QP

Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-38081

54. **TÍTULO** NUEVOS DERIVADOS DE CETO-OXADIAZOL COMO INHIBIDORES DE LAS CATEPSINAS

51. **CLASIFICACIÓN INTERNACIONAL** C070 271/06

71. **SOLICITANTE** Aventis Pharmaceuticals Inc.

DOMICILIO Bridgewater, New Jersey, Estados Unidos

74. **APODERADO** Luis Patiño Leyva

22. **BOGOTÁ, D. C.,** 21 de ABRIL de 2006

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-038081- -00000-0000 Fec: 2006-04-21 17:01:21
Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII Eva 379 FASENACIONALII
Act 411 PRESENTACION Folios: 253

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

① **SOLICITUD DE :**

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capitulo I. ☒ Capitulo II.

② **SOLICITANTE (71)**	Nombre: **AVENTIS PHARMACEUTICALS INC.** Dirección: 300 Somerset Corporate Boulevard, Bridgewater, NJ 08807 Estados Unidos Nacionalidad o Domicilio: Bridgewater, New Jersey, Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail:	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
③ **REPRESENTANTE O APODERADO**	Nombre: LUIS PATIÑO LEYVA Dirección Cra. 11ª No. 94-76 – Of. 308 Teléfono: 6161948 Fax: 6163976 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☒ Cual _____ Número 2.930.616 TP 2698
④ **INVENTOR (ES) (72)**	Nombre: THURAIRATNAM Sukathini Dirección: 6 Smoke Rise Lane, Nacionalidad o Domicilio: Bedminister, NJ 07921, Estados Unidos	

⑤ **PCT (86)**

Solicitud Internacional No. PCT/US2004/035282 Fecha Octubre 22 de 2004

Publicación Internacional No. WO 2005/040142 A1 Fecha Mayo 6 de 2005

⑥ **Titulo (54)** **NUEVOS DERIVADOS DE CETO-OXADIAZOL COMO INHIBIDORES DE LAS CATEPSINAS.**

⑦ **Clasificación Internacional (51)** C07D 271/06

⑧ **PRIORIDAD:**	(33) País de Origen	(32) Fecha	(31) Numero de Solicitud
SI ☒ NO ☐	Estados Unidos	Octubre 24 de 2003	60/514,373

⑨ **Comprobante de pago:** **Fecha:**

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

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [x] Documento que acredita existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] 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 deposito 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.
- [x] Otros Reporte de Búsqueda Internacional.

(11) FIGURA CARACTERISTICA

(12) Solicito la concesión de la patente,

NOMBRE: LUIS PATIÑO LEYVA

FIRMA:

C.C. 2.930.616 Bogotá T.P. 2698

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

Continuación nombre, dirección y domicilio de inventores:

Nombre	Dirección	Domicilio
ALDOUS David John	268 Gates Avenue,	Gillette, NJ 07933, Estados Unidos
LEROY Vincent	1 JFK Boulevard, Franklin Green Apt. #36K,	Somerset, NJ08873, Estados Unidos
TIMM Andreas Paul	97 Bonney Court, Bridgewater	New Jersey 08807, Estados Unidos

Otros anexos que se acompañan a la solicitud.

Copia del formato de solicitud de patente internacional.

Solicitud de corrección de errores obvios, de acuerdo con la regla PCT 91.1(b).

Formato No. PCT/ISA/217 respuesta a solicitud de corrección de errores obvios

Modificaciones de acuerdo con el artículo 34 del PCT.

Modificaciones de acuerdo con el artículo 19 del PCT

Copia formulario PCT/IB/308 correspondiente a la notificación informando al solicitante de la comunicación de la solicitud internacional a las oficinas designadas.

Copia formulario PCT/IPEA/402 correspondiente a la notificación de recibo de solicitud.

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

Copia formato PCT/ISA/210, correspondiente al Reporte de Búsqueda.

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
R. PETER WIDIN

3. ACTING IN THE CAPACITY OF:
COUNTY CLERK

4. BEARS THE SEAL/STAMP OF:
COUNTY OF SOMERSET

CERTIFIED

5. AT TRENTON, NEW JERSEY

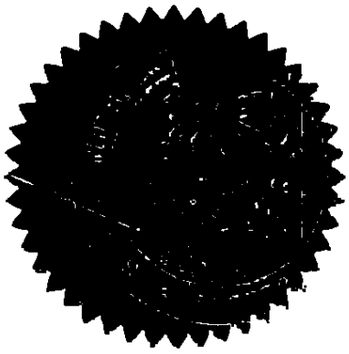
6. THE 9TH DAY OF APRIL 2002

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A149012

9. SEAL/STAMP:

10. SIGNATURE





G.HOLLMANN RESTREPO ABOGADOS 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 ensigns 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 ensigns 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 East Millstone, NJ on this 1st day of March of 2002.

ROSS J. OEHLER
ASSISTANT SECRETARY

G. HOLLMANN RESTREPO ABOGADOS LTDA

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

1) Para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, dibujos y modelos industriales, registro de marcas, registro de lemas comerciales, depósito de nombres y enseñas 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 tomas 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.

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

Firmado en el de de .

El Notario Cuarto del Círculo de Bogotá hace constar que esta fotocopia coincide con el original que tuvo a la vista
13 MAR 2002
GILBERTO CASTRO CASTRO
NOTARIO CUARTO

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

Nancy J Ingram
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 aknowledgement, proof or affidavit, a NOTARY PUBLIC OF NEW JERSEY

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

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

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

El Notario Cuarto [illegible] Segovia hace constar que [illegible] esta colonia [illegible] documento original de un [illegible] fecha
13 [illegible] 2002
GILBERTO CASTRO CASTRO
NOTARIO CUARTO

ESTADO DE NEW JERSEY, CONDADO DE SOMERSET

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

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

R. Peter Widin, Secretario

Deborah L. Anderson, Secretaria Especial Suplente

(Firma y Sello Oficial)

APOSTILLA

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

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

El Notario Cuarto del Circulo de Bogotá hace constar que la(s) foto-copia coincide con el(los) folio(s) del documento que se le(s) presentó

13 MAR 2002

GILBERTO PINZON CASTRO
NOTARIO CUARTO

Confirmado

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

M. Méndez S.

MINISTERIO DE RELACIONES EXTERIORES

223893

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

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RESPONSABILIDAD DEL TEXTO

2002 APR 22 P 12:19

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.



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 5TH DAY OF APRIL 2006

7. BY: Bradley I. Abelow, NEW JERSEY TREASURER

8. NO. A256161

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow

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 28th day of March , 2006.

SEAL

Notary Public
Nancy J. Ingram
Notary Public, State of New Jersey
My Commission Expires August 2, 2009

Notary Signature

Print or Type Name of Notary, Expiration Date, if any, Title or Jurisdiction Area

Docket No. USAV2003/0066 Co Pct

10

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

NOVEMBER 12, 2003

PTAS

70006213BA

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

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RECORDATION DATE: 11/11/2003 REEL/FRAME: 014118/0951
NUMBER OF PAGES: 3

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

ASSIGNOR:
THURAIRATNAM, SUKATHINI DOC DATE: 11/10/2003

ASSIGNOR:
ALDOUS, DAVID JOHN DOC DATE: 11/07/2003

ASSIGNOR:
LEROY, VINCENT DOC DATE: 11/10/2003

ASSIGNOR:
TIMM, ANDREAS PAUL DOC DATE: 11/10/2003

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

SERIAL NUMBER: 60514373 FILING DATE:
PATENT NUMBER: ISSUE DATE:

PAULA MCCRAY, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

12

FORM PTO-1595
1-31-92
(modified)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being transmitted via facsimile to the Commissioner for Patents, Alexandria, VA 22313-1450, Patent and Trademark Assignment System, at (703) 308-6606, on
Date 11/11/2003
Signature

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

1. Name of conveying party(ies):
1. Sukothini THURAIRATNAM
2. David John ALDOUS
1. Vincent LEROY
1. Andreas Paul TIMM
Additional name(s) of conveying party(ies) attached? ☐ YES ☒ NO

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) and address(es) attached? ☐ YES ☒ NO

3. Nature of Conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other
Execution Date: 1. 11/10/03 2. 11/07/03

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): 60/514,373 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: 08807-0800
** FAX NUMBER: (908) 231-2626 **
Our Reference No.: USAV2003/0066 US PSP

6. Total number of applications and patents involved: 1
7. Total (37 CFR 3.41): $40.00
☐ Enclosed
☒ Authorized to be charged to deposit account
8. Deposit account number: 19-1962

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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.

