metilpropano-1-sulfonyl)-
15 etil]-amida de ácido morfolino-4-carboxílico, una mezcla
de diastereoisómeros, (60 mg, 24% global) como un sólido
blanco. ¹H NMR (CDCl₃, 300 MHz): δ [7,87 (d, J=6Hz), 7,79
(d, J=7Hz), 1H], [6,10 (d, J=6,5Hz), 6,06 (d, J=6,2Hz),
1H], 5,27-5,23 (m, 1H), 4,91-4,85 (m, 1H), 3,72-3,66 (m,
20 5H), 3,48-3,34 (m, 5H), 3,17-3,05 (m, 2H), 2,42-2,38 (m,
1H), 2,24-2,19 (m, 1H), 2,15-2,07 (m, 1H), 1,90-1,81 (m,
1H), 1,17-1,15 (m, 10H), 1,01 (t, J=7Hz, 3H). LC/MS m/z=500
(M+H)

25

EJEMPLO 5

{2-(2-metilpropano-1-sulfonyl)-1-[1-(3-tiofen-2-il-1,2,4-
oxadiazol-5-carbonil)-propilcarbamoil]-etil}-amida
de ácido morfolino-4-carboxílico



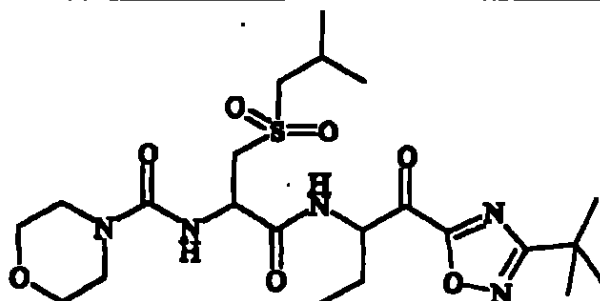
30

Al proceder de una manera similar a la descrita en
el Ejemplo 4 anteriormente, pero usando (S)-2-amino-1-(3-
tiofen-2-il-[1,2,4]oxadiazol-5-il)-butan-1-ol (Ejemplo de
Referencia 7) en lugar de (S)-2-amino-1-(3-ciclopropil-

1,2,4-oxadiazol-5-il)-butan-1-ol en la Etapa 1, se preparó {2-(2-metilpropano-1-sulfonil)-1-[1-(3-tiofen-2-il-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-etil]-amida de ácido morfolino-4-carboxílico, como una mezcla de diastereoisómeros (110 mg, 40% de rendimiento global) como un sólido blanco. ¹H NMR (CDCl₃, 300MHz): [7,97 (d, J=6,5Hz), 7,87 (d, J=6,5Hz), 1H], 7,91 (d, J=3,8Hz), 1H, 7,59 (d, J=5Hz, 1H), 7,22-7,21 (m, 1H), 6,11-6,05 (m, 1H), 5,35-5,32 (m, 1H), 4,93-4,87 (m, 1H), 3,76-3,60 (m, 5H), 3,54-3,35 (m, 5H), 3,18-3,04 (m, 2H), 2,43-2,36 (m, 1H), 2,21-2,15 (m, 1H), 2,00-1,93 (m, 1H), 1,29-1,14 (m, 6H), 1,08 (t, J=7,5Hz, 3H). LC/MS m/z=542 (M+H).

EJEMPLO 6

15 [1-[1-(3-terc-butil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-2-(2-metilpropano-1-sulfonil)-etil]-amida de ácido morfolino-4-carboxílico



Etapa 1

20 Se suspendió N-ciclohexilcarbodiimida-N'-metilpoliestireno (0,526 g, 1 milimol, carga 1,9 milimoles/g) en diclorometano (20 ml). Se añadieron ácido 3-(2-metilpropano-1-sulfonil)-2-[(morfolino-4-carbonil)-amino]-propiónico (0,242 g, 0,6 milimoles, Ejemplo de Referencia 5) y HOBt (0,114 g, 0,85 milimoles) y la mezcla de reacción se agitó durante 20 minutos. Se añadió (2S)-2-amino-1-(3-terc-butil-[1,2,4]oxadiazol-5-il)-butan-1-ol (0,107 g, 0,5 milimoles, Ejemplo de Referencia 6) y la agitación continuó durante 5 horas. Se añadió triamina Silicycle (1,27 g, 5 milimoles) y la mezcla se agitó durante 15 horas. La mezcla de reacción se filtró bajo succión y el filtrado se concentró para dar [1-{1-[(3-terc-butil-1,2,4-oxadiazol-5-il)-hidroximetil]-propilcarbamoil}-2-(2-metilpropano-1-sulfonil)-etil]-

amida de ácido morfolino-4-carboxílico (0,271 g), [LC/MS $m/z=518$ ($M+H^+$)].

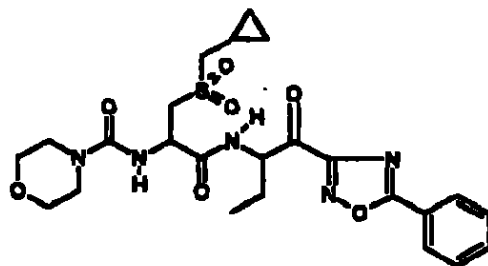
Etapa 2

Se disolvió [1-{1-[(3-terc-butil-1,2,4-oxadiazol-5-il)-hidroximetil]-propilcarbamoil}-2-(2-metilpropano-1-sulfonil)-etil]-amida de ácido morfolino-4-carboxílico (0,271 g) en diclorometano (10 ml) y se añadió peryodina-
 5 no de Dess-Martin (0,424 g, 1 milimol). La mezcla de reacción se agitó durante 2 horas y a continuación se vertió en una mezcla de solución de bicarbonato sódico saturado y tiosulfato sódico saturado (1/1, 50 ml). Las fases se separaron y la fase acuosa se extrajo con diclorometano. Las fases orgánicas combinadas se lavaron con solución de bicarbonato sódico y salmuera. La solución se se-
 10 có con sulfato magnésico y a continuación se concentró bajo vacío. El residuo se sometió a cromatografía de desarrollo rápido (gradiente de acetato de etilo al 5% en heptano a acetato de etilo al 75% en heptano) para dar [1-[1-(3-terc-butil-1,2,4-oxadiazol-5-carbonil)-
 20 propilcarbamoil]-2-(2-metilpropano-1-sulfonil)-etil]-amida de ácido morfolino-4-carboxílico, una mezcla de diastereoisómeros. ^1H NMR ($CDCl_3$, 300MHz): [7,87 (d, $J=6,5Hz$) 7,79 (d, $J=7Hz$), 1H], [6,11 (d, $J=6,5Hz$) 6,06 (d, $J=6,5Hz$), 1H], 5,38-5,30 (m, 1H), 4,92-4,13 (m, 1H),
 25 3,78-3,68 (m, 5H), 3,49-3,33 (m, 5H), 3,24-3,04 (m, 2H), 2,47-2,37 (m, 1H), 2,20-2,07 (m, 1H), 1,95-1,85 (m, 1H), 1,45 (s, 9H), 1,17 (d, $J=6,5Hz$, 6H), [1,04 (t, $J=7,5Hz$) 1,03 (t, $J=7,5Hz$), 3H]. [LC/MS $m/z=516$ ($M+H^+$)].

30

EJEMPLO 7

{2-Ciclopropilmetanosulfonil-1-[1-(5-fenil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico



Etapas 1

Una suspensión de ácido (R)-3-ciclopropilmetanosulfonil-2-[(morfolino-4-carbonil)-amino]-propiónico (110 mg, 0,344 milimoles, Ejemplo de Referencia 4) en cloruro de metileno (10 ml) se trató con N-ciclohexilcarbodiimida unida a PS (malla HL 200-400 reticulada con 2% de DVB) de Novabiochem (320 mg, 0,618 milimoles, 1,93 milimoles/g de carga) y se agitó a temperatura ambiente durante 10 minutos. Se añadió HOBt (43 mg, 0,319 milimoles) seguido por (S)-amino-1-(5-fenil-1,2,4-oxadiazol-3-il)-butan-1-ol (73 mg, 0,313 milimoles, Ejemplo de Referencia 12) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Se añadió PS-trisamina de Argonaut Technologies (413 mg, 1,549 milimoles, 3,75 milimoles/g de carga) y la reacción se agitó durante otras 3 horas. La mezcla se filtró y el filtrado se evaporó bajo presión reducida para dar (2-ciclopropilmetanosulfonil-1-{1-[hidroxi-(5-fenil-1,2,4-oxadiazol-3-il)-metil]-propilcarbamoil}-etil)-amida de ácido morfolino-4-carboxílico como un sólido naranja (183 mg). MS: 536 (MH⁺).

Etapas 2

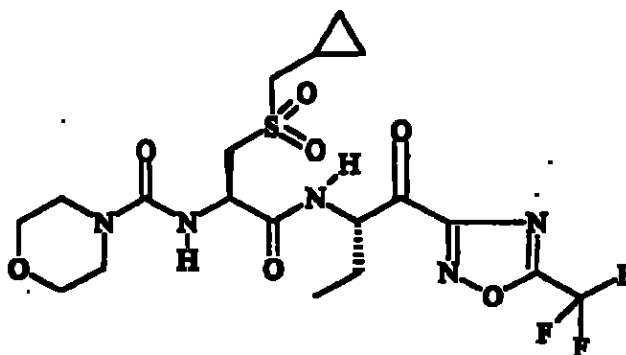
Se añadió peryodinano de Dess-Martin (200 mg, 0,47 milimoles) a una solución de (2-ciclopropilmetanosulfonil-1-{1-[hidroxi-(5-fenil-1,2,4-oxadiazol-3-il)-metil]-propilcarbamoil}-etil)-amida de ácido morfolino-4-carboxílico (183 mg, 0,34 milimoles) en cloruro de metileno (10 ml) y se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se lavó con una solución de Na₂S₂O₃ en agua (0,26M), bicarbonato saturado y agua, se secó sobre Na₂SO₄ y se concentró bajo presión reducida. El residuo se sometió a cromatografía de desarrollo rápido eluyendo con una mezcla de acetato de

etilo y heptano para dar {2-ciclopropilmetanosulfonil-1-[1-(5-fenil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico, una mezcla de diastereoisómeros, (45 mg) como un sólido blanquecino.

5 ^1H NMR (CDCl_3): 8,22 (d, $J = 7\text{Hz}$, 2H), 7,83, 7,75 (2xd, $J=7\text{Hz}$, 1H), 7,65 (m, 1H), 7,60-7,51 (m, 2H), 6,10-6,07 (2xd, $J = 7\text{Hz}$, 1H), 5,36 (m, 1H), 5,00-4,86 (m, 1H), 3,79 (m, 1H), 3,74-3,66 (m, 4H), 3,48 (m, 1H), 3,47-3,37 (m, 4H), 3,20-3,07 (m, 2H), 2,24-2,06 (m, 1H), 2,00-1,82 (m, 1H), 1,22 (m, 1H), 1,01 (t, $J = 7\text{Hz}$, 3H), 0,80-0,68 (m, 2H), 0,56-0,38 (m, 2H). MS: 534 (MH^+).

EJEMPLO 8

15 {(R)-2-ciclopropilmetanosulfonil-1-[(S)-1-(5-trifluorometil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico



Etapas 1

20 Una solución de ácido (R)-3-ciclopropilmetanosulfonil-2-[(morfolino-4-carbonil)-amino]-propiónico (266 mg, 0,83 milimoles, Ejemplo de Referencia 4) en dimetilformamida (10 ml) se trató sucesivamente con trifluoroacetato de (S)-2-amino-1-(5-trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol (282 mg, 0,83 milimoles, Ejemplo de Referencia 13), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (316 mg, 0,83 milimoles) y diisopropiletilamina (0,289 ml, 1,66 milimoles). La reacción se agitó

25 a temperatura ambiente durante la noche. El disolvente se evaporó bajo presión reducida. El residuo se recogió en acetato de etilo y se lavó con ácido clorhídrico 1N, solución acuosa saturada de bicarbonato y agua, se secó so-

30

bre Na_2SO_4 y el disolvente se evaporó bajo presión reducida para dar ((R)-2-ciclopropilmetanosulfonil-1-((S)-1-[hidroxi-(5-trifluorometil-1,2,4-oxadiazol-3-il)-metil]-propilcarbamoil)-etil)-amida de ácido morfolino-4-carboxílico como un aceite marrón (370 mg). MS: 528 (MH^+).

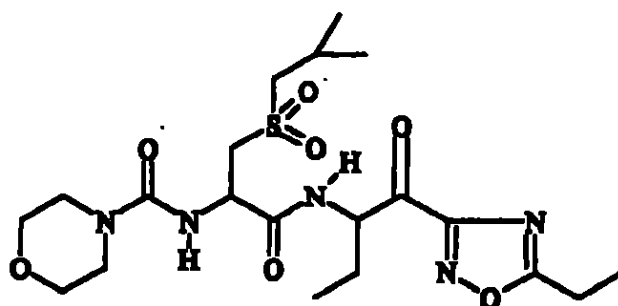
Etapa 2

Una solución de ((R)-2-ciclopropilmetanosulfonil-1-((S)-1-[hidroxi-(5-trifluorometil-1,2,4-oxadiazol-3-il)-metil]-propilcarbamoil)-etil)-amida de ácido morfolino-4-carboxílico (370 mg, 0,70 milimoles) en cloruro de metileno (10 ml) se trató con peryodinano de Dess-Martin (298 mg, 0,70 milimoles) y se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se lavó con una solución acuosa de $\text{Na}_2\text{S}_2\text{O}_3$ (0,26M), solución acuosa saturada de bicarbonato y agua, se secó sobre Na_2SO_4 y el disolvente se evaporó bajo presión reducida. El material en bruto se sometió a cromatografía de desarrollo rápido eluyendo con una mezcla de acetato de etilo y heptano. Se sometió a continuación adicionalmente a HPLC preparativa (usando un manipulador de líquidos Gilson 215 y una columna C18 de 10 micras MonoChrom - PN0504 - 100x212 de MetaChem), eluyendo con una mezcla de acetonitrilo y agua, que va desde 10% hasta 100% de acetonitrilo en agua, para dar ((R)-2-ciclopropilmetanosulfonil-1-((S)-1-(5-trifluorometil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil)-etil)-amida de ácido morfolino-4-carboxílico como un sólido blanco (9 mg). ^1H NMR (CDCl_3): 7,87 (d, $J=6\text{Hz}$, 1H), 5,99 (d, $J = 6\text{Hz}$, 1H), 5,16 (m, 1H), 4,87 (m, 1H), 3,74-3,66 (m, 1H), 3,44-3,36 (m, 5H), 3,14 (d, $J = 7\text{Hz}$, 2H), 2,20-2,02 (m, 1H), 1,98-1,78 (m, 1H), 1,21 (m, 1H), 1,02 (t, $J = 7\text{Hz}$, 3H), 0,82-0,70 (m, 2H), 0,57-0,40 (m, 2H). MS: 526 (MH^+).

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EJEMPLO 9

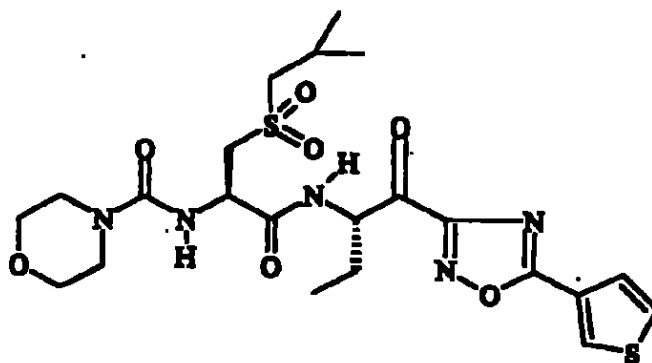
[(1-[(1-(5-Etil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-2-(2-metilpropano-1-sulfonil)-etil)-amida de ácido morfolino-4-carboxílico]



Al proceder de una manera similar al Ejemplo 8 anterior, pero usando ácido (R)-3-(2-metilpropano-1-sulfonyl)-2-[(morfolino-4-carbonil)-amino]-propiónico (Ejemplo de Referencia 5) en lugar de ácido (R)-3-ciclopropilmetanosulfonyl-2-[(morfolino-4-carbonil)-amino]-propiónico y (S)-2-amino-1-(5-etil-1,2,4-oxadiazol-3-il)-butan-1-ol (Ejemplo de Referencia 14) en lugar de trifluoroacetato de (S)-2-amino-1-(5-trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol, en la Etapa 1, se preparó [1-[1-(5-etil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-2-(2-metilpropano-1-sulfonyl)-etil]-amida de ácido morfolino-4-carboxílico, una mezcla de diastereoisómeros. ¹H NMR (CDCl₃): 7,81, 7,72 (2xd, J = 6,5Hz, 1H), 6,14-6,01 (2xd, J = 6,5Hz, 1H), 5,28 (m, 1H), 4,95-4,81 (m, 1H), 3,75-3,65 (m, 5H), 3,54-3,32 (m, 5H), 3,12 (m, 2H), 3,01 (q, J = 7,5Hz, 2H), 2,45-2,30 (m, 1H), 2,17-2,04 (m, 1H), 1,93-1,78 (m, 1H), 1,44 (t, J = 7,5Hz, 3H), 1,13 (d, J = 6,5Hz, 6H), 0,98 (t, J = 7,5Hz, 3H). MS: 488 (MH⁺).

EJEMPLO 10

{(R)-2-(2-Metilpropano-1-sulfonyl)-1-[(S)-1-(5-tiofen-3-il-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-etil}-amida



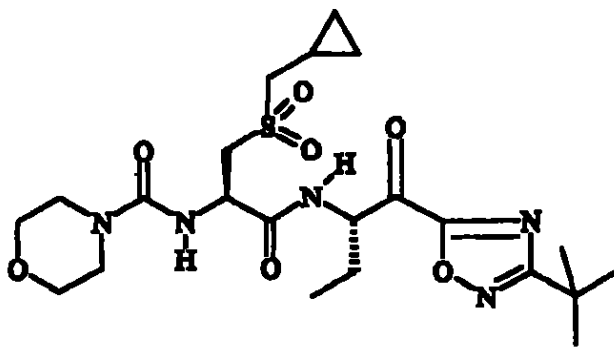
Al proceder de una manera similar al Ejemplo 8 ante-

rior, pero usando ácido (R)-3-(2-metilpropano-1-sulfonil)-2-[(morfolino-4-carbonil)-amino]-propiónico (Ejemplo de Referencia 5) en lugar de ácido (R)-3-ciclopropilmetanosulfonil-2-[(morfolino-4-carbonil)-amino]-propiónico y (S)-2-amino-1-(5-tiofen-3-il-1,2,4-oxadiazol-3-il)-butan-1-ol (Ejemplo de Referencia 16) en lugar de trifluoroacetato de (S)-2-amino-1-(5-trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol, se preparó { (R)-2-(2-metilpropano-1-sulfonil)-1-[(S)-1-(5-tiofen-3-il-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico. ¹H NMR (CDCl₃): 8,33 (dd, J= 3 y 1,1 Hz, 1H), 7,83 (d, J = 6,5Hz, 1H), 7,73 (dd, J=5,1 y 1,1 Hz, 1H), 7,48 (dd, J=5,0 y 3,0 Hz, 1H), 6,04 (d, J = 6,5Hz, 1H), 5,33 (m, 1H), 4,86 (m, 1H), 3,78-3,66 (m, 5H), 3,49-3,35 (m, 5H), 3,22-3,05 (m, 2H), 2,46-2,32 (m, 1H), 2,22-2,07 (m, 1H), 1,98-1,82 (m, 1H), 1,14 (d, J = 7Hz, 6H), 1,01 (t, J = 7,5Hz, 3H). MS : 542 (MH⁺).