George G. Wang, Reg. No. 41,419
Name of Person Signing
Signature
Date: November 11, 2003
Total number of pages comprising cover sheet: 3

OMB No. 0651-0011 (exp. 4/94)

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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, United States of America, 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 application for United States Letters Patent therefor, assigned Attorney Docket No. **USAV2003/0066 US PSP** and (if filed prior to the execution hereof) filed on 10/24/2003, as Serial No. 60/514,373, entitled

Novel Compounds and Compositions as Cathepsin Inhibitors

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 10th day of November, 2003.
(City, State and Nation)

Signature: Sukanthini Thurairatnam
Inventor's Name: Sukathini THURAIRATNAM
Residential Address: 6 Smoke Rise Lane
Bedminster, New Jersey 07921

Signed at Bridgewater on this 7th day of November, 2003.
(City, State and Nation)

Signature: _____
Inventor's Name: David John ALDOUS
Residential Address: 268 Gates Avenue
Gillette, New Jersey 07933

Signed at Bridgewater on this 10th day of November, 2003.
(City, State and Nation)

Signature: _____
Inventor's Name: Vincent LEROY
Residential Address: 1 JFK Boulevard
Franklin Greens Apt # 36K
Somerset, New Jersey 08873

Signed at Bridgewater, NJ, USA on this 10th day of November, 2003.
(City, State and Nation)

Signature: _____
Inventor's Name: Andreas Paul TIMM
Residential Address: 97 Bonney Court
Bridgewater, New Jersey 08807

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

Signature: _____
Inventor's Name:
Residential Address:

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

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 May 2005 (06.05.2005)

PCT

(10) International Publication Number
WO 2005/040142 A1

(51) International Patent Classification[7]: C07D 271/06, A61K 31/5377, A61P 35/00, C07D 271/10, 261/08, 413/04, 263/32, 263/56, 295/18, A61P 29/00, 37/00

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PCT/US2004/035282

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/514,373 24 October 2003 (24.10.2003) US

(71) Applicant *(for all designated States except US)*: AVENTIS PHARMACEUTICALS INC. [US/US]; 300 Somerset Corporate Boulevard, Bridgewater, New Jersey 08807-2854 (US).

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(54) Title: NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS

(57) Abstract: Novel difluorinated amide derivatives of Formula (II) as inhibitors of cathepsin S, K, B, and L, the pharmaceutically acceptable salts and *N*-oxides thereof, their uses as therapeutic agents and the methods of their making.

NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS

FIELD OF THE INVENTION

This invention relates to the use of novel keto-oxadiazole derivatives for treating diseases associated with cysteine protease and, particularly, diseases associated with activity of cathepsin S, K, and B. This invention also relates to processes of making such compounds.

BACKGROUND OF THE INVENTION

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, for example, as a result of increased 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, atherosclerosis, emphysema, osteoporosis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, periodontal disease, metachromatic leukodystrophy and others.

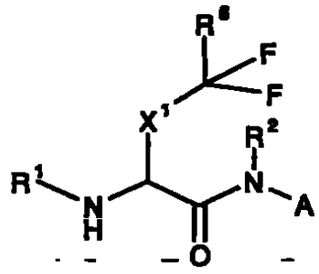
An increase in cathepsin activity such as, for example, cathepsin S, contributes to the pathology and/or symptomatology of a number of diseases such as, for example, autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythamotasus, irritable bowel disease, rheumatoid arthritis and Hashimoto's 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 is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsin S may be of use in treatment of systemic amyloidosis.

The activity of, for example, cathepsin B in synovial fluid is significantly elevated in osteoarthritis models (F. Mehraban Ann. Rheum. Dis. 1997; *56*, 108-115). Similarly, cathepsin K is a critical protease in synovial fibroblast-mediated collagen degradation (W.-S. Hou (et al.) Am. J. Pathol. 2001, 159, 2167-2177). Thus, inhibition of Cathepsin B and K, for example, is a useful method for the treatment of degenerative joint diseases such as, for example, osteoarthritis. Cathepsin K inhibition, for example, leads to inhibition of bone resorption (G. B. Stroup (et al.) J. Bone Mineral Res. 2001, 16, 1739-1746). Cathepsin K inhibitors are, therefore, useful for the treatment of osteoporosis.

It is known in the art that cathepsins play an important role in the degradation of connective tissues, the generation of bioactive proteins and antigen processing. They have been implicated in osteoporosis, muscular dystrophy, bronchitis, emphysema, viral infection, cancer metastasis and neurodegenerative diseases, such as Alzheimer's disease and Huntington's disease. Recently, increased interest in cathepsin inhibitors has been generated with potential therapeutic targets, such as cathepsin K or cathepsin L for osteoporosis and cathepsin S for immune modulation (W. Kim., K. Kang. Expert Opin. Ther. Pat. 2002, 12, 419-432). An increase in cathepsin K or B activity contributes to the pathology and/or symptomatology of a number of diseases. Accordingly, molecules that inhibit the activity of cathepsin protease are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

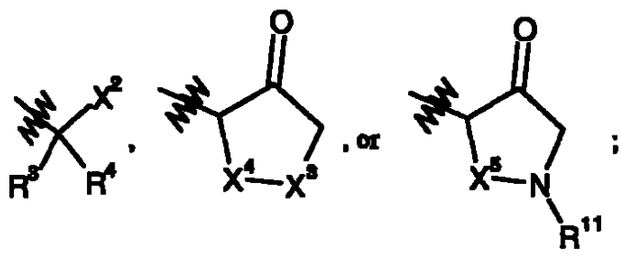
In one aspect of the present invention, compounds are provided that inhibit the enzymatic activity of cathepsin S, B, and K and have a structure of formula (I):



(I)

wherein

A is



X^1 is methylene, ethylene or a bond;

X^2 is CN, CHO, $C(O)R^6$, $C(O)C(O)NR^7R^7$, $C(O)C(O)NR^7R^8$, $C(O)C(O)R^{13}$, $C(O)C(O)OR^{13}$, $C(O)CH_2X^3R^{13}$;

X^3 is selected from the group consisting of O, $S(O)_n$, CO, CONH, NHCO, $NHSO_2$ and SO_2NH;

X^4 is $CH(R^{12})$ or $CH(R^{12})$-CH_2;

X^5 is methylene, ethylene, propylene or a bond;

X^6 is a bond or (C_{1-2})alkylene;

R^1 is H, $R^{13}C(O)$-, $R^{13}S(O)_2$-, $R^{13}OC(O)$-, $R^8R^7NC(O)$-, $R^8R^7NS(O)_2$-; $R^{13}S(O)_2NC(O)$- or $R^{13}C(O)NS(O)_2$-; or R^1 is selected from the group consisting of (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl and hetero(C_{5-13})aryl(C_{0-6})alkyl , each of which is 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, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-12})aryl(C_{0-6})alkyl;

R^3 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-13})aryl(C_{0-6})alkyl optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^4 is H or (C_{1-6})alkyl; or R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^5 is H, F, or R^5 is (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl each 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, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^6 is (C_{6-12})aryl, hetero(C_{5-13})aryl and halo substituted (C_{1-6}) alkyl; wherein R^6 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, cyano, halo, halo-substituted (C_{1-6})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^7 is H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl; wherein R^7 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^8 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, and hetero(C_{5-13})aryl(C_{0-6})alkyl, or R^7 and R^8 together with the atom attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^9 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl;

R^{10} is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl;

R^{11} is selected from the group consisting of hydrogen, (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-3})alkyl, hetero(C_{8-12})-bicycloaryl(C_{0-3})alkyl, $-C(O)R^{13}$, $-C(S)R^{13}$, $-S(O)_2R^{13}$, $-C(O)OR^{13}$, $-C(O)N(R^7)R^8$, $-C(S)N(R^7)R^8$ and $-S(O)_2N(R^7)R^8$;

R^{12} is H or C_{1-6}alkyl optionally substituted by amido, (C_{6-12})aryl, hetero(C_{5-12})aryl, hetero(C_{5-12})cycloalkyl or hydroxy;

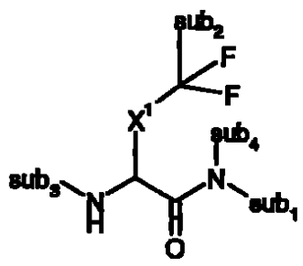
R^{13} is (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl; wherein R^{13} is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$,

$-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$; and

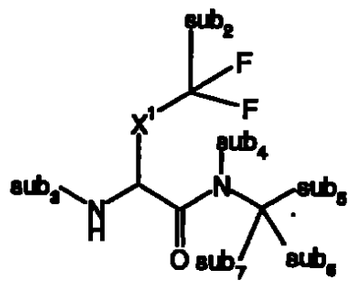
n is zero or an integer 1 or 2;

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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

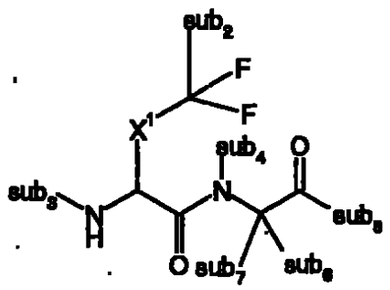
In another aspect of the present invention, the inventive subject matter is the backbone structures of Formulae II, III, IV or V, wherein sub_1-sub_8 are general substituents. The specific substituents at sub_1- sub_8 are not part of this aspect of the invention and can be any chemical groups or radicals which may be substituted at those positions (referred to as "general substituents" hereinafter), including those substitutions made possible by any conventional means or by any new technologies developed in the future. Thus, for the purpose of this application, "general substituents" do not serve as a claim element or limitation of the claim and they themselves may be novel and non-obvious, or unknown at the time of the invention.



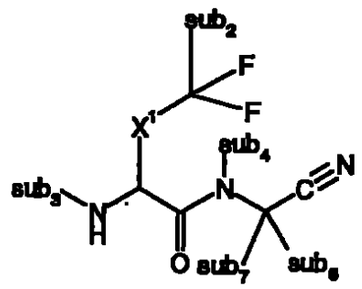
II



III



IV



V

In yet another aspect of the invention, the inventive subject matter includes the backbone structure of Formulae II, III, IV or V together with popular substituents at sub_1-sub_8. For the purpose

of this application, "a popular substituent" means a chemical group or radical which, at the time of the present invention, people of ordinary skill in the art, by using the specific substitutions disclosed hereinafter as guidance, would deem practical to substitute at sub_1-sub_8 without undue experimentation in practicing the present invention.

In still another aspect of the invention, the inventive subject matter includes the backbone structures of Formulae II, III, IV or V and specific substituents disclosed hereinafter at sub_1-sub_8. The specific substituent disclosed in the present application is refereed to as a "particular substitnent." For the purpose of the present application, a particular substitnent, if recited in the claims, serves as a claim limitation and may confer patentability on the claim by itself or in combination with the backbone structure along with other substituents therein.

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.

"A related chemical entity" of a compound, means an N-oxide derivative, a prodrug derivative, a protected derivative, an individual isomer, a mixture of isomers, or a pharmaceutically acceptable salt or solvate, of said compound, which can be prepared without undue experimentation by people with ordinary skill in the field.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as described herein.

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as described herein. Exemplary alkoxy groups include allyloxy, difluoromethoxy, methoxy, trifluoromethoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

"Alkoxycarbonyl" means an alkyl-O-CO- group in which the alkyl group is as described herein. Exemplary alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g., (C_{1-6})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., (C_{6-12})aryl(C_{0-6})alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl 3-phenylpropyl, and the like). It will be appreciated by those skilled in the art that when alkyl represents an unsaturated aliphatic radical such radicals may not be attached directly to an oxygen, nitrogen or sulphur atom via the carbon carbon multiple bond of said unsaturated aliphatic radical.

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated, (C_{1-2})alkylene includes methylene (-CH_2-) and ethylene (-CH_2CH_2-). It will be appreciated by those skilled in the art that when alkylene represents an unsaturated, aliphatic, divalent radical such radicals may not be attached directly to an oxygen, nitrogen or sulphur atom via the carbon carbon multiple bond of said unsaturated, aliphatic, divalent radical.

"Alkylenedioxy" means an -O-alkylene-O- group in which alkylene is as defined above. Exemplary alkylenedioxy groups include methylenedioxy and ethylenedioxy.

"Alkylsulfinyl" means an alkyl-SO- group in which the alkyl group is as previously described. Preferred alkylsulfinyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylsulfonyl" means an alkyl-SO_2- group in which the alkyl group is as previously described. Preferred alkylsulfonyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Exemplary alkylthio groups include methylthio, ethylthio, isopropylthio and heptylthio.

"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.

"Aroyl" means an aryl-CO- group in which the aryl group is as described herein. Exemplary aroyl groups include benzoyl and 1- and 2-naphthoyl.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as previously defined.

"Aryl" as a group or part of a group denotes: (i) an optionally substituted monocyclic or multicyclic aromatic carbocyclic moiety of 6 to 12 carbon atoms, such as phenyl or naphthyl; or (ii) an optionally substituted partially saturated multicyclic aromatic carbocyclic moiety in which an aryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure, such as a tetrahydronaphthyl, indenyl or indanyl ring. Except where otherwise defined, aryl groups may be substituted with one or more aryl group substituents, which may be the same or different, where "aryl group substituent" includes, for example, acyl, acylamino, alkoxy, alkoxycarbonyl, alkylenedioxy, alkylsulfinyl, alkylsulfonyl, alkylthio, aroyl, aroylamino, aryl, arylalkyloxy, arylalkyloxycarbonyl, arylalkylthio, aryloxy, aryloxycarbonyl, arylsulfinyl, arylsulfonyl, arylthio, carboxy (or an acid bioisostere), cyano, cycloalkyl, halo, heteroaroyl, heteroaryl, heteroarylalkyloxy, heteroaroylamino, heteroaryloxy, heterocycloalkyl, hydroxy, nitro, trifluoromethyl, -NY^3Y^4, -$CONY^3Y^4$, -$SO_2NY^3Y^4$, -NY^3-C(=O)alkyl, -NY^3SO_2alkyl or alkyl optionally substituted with aryl, heteroaryl, hydroxy, or -NY^3Y^4(in which Y^3 and Y^4 are independently hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl; or the group -NY^3Y^4 may form a cyclic amine). Exemplary optionally substituted

(C_{6-12})aryl include, but is not limited to, biphenyl, bromophenyl, chlorophenyl, dichlorophenyl, , difluoromethoxyphenyl, dimethylphenyl, ethoxycarbonylphenyl, fluorophenyl, isopropylphenyl, methoxyphenyl, methylphenyl, methylsulfonylphenyl, naphthyl, pentafluorophenyl, phenyl, trifluoromethoxyphenyl, trifluoromethylphenyl, and the like. Optionally substituted (C_{6-12})aryl as used in this Application to define a radical substituent attached to the group R^6 includes trifluoromethoxyphenyl, difluoromethoxyphenyl, 4-fluorophenyl, and the like.

"Arylalkyloxy" means an arylalkyl-O- group in which the arylalkyl groups is as previously described. Exemplary arylalkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Arylalkyloxycarbonyl" means an arylalkyl-O-CO- group in which the arylalkyl groups is as previously described. An exemplary arylalkyloxycarbonyl group is benzyloxycarbonyl.

"Arylalkylthio" means an arylalkyl-S- group in which the arylalkyl group is as previously described. An exemplary arylalkylthio group is benzylthio.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Exemplary aryloxy groups include phenoxy and naphthoxy, each optionally substituted.

"Aryloxycarbonyl" means an aryl-O-C(=O)- group in which the aryl group is as previously described. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulfinyl" means an aryl-SO- group in which the aryl group is as previously described.

"Arylsulfonyl" means an aryl-SO_2- group in which the aryl group is as previously described.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Exemplary arylthio groups include phenylthio and naphthylthio.

"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., (C_{3-12})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). It will be appreciated by those skilled in the art that when cycloalkyl represents an unsaturated cyclic ring assembly such rings may not be attached directly via the carbon carbon multiple bond to an oxygen, nitrogen or sulphur atom.

"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.

"Heteroaroyl" means a heteroaryl-C(=O)- group in which the heteroaryl group is as described herein. Exemplary heteroaryl groups include pyridylcarbonyl.

"Heteroaroylamino" means a heteroaroyl-NH- group in which the heteroaryl moiety is as previously described.

"Heteroaryl" as a group or part of a group denotes: (i) an optionally substituted aromatic monocyclic or multicyclic organic moiety of about 5 to about 13 ring members in which one or more of the ring members is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur (examples of such groups include benzimidazolyl, benzoxazolyl, benzothiazolyl, furyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl groups, optionally substituted by one or more aryl group substituents as defined above except where otherwise defined); (ii) an optionally substituted partially saturated multicyclic heterocarbocyclic moiety in which a heteroaryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure (examples of such groups include pyrindanyl groups, optionally substituted by one or more "aryl group substituents" as defined above, except where otherwise defined). Optional substituents include one or more "aryl group substituents" as defined above, except where otherwise defined. Optionally substituted hetero(C_{5-13})aryl as used in this Application to define R^6 includes benzoxazol-2-yl, 5-tert-butyl-[1,2,4]oxadiazol-3-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, 5-cyclopropyl-1,2,4-oxadiazol-5-yl, 5-cyclopropyl-1,3,4-oxadiazol-2-yl , 5-ethyl-[1,3,4]oxadiazol-2-yl, 5-(4-fluoro-phenyl)-1,2,4-oxadiazol-3-yl, 5-isopropyl-isoxazol-3-yl, 5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl, oxazol-2-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 5-phenyl-1,2,4-oxadiazol-3-yl, 3-(tetrahydro-pyran-4-yl)-1;2,4-oxadiazol-5-yl ,5-thiophen-2-yl-oxazol-2-yl, 5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl, and the like.

"Heteroarylalkyloxy" means an heteroarylalkyl-O- group in which the heteroarylalkyl group is as previously described. Exemplary heteroaryloxy groups include optionally substituted pyridylmethoxy.

"Heteroaryloxy" means an heteroaryl-O- group in which the heteroaryl group is as previously described. Exemplary heteroaryloxy groups include optionally substituted pyridyloxy.

"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, (C_{1-6})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(C_{5-12})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, (C_{1-6})alkyl or a protecting group.

"Isomers", as used in this disclosure, mean the compounds of the present invention having identical molecular formulae but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound, which has one chiral center has two enantiomeric forms of opposite chirality. A "racemic mixture" contains both enantiomers as a 1 : 1 ratio. However, in terms of this application a racemic mixture has been employed when both enantiomers were present irrespective of their ratios. 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 individual diastereomer 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*- 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 illustrations used in this disclosure to describe compounds of the present invention are meant to encompass all possible stereoisomers. Thus, for example, [the name morpholine-4-carboxylic acid {1-[1-(3-*cyclopropyl*-[1,2,4]*oxadiazole*-5-*carbonyl*)-*propylcarbamoyl*]-3,3-*difluoro*-hexyl}-amide is meant to include morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide and morpholine-4-carboxylic acid {(R)-1-[(R)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide and any mixture, racemic or otherwise, thereof.]