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EJEMPLO 11

{ (R)-1-[(S)-1-(3-terc-butil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-2-ciclopropilmetanosulfoniletil}-amida de ácido morfolino-4-carboxílico



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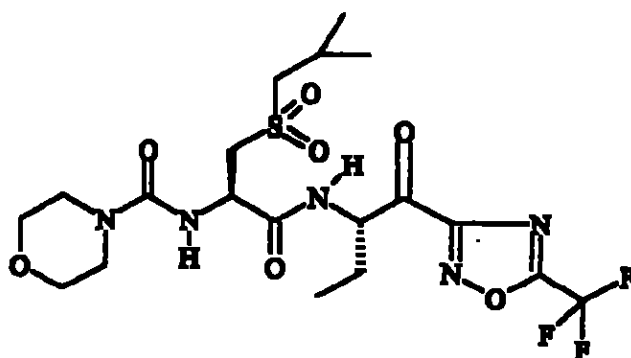
Al proceder de una manera similar al Ejemplo 8 anterior, pero usando (S)-2-amino-1-(3-terc-butil-1,2,4-oxadiazol-5-il)-butan-1-ol (Ejemplo de Referencia 6) en lugar de trifluoroacetato de (S)-2-amino-1-(5-trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol, se preparó { (R)-1-[(S)-1-(3-terc-butil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-2-ciclopropilmetanosulfoniletil}-amida de ácido morfolino-4-carboxílico. ¹H NMR (CDCl₃): 7,80 (d, J=6,5Hz, 1H), 6,02

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(d, J=6,5Hz, 1H), 5,31 (m, 1H), 4,88 (m, 1H), 3,82-3,66 (m, 5H), 3,50-3,36 (m, 5H), 3,15 (d, J = 7Hz, 2H), 2,20-2,04 (m, 1H), 1,95-1,80 (m, 1H), 1,42 (s, 9H), 1,26-1,15 (m, 1H), 1,00 (t, J=7,5Hz, 3H), 0,79-0,72 (m, 2H), 0,56-0,41 (m, 2H).
MS: 514 (MH⁺).

EJEMPLO 12

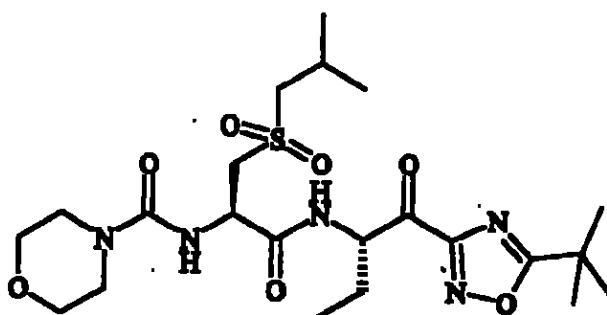
10 {(R)-2-(2-metilpropano-1-sulfonil)-1-[(S)-1-(5-trifluorometil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico



Al proceder de una manera similar al Ejemplo 8 anterior, pero usando ácido (R)-3-(2-metilpropano-1-sulfonil)-2-[(morfolino-4-carbonil)-amino]-propiónico (Ejemplo de Referencia 5) en lugar de ácido (R)-3-ciclopropilmetanosulfonil-2-[(morfolino-4-carbonil)-amino]-propiónico, se preparó {(R)-2-(2-metilpropano-1-sulfonil)-1-[(S)-1-(5-trifluorometil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico. ¹H NMR (CDCl₃): 7,90 (d, J=6Hz, 1H), 6,00 (d, J=6Hz, 1H), 5,17 (m, 1H), 4,83 (m, 1H), 3,73-3,62 (m, 5H), 3,45-3,36 (m, 5H), 3,13 (m, 2H), 2,45-2,32 (m, 1H), 2,18-2,04 (m, 1H), 1,96-1,80 (m, 1H), 1,14 (d, J=7Hz, 6H), 1,03 (t, J=7,5Hz, 3H). MS: 528 (MH⁺).

EJEMPLO 13

30 {(R)-1-[(S)-1-(5-terc-butil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-2-fenilmetanosulfoniletil}-amida de ácido morfolino-4-carboxílico

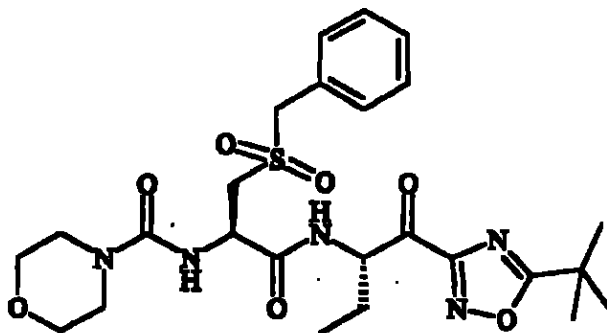


Al proceder de una manera similar al Ejemplo 8 anterior, pero usando ácido (R)-3-(2-metilpropano-1-sulfonil)-2-[(morfolino-4-carbonil)-amino]-propiónico
 5 (Ejemplo de Referencia 5) en lugar de ácido (R)-3-ciclopropilmetanosulfonil-2-[(morfolino-4-carbonil)-amino]-propiónico y (S)-2-amino-1-(5-terc-butyl-1,2,4-oxadiazol-3-il)-butan-1-ol (Ejemplo de Referencia 9) en lugar de trifluoroacetato de (S)-2-amino-1-(5-
 10 trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol, se preparó { (R)-1-[(S)-1-(5-terc-butyl-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-2-fenilmetanosulfoniletil}-amida de ácido morfolino-4-carboxílico. ^1H NMR (CDCl_3): 7,78 (d, $J=7\text{Hz}$, 1H), 6,04 (d, $J=6,5\text{Hz}$, 1H), 5,30 (m, 1H),
 15 4,85 (m, 1H), 3,76-3,64 (m, 5H), 3,48-3,34 (m, 5H), 3,13 (m, 2H), 2,47-2,31 (m, 1H), 2,19-2,02 (m, 1H), 1,95-1,80 (m, 1H), 1,48 (s, 9H), 1,14 (d, $J=6,5\text{Hz}$, 6H), 0,99 (t, $J=7,5\text{Hz}$, 3H). MS : 516 (MH^+).

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EJEMPLO 14

{ (R)-1-[(S)-1-(5-terc-butyl-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-2-fenilmetanosulfoniletil}-amida
de ácido morfolino-4-carboxílico



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Al proceder de una manera similar al Ejemplo 8 anterior, pero usando ácido (R)-2-[(morfolino-4-carbonil)-amino]-3-fenilmetanosulfonilpropiónico en lugar de ácido

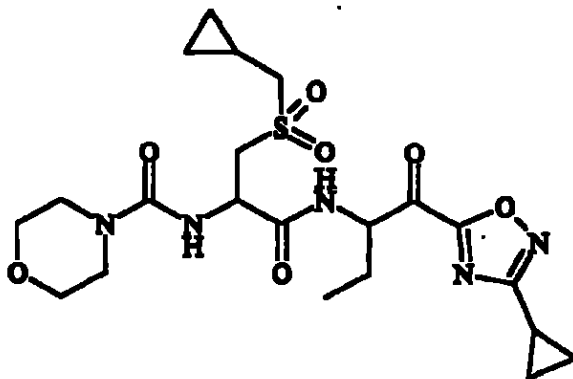
195

(R)-3-ciclopropilmetanosulfonil-2-[(morfolino-4-carbonil)-amino]-propiónico y (S)-2-amino-1-(5-terc-butyl-1,2,4-oxadiazol-3-il)-butan-1-ol (Ejemplo de Referencia 9) en lugar de trifluoroacetato de (S)-2-amino-1-
 5 (5-trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol, se preparó { (R)-1-[(S)-1-(5-terc-butyl-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-2-fenilmetanosulfoniletil}-amida de ácido morfolino-4-carboxílico. ¹H NMR (CDCl₃): 7,67 (d, J=7Hz, 1H), 7,50-7,34 (m, 5H), 6,01 (d, J=7Hz, 1H), 5,31 (m, 1H), 4,93 (m, 1H), 4,52 y 4,40 (2xd, J=14Hz, 2H), 3,76-3,64 (m, 5H), 3,46-3,26 (m, 5H), 2,20-2,06 (m, 1H), 1,94-1,78 (m, 1H), 1,48 (s, 9H), 0,98 (t, J=7,5Hz, 3H).
 MS: 550 (MH⁺).

15

EJEMPLO 15

{2-Ciclopropilmetanosulfonil-1-[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico



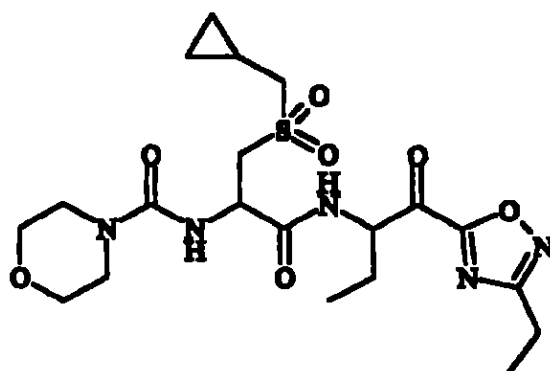
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Al proceder de una manera similar al Ejemplo 8 anterior, pero usando (S)-2-amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol (Ejemplo de Referencia 10) en lugar de trifluoroacetato de (S)-2-amino-1-(5-trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol, se preparó {2-ciclopropilmetanosulfonil-1-[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico, una mezcla de diastereoisómeros, como un sólido blanco. ¹H NMR (CDCl₃): δ
 30 7,83, 7,74 (d, J = 7Hz, 1H), 6,02 (d, J = 7Hz, 1H), 5,22 (m, 1H); 4,87 (m, 1H), 3,72 (m, 5H), 3,41 (m, 5H), 3,16 (d, 2H), 2,21 (m, 1H), 2,15 (m, 1H), 1,86 (m, 1H), 1,03-

1,24 (m, 5H), 0,99 (t, J = 7Hz, 3H), 0,76 (m, 2H), 0,48 (m, 2H). MS (M/Z) = 498 (M+H). LC Kromasil KR 100-10 Sil, 2504,6 mm de DI (90% de (heptano/THF/ACN// (220/60/14, v/v/v) tiempo de retención = 24,1 minutos, caudal 1,5 ml/minuto.

EJEMPLO 16

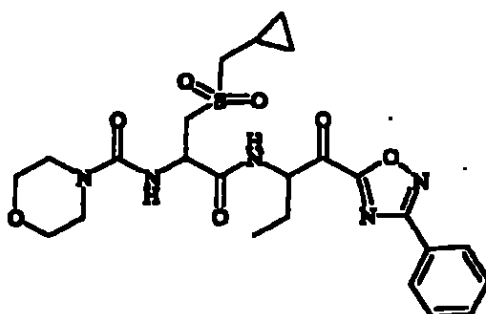
10 {2-Ciclopropilmetanosulfonil-1-[1-(3-etil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico



Al proceder de una manera similar al Ejemplo 8 anterior, pero usando trifluoroacetato de (S)-2-amino-1-(3-etil-1,2,4-oxadiazol-5-il)-butan-1-ol (Ejemplo de Referencia 14) en lugar de trifluoroacetato de (S)-2-amino-1-(5-trifluorometil-1,2,4-oxadiazol-3-il)-butan-1-ol, se preparó {2-ciclopropilmetanosulfonil-1-[1-(3-etil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico, como una mezcla 1:1 de diastereoisómeros. ¹H NMR (CDCl₃): δ 7,85 y 7,75 (2xd, J = 6Hz, 1H), 6,07 (m, 1H), 5,28 (m, 1H), 4,92 (m, 1H), 3,8-3,6 (m, 5H), 3,42 (m, 5H), 3,2-3,1 (m, 2H), 2,88 (q, J = 7Hz, 2H), 2,13 (m, 1H), 1,87 (m, 1H), 1,39 (t, J = 7Hz, 3H), 1,22 (m, 1H), 1,02 (t, J = 7Hz, 3H), 0,75 (m, 2H), 0,48 (m, 2H). MS m/z 486 (M+H).

EJEMPLO 17

30 {2-Ciclopropilmetanosulfonil-1-[1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico



Etapas 1

Se añadió ciclohexilcarbodiimida unida a poliestireno (2,0 eq., 0,82 milimoles, 432 mg) seguida por monohidrato de HOBt (1,7 eq., 0,70 milimoles, 94,2 mg) a una solución de ácido (R)-3-ciclopropilmetanosulfonil-2-
 5 [(morfolino-4-carbonil)-amino]-propiónico (130,5 mg, 0,41 milimoles) y di-isopropiletilamina (0,41 milimoles, 53,0 mg, 0,0714 ml) en diclorometano seco (6 ml). La mezcla se
 10 agitó a temperatura ambiente durante 15 minutos y a continuación se añadió el (2S)-2-amino-1-(3-fenil-[1,2,4]oxadiazol-5-il)-butan-1-ol (0,41 milimoles, 95 mg). La mezcla se agitó durante otras 64 horas y a continuación se añadió trisamina unida a sílice (5,0 eq., 2,05
 15 milimoles, 569,4 mg). La mezcla se agitó durante otras 2 horas y a continuación se filtró. El filtrado se concentró a vacío y se purificó sobre 12 g de gel de sílice, se eluyó con una mezcla de acetato de etilo y heptano (2:1 y a continuación 1:0) para proporcionar 182 mg (83%) del
 20 alcohol deseado. (LC/MS 100% M+1 536).

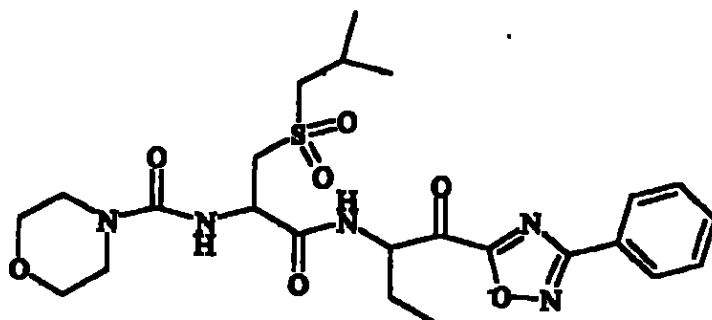
Etapas 2

Se añadió una solución de reactivo de Dess-Martin (solución al 15% en peso, 2 eq., 0,63 milimoles, 1,80 g) a una solución de alcohol (170 mg, 0,32 milimoles) en 5
 25 ml de diclorometano seco. La mezcla se agitó a temperatura ambiente durante 2 horas y a continuación se extinguió añadiendo una solución de $\text{Na}_2\text{S}_2\text{O}_3$ (4,0 eq., 1,28 milimoles, 202,4 mg) en bicarbonato sódico saturado (30 ml). La capa acuosa se extrajo dos veces con diclorometano (20
 30 ml). Las capas orgánicas se secaron (MgSO_4) y se concentraron a vacío. El residuo se purificó sobre 12 g de gel de sílice, eluyendo con una mezcla de acetato de etilo y heptano (1,5:1 y a continuación 2:1) para proporcionar {2-ciclopropilmetanosulfonil-1-[1-(3-fenil-1,2,4-

oxadiazol-5-carbonil)-propilcarbamoil]-etil}-amida de
 ácido morfolino-4-carboxílico, una mezcla 3:1 de diaste-
 reoisómeros (139 mg, 82%). ¹H NMR (CDCl₃): 8,15 (d, J =
 7,6 Hz, 2H), 8,0 (d, J = 6,6 Hz, 1H, principal), 7,9 (d,
 5 J = 7 Hz, 1H secundario), 7,6 (m, 3H), 6,08 (2xd, J = 6,5
 Hz, 1H), 5,4 (m, 1H), 4,95 (m, 1H), 3,8-3,69 (m, 5H),
 3,53-3,35 (m, 5H), 3,15 (m, 2H), 2,2 (m, 1H), 1,95 (m,
 1H), 1,2 (m, 1H), 1,06 (t, J= 7,5 Hz, 3H), 0,8 (m, 2H),
 0,5 (m, 2H). LC/MS muestra 35% M+1 534 así como 65% de
 10 hidrato M+18 552.

EJEMPLO 18

{2-(2-Metilpropano-1-sulfonil)-1-[1-(3-fenil-1,2,4-
oxadiazol-
 15 5-carbonil)-propilcarbamoil]-etil}-amida de
ácido morfolino-4-carboxílico

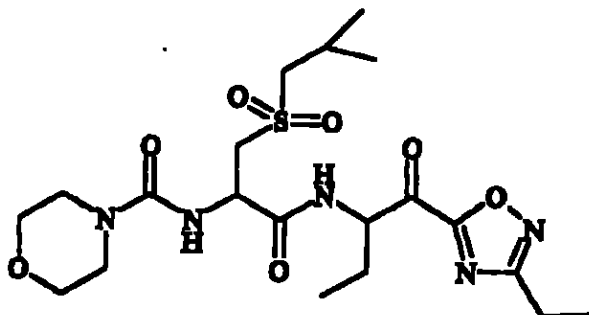


Al proceder de una manera similar al Ejemplo 17 an-
 terior, pero usando ácido (R)-3-(2-metilpropano-1-
 20 sulfonil)-2-[(morfolino-4-carbonil)-amino]-propiónico
 (Ejemplo de Referencia 5) en lugar de ácido (R)-3-
 ciclopropilmetanosulfonil-2-[(morfolino-4-carbonil)-
 amino]-propiónico, en la Etapa 1, se preparó {2-(2-
 metilpropano-1-sulfonil)-1-[1-(3-fenil-1,2,4-oxadiazol-5-
 25 carbonil)-propilcarbamoil]-etil}-amida de ácido morfoli-
 no-4-carboxílico. ¹H NMR (CDCl₃): 8,15 (dd, 2H), 7,95-7,85
 (2xd, 1H), 7,45 (m, 3H), 6,14-6,0 (2xd, 1H), 5,35 (m,
 1H), 4,90 (m, 1H), 3,70 (m, 5H), 3,40 (m, 5H), 3,2-3,0
 (m, 2H), 2,50-2,30 (m, 1H), 2,30-2,10 (m, 1H), 2,05-1,90
 30 (m, 1H), 1,10 (t, 6H), 1,05 (t, 3H). MS: 536 (MH⁺).

EJEMPLO 19

[1-[1-(3-Etil-1,2,4-oxadiazol-5-carbonil)-

propilcarbamoil]-2-(2-metilpropano-1-sulfonil)-etil}-
amida de
ácido morfolino-4-carboxílico



- 5 Se añadió PyBOP (1,1 eq., 200 mg) a una suspensión del ácido (R)-3-(2-metilpropano-1-sulfonil)-2-[(morfolino-4-carbonil)-amino]-propiónico (113 mg, 0,35 milimoles, Ejemplo de Referencia 5), (S)-2-amino-1-(3-etil-1,2,4-oxadiazol-5-il)-butan-1-ol (0,35 mg, 65 mg) y
- 10 diisopropiletilamina (1,2 eq., 0,073 ml) en diclorometano seco (7 ml). La mezcla se agitó a temperatura ambiente durante la noche y a continuación se extinguió con solución de NaHCO_3 . Los materiales volátiles se retiraron a vacío y la mezcla acuosa se extrajo en acetato de etilo.
- 15 Las capas orgánicas se secaron (Na_2SO_4) y a continuación se concentraron a vacío. El residuo se purificó sobre gel de sílice, eluyendo con acetato de etilo:diclorometano para proporcionar el alcohol deseado. Se añadió una solución de reactivo de Dess-Martin a una solución del alcohol en diclorometano seco (solución al 15% en peso, 2
- 20 eq.). La mezcla se agitó a temperatura ambiente durante 2 horas y a continuación se extinguió añadiendo una solución de $\text{Na}_2\text{S}_2\text{O}_3$ (4,0 eq.) en bicarbonato sódico saturado. La capa acuosa se extrajo con diclorometano. Las capas
- 25 orgánicas se secaron (MgSO_4) y se concentraron a vacío. El residuo se purificó sobre gel de sílice, se eluyó con una mezcla de acetato de etilo y diclorometano para proporcionar [1-[1-(3-etil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-2-(2-metilpropano-1-sulfonil)-etil]-
- 30 amida de ácido morfolino-4-carboxílico (98 mg, 57%).
- ^1H NMR (CDCl_3) mezcla 4:1 de isómeros 7,9 (d, $J = 6,4$ Hz, 1H, principal), 7,8 (d, $J = 6$ Hz, 1H, secundario), 6,1 (d, $J = 6,1$ Hz, 1H, secundario), 6,0 (d, $J = 6,1$ Hz, 1H, principal), 5,25 (m, 1H), 4,95 (m, 1H), 3,74-3,67 (m,

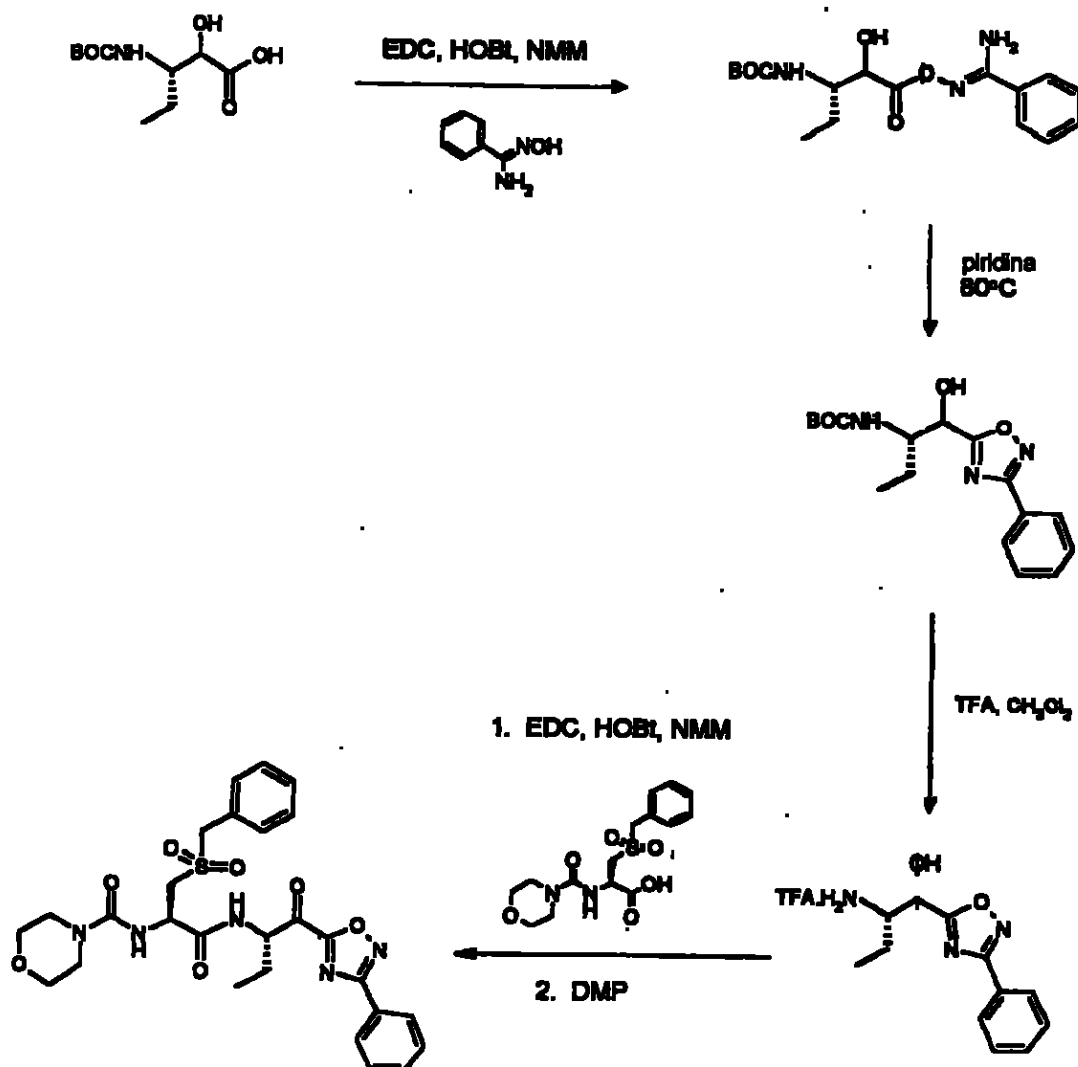
180

5H), 3,4 (m, 5H), 3,2 (m, 2H), 2,2 (m, 1H), 2,9 (q, J = 7,5 Hz, 2H), 2,4 (m, 1H), 2,2 (m, 1H), 1,9 (m, 1H), 1,4 (t, J= 7,6 Hz, 3H), 1,2 (d, J = 6,6 Hz, 6H), 1,0 (t, J = 7,4 Hz, 3H). LC/MS muestra 52% M+1 588 así como 37% de 5 hidrato M+18 506.

EJEMPLO 20

{2-Fenilmetanosulfonil-1-[1-(3-fenil-[1,2,4]-oxadiazol-5-carbonil)-propilcarbamoil]-etil}-amida de
ácido morfolino-4-carboxílico

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Etapa 1

Se combinó ácido 3-terc-butoxicarbonilamino-2-hidroxipentanoico (500 mg, 2,14 milimoles) con EDC (600 mg, 3,14 milimoles), HOBT (600 mg, 3,92 milimoles) y N-hidroxibenzamidina (292 mg, 2,14 milimoles). Se añadió diclorometano (10 ml) y a continuación 4-metilmorfolina (1 ml). La mezcla se agitó a temperatura ambiente durante

16 horas. Después de la dilución con acetato de etilo (200 ml), la solución se lavó con agua (300 ml), solución acuosa saturada de NaHCO_3 y salmuera, a continuación se secó con MgSO_4 y a continuación se evaporó bajo vacío.

5 Etapa 2

El producto de la etapa 1 se disolvió en piridina (10 ml) y la solución se calentó a 80°C durante 15 horas. La piridina se evaporó bajo vacío y el residuo se sometió a cromatografía de desarrollo rápido sobre gel de sílice (eluyente: acetato de etilo) para dar éster terc-butílico de ácido {1-[hidroxi-(3-fenil-[1,2,4]oxadiazol-5-il)-metil]-propil}-carbámico (290 mg, 0,83 milimoles).

Etapa 3

Se disolvió éster terc-butílico de ácido {1-[hidroxi-(3-fenil-[1,2,4]oxadiazol-5-il)-metil]-propil}-carbámico (145 mg, 0,41 milimoles) en CH_2Cl_2 (4 ml) y se añadió TFA (4 ml). Después de agitar durante 1 hora, la mezcla se evaporó hasta sequedad.

Etapa 4

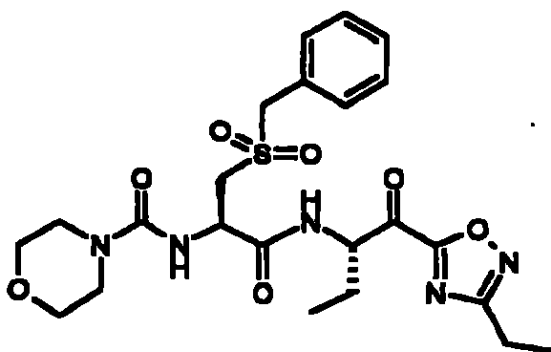
Se añadieron ácido 2-[(morfolino-4-carbonil)-amino]-3-fenilmetanosulfonil-propiónico (200 mg, 0,56 milimoles), EDC (200 mg, 1,05 milimoles), HOBt (200 mg, 1,30 milimoles) y CH_2Cl_2 (4 ml) al producto de la etapa 3 anterior. Se añadió 4-metilmorfolina (0,5 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Después de la dilución con acetato de etilo (150 ml), la solución se lavó con agua (30 ml), solución acuosa saturada de NaHCO_3 y salmuera, a continuación se secó con MgSO_4 y a continuación se evaporó bajo vacío. El residuo se disolvió en diclorometano seco (10 ml) y se añadió peryodinano de Dess-Martin (500 mg, 1,2 milimoles). Después de agitar a temperatura ambiente durante 1 hora, la mezcla se diluyó con acetato de etilo (150 ml) y la mezcla se trató con solución de $\text{Na}_2\text{S}_2\text{O}_3$ 0,26M en NaHCO_3 acuoso saturado. La fase orgánica se lavó con NaHCO_3 acuoso saturado y salmuera, a continuación se secó con MgSO_4 y a continuación se evaporó. El residuo se sometió a cromatografía de desarrollo rápido sobre gel de sílice (hexano/acetato de etilo 1:2 hasta acetato de etilo) para dar {2-fenilmetanosulfonil-1-[1-(3-fenil-[1,2,4]-oxadiazol-5-

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carbonil)-propilcarbamoil]-etil}-amida de ácido morfoli-
no-4-carboxílico (40 mg, 0,07 milimoles). ^1H NMR (DMSO):
8,79 (d, $J=6$ Hz, 1H), 8,04 (d, $J=8$ Hz, 2H), 7,65-7,53 (m,
3H), 7,41-7,32 (m, 5H), 7,02 (d, $J=8$ Hz, 1H), 4,96-4,90
5 (m, 1H), 4,73-4,66 (m, 1H), 4,45 (s, 2H), 3,57-3,19 (m,
10H), 2,04-1,95 (m, 1H), 1,80-1,71 (m, 1H), 0,95 (t,
 $J=7,6$ Hz, 3H). MS: (M^++1) 570.

EJEMPLO 21

10 {1-[1-(3-Etil-[1,2,4]-oxadiazol-5-carbonil)-
propilcarbamoil]-2-fenilmetanosulfoniletil}-amida de áci-
do
morfolino-4-carboxílico

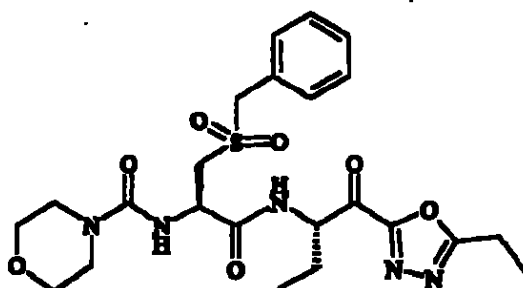


15 Al proceder de una manera similar a la descrita en
el Ejemplo 20 anterior, pero usando N-
hidroxipropionamidina en lugar de N-hidroxibencimidazol
en la etapa 1, se preparó {1-[1-(3-etil-[1,2,4]-
oxadiazol-5-carbonil)-propilcarbamoil]-2-
20 fenilmetanosulfoniletil}-amida de ácido morfolino-4-
carboxílico. ^1H NMR (DMSO): 8,73 (d, $J=6,4$ Hz, 1H), 7,40-
7,33 (m, 5H), 7,01 (d, $J=8$ Hz, 1H), 4,88-4,82 (m, 1H),
4,71-4,65 (m, 1H), 4,47 (s, 2H), 3,57-3,24 (m, 10H), 2,81
(q, $J=7,6$ Hz, 2H), 1,99-1,88 (m, 1H), 1,75-1,64 (m, 1H),
25 1,26 (t, $J=7,6$ Hz, 3H), 0,92 (t, $J=7,6$ Hz, 3H). MS: (M^++1)
522.

EJEMPLO 22

30 {1-[1-(5-Etil-[1,3,4]-oxadiazol-2-carbonil)-
propilcarbamoil]-2-fenilmetanosulfoniletil}-amida de áci-
do morfolino-4-carboxílico

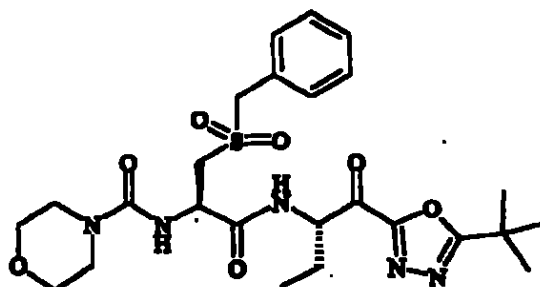
183



Al proceder de una manera similar a la descrita en el Ejemplo 1, se preparó {1-[1-(5-etil-[1,3,4]-oxadiazol-2-carbonil)-propilcarbamoil]-2-fenilmetanosulfoniletil}-
 5 amida de ácido morfolino-4-carboxílico. ^1H NMR (DMSO): 8,64 (d, $J=6,8\text{Hz}$, 1H), 7,42-7,32 (m, 5H), 7,02 (d, $J=8,8\text{Hz}$, 1H), 5,04-4,96 (m, 1H), 4,62-4,72 (m, 1H), 4,47 (s, 2H), 3,64-3,24 (m, 10H), 2,96 (q, $J=7,6\text{Hz}$, 2H), 1,89-1,79 (m, 1H), 1,72-1,60 (m, 1H), 1,38-1,16 (m, 2H), 1,29 (t, $J=7,6\text{Hz}$, 3H), 0,89 (t, $J=7,2\text{Hz}$, 3H). MS: (M^++1) 536.

EJEMPLO 23

{1-[1-(5-Terc-butil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-2-fenilmetanosulfoniletil}-amida
 15 de ácido morfolino-4-carboxílico



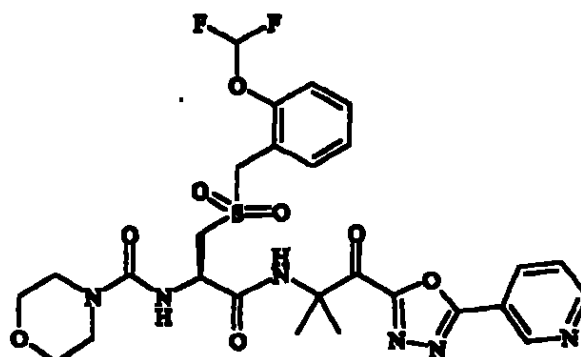
Al proceder de una manera similar a la descrita en el Ejemplo 1, se preparó {1-[1-(5-terc-butil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-2-fenilmetanosulfoniletil}-amida de ácido morfolino-4-carboxílico. ^1H NMR (DMSO): 8,63 (d, $J=5,2\text{Hz}$, 1H), 7,26-7,46 (m, 5H), 7,02 (d, $J=8,8\text{Hz}$, 1H), 4,98-5,08 (m, 1H), 4,62-4,72 (m, 1H), 4,48 (s, 2H), 3,24-3,64 (m, 10H), 1,76-1,92 (m, 1H), 1,58-1,74 (m, 1H), 1,39 (s, 9H), 1,16-
 20 1,38 (m, 2H), 0,89 (t, $J=7,6\text{Hz}$, 3H). MS: (M^++1) 564.

EJEMPLO 24

{2-(2-Difluorometoxifenilmetanosulfonil)-1-[1,1-dimetil-2-oxo-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-il)-

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etilcarbamoil]-etil)-amida de ácido morfolino-4-
carboxílico



Al proceder de una manera similar a la descrita en
5 el Ejemplo 2, se preparó {2-(2-Difluorometoxifenilmetanosulfonil)-1-[1,1-dimetil-2-oxo-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-il)-etilcarbamoil]-etil}-amida de ácido morfolino-4-carboxílico ¹H NMR (DMSO-d): 9,33 (1H, s, NH), 9,22 (1H, dd, J=1,74Hz), 8,84
10 (1H, dd), 8,43 (1H, dt), 7,68 (1H, dd, J=1,75Hz, J=6,7Hz), 7,42 (2H, m), 7,3-7,2 (2H, m), 7,07 (1H, t, J=74,1Hz), 6,76 (1H, d, J=8,6Hz, NH), 4,7-4,6 (1H, m), 4,45 (2H, s), 3,5-3,4 (4H, m), 3,38-3,2 (2H, m), 3,2-3,1 (4H, m), 1,52 (6H, s). MS: 635,6 (M-1), 637,4 (M+1).

15

EJEMPLO 25

Ensayo de Catepsina S

Se prepararon soluciones de compuestos de prueba en concentraciones variables en 10 µl de dimetilsulfóxido
20 (DMSO) y a continuación se diluyeron en tampón de ensayo (40 µl, que comprendía: MES, 50 mM (pH 6,5); EDTA, 2,5 mM y NaCl, 100 mM). Se añadió catepsina S humana (0,158 picomoles en 25 µl de tampón de ensayo) a las diluciones. Las soluciones de ensayo se mezclaron durante 5-10 segun-
25 dos en una placa agitadora, se cubrieron y se incubaron durante 30 minutos a temperatura ambiente. Se añadió Z-Val-Val-Arg-AMC (9 nanomoles en 25 µl de tampón de ensayo) a las soluciones de ensayo y la hidrólisis fue seguida espectrofotométricamente a λ 460 nm durante 5 minutos.
30 Las constantes de inhibición aparentes (K_i) se calcularon a partir de las curvas de progreso enzimático usando modelos matemáticos estándar.