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

"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.

"Pharmaceutically acceptable salts" means salts of compounds of present invention 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, cyclopentane propionic 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, methylsulfonic 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, which is convertible in vivo by metabolic means to a compound of present invention. For example an ester of a compound of present invention containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of present invention containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of present invention 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*-tolnoyltartrates, methylsulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates and quinates. Suitable esters of compounds of present invention 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 present invention 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 present invention in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of

present invention are useful in the preparation of compounds of present invention 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.

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

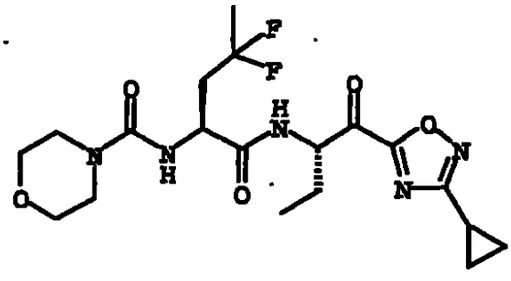
(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(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 present invention 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) wherein R^1 is morpholine-4-carbonyl, X^1 is methylene, R^5 is methyl, R^2 is H and A is  , in which R^3 is ethyl, R^4 is H and X^2 is $C(O)R^6$ where R^6 is 3-cyclopropyl-1,2,4-oxadiazol-5-yl; that is, a compound having the following structure:



is named morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide

However, it is understood that, for a particular compound referred to by both a structural formula and a nomenclature name, if the structural formula and the nomenclature name are inconsistent with each other, the structural formula takes the precedence over the nomenclature name.

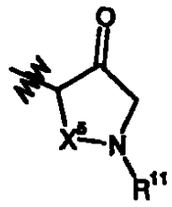
The various features of novelty which characterize the invention are pointed out with particularity in the claims annexed to and forming a part of this disclosure. For a better understanding of the invention, its operating advantages, and specific objects attained by its use, reference should be made to the following description in which there are illustrated and described preferred embodiments of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

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

X^1 may particularly represent methylene.

A may particularly represent  wherein: R^3 is H, (C_{6-12})aryl(C_{2-6})alkyl or (C_{1-6})alkyl optionally substituted by $-X^6OR^9$ [in which X^6 is a bond and R^9 is (C_{1-6})alkyl]; R^4 is H or (C_{1-6})alkyl; and X^2 is CHO, CN or $C(O)R^6$ [in which R^6 is hetero(C_{5-13})aryl optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl].

A may also particularly represent  wherein X^5 is propylene and R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$, in which R^{13} is alkyl or (C_{6-12})aryl.

R^1 may particularly represent $R^{13}C(O)-$ in which R^{13} is hetero(C_{5-12})cycloalkyl.

R^1 may also particularly represent $R^{13}OC(O)-$ in which R^{13} is (C_{6-12})aryl(C_{1-6})alkyl.

R^1 may also particularly represent (C_{1-9})alkyl.

R^1 may also particularly represent hetero(C_{5-12})cycloalkyl.

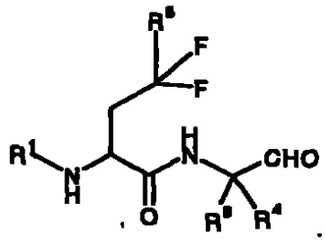
R^2 may particularly represent H.

R^5 may particularly represent (C_{1-9})alkyl.

R^5 may also particularly represent (C_{6-12})aryl(C_{1-6})alkyl.

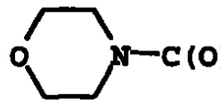
Particular Genera:

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

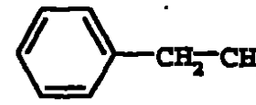


(Ia)

wherein R^1, R^3, R^4 and R^5 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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

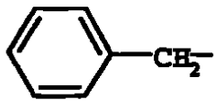
Compounds of Formula (Ia) in which R^1 is $R^{13}C(O)$- and R^{13} is hetero(C_{5-12})cycloalkyl are examples. Compounds of Formula (Ia) in which R^1 is  are particular examples.

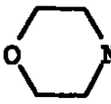
Compounds of Formula (Ia) in which R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl or (C_{1-6})alkyl are examples.

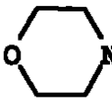
Compounds of Formula (Ia) in which R^3 is H,  or CH_3—CH_2—CH_2— are particular examples.

Compounds of Formula (Ia) in which R^4 is H or methyl are examples.

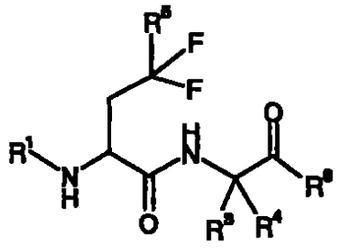
Compounds of Formula (Ia) in which R^5 is (C_{6-12})aryl(C_{1-6})alkyl are examples.

Compounds of Formula (Ia) in which R^5 represents  are particular examples.

A particular group of compounds of the invention are compounds of formula (Ia) in which: R^1 is $R^{13}C(O)$- (especially ); R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl (especially ) or (C_{1-6})alkyl (especially $CH_3-CH_2-CH_2-$); R^4 is H or methyl and R^5 is (C_{6-12})aryl(C_{1-6})alkyl (especially ).

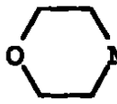
A particular group of compounds of the invention are compounds of formula (Ib) in which: R^1 is $R^{13}C(O)$- (especially ); R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl (especially ) or (C_{1-6})alkyl (especially CH_3-CH_2-); R^4 is H or methyl and R^5 is (C_{6-12})aryl(C_{1-6})alkyl (especially ).

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



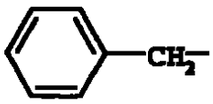
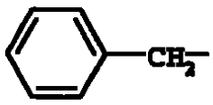
(Ic)

wherein R^1, R^3, R^4, R^5 and R^6 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 (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^1 is $R^{13}C(O)$- and R^{13} is hetero(C_{5-12})cycloalkyl are examples. Compounds of Formula (Ic) in which R^1 is  are particular examples.

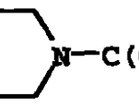
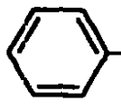
Compounds of Formula (Ic) in which R^3 is (C_{1-6})alkyl optionally substituted by $-X^6OR^9$ [in which X^6 is a bond and R^9 is (C_{1-6})alkyl] are examples. Compounds of Formula (Ic) in which R^3 is CH_3-CH_2- , $CH_3-CH_2-CH_2-$ or CH_3-O-CH_2- are particular examples.

Compounds of Formula (Ic) in which R^4 is H or methyl are examples. Compounds of Formula (Ic) in which R^4 is H are examples.

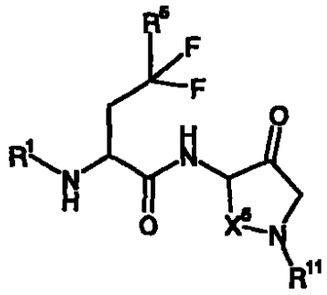
Compounds of Formula (Ic) in which R^5 is (C_{1-9})alkyl or (C_{6-12})aryl(C_{1-6})alkyl are examples. Compounds of Formula (Ic) in which R^5 represents $CH_3CH_2CH_2$ or CH_3 CH_2 or CH_3 or  are particular examples. Compounds of Formula (Ic) in which R^5 represents  are particular examples.

Compounds of Formula (Ic) in which R^6 is hetero(C_{5-13})aryl, optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl, are examples. Exemplary optionally substituted hetero(C_{5-13})aryl groups include optionally substituted benzoxazolyl, oxadiazolyl, isoxazolyl, or oxazolyl. Compounds of Formula (Ic) in which R^6 is benzoxazol-2-yl, 5-tert-butyl-[1,2,4]oxadiazol-3-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, 5-cyclopropyl-1,2,4-oxadiazol-2-yl, 5-cyclopropyl-1,3,4-oxadiazol-2-yl , 5-ethyl-1,3,4-oxadiazol-2-yl, 5-(4-fluoro-phenyl)-1,2,4-oxadiazol-3-yl, 5-isopropyl-

isoxazol-3-yl, 5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl, 5-(5-methyl-thien-2-yl)-oxazol-2-yl, oxazol-2-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 5-phenyl-1,2,4-oxadiazol-3-yl, 5-thiophen-2-yl-oxazol-2-yl, 5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl and the like, are examples. Compounds of Formula (Ic) in which R^6 is benzoxazol-2-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, oxazol-2-yl, are particular examples.

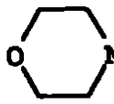
A particular group of compounds of the invention are compounds of formula (Ic) in which: R^1 is $R^{13}C(O)$- (especially ); R^3 is (C_{1-6})alkyl optionally substituted by -X^6OR^9 (especially CH_3-CH_2-, $CH_3-CH_2-CH_2-$ or CH_3-O-CH_2-); R^4 is H and R^5 is (C_{1-9})alkyl or (C_{6-12})aryl(C_{1-6})alkyl (especially ); R^6 is hetero(C_{5-13})aryl, optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, hetero(C_{5-12}) cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl (especially benzoxazol-2-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, oxazol-2-yl and 5-methyl-isoxazol-3-yl)-oxazole-2-yl).