EJEMPLO 26

Ensayo de Catepsina B

Se prepararon soluciones de compuestos de prueba en concentraciones variables en 10 μ l de dimetilsulfóxido (DMSO) y a continuación se diluyeron en tampón de ensayo (40 μ l, que comprendía: ácido N,N-bis(2-hidroxietil)-2-aminoetanosulfónico (BES), 50 mM (pH 6); monolaurato de polioxietilensorbitán, 0,05%; y ditioneitol (DTT), 2,5 mM). Se añadió a las diluciones catepsina B humana (0,025 picomoles en 25 μ l de tampón de ensayo). Las soluciones de ensayo se mezclaron durante 5-10 segundos en una placa agitadora, se cubrieron y se incubaron durante 30 minutos a temperatura ambiente. Se añadió Z-FR-AMC (20 nanomoles en 25 μ l de tampón de ensayo) a las soluciones de ensayo y la hidrólisis fue seguida espectrofotométricamente a λ 460 nm durante 5 minutos. Las constantes de inhibición aparentes (K_i) se calcularon a partir de las curvas de progreso enzimático usando modelos matemáticos estándar.

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EJEMPLO 27

Ensayo de Catepsina K

Se prepararon soluciones de compuestos de prueba en concentraciones variables en 10 μ l de dimetilsulfóxido (DMSO) y a continuación se diluyeron en tampón de ensayo (40 μ l, que comprende: MES, 50 mM (pH 5,5); EDTA, 2,5 mM y DTT, 2,5 mM). Se añadió catepsina K humana (0,0906 picomoles en 25 μ l de tampón de ensayo) a las diluciones. Las soluciones de ensayo se mezclaron durante 5-10 segundos en una placa agitadora, se cubrieron y se incubaron durante 30 minutos a temperatura ambiente. Se añadió Z-Phe-Arg-AMC (4 nanomoles en 25 μ l de tampón de ensayo) a las soluciones de ensayo y la hidrólisis se siguió espectrofotométricamente a λ 460 nm durante 5 minutos. Las constantes de inhibición aparentes (K_i) se calcularon a partir de las curvas de progreso enzimático usando modelos matemáticos estándar.

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EJEMPLO 28

Ensayo de Catepsina L

Se prepararon soluciones de compuestos de prueba en

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concentraciones variables en 10 μ l de dimetilsulfóxido (DMSO) y a continuación se diluyeron en tampón de ensayo (40 μ l, que comprende: MES, 50 mM (pH 5,5); EDTA, 2,5 mM y DTT, 2,5 mM). Se añadió catepsina L humana (0,05 picomoles en 25 μ l de tampón de ensayo) a las diluciones. Las soluciones de ensayo se mezclaron durante 5-10 segundos en una placa agitadora, se cubrieron y se incubaron durante 30 minutos a temperatura ambiente. Se añadió Z-Phe-Arg-AMC (1 nanomol en 25 μ l de tampón de ensayo) a las soluciones de ensayo y la hidrólisis se siguió espectrofotométricamente a λ 460 nm durante 5 minutos. Las constantes de inhibición aparentes (K_i) se calcularon a partir de las curvas de progreso enzimático usando modelos matemáticos estándar.

Los compuestos de la invención se probaron de acuerdo con los ensayos descritos anteriormente con respecto a la inhibición de proteasas y se observó que exhibían actividad inhibidora de catepsina S selectiva. Por ejemplo, se encontró que los compuestos de la invención inhibían la actividad de la proteasa catepsina S a concentraciones que son menos de 50 veces menores que las concentraciones requeridas para producir una inhibición equiactiva de actividad de la proteasa catepsina K. Las constantes de inhibición aparentes (K_i) para los compuestos de la invención, contra catepsina S, estaban en el intervalo de aproximadamente 10^{-10} M a aproximadamente 10^{-7} M.

EJEMPLO 29

Formulaciones Farmacéuticas Representativas que Contienen un Compuesto de Fórmula I

FORMULACIÓN ORAL

Compuesto de Fórmula I	10-100 mg
Monohidrato de Ácido Cítrico	105 mg
Hidróxido Sódico	18 mg
Saboreante	
Agua	c.s. hasta 100 ml

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FORMULACIÓN INTRAVENOSA

Compuesto de Fórmula I	0,1-10 mg
Monohidrato de Dextrosa	c.s. para hacerla isotónica
Monohidrato de Ácido Cítrico	1,05 mg
Hidróxido Sódico	0,18 mg
Agua para Inyección	c.s. hasta 1,0 ml

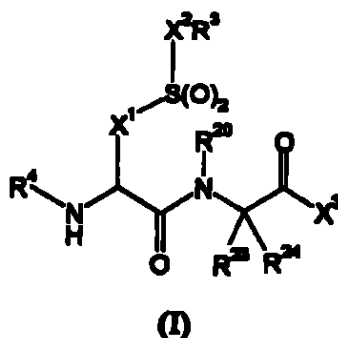
FORMULACIÓN DE TABLETA

Compuesto de Fórmula I	1%
Celulosa Microcristalina	73%
Ácido Esteárico	25%
Sílice Coloidal	1%

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REIVINDICACIONES

1. Un compuesto de Fórmula (I):



5 en la que:

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

R^3 es $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$, $-CR^7=NR^8$ o cicloalquilo(C_{3-12}), en donde R^5 y R^6 son independientemente hidrógeno o 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 cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), arilo(C_{6-12}), hetero-arilo(C_{5-12}), bicicloarilo(C_{9-12}) o hetero-bicicloarilo(C_{8-12}) y R^7 y R^8 junto con los átomos a los que R^7 y R^8 están unidos forman hetero-cicloalquilo(C_{3-12}), hetero-arilo(C_{5-12}) o hetero-bicicloarilo(C_{8-12}), en donde R^3 opcionalmente está sustituido por 1 a 5 radicales seleccionados independientemente de un grupo que consiste en alquilo(C_{1-4}), ciano, halo, alquilo(C_{1-4}) sustituido por halo, 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 donde X^4 es un enlace o alquileno(C_{1-2}), R^9 en cada presencia es independientemente hidrógeno, alquilo(C_{1-3}) o alquilo(C_{1-3}) sustituido por halo y R^{10} es alquilo(C_{1-3}) o alquilo(C_{1-3}) sustituido por halo; y

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

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alquilo(C₀₋₃), bicicloaril(C₉₋₁₂)-alquilo(C₀₋₃) o hetero-
 bicicloaril(C₉₋₁₂)-alquilo(C₀₋₃) y R¹⁴ en cada presencia es
 independientemente hidrógeno o alquilo(C₁₋₆), o (ii) ci-
 cloalquil(C₃₋₁₂)-alquilo(C₀₋₃), hetero-cicloalquil(C₅₋₁₂)-
 5 alquilo(C₀₋₃), aril(C₆₋₁₂)-alquilo(C₀₋₃), hetero-aril(C₅₋₁₂)-
 alquilo(C₀₋₃), bicicloaril(C₉₋₁₂)-alquilo(C₀₋₃) o hetero-
 bicicloaril(C₉₋₁₂)-alquilo(C₀₋₃) o (iii) cicloalquil(C₃₋₆)-
 alquilo(C₀₋₃), hetero-cicloalquil(C₅₋₆)-alquilo(C₀₋₃), fe-
 nil-alquilo(C₀₋₃) o hetero-aril(C₅₋₆)-alquilo(C₀₋₃) susti-
 10 tuido por -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 donde X⁶ es un enla-
 ce o metileno,
 15 R¹⁵ es cicloalquil(C₃₋₆)-alquilo(C₀₋₃), hetero-
 cicloalquil(C₅₋₆)-alquilo(C₀₋₃), fenil-alquilo(C₀₋₃) o hete-
 ro-aril(C₅₋₆)-alquilo(C₀₋₃) y R¹⁶ es hidrógeno o alquilo(C<sub>1-
 6</sub>); en donde R⁴ contiene además opcionalmente 1 a 5 susti-
 tuyentes que cuando están presentes dentro de un sistema
 20 anular alicíclico o aromático son radicales seleccionados
 independientemente de un grupo que consiste en alquilo(C<sub>1-
 6</sub>), alquilideno(C₁₋₆), ciano, halo, nitro, alquilo(C₁₋₃)
 sustituido por halo, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -
 X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -
 25 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 cuando
 están presentes dentro de un resto alifático son radica-
 les seleccionados independientemente del grupo que con-
 siste en ciano, halo, nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -
 30 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 donde X⁶ es un enlace o alquile-
 35 no(C₁₋₆), R¹⁷ en cada presencia es independientemente hi-
 drógeno, alquilo(C₁₋₆) o alquilo(C₁₋₃) sustituido por halo
 y R¹⁸ es alquilo(C₁₋₆) o alquilo(C₁₋₃) sustituido por halo;

R²⁰ se selecciona del grupo que consiste en hidróge-
 40 no, alquilo(C₁₋₆), cicloalquil(C₃₋₁₂)-alquilo(C₀₋₆), hetero-

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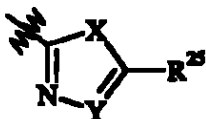
cicloalquil (C₃₋₁₂)-alquilo (C₀₋₆), aril (C₆₋₁₂)-alquilo (C₀₋₆) o hetero-aril (C₅₋₁₂)-alquilo (C₀₋₆);

R²³ se selecciona de hidrógeno, alquilo (C₁₋₆), alcoxi-
alquilo (C₁₋₃), halo-alquilo (C₁₋₃), cicloalquil (C₃₋₁₂)-
5 alquilo (C₀₋₆), hetero-cicloalquil (C₅₋₁₂)-alquilo (C₀₋₆),
aril (C₆₋₁₂)-alquilo (C₀₋₆) y hetero-aril (C₅₋₁₂)-alquilo (C₀₋₆)
opcionalmente sustituido con amino, -NHC(O)R¹⁵ o -R¹⁵ en
donde R¹⁵ es como se describe anteriormente; y

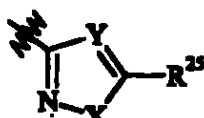
R²⁴ se selecciona de hidrógeno o alquilo (C₁₋₆); o

10 R²³ y R²⁴ tomados junto con el átomo de carbono al
que tanto R²³ como R²⁴ están unidos forman cicloalquile-
no (C₃₋₈) o heterocicloalquilenos (C₃₋₈);

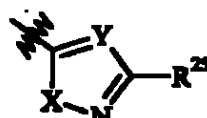
X³ se selecciona del grupo (a), (b) o (c);



(a)



(b)



(c)

15 en donde X es O e Y es N;

R²⁵ se selecciona de hidrógeno, alquilo (C₁₋₆), ci-
cloalquil (C₃₋₁₂)-alquilo (C₀₋₆), hetero-cicloalquil (C₃₋₁₂)-
alquilo (C₀₋₆), aril (C₆₋₁₂)-alquilo (C₀₋₆), hetero-aril (C₅₋₁₂)-
alquilo (C₀₋₆), -X⁴NHR¹⁵, -X⁴S(O)₂R²⁶ o -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷
20 en donde R¹⁵, R¹⁷ y X⁴ son como se describen anteriormente;

R²⁶ se selecciona del grupo que consiste en hidróge-
no, alquilo (C₁₋₆), cicloalquil (C₃₋₁₂)-alquilo (C₀₋₆), hetero-
cicloalquil (C₅₋₁₂)-alquilo (C₀₋₆), aril (C₆₋₁₂)-alquilo (C₀₋₆),
hetero-aril (C₅₋₁₂)-alquilo (C₀₋₆), bicicloaril (C₉₋₁₂)-
25 alquilo (C₀₋₃) y hetero-bicicloaril (C₈₋₁₂)-alquilo (C₀₋₃);

en la que R²⁵ contiene además opcionalmente 1 a 5
sustituyentes que cuando están presentes dentro de un
sistema anular alicíclico o aromático son radicales se-
leccionados independientemente de un grupo que consiste
30 en alquilo (C₁₋₆), alquilideno (C₁₋₆), ciano, halo, nitro,
alquilo (C₁₋₃) sustituido por halo, -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,
35 -X⁶OP(O)(OR⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ y
-X⁶C(O)R¹⁸ y cuando están presentes dentro de un resto

alifático son radicales seleccionados independientemente de un grupo que consiste en ciano, halo, nitro, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$, $-NR^{17}C(NR^{17})NR^{17}R^{17}$, $-OR^{17}$, $-SR^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-P(O)(OR^{17})OR^{17}$, $-OP(O)(OR^{17})OR^{17}$, $-NR^{17}C(O)R^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$ y $-C(O)R^{18}$, en donde R^{15} , R^{17} , R^{18} y X^6 son como se describen anteriormente; o

un derivado de dicho compuesto seleccionado del grupo que consiste en derivados de N-óxido, derivados de profármaco, derivados protegidos, isómeros y mezclas de isómeros de dicho compuesto, o una sal o un solvato farmacéuticamente aceptable de dicho compuesto o dicho derivado.

2. Un compuesto de acuerdo con la reivindicación 1, en el que:

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

R^3 es $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$, $-CR^7=NR^8$ o cicloalquilo(C_{3-12}), en donde R^5 y R^6 son independientemente hidrógeno o 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 cicloalquilo(C_{3-12}), arilo(C_{6-12}), hetero-arilo(C_{5-12}) o bicicloarilo(C_{9-12}), R^7 y R^8 junto con los átomos a los que R^7 y R^8 están unidos forman hetero-arilo(C_{5-12});

en donde dentro de R^3 , cualquier grupo cicloalquilo, arilo, heteroarilo o bicicloarilo puede estar sustituido con 1 a 5 radicales seleccionados independientemente de un grupo que consiste en alquilo(C_{1-4}), ciano, halo, alquilo(C_{1-4}) sustituido por halo, $-X^4OR^9$ y $-X^4C(O)OR^9$, en donde X^4 es un enlace o alquileno(C_{1-2}) y R^9 en cada presencia es independientemente alquilo(C_{1-3}) y alquilo(C_{1-3}) sustituido por halo;

R^4 es $-C(O)X^5R^{11}$ o $-S(O)_2X^5R^{11}$, en donde X^5 es un enlace, $-O-$ o $-NR^{12}-$, en donde R^{12} es hidrógeno o alquilo(C_{1-6}) y R^{11} es (i) alquilo(C_{1-6}) o (ii) hetero-cicloalquil(C_{5-12})-alquilo(C_{0-3}), aril(C_{6-12})-alquilo(C_{0-3}), hetero-aril(C_{5-12})-alquilo(C_{0-3}), bicicloaril(C_{9-12})-alquilo(C_{0-3}) o hetero-bicicloaril(C_{8-12})-alquilo(C_{0-3}) o (iii) hetero-cicloalquil(C_{5-6})-alquilo(C_{0-3}) o fenil-alquilo(C_{0-3}) susti-

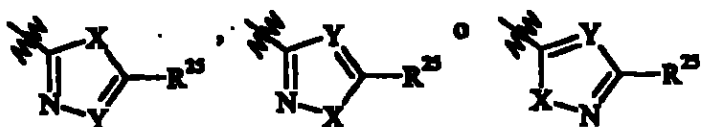
tuido por $-X^6OR^{15}$, $-X^6C(O)R^{15}$ o $-X^6NR^{16}C(O)OR^{16}$, en donde X^6 es un enlace o metileno, R^{15} es fenil-alquilo(C_{0-3}) o hetero-aril(C_{5-6})-alquilo(C_{0-3}) y R^{16} es hidrógeno o alquilo(C_{1-6});

5 en donde dentro de R^4 , cualquier sistema anular alicíclico o aromático puede estar sustituido con 1 a 5 radicales seleccionados independientemente de un grupo que consiste en alquilo(C_{1-6}), halo, $-X^6NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6C(O)OR^{17}$, $-X^6NC(O)R^{16}$ y $-X^6C(O)R^{18}$, en donde R^{17} en cada
10 presencia es independientemente hidrógeno, alquilo(C_{1-6}) o alquilo(C_{1-3}) sustituido por halo y R^{18} es alquilo(C_{1-6}) o alquilo(C_{1-3}) sustituido por halo;

R^{20} es hidrógeno o alquilo(C_{1-6});

R^{23} es alquilo(C_{1-6}) o aril(C_{6-12})-alquilo(C_{0-6});

R^{24} es hidrógeno o alquilo(C_{1-6});

20 X^3 es , en

25 donde X es O, Y es N y R^{25} se selecciona de hidrógeno, halo-alquilo(C_{1-3}), alquilo(C_{1-6}), cicloalquil(C_{3-12})-alquilo(C_{0-6}), aril(C_{6-12})-alquilo(C_{0-6}) o hetero-aril(C_{5-13})-alquilo(C_{0-6}), en donde dentro de R^{25} , cualquier sistema anular alicíclico o aromático puede estar sustituido con
30 1 a 5 radicales seleccionados independientemente de alquilo(C_{1-6}) y alquilo(C_{1-3}) sustituido por halo; o

un derivado de dicho compuesto seleccionado del grupo que consiste en derivados de N-óxido, derivados de profármaco, derivados protegidos, isómeros y mezclas de
35 isómeros de dicho compuesto; o una sal o un solvato farmacéuticamente aceptable de dicho compuesto o dicho derivado.

3. Un compuesto de acuerdo con la reivindicación 2,
40 en el que R^3 se selecciona del grupo que consiste en fenilo, piridin-2-ilo, piridin-3-ilo, piridin-4-ilo, vinilo, 2-difluorometoxifenilo, 1-oxipiridin-2-ilo, 4-metoxifenilo, 4-metilfenilo, 2-metilfenilo, 4-clorofenilo, 3,5-dimetilfenilo, 4-trifluorometilfenilo,
45 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, 5 4-bromofenilo, 2-fluoro-3-clorofenilo, 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, 4-10 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-trifluorometilfenilo, 2-fluoro-4-trifluorometilfenilo, 2-15 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, 2,6-20 diclorofenilo, 4-carboxifenilo, ciclohexilo, ciclopropilo, isopropilo, tiofen-2-ilo, 5-clorotiofen-2-ilo y 3,5-dimetilisoxazol-4-ilo; o

un derivado de dicho compuesto seleccionado del grupo que consiste en derivados de N-óxido, derivados de 25 profármaco, derivados protegidos, isómeros y mezclas de isómeros de dicho compuesto; o una sal o un solvato farmacéuticamente aceptable de dicho compuesto o dicho derivado.

30 4. Un compuesto de acuerdo con la reivindicación 3, en el que R⁴ es benzoílo, morfolino-4-carbonilo, acetilo, furano-3-carbonilo, 2-metoxibenzoílo, 3-metoxibenzoílo, naftaleno-2-carbonilo, benzo[1,3]dioxol-5-carbonilo, 3-piridin-3-il-acrilóilo, benzofurano-2-carbonilo, furano-35 2-carbonilo, terc-butoxicarbonilo, bifenil-4-carbonilo, quinolino-2-carbonilo, quinolino-3-carbonilo, 3-acetilbenzoílo, 4-fenoxibenzoílo, 3-hidroxibenzoílo, 4-hidroxibenzoílo, piridino-3-carbonilo, 3-(terc-butoxicarbonilaminometil)-benzoílo, éster terc-butílico 40 de ácido 4-carbonilpiperacina-1-carboxílico, éster etílico

de ácido 4-carbonilpiperacin-1-carboxílico, 4-(furano-2-carbonil)-piperacin-1-carbonilo, piridino-4-carbonilo, 1-oxipiridino-4-carbonilo, 1-oxipiridino-3-carbonilo, tiofeno-2-carbonilo, tiofeno-3-carbonilo, 4-benzoilbenzoílo, 5 5-metiltiofeno-2-carbonilo, 3-clorotiofeno-2-carbonilo, 3-bromotiofeno-2-carbonilo, 4-clorobenzoílo, 3-fluoro-4-metoxibenzoílo, 4-metoxibenzoílo, 4-trifluorometoxibenzoílo, 3,4-difluorobenzoílo, 4-fluorobenzoílo, 3,4-dimetoxibenzoílo, 3-metilbenzoílo, 4-bromobenzoílo, 4-trifluorometilbenzoílo, 3-benzoilbenzoílo, ciclopentanocarbonilo, benzo[b]tiofeno-2-carbonilo, 3-clorobenzo[b]tiofeno-2-carbonilo, benceno-sulfonilo, naftaleno-2-sulfonilo, 5-metiltiofeno-2-sulfonilo, tiofeno-2-sulfonilo, éster formamilmetílico, 15 4-metilpentanoílo, éster formamilisobutílico, éster formamilmonoalílico, éster formamilisopropílico, N,N-dimetilformamilo, N-isopropilformamilo, N-piridin-4-ilformamilo, N-piridin-3-ilformamilo, 3-fenilacrilóílo, 1H-indol-5-carbonilo, piridino-2-carbonilo, piracino-2-carbonilo, 3-hidroxipiridino-2-carbonilo, 2-aminopiridino-3-carbonilo, 2-hidroxipiridino-3-carbonilo, 6-aminopiridino-3-carbonilo, 6-hidroxipiridino-3-carbonilo, piridacino-4-carbonilo, 3-fenoxibenzoílo y 1-oxo-1,3-dihidroisoindol-2-carbonilo; o 25 un derivado de dicho compuesto seleccionado del grupo que consiste en derivados de N-óxido, derivados de profármaco, derivados protegidos, isómeros y mezclas de isómeros de dicho compuesto; o una sal o un solvato farmacéuticamente aceptable de dicho compuesto o dicho derivado. 30 vado.

5. Un compuesto de acuerdo con la reivindicación 4, en el que R²⁵ es terc-butilo, ciclopropilo, etilo, fenilo, piracinilo, piridacinilo, piridinilo, tienilo o trifluorometilo; o 35 rometilo; o

un derivado de dicho compuesto seleccionado del grupo que consiste en derivados de N-óxido, derivados de profármaco, derivados protegidos, isómeros y mezclas de isómeros de dicho compuesto; o una sal o un solvato farmacéuticamente aceptable de dicho compuesto o dicho derivado. 40 macéuticamente aceptable de dicho compuesto o dicho derivado.

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vado.

6. Un compuesto de acuerdo con la reivindicación 2, en el que R^3 es $-CR^5=CHR^6$ en donde R^5 y R^6 junto con los átomos a los que R^5 y R^6 están unidos forman arilo(C_6-12), opcionalmente sustituido por 1 a 5 radicales seleccionados independientemente de un grupo que consiste en alquilo(C_{1-4}), ciano, halo, alquilo(C_{1-4}) sustituido por halo, $-X^4OR^9$ y $-X^4C(O)OR^9$, en donde R^9 es un enlace o alquilo(C_{1-2}), R^9 en cada presencia es independientemente alquilo(C_{1-3}) o alquilo(C_{1-3}) sustituido por halo.

7. Un compuesto de acuerdo con la reivindicación 6, en el que R^3 es fenilo o 2-difluorometoxifenilo.

15

8. Un compuesto de acuerdo con la reivindicación 2, en el que R^3 es $-CR^5(CR^6_3)_2$ en donde R^5 es hidrógeno y R^6 es alquilo(C_{1-4}).

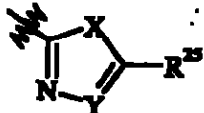
9. Un compuesto de acuerdo con la reivindicación 8, en el que R^3 es $-CH(CH_3)_2$.

10. Un compuesto de acuerdo con la reivindicación 2, en el que R^3 cicloalquilo(C_{3-12}).

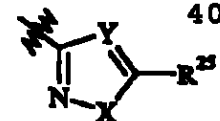
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11. Un compuesto de acuerdo con la reivindicación 10, en el que R^3 es ciclopropilo.

12. Un compuesto de acuerdo con la reivindicación 5, en el que R^3 es



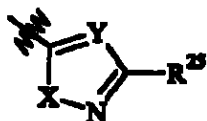
13. Un compuesto de acuerdo con la reivindicación 5, en el que R^3 es



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19b

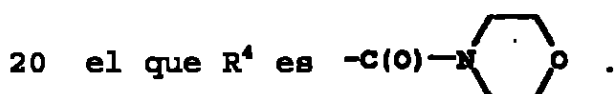
14. Un compuesto de acuerdo con la reivindicación 5, en el que R^3 es



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15. El compuesto de acuerdo con la reivindicación 2, en el que R^4 es $-C(O)X^5R^{11}$ en donde X^5 es un enlace y R^{11} es hetero-cicloalquil (C_{5-12})-alquilo (C_{0-3}).

15 16. El compuesto de acuerdo con la reivindicación 15, en



17. El compuesto de acuerdo con la reivindicación 2, en el que R^{20} es hidrógeno, R^{23} es alquilo (C_{1-6}), R^{24} es hidrógeno, R^{25} es terc-butilo, ciclopropilo, etilo, fenilo, piridin-3-ilo, piridin-4-ilo, tien-3-ilo o trifluorometilo.

18. El compuesto de acuerdo con la reivindicación 1, seleccionado de grupo que consiste en:

- {2-(2-difluorometoxifenilmetanosulfonil-1-[1,1-dimetil-2-oxo-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-il)-etilcarbamoil]-etil)-amida de ácido morfolino-4-carboxílico;
- {2-fenilmetanosulfonil-1-[1-(5-fenil-[1,3,4]oxadiazol-2-carbonil)pentilcarbamoil]etil}amida de ácido morfolino-4-carboxílico;
- {2-(2-difluorometoxifenilmetanosulfonil-1-[1-(5-piridin-3-il-[1,3,4]oxadiazol-2-carbonil)pentilcarbamoil]etil}amida de ácido morfolino-4-carboxílico;
- [1-[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-2-(2-metilpropano-1-sulfonil)-etil]amida de ácido morfolino-4-carboxílico;
- {2-(2-metilpropano-1-sulfonil)-1-[1-(3-tiofen-2-il-1,2,4-oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido

- morfolino-4-carboxílico;
 [1-[1-(3-terc-butil-1,2,4-oxadiazol-5-carbonil)-
 propilcarbamoil]-2-(2-metilpropano-1-sulfonil)etil]amida
 de ácido morfolino-4-carboxílico;
- 5 {2-ciclopropilmetanosulfonil-1-[1-(5-fenil-1,2,4-
 oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido
 morfolino-4-carboxílico;
 {(R)-2-ciclopropilmetanosulfonil-1-[(S)-1-(5-
 trifluorometil-1,2,4-oxadiazol-3-
 10 carbonil)propilcarbamoil]etil}amida de ácido morfolino-4-
 carboxílico;
 [(1)-[(1-(5-etil-1,2,4-oxadiazol-3-
 carbonil)propilcarbamoil]-2-(2-metilpropano-1-
 sulfonil)etil]amida de ácido morfolino-4-carboxílico;
- 15 {(R)-2-(2-metilpropano-1-sulfonil)-1-[(S)-1-(5-tiofen-3-
 il-1,2,4-oxadiazol-3-carbonil)propilcarbamoil]etil}amida;
 {(R)-1-[(S)-1-(3-terc-butil-1,2,4-oxadiazol-5-carbonil)-
 propilcarbamoil]-2-ciclopropilmetanosulfoniletil}amida de
 ácido morfolino-4-carboxílico;
- 20 {(R)-2-(2-metilpropano-1-sulfonil)-1-[(S)-1-(5-
 trifluorometil-1,2,4-oxadiazol-3-
 carbonil)propilcarbamoil]-etil}amida de ácido morfolino-
 4-carboxílico;
 {(R)-1-[(S)-1-(5-terc-butil-1,2,4-oxadiazol-3-carbonil)-
 25 propilcarbamoil]-2-fenilmetanosulfoniletil}amida de ácido
 morfolino-4-carboxílico;
 {(R)-1-[(S)-1-(5-terc-butil-1,2,4-oxadiazol-3-carbonil)-
 propilcarbamoil]-2-fenilmetanosulfoniletil}amida de ácido
 morfolino-4-carboxílico;
- 30 {2-ciclopropilmetanosulfonil-1-[1-(3-ciclopropil-1,2,4-
 oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido
 morfolino-4-carboxílico;
 {2-ciclopropilmetanosulfonil-1-[1-(3-etil-1,2,4-
 oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido
 35 morfolino-4-carboxílico;
 {2-ciclopropilmetanosulfonil-1-[1-(3-fenil-1,2,4-
 oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido
 morfolino-4-carboxílico;
 {2-(2-metilpropano-1-sulfonil)-1-[1-(3-fenil-1,2,4-
 40 oxadiazol-5-carbonil)propilcarbamoil]etil}amida de ácido

morfolino-4-carboxílico;
 [1-[1-(3-etil-1,2,4-oxadiazol-5-
 carbonil)propilcarbamoil]-2-(2-metilpropano-1-
 sulfonil)etil}amida de ácido morfolino-4-carboxílico;
 5 {2-fenilmetanosulfonil-1-[1-(3-fenil-[1,2,4]-oxadiazol-5-
 carbonil)propilcarbamoil]etil}amida de ácido morfolino-4-
 carboxílico;
 {1-[1-(3-etil-[1,2,4]-oxadiazol-5-
 carbonil)propilcarbamoil]-2-fenilmetanosulfoniletil}amida
 10 de ácido morfolino-4-carboxílico;
 {1-[1-(5-etil-[1,3,4]-oxadiazol-2-
 carbonil)propilcarbamoil]-2-fenilmetanosulfoniletil}amida
 de ácido morfolino-4-carboxílico;
 {1-[1-(5-terc-butil[1,3,4]-oxadiazol-2-carbonil)-
 15 propilcarbamoil]-2-fenilmetanosulfoniletil}amida de ácido
 morfolino-4-carboxílico; y
 {2-(2-difluorometoxifenilmetanosulfonil)-1-[1,1-dimetil-
 2-oxo-2-(5-piridin-3-il-[1,3,4]oxadiazol-2-
 il)etilcarbamoil]-etil}amida de ácido morfolino-4-
 20 carboxílico.

19. Un derivado seleccionado del grupo que consiste
 en derivados de N-óxido, derivados de profármaco, deriva-
 dos protegidos, isómeros y mezclas de isómeros de un com-
 25 puesto de acuerdo con la reivindicación 18, o una sal o
 un solvato farmacéuticamente aceptable de un compuesto de
 acuerdo con la reivindicación 18 o dicho derivado.

20. Una composición farmacéutica que comprende una
 30 cantidad terapéuticamente eficaz de un compuesto de
 acuerdo con la reivindicación 1 en combinación con un ex-
 cipiente farmacéuticamente aceptable.

21. Un método para tratar una enfermedad en un ani-
 35 mal en el que la inhibición de catepsina S puede preve-
 nir, inhibir o mejorar la patología y/o la sintomatología
 de la enfermedad, método que comprende administrar al
 animal una cantidad terapéuticamente eficaz de compuesto
 de acuerdo con la reivindicación 1 o uno de sus derivados
 40 de N-óxido o isómeros individuales o mezclas de isómeros;

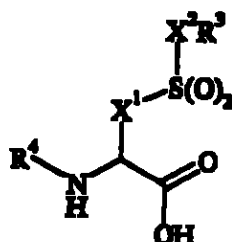
o una sal o un solvato farmacéuticamente aceptable de tal compuesto y sus derivados de N-óxido, derivados de pro-fármaco, derivados protegidos, isómeros individuales y mezclas de isómeros.

5

22. Un método para fabricar una composición farma-céutica que usa un compuesto de acuerdo con la reivindi-cación 1 para tratar una enfermedad en un animal en el que la actividad de catepsina S contribuye a la patología
10 y/o la sintomatología de la enfermedad.

23. Un procedimiento para preparar un compuesto de acuerdo con la reivindicación 1, al:

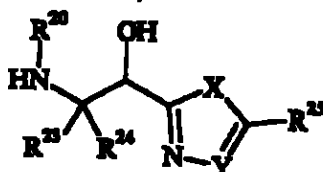
(A) hacer reaccionar un compuesto de Fórmula (II):



(II)

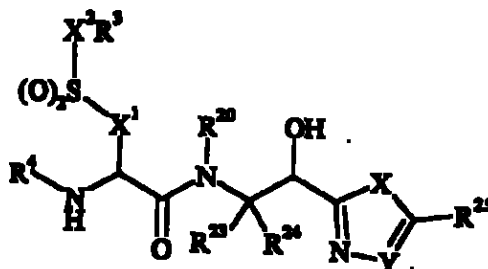
15

con un compuesto de la Fórmula (III):



(III)

seguido por la oxidación de la β-hidroxiamida (IV) resultante:

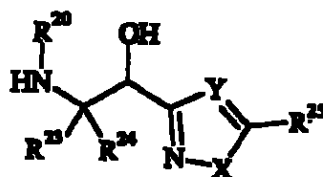


(IV)

20

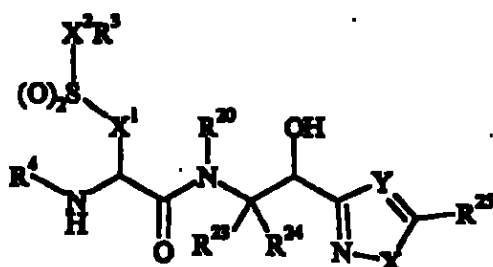
y a continuación oxidar dicha β-hidroxiamida para proporcionar un compuesto de acuerdo con la reivin-dicación 1; o

- (B) hacer reaccionar un compuesto de Fórmula (II) con un compuesto de la Fórmula (VI):



(VI)

para proporcionar una β-hidroxiamida (VIII):



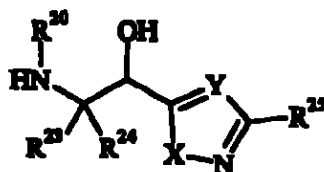
(VIII)

5

y a continuación oxidar dicha β-hidroxiamida para proporcionar un compuesto de acuerdo con la reivindicación 1; o

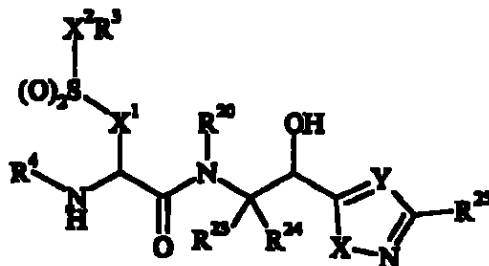
- (C) hacer reaccionar un compuesto de Fórmula (II) con un compuesto de la Fórmula (VII):

10



(VII)

para proporcionar una β-hidroxiamida (IX):



(IX)

y a continuación oxidar dicha β-hidroxiamida para proporcionar un compuesto de acuerdo con la reivin-

15

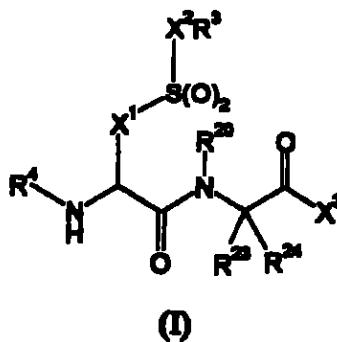
dicación 1;

en donde X , Y , X^1 , X^2 , R^3 , R^4 , R^{20} , R^{23} , R^{24} y R^{25} son iguales que en la Fórmula (I) definida en la reivindicación 1.

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RESUMEN

La presente invención se refiere a nuevos inhibidores de catepsina S selectivos, a sus sales farmacéuticamente aceptables y N-óxidos, a sus usos como agentes terapéuticos y a los métodos para su elaboración.



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PCT REQUEST

US20010197WO

Original (for SUBMISSION) - printed on 14.11.2002 11:05:59 AM

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	US20010197WO
I	Title of invention	NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN S 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	AXYS PHARMACEUTICALS, INC.
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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US20010197WO

Original (for SUBMISSION) - printed on 14.11.2002 11:05:59 AM

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)	LI, Jiayao
III-2-5	Address:	442 Milton Avenue Apartment 3 San Bruno, CA 94066 United States of America
III-2-6	State of nationality	CN
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)	ALDOUS, David, J.
III-3-5	Address:	268 Gates Avenue Gillette, NJ 07933 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)	THURAIRATNAM, Sukanthini
III-4-5	Address:	6 Smoke Rise Lane Bedminster, NJ 07921 United States of America
III-4-6	State of nationality	GB
III-4-7	State of residence	US
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	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

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US20010197WO

Original (for SUBMISSION) - printed on 14.11.2002 11:05:59 AM

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.; DUBBERLEY, F., Aaron; 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
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

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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 November 2001 (14.11.2001)
VI-1-2	Number	60/332,605
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	-

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VII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to the international application of which it forms a part (if filing declaration with application). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VII-4-1 -1	Prior applications:	60/332,605, US, 14 November 2001 (14.11.2001)

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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:	LI, Jiayao
VIII-4-1 -1-2	Residence: (city and either US State, if applicable, or country)	San Bruno, California
VIII-4-1 -1-3	Mailing address:	442 Milton Avenue Apartment 3 San Bruno, California 94066
VIII-4-1 -1-4	Citizenship:	CN
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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PCT REQUEST

US20010197WO

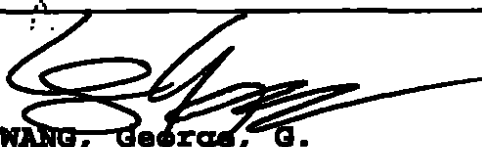
Original (for SUBMISSION) - printed on 14.11.2002 11:05:59 AM

VIII-4-1 -2-1	Name:	ALDOUS, David, J.
VIII-4-1 -2-2	Residence: (city and either US State, if applicable, or country)	Gillette, New Jersey
VIII-4-1 -2-3	Mailing address:	268 Gates Avenue Gillette, NJ 07933
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:	THURAIRATNAM, Sukanthini
VIII-4-1 -3-2	Residence: (city and either US State, if applicable, or country)	Bedminster, New Jersey
VIII-4-1 -3-3	Mailing address:	6 Smoke Rise Lane Bedminster, NJ 07921
VIII-4-1 -3-4	Citizenship:	GB
VIII-4-1 -3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -3-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

PCT REQUEST

US20010187WO

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	8	-
IX-2	Description	96	-
IX-3	Claims	13	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	118	
	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	
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PCT (ANNEX - FEE CALCULATION SHEET)

US20010197WO

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

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.06.2002)
0-8	Applicant's or agent's file reference	US20010197WO
2	Applicant	AVENTIS PHARMACEUTICALS INC., et al.
12	Calculation of prescribed fees	fee amount/multiplier Total amounts (USD)
12-1	Transmittal fee T	⇒ 240
12-2-1	Search fee S	⇒ 866
12-2-2	International search to be carried out by	EP
12-3	International fee	
	Basic fee	
	(first 30 sheets) b1	407
12-4	Remaining sheets	88
12-5	Additional amount (X)	9
12-6	Total additional amount b2	792
12-7	b1 + b2 = B	1,199
12-8	Designation fees	
	Number of designations contained in international application	94
12-9	Number of designation fees payable (maximum 5)	5
12-10	Amount of designation fee (X)	88
12-11	Total designation fees D	440
12-12	PCT-EASY fee reduction R	-125
12-13	Total international fee (B+D-R) I	⇒ 1,514
12-14	Fee for priority document	
	Number of priority documents requested	1
12-15	Fee per document (X)	15
12-16	Total priority document fee P	⇒ 15
12-17	TOTAL FEES PAYABLE (T+S+H+P)	⇒ 2,635
12-18	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions	
	The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)
12-20-1	Authorization to charge the total fees indicated above.	✓

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PCT (ANNEX - FEE CALCULATION SHEET)

US20010197WO

Original (for SUBMISSION) - printed on 14.11.2002 11:05:59 AM

12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	18-1982
12-22	Date	14 November 2002 (14.11.2002)
12-23	Name and signature	WANG, George, G. 