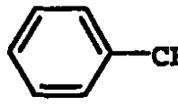
A further particular group of compounds of the invention are compounds of Formula (Id):

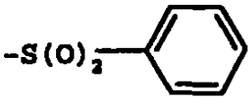


(Id)

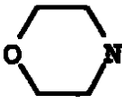
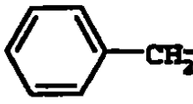
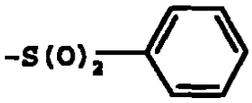
wherein R^1, R^5, R^{11} and X^5 are as hereinbefore described, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Id) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Compounds of Formula (Id) in which R^1 is $R^{13}C(O)$- and R^{13} is hetero(C_{5-12})cycloalkyl are examples. Compounds of Formula (Id) in which R^1 is  are particular examples.

Compounds of Formula (Id) in which R^5 is (C_{6-12})aryl(C_{1-6})alkyl are examples. Compounds of Formula (Id) in which R^5 represents  are particular examples.

Compounds of Formula (Id) in which R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$, in which R^{13} is alkyl or (C_{6-12})aryl are example. Compounds of Formula (Id) in which R^{11} represents $-C(O)OC(CH_3)_3$ or  are particular examples.

Compounds of Formula (Id) in which X^1 is propylene are examples.

A particular group of compounds of the invention are compounds of formula (Id) in which: R^1 is $R^{13}C(O)$- (especially ); R^5 is (C_{6-12})aryl(C_{1-6})alkyl (especially ); R^{11} is $-C(O)OR^{13}$ [especially $-C(O)OC(CH_3)_3$] or $-S(O)_2R^{13}$ (especially ) and X^1 is propylene are examples.

Particular compounds of the present invention include:

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

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

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;
morpholine-4-carboxylic acid {1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-5-methyl-hexyl}-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;
morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide;
morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-butyl}-amide;
morpholine-4-carboxylic acid {1-[1-(5-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;
morpholine-4-carboxylic acid {3,3-difluoro-1-[1-(5-isopropyl-isoxazole-3-carbonyl)-propylcarbamoyl]-hexyl}-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(5-methyl-isoxazol-3-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(oxazole-2-carbonyl)-propylcarbamoyl]-4-phenyl-butyl}-amide;
morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-thiophen-2-yl-oxazole-2-carbonyl)-propylcarbamoyl]-butyl}-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;
morpholine-4-carboxylic acid [1-(2-benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-1-methyl-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;
morpholine-4-carboxylic acid [(S)-1-((S)-1-cyano-3-phenyl-propylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;
morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;
morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-formyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide;
morpholine-4-carboxylic acid {(S)-1-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;
morpholine-4-carboxylic acid {(S)-1-[1-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-propylcarbamoyl]-

3,3-difluoro-4-phenyl-butyl}-amide;
morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propylcarbamoyl]-butyl}-amide;
[(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-carbamic acid benzyl ester;
(S)-4,4-difluoro-5-phenyl-2-(tetrahydro-pyran-4-ylamino)-pentanoic acid cyanomethyl-amide;
(S)-4,4-difluoro-2-isobutylamino-5-phenyl-pentanoic acid cyanomethyl-amide;
morpholine-4-carboxylic acid [(S)-1-((S)-1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;
(S)-4-{(S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoylamino}-3-oxo-azepane-1-carboxylic acid tert-butyl ester;
morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-ethyl-1,3,4-oxadiazol-2-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide;
morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,3,4-oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;
morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;
morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Pharmacology and Utility:

The compounds of the invention are inhibitors of cathepsin S and, as 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 may be useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, irritable bowel disease, rheumatoid arthritis and Hashimoto's 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 is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsin S may be 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 31, 32, 33, 34, *infra*.

The compounds of the invention are also inhibitors of cathepsin K and B and, as such, are useful for treating diseases in which cathepsin K and B activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention may be useful in treating pain, osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer or skin cancer.

Administration and Pharmaceutical Compositions:

In general, compounds of the present invention 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 the invention may range from about 1 micrograms per kilogram body weight (μg/kg) per day to about 60 milligram per kilogram body weight (mg/kg) per day, typically from about 1 μg/kg/day to about 20 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 80 μg /day to about 4.8 g/day, typically from about 80 μg /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 the invention for treating a given disease.

The compounds of the invention 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 the invention 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., 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 the invention in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of the invention for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of the invention are described in Example 35.

Chemistry:

Processes for Making Compounds of the invention:

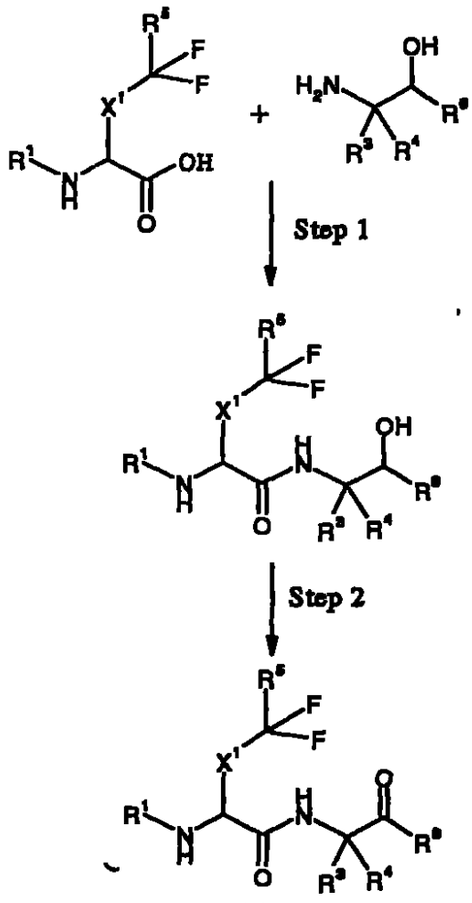
Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R.C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

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 examples see T.W. Greene and P. G. M. Wuts in

"Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

Compounds of the invention can be prepared by proceeding according to Reaction Scheme 1:

Reaction Scheme 1



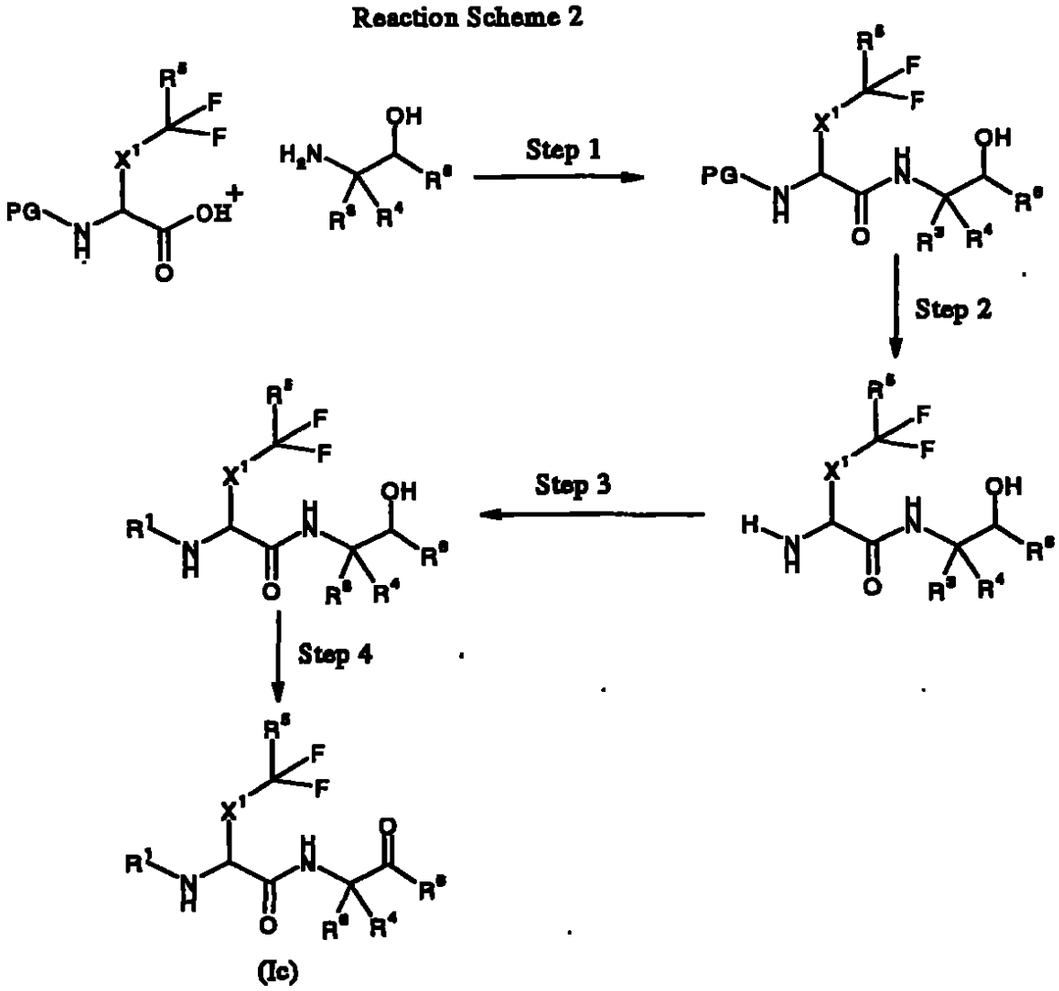
(Ic)

in which each X^1, R^1, R^3, R^4, R^5, and R^6 are as defined in the Summary of the Invention. Thus, in step 1, an acid may be condensed with an amino compound of formula to give a β-hydroxy amide. The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *O*-(7-azabenzotrizol-1-yl)-1,1,3,3, tetramethyluroniumhexafluorophosphate (HATU), or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature and requires 2 to 10 hours to complete. The β-hydroxy amide may then be oxidized, in step 2, to give a compound of formula (Ic). The oxidation reaction may conveniently be carried out

using Dess-Martin periodinane in an inert solvent, such as dichloromethane, and at a temperature from about 0°C to about room temperature.