VALIDATION LOG AND REMARKS

13-2-6	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
13-2-7	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
		Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Fees	Green? Please confirm that fee schedule utilized is the latest available
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

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0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 92.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.06.2002)
1	The undersigned applicant(s)	AVENTIS PHARMACEUTICALS INC.; AXYS PHARMACEUTICALS, INC.; LI, Jiayao; ALDOUS, David, J.; THURAIRATNAM, Sukanthini
1-1-1	hereby appoints (appoint) the following person	WANG, George, G.; BARNEY, Charlotte, L.; COPPOLA, William, C.; DAHLING, Gerald, V.; DARKES, Paul, R.; DOLAN, Peter, L.; DUBBERLEY, F., Aaron; 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. AVENTIS PHARMACEUTICALS INC. P. O. Box 6800 Route 202-206 Bridgewater, NJ 08807-0800 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	In connection with the international application identified below:	
1-4-1	Title of the invention	NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN S INHIBITORS
1-4-2	Applicant's or agent's file reference	US20010197WO
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

PCT POWER OF ATTORNEY

2/2

U820010197WO

Printed on 14.11.2002 10:48:34 AM

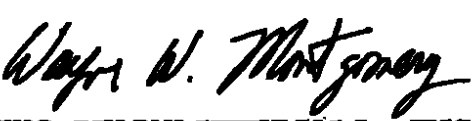
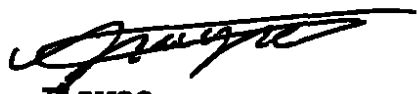
2-1	Signature of applicant	
2-1-1	Name	AVENTIS PHARMACEUTICALS INC.
2-1-2	Name of signatory	Ross J. Oehler
2-1-3	Capacity	Assistant Secretary
2-2	Signature of applicant	
2-2-1	Name	AXYS PHARMACEUTICALS, INC.
2-2-2	Name of signatory	Wayne W. Montgomery
2-2-3	Capacity	Vice President
2-3	Signature of applicant	
2-3-1	Name	LI, Jiayao
2-4	Signature of applicant	
2-4-1	Name	ALDOUS, David, J.
2-5	Signature of applicant	
2-5-1	Name	THURAIRATNAM, Sukanthini
3	Date	14 November 2002 (14.11.2002)

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PCT POWER OF ATTORNEY

Printed on 14.11.2002 10:48:34 AM

US20010187WO

2-1	Signature of applicant	
2-1-1	Name	AVENTIS PHARMACEUTICALS INC.
2-1-2	Name of signatory	Ross J. Oehler
2-1-3	Capacity	Assistant Secretary
2-2	Signature of applicant	
2-2-1	Name	AXYS PHARMACEUTICALS, INC.
2-2-2	Name of signatory	Wayne W. Montgomery
2-2-3	Capacity	Vice President
2-3	Signature of applicant	
2-3-1	Name	LI, Jiayao
2-4	Signature of applicant	
2-4-1	Name	ALDOUS, David, J.
2-5	Signature of applicant	
2-5-1	Name	THURAIRATNAM, Sukanthini
3	Date	14 November 2002 (14.11.2002)

216

PCT POWER OF ATTORNEY

US20010197WO

Printed on 14.11.2002 10:48:34 AM

2-1	Signature of applicant	
2-1-1	Name	AVENTIS PHARMACEUTICALS INC.
2-1-2	Name of signatory	Ross J. Oehler
2-1-3	Capacity	Assistant Secretary
2-2	Signature of applicant	
2-2-1	Name	AXYS PHARMACEUTICALS, INC.
2-2-2	Name of signatory	Wayne W. Montgomery
2-2-3	Capacity	Vice President
2-3	Signature of applicant	
2-3-1	Name	LI, Jiayao
2-4	Signature of applicant	<i>David J. Aldous</i> 01/06/03
2-4-1	Name	ALDOUS, David, J.
2-5	Signature of applicant	<i>Sukanthini Thurai</i> 01/06/03
2-5-1	Name	THURAIRATNAM, Sukanthini
3	Date	14 November 2002 (14.11.2002)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference USAV2001/0197 WO PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/418)	
International application No. PCT/US 02/38398	International filing date (day/month/year) 14.11.2002	Priority date (day/month/year) 14.11.2001	
International Patent Classification (IPC) or both national classification and IPC G07D271/08, G07D271/06			
Applicant AVENTIS PHARMACEUTICALS INC. et al.			
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 5 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 70.18 and Section 807 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.			
3. This report contains indications relating to the following items: I ☒ Basis of the opinion 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 Rule 96.2(a)(i) 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 21.05.2003		Date of completion of this report 08.03.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office - Glashöfer Str. 103 D-10885 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840		Authorized Officer Telephone No. +49 30 25901- 337  	

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. **PCT/US 02/36396****1. Basis of the report**

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-96 as originally filed

Claims, Numbers

1-23 as originally filed.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination 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.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(e)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REP RT**International application No. **PCT/US 0236396****III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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

☐ the entire international application,

☒ claims Nos. 21

because:

☒ the said international application, or the said claims Nos. 21 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

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

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

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

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Yes: Claims	1-23
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-23
Industrial applicability (IA)	Yes: Claims	1-20,22,23
	No: Claims	

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARYInternational application No. **PCT/US 02/36398****EXAMINATION REPORT - SEPARATE SHEET****Re Item III****Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 21 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 87.1(iv) PCT. Consequently, the International Examination Authority fully concurs with the objection put forward by the International Search Authority and no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1: WO-A-0119808

D2: US-B-6255453

Novelty

The document D1 discloses cathepsin B protease inhibitors which structurally differ from the compounds of the present claim 1 in that they have a cyano group in lieu of the present group $-C(O)X^*$ wherein X^* stands for an oxadiazole residue (see page 1, lines 5-21; page 2, formula I; Examples 1-4; claims 1, 9).

The document D2 discloses cathepsin B protease inhibitors which structurally differ from the compounds of the present claim 1 in that they lack the sulfonyl group-containing side chain $-X^1S(O)_2X^2R^3$ and in that one amino group forms part of a pyrrolidine moiety (see column 1, lines 15-55; column 2, formula (I); column 3, lines 40-61; claim 1).

Consequently, novelty has to be acknowledged for the subject-matter of the present independent claims 1 and 19-23 and the present dependent claims 2-18.

Inventive step

The document D1 can be seen as the closest prior art for the novel subject-matter, since it addresses the same technical problem and since the compounds of D1 come structurally close to the compounds of claim 1.

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INTERNATIONAL PRELIMINARY

International application No. PCT/US 02/36398

EXAMINATION REPORT - SEPARATE SHEET

The distinguishing feature is the exchange of the group $-C\equiv N$ with the group $-C(O)X^3$. However, in the absence of any unexpected technical effect linked to this feature, the objective problem solved by the novel subject-matter in view of D1 can merely be seen as the provision of further cathepsin S protease inhibitors, methods for their preparation and their use as medicaments for the treatment of related diseases.

The document D2, which can likewise be seen as relevant prior art, teaches cathepsin S protease inhibitors having an oxadiazolylcarbonyl group at this position. One possible solution to the above formulated very general problem would therefore have been the exchange of the cyano group of D1 with the oxadiazolylcarbonyl group of D2.

Consequently, for the time being, the presence of an inventive activity cannot be acknowledged for the novel subject-matter, since there is no evidence that such a solution brings about unexpected advantages when compared to the solution already provided by D1.

Formal matters, clarity

The appropriate form for claim 22 would be a use claim (Use in the manufacture of a medicament ...).

In the claims 1-5, 19 and 21, language such as "prodrug derivatives", "protected derivatives", "isomers", mixtures of isomers" and the like introduces obscurity in that the subject-matter, for which protection is sought, is not clearly defined.

In any event, it appears that the subject-matter of the present claim 1 lacks sufficient support from the description anyway, if one compares the almost unlimited number of compounds covered by the present formula (I) to the very restricted number of compounds presented in the worked Examples on file, which can hardly be deemed representative.

Industrial applicability

There is no doubt that the subject-matter of the present claims on file (except claim 21) is industrially applicable.

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

Referencia de asunto de solicitante o agente
USAV2001/0197WOPCT

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

Solicitud Internacional No. PCT/US02/36396
Fecha de presentación internacional (día/mes/año) 14.11.2002
Fecha de prioridad (día/mes/año) 14.11.2001

Clasificación Internacional de Patentes (IPC) o ambas clasificación nacional e IPC
C07D271/06, C07D271/06

Solicitante
AVENTIS PHARMACEUTICALS INC. y otros

1. Este reporte de examen preliminar ha sido preparado por esta Autoridad Internacional de Examen Preliminar y es transmitida al solicitante de acuerdo con el Artículo 38..
2. Este reporte consiste de un total de 5 hojas, incluyendo esta hoja de cubierta.

Este REPORTE está también acompañado de ANEXOS, es decir, hojas de la descripción, reivindicaciones y/o dibujos que han sido modificados y son la base de este reporte y/o, hojas que contienen rectificaciones elaboradas ante esta Autoridad (ver Regla 70.18 y Sección 507 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 con razones bajo la Regla 66.2(a)(ii) con respecto a novedad, paso inventivo o aplicabilidad industrial: citas y explicaciones que soportan cada declaración
VI		Algunos documentos citados
VII		Algunos defectos en la solicitud internacional
VIII		Algunas observaciones sobre la solicitud internacional

Fecha de entrega de la demanda 21.06.2003

Fecha de completado este reporte 08.03.2004

Nombre y dirección de envío de la autoridad de examen preliminar internacional
Oficina Europea de Patentes, Gitschiner Str. 103
D-10958 Berlín
Tel. +49 30 25901-0

223

Fax: +49 30 25901-840

Funcionario autorizado

Teléfono No. +49 30 25901-337

Hopfner

Forma PCT/IPEA/408 (Hoja de cubierta) (Enero 2004)

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No. PCT/US02/36396

I. Base del reporte

1. Con respecto a los elementos de la solicitud internacional (Se hace referencia a las hojas de reemplazo que han sido suministradas a la Oficina receptora como respuesta a una invitación bajo el Artículo 14 en este reporte como "presentados originalmente")

Descripción, Páginas

1-96 como se presentaron originalmente

Reivindicaciones, Números

1-23 como se presentaron originalmente

2. Con respecto al idioma, todos los elementos marcados arriba estaban disponibles o fueron suministrados a esta Autoridad en el idioma en el cual se presentó la solicitud internacional, a menos que se indique de otra forma bajo este ítem.
Estos elementos estaban disponibles o fueron suministrados a esta Autoridad en el siguiente idioma , el cual es:
el idioma de una traducción suministrada para el propósito de la búsqueda internacional (bajo la Regla 23.1(b)),
el idioma de la publicación de la solicitud internacional (bajo la Regla 48.3(b)),
el idioma de una traducción suministrada para el propósito del examen preliminar internacional (bajo la Regla 55.2 y/o 55.3),
3. Con respecto a cualquier nucleótido y/o secuencia de aminoácidos divulgados en la solicitud internacional, el examen preliminar internacional se llevó a cabo en la base del listado de secuencias:
contenido en la solicitud internacional en forma escrita
presentado conjuntamente con la solicitud internacional en forma legible por computador,
suministrado subsecuentemente a esta Autoridad en forma escrita,
suministrado subsecuentemente a esta Autoridad en forma legible por computador,
Se ha suministrado la declaración de que el listado de secuencias escrito suministrado subsecuentemente no entra más allá de la divulgación en la solicitud internacional como se presentó.
Se ha suministrado la declaración de que la información registrada en forma legible por computador subsecuentemente es idéntica al listado de secuencias escrito.
4. Las modificaciones han dado como resultado la cancelación de la descripción, páginas:

las reivindicaciones, Nos.:
los dibujos, hojas:

5. Este reporte ha sido establecido como si (algunas de) las correcciones no se hayan hecho, pues han sido consideradas como más allá de las divulgaciones como se presentaron (Regla 70.2(c)).

(Debe hacerse referencia a cualquier hoja de reemplazo que contiene dichas modificaciones bajo el ítem 1 y anexarse a esta opinión.)

6. Observaciones adicionales, si es necesario:

Forma PCT/IPEA/408 (Enero 2004)

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No. PCT/US02/36396

III. No establecimiento de opinión con respecto a novedad, paso inventivo y aplicabilidad industrial.

1. Las preguntas de si la invención reivindicada parece ser novedosa, involucra un paso inventivo (no es obvia) o es industrialmente aplicable no han sido y no serán examinadas con respecto a:

la solicitud internacional completa,
X las reivindicaciones Nos. 21
debido a

X la mencionada solicitud internacional, o las mencionadas reivindicaciones Nos. 12 se relacionan con la siguiente materia sujeto lo cual no requiere de un examen preliminar internacional (especificar):

ver hoja separada

la descripción, reivindicaciones o dibujos (indicar abajo los elementos particulares) o dichas reivindicaciones Nos. Son tan poco claras que no se puede formar una opinión importante (especificar):

las reivindicaciones o dichas reivindicaciones Nos. están tan inadecuadamente soportadas en la descripción que no se puede formar una opinión importante.

no se ha establecido un reporte de búsqueda internacional para las dichas reivindicaciones Nos.

2. No se puede dirigir una opinión escrita debido a la falta del listado de nucleótidos y/o secuencia de aminoácidos para cumplir con el Estándar provisto en el Anexo C de las instrucciones administrativas:

la forma escrita no se ha suministrado o no cumple con el Estándar,

la forma leíble por computador no se ha suministrado o no cumple con el Estándar.

- V. Declaración justificada bajo la Regla 66.2(a)(ii) con respecto a novedad, altura inventiva o aplicabilidad industrial, citas y explicaciones que sustentan dicha declaración

1. Declaración

Novedad (N)

Si: Reivindicaciones 1-23

No: Reivindicaciones

Altura inventiva (IS)	Si:	Reivindicaciones	
	No:	Reivindicaciones	1-23
Aplicabilidad industrial (IA)	Si:	Reivindicaciones	1-20. 22,23
	No:	Reivindicaciones	

2. Citaciones y explicaciones
ver hoja separada

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL - HOJA SEPARADA
Solicitud internacional PCT/US02/36396

Re Ítem III

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

La reivindicación 21 se relaciona con materia sujeto considerada por esta Autoridad cubierta por las provisiones de la Regla 67.1(iv) PCT. Consecuentemente, la Autoridad de Examen Internacional concurre completamente con las objeción adelantada por la Autoridad de Búsqueda Internacional y no se formulará opinión con respecto a la aplicabilidad industrial de la materia sujeto de esta reivindicación (Artículo 34(4)(a)(i) PCT).

Re Ítem V

Establecimiento justificado bajo la Regla 66.2(a)(ii) con respecto a novedad, altura inventiva o aplicabilidad industrial citaciones y explicaciones que sustentan dicha declaración

Se hace referencia a los siguientes documentos:

D1: WO-A-0119808

D2: US-B-6255453

Novedad

El documento D1 divulga inhibidores de proteasa catepsina S que difieren estructuralmente de los compuestos de la presente reivindicación 1 en cuanto a que tienen un grupo ciano en lugar del grupo presente $-C(O)X^3$ donde X^3 permanece para un residuo de oxadiazolo (ver página 1, líneas 5-21; página 2, fórmula 1; Ejemplos 1-4; reivindicaciones 1, 9).

El documento D2 divulga inhibidores de proteasa catepsina S que difieren estructuralmente de los compuestos de la presente reivindicación 1 en cuanto a que no tienen el grupo sulfonil que contiene la cadena lateral $-X^1S(O)_2-X^2R^3$ y en cuanto a que un grupo amino forma parte de una fracción de pirrolidina (ver columna 1, líneas 15-55; columna 2, fórmula (I); columna 3, líneas 49-61; reivindicación 1).

Consecuentemente, la novedad debe reconocerse para la materia sujeto de las presentes reivindicaciones independientes 1 y 19-23 y las presentes reivindicaciones independientes 2-18.

Actividad inventiva

El documento D1 puede verse como el arte previo más cercano para dicha materia sujeto, puesto que se dirige al mismo problema técnico y puesto que los compuestos de D1 son estructuralmente más cercanos a los compuestos de la reivindicación 1.

La característica distintiva puede ser el intercambio del grupo $-C=N$ con el grupo $-C(O)X^3$. Sin embargo, en ausencia de cualquier efecto técnico inesperado enlazado a una tal característica, el problema objetivo resuelto por la materia sujeto novedosa en

vista de D1 puede meramente verse como la provisión de adicionales inhibidores de proteasa catepsina S, métodos para su preparación y su uso como medicamentos para el tratamiento de enfermedades relacionadas.

El documento D2, el cual puede verse similarmente como arte previo relevante, enseña inhibidores de proteasa de catepsina S que tienen un grupo oxadiazolilcarbonil en esa posición. Una posible solución al anteriormente formulado problema muy técnico puede haber sido consecuentemente el intercambio del grupo ciano de D1 con el grupo oxadiazolilcarbonil de D2.

Consecuentemente, hasta el presente, la presencia de una actividad inventiva no puede reconocerse para la materia sujeto novedosa, puesto que no hay evidencia de que una solución tal provea ventajas inesperadas cuando se compara con la solución ya provista por D1.

Aplicabilidad industrial

No ha duda de que la materia sujeto de las presentes reivindicaciones (excepto la reivindicación 21) es aplicable industrialmente.

Forma PCT/ Hoja separada/408 (Hoja 2) (EPO-Abril 1997)

A circular stamp from the Patent Department, dated JUN 2003. The stamp features a central star and the text "PATENT DEPT." and "JUN 2003". The outer ring of the stamp contains the numbers 1 through 31. Handwritten numbers "227" and "228" are visible on the right side of the stamp.

To:

WRITTEN OPINIO

(PCT Rule 66)

**COMPUTER
ENTERED**

Date of mailing
(day/month/year)

17/06/2003

Applicant's or agent's file reference:

US20010197WOPCT

REPLY DUE

within 2 / 00 months/days
from the above date of mailing

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US 02/ 36396

14/11/2002

14/11/2001

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

C07D271/06

Applicant

AVENTIS PHARMACEUTICALS INC. et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
- I ☒ Basis of the opinion
- 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 Rule 66.2(a)(ii) 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
3. The applicant is hereby invited to reply to this opinion.
- When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).
- How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
- Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.
- If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is:
- 14/03/2004

Name and mailing address of the IPBA/



European Patent Office, Glitschiner Str. 103
D-10969 Berlin - Germany
Tel.: (+49-30) 25901-0
Fax: (+49-30) 25901-340

Authorized officer

Examiner

Formalities officer
(incl. extension of time limits)
Tel. (+49-89) 2399 2828

Form PCT/IPEA/408 (cover sheet) (march 2002)

I. Basis of the opinion

The basis of this written opinion 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 and will not be 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

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:
2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).
3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

Previously Documented

ACTION DUE	Prepare Reply 6/25/03
	Reply to PCT 8-17-03
DUE DATE	
DKTD BY	
ATTY	GGW

TRATADO DE COOPERACIÓN DE PATENTES

**De la
AUTORIDAD INTERNACIONAL DE EXAMEN PRELIMINAR**

**Para:
Wang, George G.
AVENTIS PHARMACEUTICALS INC.
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800
ESTADOS UNIDOS DE AMÉRICA**

**SELLO DEL DEPARTAMENTO DE PATENTES – JUNIO 2003
ENTRADA AL COMPUTADOR 6-24-03
VER 2 PÁGINA PARA FECHAS DE RESPUESTA**

**PCT
OPINIÓN ESCRITA
(REGLA 66 PCT)**

Fecha de envío (día/mes/año) 17.02.2003

**Referencia de asunto de solicitante o agente
US20010197WOPCT**

RESPUESTA dentro de 2/00 meses/días de la anterior fecha de envío

**Solicitud Internacional No. PCT/US02/36396
Fecha de presentación internacional (día/mes/año) 14/11/2002
Fecha de prioridad (día/mes/año) 14/11/2001**

**Clasificación Internacional de Patentes (IPC) o ambas clasificación nacional e IPC
C07D271/06**

**Solicitante
AVENTIS PHARMACEUTICALS INC. y otros**

1. Esta opinión escrita es la primera llevada a cabo por esta Autoridad Internacional de Examen Preliminar.
2. Esta opinión 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 con razones bajo la Regla 66.2(a)(ii) con respecto a novedad, paso inventivo o aplicabilidad industrial: citaciones y explicaciones que soportan cada declaración
VI		Algunos documentos citados
VII		Algunos defectos en la solicitud internacional

VIII Algunas observaciones sobre la solicitud internacional

3. Se invita por este medio al solicitante a contestar a esta opinión:
 - Cuándo?** Ver el tiempo límite indicado arriba. El solicitante puede, antes de expirar de ese tiempo límite, solicitar a esta Autoridad conceder una extensión, ver Regla 66.2(d).
 - Cómo?** Presentando una respuesta por escrito, acompañada, cuando sea apropiado, mediante correcciones, de acuerdo con la Regla 66.3. para la forma y el idioma de las correcciones, ver Reglas 66.8 y 66.9.
 - Además:** Para una oportunidad adicional para presentar correcciones, ver Regla 66.4.

Si no se presenta respuesta, el reporte internacional preliminar se establecerá sobre la base de esta opinión.
4. La fecha final en la cual el reporte de examen preliminar internacional debe establecerse de acuerdo con la Regla 69.2 es: 14/03/2004

Nombre y dirección de envío de la autoridad de examen preliminar internacional
 Oficina Europea de Patentes, Gitschiner Str. 103
 D-10969 Berlín Alemania
 Tel. (+49-30) 25901-0
 Fax: (+49-30) 25901-840

Funcionario autorizado
 Examinador

Funcionario de formalidades (Prórroga de límites de tiempo)
 Tel. (+49-89) 2399-2828

Forma PCT/IPEA/408 (Primera hoja) (Marzo 2002)

OPINIÓN ESCRITA Solicitude Internacional No. PCT/US02/36396

- I. Base de la opinión

La base de esta opinión escrita es la solicitud tal como se presentó originalmente.

La pregunta de si la invención reivindicada parece ser novedosa, involucra una actividad inventiva, o es aplicable industrialmente no ha sido y no será el sujeto del examen preliminar internacional con respecto a las reivindicaciones que no han sido buscadas (Artículo 17(2)(a) o (3) y Regla 66.1(e) PCT; ver también el reporte de búsqueda internacional).
- V. Declaración justificada bajo la Regla 66.2(a)(ii) con respecto a novedad, la altura inventiva o la aplicabilidad industrial.
 1. En la extensión en que se ha llevado a cabo el examen preliminar internacional (ver ítem III de arriba), se puntualiza lo siguiente:
 2. A la luz de los documentos citados en el reporte de búsqueda internacional, se considera que la invención tal como se definió en por lo menos algunas de las reivindicaciones, las cuales han sido el sujeto de un reporte de búsqueda internacional, no parecen cumplir con los criterios mencionados en el Artículo 33(1) PCT, es decir, no parecen ser novedosas y/o involucrar actividad

inventiva (ver el reporte de búsqueda internacional, en particular los documentos citados X y/o Y, y las correspondientes referencias de las reivindicaciones).

3. Si se presentan modificaciones, el solicitante debe cumplir con los requerimientos de la Regla 66.8 PCT e indicar la base de las modificaciones en los documentos de la solicitud tal como se presentó originalmente (Artículo 34(2) (b) PCT) de otra manera estas modificaciones pueden no ser tomadas en consideración para el establecimiento del reporte de examen preliminar internacional. Se dirige la atención del solicitante al hecho de que si la solicitud contiene una pluralidad innecesaria de reivindicaciones independientes, no se llevará a cabo un examen de ninguna de las reivindicaciones.

NB: Si el solicitante decide solicitar un examen sustantivo detallado, entonces normalmente se establecerá directamente un reporte de examen preliminar. Excepcionalmente el examinador puede llevar a cabo una segunda opinión escrita, solicitada explícitamente.

SELLO ACCIÓN DEBIDA Preparar Respuesta 6/25/03 Respuesta a PCT 6-17-03
Forma PCT/408AE2 (EPO-03-2002) P20725

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PCT

In the European Patent Office

Applicants File Reference:
USAV2001/0197WOPCT

International Filing Date:
14 November 2002 (14.11.02)

International Application No.:
PCT/US02/36396

Priority Date:
14 November 2001 (14.11.01)

Title of Invention:
**OLIGOPEPTIDES AND COMPOSITIONS CONTAINING THEM AS CATHESPIN S
INHIBITORS**

Applicant(s):
AVENTIS PHARMACEUTICALS INC, et al.

Authorized Officer:

RESPONSE TO WRITTEN OPINION

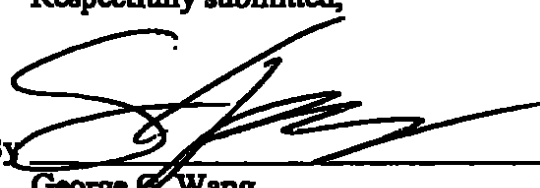
IPEA/European Patent Office
Gitschiner Str. 103
D-10969 Berlin, Germany

Sir:

This is in response to the Written Opinion mailed 17/06/2003. The Applicants respectfully disagree with IPEA's conclusion that the subject matter of the above-referenced application does not appear to meet the criteria set forth in PCT Article 33(1). Since the IPEA Written Opinion did not "fully state the reasons for the opinion" as required by PCT Rule 66.2(b), The Applicants are unable to respond more specifically to the Written Opinion.

Therefore, the Applicants respectfully request that a detailed substantive examination be conducted and the Applicants be furnished with the specific reasons supporting the conclusions stated in the Written Opinion so that the Applicants can response fully to the Written Opinion.

Respectfully submitted,

By 

George G. Wang
Attorney for Applicants

Aventis Pharmaceuticals Inc.
Patent Department
Route #202-206 / P.O. Box 6800
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Telephone (908) 231-2843
Telefax (908) 231-2626

Aventis Docket No. USAV2001/0197 WO PCT
Dated: July 28, 2003

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PCT

In the European Patent Office

Applicants File Reference:
USAV2001/0197WOPCT

International Filing Date:
14 November 2002 (14.11.02)

International Application No.:
PCT/US02/36396

Priority Date:
14 November 2001 (14.11.01)

Title of Invention:
**OLIGOPEPTIDES AND COMPOSITIONS CONTAINING THEM AS CATHESPIN S
INHIBITORS**

Applicant(s):
AVENTIS PHARMACEUTICALS INC, et al.

RESPONSE TO SECOND WRITTEN OPINION

IPEA/European Patent Office
Gitschiner Str. 103
D-10969 Berlin, Germany

Dear Sir:

**Responsive to the Written Opinion of the International Preliminary Examining Authority, mailed
14 November 2003, Applicants respectfully request reconsideration.**

Remarks

**Applicants respectfully disagree with the Examiner, particularly concerning the "Clarity" and
"Inventive Step" requirements.**

Clarity:

**The Examiner alleges that "language such as 'prodrug derivatives', 'protected derivatives',
'isomers', 'mixture of isomers' introduces obscurity in that the subject-matter, for which protection
is sought, is not clearly defined." Applicants respectfully point out that not only are those terms
commonly understandable to people skilled in the art, they are also clearly defined in the
specification. For example, an "isomers" is defined as "compounds of Formula (I) having identical
molecular formulae but differ in the nature or sequence of bonding of their atoms or in the
arrangement of their atoms in space (page 11). This clearly defines what an isomer is and there is
nothing unclear about it. Once "isomer" is clearly defined, the meaning of "mixture of isomers" is
self-evident. Similarly, "prodrug" is clearly defined ("prodrug means a compound that is**

convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of Formula I", page 13).

In view of the definition of "prodrug", the definition of "prodrug derivative" is self-evident to anyone with ordinary skill in the art. Lastly, "protective derivative" is defined as derivatives of compounds of Formula (I) in which reactive site or sites are blocked with protecting groups." (page 14). The scopes defined by those terms may be broad but the broad scopes are nonetheless clearly defined. A broad scope is not the same thing as an unclearly defined scope. Applicants respectfully submit that the use of those terms does not introduce obscurity and clearly define the intended scope.

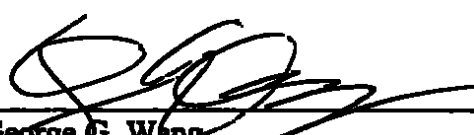
Inventive Step:

The Examiner acknowledged that the present invention distinguishes the closest known prior art, i.e., D1, by having a -CN group instead of a -C(O)X3 group as in D1. However, the Examiner concluded that the novel compounds of the present invention need to show "unexpected technical effect link to the feature" distinguishing them from the prior art. Applicants respectfully submit that the Examiner's conclusion is incorrect because it presumes that it is known or obvious to people skilled in the art that a -CN group and a -C(O)X3 are readily interchangeable. This presumption is not true. No chemist can be certain that a chemical compound having a -CN group would maintain substantially the same chemical, physical or biological properties after its -CN group being replaced with a -C(O)X3 group. The differences between the two chemical groups are not trivial and their interchangeability was not obvious at the time of the invention. Thus, the present invention is believed to have meet the inventive step requirement and should be properly acknowledged Under PCT Article 33(3) ("For purposes of the international preliminary examination, a claimed invention shall be considered to involve an inventive step if, having regard to the prior art as defined in the Regulations, it is not, at the prescribed relevant date, obvious to a person skilled in the art.")

Accordingly, Applicants respectfully request an indication that the claimed subject matter of the instant application meets the criteria set forth in PCT Article 33(2)-(3).

Respectfully submitted,

By


George G. Wang

Attorney for Applicants

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Aventis Docket No. USAV2001/0197 WO PCT

Dated: December 1, 2003

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PCT
En la
Oficina Europea de Patentes

Referencia de asunto de solicitante:

USAV2001/0197WOPCT

Solicitud Internacional No. PCT/US02/36396

Fecha de presentación internacional 14 Noviembre 2002 (14.11.02)

Fecha de prioridad 14 Noviembre 2001 (14.11.2001)

Título de la Invención:

OLIGOPÉPTIDOS Y COMPOSICIONES QUE LOS CONTIENEN COMO
INHIBIDORES DE CATESPIN S

Solicitante(s):

AVENTIS PHARMACEUTICALS INC. y otros

RESPUESTA A LA SEGUNDA OPINIÓN ESCRITA

IPEA/ Oficina Europea de Patentes
Gitschiner Sr. 103

Apreciado señor:

Como respuesta a la Opinión Escrita de la Autoridad de Examen Preliminar Internacional, enviada el 14 de Noviembre 2003, los Solicitantes solicitan respetuosamente reconsideración.

Observaciones

Los solicitantes respetuosamente discrepan con el Examinador, particularmente concerniente a los requerimientos de "Claridad" y "Altura inventiva".

Claridad:

El Examinador considera que lenguaje tal como "derivados de pro-droga", "derivados protegidos", "isómeros", "mezcla de isómeros" introduce oscuridad en la materia sujeto, para la cual se espera protección, no está claramente definido. Los solicitantes puntualizan respetuosamente que no solamente esos términos son comúnmente entendibles por aquellas personas expertas en el arte, sino que además están claramente definidos en la especificación. Por ejemplo, un "isómero" está definido como "compuesto de Fórmula (I) que tienen idénticas fórmulas moleculares pero difieren en la naturaleza o secuencia de enlace en sus átomos o en el arreglo de sus átomos en el espacio (página 11). Esto define claramente cual isómero es y no hay nada claro acerca de él. Una vez el "isómero" se define claramente, el significado de "mezcla de isómeros" es auto evidente. Similarmente, "pro-droga" está claramente definido ("pro-droga" significa un compuesto que es convertible in vivo por medio metabólico (por ejemplo, por hidrólisis) a un compuesto de Fórmula I", página 13). En vista de la definición de "pro-droga", la definición de derivado de pro-droga es auto evidente para cualquier persona con experiencia ordinaria en el arte. En último lugar, "derivado protector" se define como derivados de compuestos de Fórmula (I) donde el lugar o lugares reactivos están bloqueados con grupos de protección (página 14). Los alcances definidos por estos términos pueden ampliarse pero los alcances amplios están sin embargo claramente definidos. Un alcance amplio no es la misma cosa que un alcance no claramente definido. Los solicitantes indican respetuosamente

que el uso de estos términos no introduce oscuridad y define claramente el alcance pretendido.

Altura inventiva:

El Examinador reconoce que la presente invención distingue el arte previo conocido más cercano, es decir, D1, teniendo un grupo -CN en vez de un grupo -C(O)X3 como en D1. Sin embargo, el Examinador concluyó que los novedosos compuestos de la presente invención requieren mostrar "un inesperado efecto técnico enlazado a la característica" distinguiéndolos del arte previo. Los solicitantes respetuosamente consideran que la conclusión del Examinador es incorrecta debido a que presume que es conocido u obvio para personas expertas en el arte que un grupo -C(O)X3 es fácilmente intercambiable. Esta presunción no es cierta. Ningún químico puede asegurar que un compuesto químico que tien un grupo -CN puede mantener sustancialmente las mismas propiedades químicas, físicas o biológicas después de que su grupo -CN ha sido reemplazado con un grupo -C(O)X3. Las diferencias entre los dos grupos químicos no son triviales y su capacidad de intercambio no fue obvio en el momento de la invención. Así, se considera que la presente invención ha cumplido con el requerimiento de altura inventiva y debe reconocerse adecuadamente bajo el Artículo 33(3) del PCCT ("Para el propósito del examen preliminar internacional, una invención reivindicada se considerará que involucra un paso inventivo si, con respecto al arte previo como se define en las Regulaciones, no es, en la fecha prescrita relevante, obvia para una persona experta en el arte.")

De acuerdo con lo anterior, los Solicitantes respetuosamente solicitan una indicación de que la materia sujeto reivindicada de la presente solicitud cumple con los criterios establecidos en el Artículo 33(2)-(3) del PCT.

Presentado respetuosamente,

Por firma (ilegible)
George G. Wang
Apoderado de los Solicitantes

Aventis Pharmaceuticals Inc.
Departamento de Patentes
Route #202-206 / P.O. Box 6800
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Archivo Aventis No. USAV2001/0197 WO PCT
Fechado: Diciembre 1, 2003

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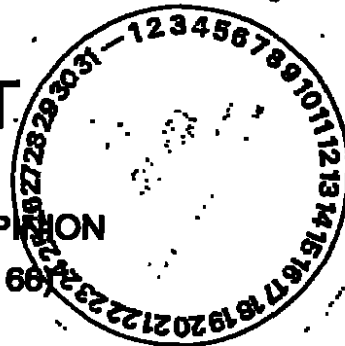
From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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

PCT

WRITTEN OPINION
(PCT Rule 68)



Applicant's or agent's file reference US20010197WOPCT		Date of mailing (day/month/year) 24.09.2003	
International application No. PCT/US02/36396	International filing date (day/month/year) 14.11.2002	Priority date (day/month/year) 14.11.2001	
International Patent Classification (IPC) or both national classification and IPC C07D271.08		ACTION DUE <i>Prepare Reply To PCT - 11/24/03</i>	
Applicant AVENTIS PHARMACEUTICALS INC. et al.		DUE DATE <i>12/24/03</i>	

1. This written opinion is the second drawn up by the International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basic of the opinion
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 Rule 68.2(a)(II) 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

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 68.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 68.3. For the form and the language of the amendments, see Rules 68.8 and 68.9.