Alternatively the compounds of this invention can be prepared by proceeding according to Reaction Scheme 2:

Reaction Scheme 2



(Ic)

in which each X^1, R^1, R^3, R^4, R^5, and R^6 are as defined in the Summary of the Invention and PG is a suitable protecting group. Thus, in step 1, an acid may be condensed with an amino compound of formula to give a β-hydroxy amide. Removal of the protecting group (Step 2) followed by introduction of R^1 group (Step 3) and oxidation (Step 4) to give a compound of formula (Ic).

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.

^{1}H nuclear magnetic resonance spectra (NMR) were recorded on Varian Mercury-300 or Unity-400 or UnityPlus-500 or Inova-500machines. In the nuclear magnetic resonance spectra (NMR) the chemical shifts (δ) are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significances: s = singlet; d = doublet; t = triplet; m = multiplet; q = quartet; dd = doublet of doublets; ddd = doublet of double doublets.

The high pressure liquid chromatography (HPLC) was run on Kromasil 10 micron, 100A Silica, 4.6mmID x 250 mm column using mixture of Heptane/THF/1,2-Dichloroethane as Mobile Phase.
Mass spectra were run on Agilent 1100 series or MICROMASS LCT-TOF MS.
The thin layer chromatography (TLC) R_f values were determined using Merck silica plates.

Abbreviations

CBZ- Benzyloxy carbonyl

DAST- (Diethylamino)sulfur trifluoride

DCM- Dichloromethane

DMF- Dimethyl formamide

DMSO - Dimethyl sulfoxide

DTT - Dithiothreitol

EDCI - N-(3-Dimethylaminopropyl)-N^1-ethylcarbodiimide hydrochloride

EDTA - Ethylenediaminetetraacetic acid

EtOAc – Ethyl acetate

HOBT - 1-Hydroxybenzotriazole hydrate

MeOH - Methanol

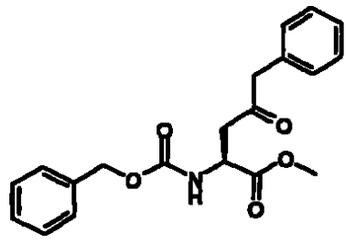
MES - 2-Morpholinoethanesulfonic acid

PyBOP - (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

THF - Tetrahydrofuran

REFERENCE 1

(S)-2-Benzyloxycarbonylamino-4-oxo-5-phenyl-pentanoic acid methyl ester:

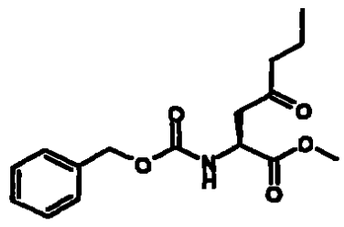


To a suspension of copper (I) bromide (4.26 mmol, 611.1 mg) in 3 mL of dry THF under N_2 was added a solution of lithium bromide (8.52 mmol, 740 mg) in 5 mL of dry THF. The mixture was stirred at room temperature for 20 min, and then cooled to –78°C. A solution of benzyl magnesium chloride (20 wt. % in THF, 4.26 mmol, 3.25 mL) followed by a solution of (S)-2-benzyloxycarbonylamino-3-chlorocarbonyl-propionic acid methyl ester [Ref: Synth. Comm 1993, 23(18), 2511-2526] (3.59 mmol) in 7 mL of dry THF was added. The mixture was stirred at –78 °C for 30 min and then quenched with saturated NH_4Cl (50 mL). The mixture was extracted twice with ethyl acetate (30 mL). The organic layers were dried over magnesium sulfate and then concentrated in vacuum. The residue was purified over 35 g silica gel, eluting with EtOAc:Heptane (1:1) to afford (S)-2-benzyloxycarbonyl-amino-4-oxo-5-phenyl-pentanoic acid methyl ester (1.07 g, 84%).

^{1}H NMR ($CDCl_3$): δ 7.4-7.17 (m, 10H), 5.73 (d, J = 8.2 Hz, 1H), 5.11 (s, 2H), 4.57 (m, 1H), 3.7 (2xs, 5H), 3.24 (dd, J = 18.5, 4.4 Hz, 1H), 3.0 (dd, J = 18.2, 4.1 Hz, 1H); LC/MS: 100% 378 (M+Na).

REFERENCE 2

(S)-2-Benzyloxycarbonylamino-4-oxo-heptanoic acid methyl ester

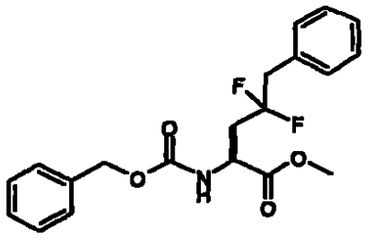


By proceeding in a similar manner to Reference Example 1 above but using propyl magnesium chloride instead of benzyl magnesium chloride there was prepared (S)-2-benzyloxycarbonylamino-4-oxo-heptanoic acid methyl ester.

^{1}H NMR ($CDCl_3$): δ 7.35 (m, 5H), 5.78 (d, J = 8.5 Hz, 1H), 5.13 (s, 2H), 4.58 (m, 1H), 3.75 (s, 3H), 3.2 (dd, J = 18.3, 4.2 Hz, 1H), 2.96 (dd, J = 18.3, 4.1 Hz, 1H), 2.4 (m, 2H), 1.6 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); LC/MS: 330 (M+Na).

REFERENCE 3

(S)-2-Benzyloxycarbonylamino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester:

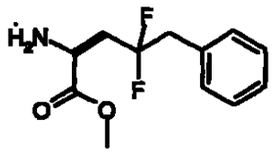


A mixture of 2-benzyloxycarbonylamino-4-oxo-5-phenyl-pentanoic acid methyl ester (3.310g, 9.31 mmol) and DAST (7 mL) was stirred at room temperature over 3 days. The mixture was diluted with dichloromethane (100 mL) and carefully added to 0.5N NaOH solution (150 mL). The aqueous layer was extracted with dichloromethane (50 mL). The organic layers were dried over magnesium sulfate and then concentrated in vacuum. The residue was purified over 110 g silica gel, eluting with EtOAc:Heptane (1:4 then 1:3) to afford (S)-2-benzyloxycarbonylamino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester (1.797g, 51.1%).

^{1}H NMR ($CDCl_3$) δ 7.3 (m, 10H), 5.43 (d, J = 7.6 Hz, 1H), 5.14 (s, 2H), 4.65 (m, 1H), 3.74 (s, 3H), 3.2 (t, J = 16.5 Hz, 2H), 2.4 (m, 2H); LC/MS: 97% 400 (M+Na).

REFERENCE 4

(S)-2-Amino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester hydrochloride:

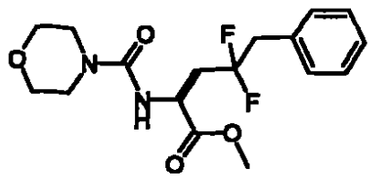


A solution of (S)-2-benzyloxycarbonylamino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester (7.806g, 20.68 mmol) in 120 mL of methanol and 4 M HCl in dioxane (41.4 mmol, 10.3 mL) was hydrogenated over 10% Pd/C (1.0g) at 50 psi. After 8 hr, another portion of 10% Pd/C (1.0g) was added. After 24 hr, the catalyst was removed by filtration over a pad of Celite, and the filtrate was concentrated in vacuum. The resulting light yellow solid was dissolved in a minimum amount of methanol and slowly added to ether (150 mL). The resulting slurry was aged for 30 min and then filtered. The white solid was dried under suction to afford (S)-2-amino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester hydrochloride (4.950g, 85.5%).

^{1}H NMR (DMSO-D_6): δ 8.6 (b, 3H), 7.3 (m, 5H), 4.26 (t, J = 6 Hz, 1H), 3.73 (s, 3H), 3.3 (t, J = 17.5 Hz, 2H), 2.55 (m, 2H); LC/MS: 100% 244 (M+1).

REFERENCE 5

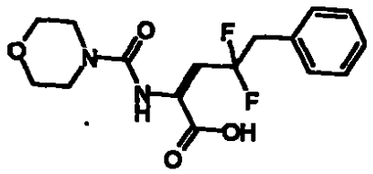
(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid methyl ester:



To a mixture of (S)-2-amino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester hydrochloride (2.50g, 8.94 mmol) and diisopropyl amine (22.3 mmol, 2.89 g) in dry dichloromethane (40 mL) under N_2 was added drop wise morpholine carbonyl chloride (13.4 mmol, 2.0 g). The mixture was stirred at room temperature for 15 hours, and then diluted with water (50 mL). The aqueous layer was extracted with dichloromethane (30 mL). The organic layers were dried over magnesium sulfate and then concentrated in vacuum. Purification over 110 g silica gel, eluting with EtOAc:Heptane (1:1, then 2:1) afforded (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid methyl ester (2.82g, 88.5%). ^{1}H NMR ($CDCl_3$): δ 7.3 (m, 5H), 5.16 (d, J = 7.5 Hz, 1H), 4.75 (dd, J = 13, 6 Hz, 1H), 3.73 (s, 3H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, J = 16.7 Hz, 2H), 2.4 (m, 2H). LC/MS: 100% 357 (M+1).

REFERENCE 6

(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid:

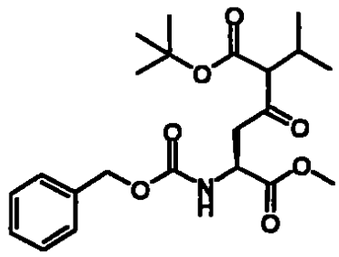


To a solution of (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid methyl ester (2.81 g, 7.88 mmol) in MeOH:H_2O (2:1 vol, 40 mL) was added LiOH mono hydrate (662 mg, 15.76 mmol). The mixture was stirred at room temperature for 2.5h, and then diluted with water (30 mL). Methanol was removed in vacuum. The pH was adjusted to pH 1 with 6N HCl and the aqueous layer was extracted with dichloromethane (2x30 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum to afford (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid (2.509g, 93%).

^{1}H NMR ($CDCl_3$): δ 8.2 (b, 1H), 7.3 (m, 5H), 5.3 (m, 1H), 4.6 (m, 1H), 3.65 (m, 4H), 3.4 (m, 4H), 3.2 (t, J = 16.5 Hz, 2H), 2.4 (m, 2H); LC/MS: 94% 343 (MH^+)

REFERENCE 7

(S)-5-Benzyloxycarbonylamino-2-isopropyl-3-oxo-hexanedioic acid 1-tert-butyl ester 6-methyl ester:

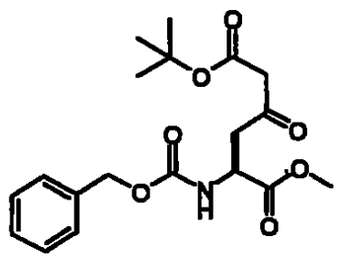


To a cooled to –78 °C solution of diisopropyl amine (3.53g, 34.88 mmol) in dry THF (20 mL) under N_2 was added drop wise a solution of n-butyl lithium (2.5 M in hexane, 34.88 mmol, 13.95 mL). The mixture was stirred at –78°C for 30 min then a solution of 3-Methyl-butyric acid tert-butyl ester (34.88 mmol, 5.52 g) in THF (40 mL) was added. The mixture was stirred at –78 °C for 30 min then a solution of (S)-2-Benzyloxycarbonylamino-3-chlorocarbonyl-propionic acid methyl (Ref: Synth. Comm 1993, 23(18), 2511-2526) (16.6 mmol) in 30 mL of dry THF was added drop wise. After stirring for another 2 hr at –78 °C, the reaction was quenched with 50 mL of 1N HCl and warmed to room temperature. The pH was adjusted to pH 3 with 1N NaOH and the THF was removed in vacuum. The organic layer was extracted with EtOAc (2x60 mL). The organic layers were dried over magnesium sulfate and then concentrated in vacuum. The residue was purified over 90 g silica gel, eluting with EtOAc:Heptane (1:3 then 1:2) afforded (S)-5-Benzyloxycarbonylamino-2-isopropyl-3-oxo-hexanedioic acid 1-tert-butyl ester 6-methyl ester (2.417 g, 34.5%).

^{1}H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.73 (d, J = 8.4 Hz, 1H), 5.12 (s, 2H); 4.6 (m, 1H), 3.74 (s, 3H), 3.39-3.06 (m, 3H), 2.4 (m, 1H), 1.45 (2s, 9H), 0.98 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H); LC/MS: 100% 422 (M+1).

REFERENCE 8

(S)-2-Benzyloxycarbonylamino-4-oxo-hexanedioic acid 6-tert-butyl ester 1-methyl ester:



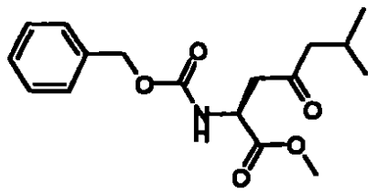
To a solution of N-CBZ L-aspartic acid 1-methyl ester (1.00 g, 3.55 mmol) in dry tetrahydrofuran (17 mL) was added carbonyl diimidazole (634.1 mg, 3.91 mmol). The mixture was stirred at room temperature for 6 hr then the magnesium salt of mono-tert butyl malonate (1.339 g, 3.91 mmol) (prepared according to Angew. Chem. Int. Ed. Engl. 1979, 18(1), 72-74) was added. The mixture was stirred at room temperature for another 20 h, then concentrated in vacuum. The residue was

partitioned between ether (60 mL) and 0.5 N HCl (60 mL). The organic layer was washed with saturated $NaHCO_3$ solution (50 mL) then dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 35 g of silica gel, eluted with EtOAc:Heptane (1:1) to afford (S)-2-Benzyloxycarbonylamino-4-oxo-hexanedioic acid 6-tert-butyl ester 1-methyl ester (1.17 g, 87%).

^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.73 (d, J = 8.3 Hz, 1H), 5.1 (s, 2H), 4.6 (m, 1H), 3.75 (s, 3H), 3.37 (s, 2H), 3.32 (dd, J = 18.7, 4.3 Hz, 1H), 3.13 (dd, J = 18.5, 4.1 Hz, 1H), 1.47 (s, 9H);
LC/MS: 93% 402 (M+Na).

REFERENCE 9

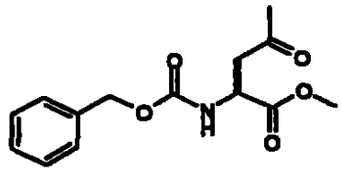
(S)-2-Benzyloxycarbonylamino-6-methyl-4-oxo-heptanoic acid methyl ester:



A solution of 5-Benzyloxycarbonylamino-2-isopropyl-3-oxo-hexanedioic acid 1-tert-butyl ester 6-methyl ester (1.06 g, 2.51 mmol) and p-toluenesulfonic acid monohydrate (35.8 mg, 0.19 mmol) in toluene (20 mL) was heated to reflux under N_2 for 6.5 hr. The mixture was cooled to room temperature, and concentrated in vacuum. The residue was purified over 35 g silica gel, eluting with EtOAc:Heptane (1:4) to afford (S)-2-Benzyloxycarbonylamino-6-methyl-4-oxo-heptanoic acid methyl ester (727 mg, 90%). ^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.78 (d, J = 9.1 Hz, 1H), 5.13 (s, 2H), 4.6 (m, 1H), 3.74 (s, 3H), 3.2 (dd, J = 18.3, 4.4 Hz, 1H), 2.95 (dd, J = 18.2, 4.0 Hz, 1H), 2.3 (m, 2H), 2.1 (m, 1H), 0.92 (d, J = 6.7 Hz, 6H); LC/MS: 77% 322 (MH^+).

REFERENCE 10

(S)-2-Benzyloxycarbonylamino-4-oxo-pentanoic acid methyl ester:



By proceeding in a similar manner to Reference Example 9 above but using 2-benzyloxycarbonylamino-4-oxo-hexanedioic acid 6-tert-butyl ester 1-methyl ester there was prepared (S)-2-benzyloxycarbonylamino-4-oxo-pentanoic acid methyl ester

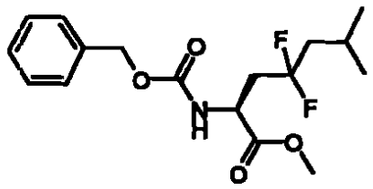
^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.76 (d, J = 8.1 Hz, 1H), 5.14 (s, 2H), 4.57 (m, 1H), 3.75 (s, 3H), 3.23 (dd, J = 18.4, 4.3 Hz, 1H), 3.0 (dd, J = 18.4, 4.3 Hz, 1H), 2.18 (s, 3H); LC/MS: >85% 280 (MH^+).

Alternate Method

To a cooled to 0°C suspension of copper (I) iodide in ether (20 mL) under N_2 was slowly added methyl lithium (1.6 M solution in ether, 21.3 mmol, 13.3 mL). The mixture was stirred at 0°C for 10 min then cooled to -78°C. A solution of 3.55 mmol of (S)-2-Benzyloxycarbonylamino-3-chlorocarbonyl-propionic acid methyl ester (Ref: Synth. Comm 1993, 23(18), 2511-2526) in 12 mL of dry THF was added drop wise. The mixture was stirred at -78 °C for 30 min then quenched by adding methanol (2 mL). The mixture was poured into saturated NH_4Cl (80 mL) and extracted with ether (2x40 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 35 g silica gel, eluted with EtOAc:Heptane (1:1) to afford (S)-2-benzyloxycarbonylamino-4-oxo-pentanoic acid methyl ester (261 mg, 26%).