Also: For an additional opportunity to submit amendments, see Rule 68.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 68.4 bis. For an informal communication with the examiner, see Rule 68.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 14.03.2004

Name and mailing address of the international preliminary examining authority:	Authorized Officer
 European Patent Office - Gluckstr. 103 D-10855 Berlin Tel. +49 30 25901-0 Fax +49 30 25901-840	Hoepfner, W Formalities officer (incl. extension of time limits) Geier, A Telephone No. +49 30 25901-706



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WRITTEN OPINION

International application No. PCT/US02/36396

I. Basis of the opinion

1. With regard to the elements of the International application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, Pages

1-96 as originally filed

Claims, Numbers

1-23 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the International search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination 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.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this opinion.)

6. Additional observations, if necessary:

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

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

- ☐ the entire international application,
- ☒ claims Nos. 12

because:

- ☒ the said international application, or the said claims Nos. 12 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the Standard.
- ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 68.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	
Industrial applicability (IA)	Claims	12

2. Citations and explanations

see separate sheet

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Re Item III

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

Claim 21 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, the International Examination Authority fully concurs with the objection put forward by the International Search Authority and no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO-A-0119808

D2: US-B-6255453

Formal matters

The appropriate form for claim 22 would be a use claim (Use in the manufacture of a medicament ...).

Clarity

In the claims 1-5, 19 and 21, language such as "prodrug derivatives", "protected derivatives", "isomers", mixtures of isomers" introduces obscurity in that the subject-matter, for which protection is sought, is not clearly defined. Therefore, the claims should be rendered more precise by limiting these vague and imprecise terms to the more concrete definitions given in the description (see e.g. pages 11-14).

In any event, it appears that the subject-matter of the present claim 1 lacks sufficient support from the description anyway, if one compares the almost unlimited number of compounds covered by the present formula (I) to the very restricted number of compounds presented in the worked Examples on file, which hardly can be deemed representative.

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Novelty

The document D1 discloses cathepsin S protease inhibitors which structurally differ from the compounds of the present claim 1 in that they have a cyano group in lieu of the present group $-C(O)X^3$ wherein X^3 stands for an oxadiazole residue (see page 1, lines 5-21; page 2, formula I; Examples 1-4; claims 1, 9).

The document D2 discloses cathepsin S protease inhibitors which structurally differ from the compounds of the present claim 1 in that they lack the sulfonyl group-containing side chain $-X^1S(O)_2-X^2R^3$ and in that one amino group forms part of a pyrrolidine moiety (see column 1, lines 15-55; column 2, formula (I); column 3, lines 49-61; claim 1).

Consequently, novelty could presumably be acknowledged for the subject-matter of (an) amended claim(s) taking into account the foregoing objections.

Inventive step

The document D1 could be seen as the closest prior art for such subject-matter, since it addresses the same technical problem and since the compounds of D1 would possibly come structurally closer to the subject-matter of such (an) amended claim(s).

The distinguishing feature would be the exchange of the group $-C=N$ with the group $-C(O)X^3$.

However, in the absence of any unexpected technical effect linked to such a feature, the objective problem in view of D1 could merely be seen as the provision of further cathepsin S protease inhibitors, methods for their preparation and their use as medicaments for the treatment of related diseases.

The document D2, which could likewise be seen as relevant prior art, teaches cathepsin S protease inhibitors having an oxadiazolylcarbonyl group at this position. One possible solution to the above formulated very technical problem would therefore have been the exchange of the cyano group of D1 with the oxadiazolylcarbonyl group of D2.

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/US02/36396

Consequently, the presence of an inventive activity could only be acknowledged for the subject-matter of (an) amended claim(s), if it could be convincingly shown that such a solution would bring about unexpected advantages when compared to the solution already provided by D1.

Industrial applicability

There is no doubt that the subject-matter of the present claims on file (except claim 21) is industrially applicable.

TRATADO DE COOPERACIÓN DE PATENTES

**De la
AUTORIDAD INTERNACIONAL DE EXAMEN PRELIMINAR**

**Para:
Wang, George G.
AVENTIS PHARMACEUTICALS INC.
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800
ESTADOS UNIDOS DE AMÉRICA**

**PCT
OPINIÓN ESCRITA
(REGLA 66 PCT)**

Fecha de envío (día/mes/año) 24.09.2003

**Referencia de asunto de solicitante o agente
US20010197WOPCT**

RESPUESTA dentro de 3 mes(es) de la anterior fecha de envío

**Solicitud Internacional No. PCT/US02/36396
Fecha de presentación internacional (día/mes/año) 14/11/2002
Fecha de prioridad (día/mes/año) 14/11/2001**

**Clasificación Internacional de Patentes (IPC) o ambas clasificación nacional e IPC
C07D271/06**

**Solicitante
AVENTIS PHARMACEUTICALS INC. y otros**

1. Esta opinión escrita es la **segunda** llevada a cabo por esta Autoridad Internacional de Examen Preliminar.
2. Esta opinión 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 con razones bajo la Regla 66.2(a)(ii) con respecto a novedad, paso inventivo o aplicabilidad industrial: citasiones y explicaciones que soportan cada declaración
VI		Algunos documentos citados
VII		Algunos defectos en la solicitud internacional
VIII		Algunas observaciones sobre la solicitud internacional
3. Se invita por este medio al solicitante a contestar a esta opinión:

Si no se presenta respuesta, el reporte internacional preliminar se establecerá sobre la base de esta opinión.

- el idioma de la publicación de la solicitud internacional (bajo la Regla 48.3(b)).

el idioma de una traducción suministrada para el propósito del examen preliminar internacional (bajo la Regla 55.2 y/o 55.3),

3. Con respecto a cualquier nucleótido y/o secuencia de aminoácidos divulgados en la solicitud internacional, el examen preliminar internacional se llevó a cabo en la base del listado de secuencias:
 contenido en la solicitud internacional en forma escrita
 presentado conjuntamente con la solicitud internacional en forma leíble por computador,
 suministrado subsecuentemente a esta Autoridad en forma escrita,
 suministrado subsecuentemente a esta Autoridad en forma leíble por computador,
 Se ha suministrado la declaración de que el listado de secuencias escrito suministrado subsecuentemente no entra más allá de la divulgación en la solicitud internacional como se presentó.
 Se ha suministrado la declaración de que la información registrada en forma leíble por computador subsecuentemente es idéntica al listado de secuencias escrito.
4. Las correcciones han dado como resultado la cancelación de la descripción, páginas:
 las reivindicaciones, Nos.:
 los dibujos, hojas:
5. Esta opinión ha sido establecida como si (algunas de) las correcciones no se hayan hecho, pues han sido consideradas como más allá de las divulgaciones como se presentaron (Regla 70.2(c)).
 (Debe hacerse referencia a cualquier hoja de reemplazo que contiene dichas modificaciones bajo el ítem 1 y anexarse a esta opinión.)
6. Observaciones adicionales, si es necesario:
- III. No establecimiento de opinión con respecto a novedad, paso inventivo y aplicabilidad industrial.

Forma PCT/IPEA/408 (Julio 1999)

Opinión ESCRITA

Solicitud Internacional No. PCT/US02/36396

1. Las preguntas de si la invención reivindicada parece ser novedosa, involucra un paso inventivo (no es obvia) o es industrialmente aplicable no han sido y no serán examinadas con respecto a:
 la solicitud internacional completa,
 X las reivindicaciones Nos. 12
 debido a
 X la mencionada solicitud internacional, o las mencionadas reivindicaciones Nos. 12 se relacionan con la siguiente materia sujeto lo cual no requiere de un examen preliminar internacional (especificar):
 ver hoja separada
 la descripción, reivindicaciones o dibujos (indicar abajo los elementos particulares) o dichas reivindicaciones Nos. Son tan poco claras que no se puede formar una opinión importante (especificar):

las reivindicaciones o dichas reivindicaciones Nos. están tan inadecuadamente soportadas en la descripción que no se puede formar una opinión importante.
no se ha establecido un reporte de búsqueda internacional para las dichas reivindicaciones Nos.

2. No se puede dirigir una opinión escrita debido a la falta del listado de nucleótidos y/o secuencia de aminoácidos para cumplir con el Estándar provisto en el Anexo C de las instrucciones administrativas:

la forma escrita no se ha suministrado o no cumple con el Estándar,
la forma legible por computador no se ha suministrado o no cumple con el Estándar.

V. Declaración justificada bajo la Regla 66.2(a)(ii) con respecto a novedad, altura inventiva o aplicabilidad industrial, citas y explicaciones que sustentan dicha declaración

1. Declaración

Novedad (N)	Reivindicaciones
Altura inventiva (IS)	Reivindicaciones
Aplicabilidad industrial (IA)	Reivindicaciones 12

2. Citaciones y explicaciones
ver hoja separada

OPINIÓN ESCRITA HOJA SEPARADA Solicitud internacional PCT/US02/36396

Re Ítem III

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

La reivindicación 21 se relaciona con materia sujeto considerada por esta Autoridad cubierta por las provisiones de la Regla 67.1(iv) PCT. Consecuentemente, la Autoridad de Examen Internacional concurre completamente con las objeción adelantada por la Autoridad de Búsqueda Internacional y no se formulará opinión con respecto a la aplicabilidad industrial de la materia sujeto de esta reivindicación (Artículo 34(4)(a)(i) PCT).

Re Ítem V

Establecimiento justificado bajo la Regla 66.2(a)(ii) con respecto a novedad, altura inventiva o aplicabilidad industrial citas y explicaciones que sustentan dicha declaración

Se hace referencia a los siguientes documentos:

D1: WO-A-0119808

D2: US-B-6266453

Asuntos formales

La forma apropiada para la reivindicación 22 debe ser una reivindicación de uso (Uso en la fabricación de un medicamento...).

Claridad

En las reivindicaciones 1-5, 19 y 21, el lenguaje tal como "derivados de pro-drogas", "derivados protegidos", "isómeros", "mezclas de isómeros" introducen oscuridad en cuanto a que la materia sujeto, para la cual se espera protección, no está claramente definida. Consecuentemente, las reivindicaciones deben volverse más precisas

limitando esos términos vagos e imprecisos a las definiciones más concretas dadas en la descripción (ver por ejemplo páginas 11-14).

En cualquier evento, parece que la materia sujeto de la presente reivindicación 1 falla en el soporte suficiente en la descripción en cualquier forma, si se compara el casi ilimitado número de compuestos cubiertos por la presente fórmula (I) con respecto al muy restringido número de compuestos presentados en los Ejemplos trabajados en archivo, lo cual difícilmente puede considerarse representativo.

Forma PCT/ Hoja separada/408 (Hoja 1) (EPO-Abril 1997)

OPINIÓN ESCRITA HOJA SEPARADA Solicitud internacional PCT/US02/36396

Novedad

El documento D1 divulga inhibidores de proteasa catepsina S que difieren estructuralmente de los compuestos de la presente reivindicación 1 en cuanto a que tienen un grupo ciano en lugar del grupo presente $-C(O)X^3$ donde X^3 permanece para un residuo de oxadiazolo (ver página 1, líneas 5-21; página 2, fórmula 1; Ejemplos 1-4; reivindicaciones 1, 9).

El documento D2 divulga inhibidores de proteasa catepsina S que difieren estructuralmente de los compuestos de la presente reivindicación 1 en cuanto a que no tienen el grupo sulfonil que contiene la cadena lateral $-X^1S(O)_2-X^2R^3$ y en cuanto a que un grupo amino forma parte de una fracción de pirrolidina (ver columna 1, líneas 15-55; columna 2, fórmula (I); columna 3, líneas 49-61; reivindicación 1).

Consecuentemente, la novedad podría presumiblemente reconocerse para la materia sujeto de (una) reivindicación(es) modificada(s) teniendo en cuenta las anteriores objeciones.

Actividad inventiva

El documento D1 puede verse como el arte previo más cercano para dicha materia sujeto, puesto que se dirige al mismo problema técnico y puesto que los compuestos de D1 pueden posiblemente ser estructuralmente más cercanos a la materia sujeto de dicha(s) (una) reivindicación(es) modificada(s).

La característica distintiva puede ser el intercambio del grupo $-C=N$ con el grupo $-C(O)X^3$.

Sin embargo, en ausencia de cualquier efecto técnico inesperado enlazado a una tal característica, el problema objetivo en vista de D1 puede meramente verse como la provisión de adicionales inhibidores de proteasa catepsina S que tienen un grupo oxadiazolilcarbonil en esa posición. Una posible solución al anteriormente formulado problema muy técnico puede haber sido consecuentemente el intercambio del grupo ciano de D1 con el grupo oxadiazolilcarbonil de D2.

Forma PCT/ Hoja separada/408 (Hoja 2) (EPO-Abril 1997)

OPINIÓN ESCRITA HOJA SEPARADA Solicitud internacional PCT/US02/36396

Consecuentemente, la presencia de una actividad inventiva puede reconocerse solamente para la materia sujeto de (una) reivindicación(es) modificada(s), si se muestra convincentemente que una solución tal deja inesperadas ventajas cuando se compara a la solución ya provista por D1.

Aplicabilidad industrial

No ha duda de que la materia sujeto de las presentes reivindicaciones (excepto la reivindicación 21) es aplicable industrialmente.

Forma PCT/ Hoja separada/408 (Hoja 3) (EPO-Abril 1997)

From the INTERNATIONAL BUREAU

PCT**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 8800
Route 202-206
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

PATENT DEPT.

Date of mailing(day/month/year)
22 May 2003 (22.05.03)

Applicant's or agent's file reference
US20010197WO

IMPORTANT NOTICE

International application No.
PCT/US02/36396

International filing date(day/month/year)
14 November 2002 (14.11.02)

Priority date(day/month/year)
14 November 2001 (14.11.01)

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 22 May 2003 (22.05.03) under No. 03/042197

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.

DUE DATE

DKTD BY

Appointed officer

Judith Zahra

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

Facsimile No.(41-22) 740.14.35

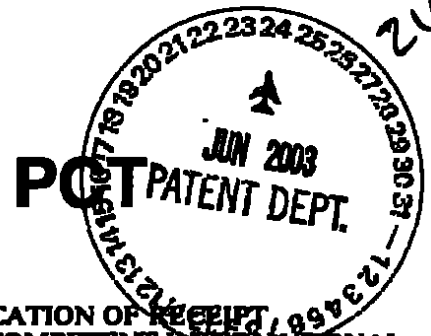
Telephone No.(41-22) 338.91.11

PATENT C OPERATION TREAT

66W

249

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

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))

Date of mailing
(day/month/year) 17-06-2003

Applicant's or agent's file reference
US20010197WOPCT

IMPORTANT NOTIFICATION

International application No. PCT/US 02/ 36396	International filing date (day/month/year) 14/11/2002	Priority date (day/month/year) 14/11/2001
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Applicant

AVENTIS PHARMACEUTICALS INC. et al.

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

21/05/2003

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.

N ACTION DUE comments

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

DUE DATE

DKTD BY

ATTY

12 6-24-03

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, Gitschiner Str. 103 D-10969 Berlin - Germany Tel.: (+49-30) 25901-0 Fax: (+49-30) 25901-840	Authorized officer HALBARTSCHLAGER M Tel. (+49-30) 25901-714
---	--



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)

19 September 2003 (19.09.03)

Applicant's or agent's file reference

US20010197WO

IMPORTANT INFORMATION

International application No.

PCT/US02/36396

International filing date (day/month/year)

14 November 2002 (14.11.02)

Priority date (day/month/year)

14 November 2001 (14.11.01)

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 : 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, AU, 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

DUE DATE

DKTD BY

ATTY

Authorized officer:

Sun LEE

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

Facsimile No. (41-22) 338-70-80

Telephone No. (41-22) 338 8710

PATENT COOPERATION TREATY

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

MAR 2003
PATENT DEPT

Date of mailing (day/month/year) 25 February 2003 (25.02.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference US20010197WO	
International application No. PCT/US02/36396	
International publication date (day/month/year) Not yet published	
International filing date (day/month/year) 14 November 2002 (14.11.02)	Priority date (day/month/year) 14 November 2001 (14.11.01)
Applicant AVENTIS PHARMACEUTICALS INC. et al	

1. 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).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. 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.
4. 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.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
14 Nove 2001 (14.11.01)	60/332,605	US	31 Deca 2002 (31.12.02)

ACTION DUE Comments

DUE DATE
DKTD BY
ATTY

14-11-03
GG

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer David MALEK
Facsimile No. (41-22) 740-1435	Telephone No. (41-22) 338 9988

PATENT COOPERATION TREATY

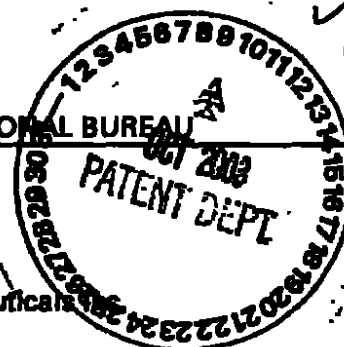
PCT

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
P.O. Box 6800
Route 202-206
Bridgewater, NJ 08807-0800
United States of America



Date of mailing (day/month/year) 19 September 2003 (19.09.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference US20010197WO	
International application No. PCT/US02/36396	International filing date (day/month/year) 14 November 2002 (14.11.02)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address Li, Jiayao 442 Milton Avenue Apartment 3 San Bruno, CA 94066 United States of America	State of Nationality CN	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 Li, Jiayao 888 Foster City Blvd., E5 Foster City, CA 94404 United States of America	State of Nationality CN	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

NO ACTION DUE File USA2001/0197-W

DATE 10/10/03
DKTD BY G. Wang

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:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Sun LEE
Facsimile No. (41-22) 338-70-80	Telephone No. (41-22) 338 8710

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADIADOR
PATENTE DE INVENCION	MODELO DE UTILIDAD	()	(>)
- Indicación de que se solicita la concesión de una patente.		()	(>)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	(>)
- Descripción de la invención.		()	(>)
- Dibujos de ser estos pertinentes.		()	(>)
- Comprobante de Pago de las tasas establecidas.			
COMPLETA ()	INCOMPLETA ()		
DISEÑO INDUSTRIAL ()			
- Indicación de que se solicita el registro de Diseño Industrial		()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.		()	()
- Representación gráfica o 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:

Eduar Navarrio

Fecha: 12-05-2004.

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
HOLLMANN RESTREPO GUSTAVO
Apoderado(a) y/o Representante de
AVENTIS PHARMACEUTICALS INC.
AXYS PHARMACEUTICALS INC.

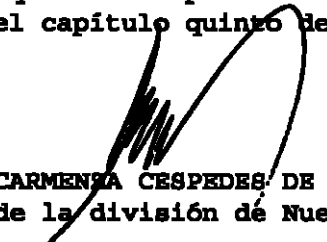
REFERENCIA	Radicación No.	04 43885
	Solicitud internacional	US02/36396
	Fecha inicio fase nacional	14/06/2004
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	U 8000

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

1. En la documentación allegada no se evidencia la existencia y representación de la sociedad Axys Pharmaceuticals, Inc., por lo tanto debe allegar el documento que así lo acredite.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.


ALIX CARMEN CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha _____
adpal 09 SET. 2005