REFERENCE 11

(S)-2-Benzyloxycarbonylamino-4,4-difluoro-6-methyl-heptanoic acid methyl ester:

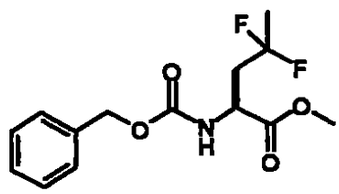


A mixture of (S)-2-benzyloxycarbonylamino-6-methyl-4-oxo-heptanoic acid methyl ester (915 mg, 2.85 mmol) and DAST (3 mL, XS) was stirred at 35°C for 47h. The mixture was diluted with dichloromethane (50 mL) and carefully added to saturated $NaHCO_3$ solution (150 mL). The aqueous layer was extracted with dichloromethane (30 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 35 g silica gel, eluting with EtOAc:Heptane (1:4) to afford (S)-2-Benzyloxycarbonylamino-4,4-difluoro-6-methyl-heptanoic acid methyl ester (156 mg, 16%).

^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.48 (d, J = 7.9 Hz, 1H), 5.15 (s, 2H), 4.61 (q, J = 5.9 Hz, 1H), 3.78 (s, 3H), 2.4 (m, 2H), 1.95 (m, 1H), 1.8 (m, 2H), 0.98 (d, J = 6.6 Hz, 6H); LC/MS: 98% 366 (M+Na).

REFERENCE 12

(S)-2-Benzyloxycarbonylamino-4,4-difluoro-pentanoic acid methyl ester

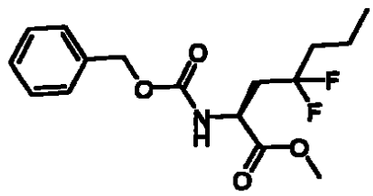


By proceeding in a similar manner to Reference Example 11 above but using (S)-2-benzyloxycarbonylamino-4-oxo-pentanoic acid methyl ester there was prepared (S)-2-benzyloxycarbonylamino-4,4-difluoro-pentanoic acid methyl ester

^{1}H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.46 (d, J = 7.1 Hz, 1H), 5.15 (s, 2H), 4.61 (q, J = 7.3 Hz, 1H), 3.78 (s, 3H), 2.45 (m, 2H), 1.67 (t, J = 18.8 Hz, 3H); LC/MS: 94% 324 (M+Na).

REFERENCE 13

(S)-2-Benzyloxycarbonylamino-4,4-difluoro-heptanoic acid methyl ester

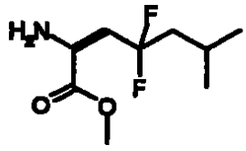


By proceeding in a similar manner to Reference Example 11 above but using (S)-2-benzyloxycarbonylamino-4-oxo-heptanoic acid methyl ester there was prepared (S)-2-benzyloxycarbonylamino-4,4-difluoro-heptanoic acid methyl ester.

LC/MS: 96% 330 (MH^+), 352 (M+Na).

REFERENCE 14

(S)-2-Amino-4,4-difluoro-6-methyl-heptanoic acid methyl ester hydrochloride:

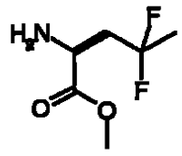


A solution of (S)-2-benzyloxycarbonylamino-4,4-difluoro-6-methyl-heptanoic acid methyl ester: (333 mg, 0.97 mmol) in methanol (10 mL) and 4 M HCl in dioxane (4 mmol, 1 mL) was hydrogenated over 10% Pd/C (150 mg) at 55 psi. After 7 hr, another portion of 10% Pd/C (200 mg) was added and the hydrogenation resumed. After 5.5 hr, the reaction did not progress. Catalyst was filtered and the filtrate was concentrated in vacuum and subjected to the hydrogenation conditions. After 6.5 hr, the catalyst was removed by filtration over a pad of Celite, and the filtrate was concentrated in vacuum to afford (S)-2-amino-4,4-difluoro-6-methyl-heptanoic acid methyl ester hydrochloride as a yellow sticky solid (240 mg, quant.).

^{1}H NMR ($CDCl_3$): δ 4.8 (b, 3H), 4.35 (b, 1H), 3.84 (s, 3H), 2.6 (m, 2H), 1.9 (m, 3H), 0.99 (d, J = 6.2 Hz, 6H); LC/MS: 90% 210 (M+1).

REFERENCE 15

(S)-2-Amino-4,4-difluoro-pentanoic acid methyl ester hydrochloride:

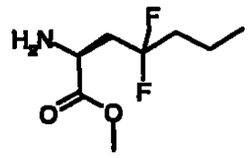


By proceeding in a similar manner to Reference Example 14 above but using (S)-2-benzyloxycarbonylamino-4,4-difluoro-pentanoic acid methyl ester there was prepared (S)-2-amino-4,4-difluoro-pentanoic acid methyl ester hydrochloride.

^{1}H NMR ($CDCl_3$): δ 4.8 (s, 3H), 4.37 (m, 1H), 3.86 (s, 3H), 2.4-2.8 (m, 2H), 1.73 (t, J = 18.9 Hz, 3H); LC/MS: 100% 168 (M+1).

REFERENCE 16

(S)-2-Amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride

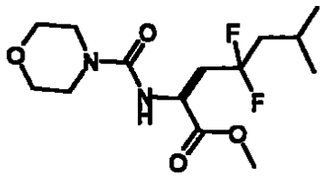


By proceeding in a similar manner to Reference Example 14 above but using (S)-2-benzyloxycarbonylamino-4,4-difluoro-heptanoic acid methyl ester there was prepared (S)-2-amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride

LC/MS: 100% 196 (MH^+).

REFERENCE 17

(S)-4,4-Difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester:

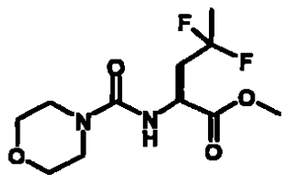


To a mixture of (S)-2-amino-4,4-difluoro-6-methyl-heptanoic acid methyl ester hydrochloride (238 mg, 0.97 mmol) and diisopropyl amine (2.42 mmol, 313 mg) in dry dichloromethane (5 mL) under N_2 was added drop wise morpholine carbonyl chloride (1.45 mmol, 218 mg). The mixture was stirred at room temperature for 23 h, then diluted with dichloromethane (25 mL) and washed with dilute HCl (30 mL), and saturated $NaHCO_3$ (30 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum. Purification over 12 g silica gel, eluting with EtOAc:Heptane (1:1, then 2:1) afforded (S)-4,4-Difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester (206 mg, 66%).

^{1}H NMR ($CDCl_3$): δ 5.2 (d, J = 7.4 Hz, 1H), 4.72 (dd, J = 13, 6 Hz, 1H), 3.78 (s, 3H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 1.95 (m, 1H), 1.8 (m, 2H), 0.99 (d, J = 6.4 Hz, 6H);LC/MS: 90% 345 (M+Na).

REFERENCE 18

(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid methyl ester:

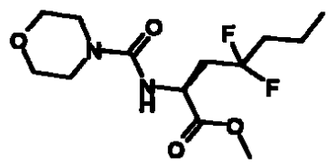


By proceeding in a similar manner to Reference Example 17 above but using (S)-2-amino-4,4-difluoro-pentanoic acid methyl ester hydrochloride there was prepared (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid methyl ester.

^{1}H NMR ($CDCl_3$): δ 5.18 (d, J = 7.5 Hz, 1H), 4.71 (q, J = 7 Hz, 1H), 3.78 (s, 3H), 3.71 (m, 4H), 3.4 (m, 4H), 2.37-2.55 (m, 2H), 1.67 (t, J = 18.7 Hz, 3H); LC/MS: 100% 303 (M+ Na).

REFERENCE 19

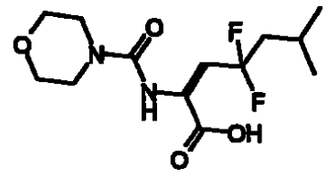
(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester



By proceeding in a similar manner to Reference Example 17 above but using (S)-2-amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride there was prepared (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester LC/MS: 100% 309 (MH^+).

REFERENCE 20

(S)-4,4-Difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid:



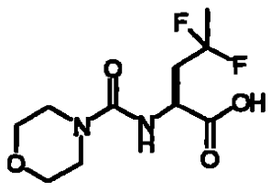
To a solution of methyl ester (205mg, 0.63 mmol) in MeOH: H2O (2:1 vol, 4 mL) was added LiOH-mono hydrate (80 mg, 1.9 mmol). The mixture was stirred at room temperature for 21h, then diluted with water (15 mL) and extracted with ether (20 mL). The pH of the aqueous layer was adjusted to pH 1 with 1N HCl and it was extracted with dichloromethane (2x20 mL). The organic layers were

dried over magnesium sulfate and concentrated in vacuum to afford (S)-4,4-dDifluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (168 mg, 86%).

^{1}H NMR ($CDCl_3$): δ 6.4 (b, 1H), 5.3 (d, J = 6.2 Hz, 1H), 4.6 (m, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.5 (m, 2H), 2.0 (m, 1H), 1.8 (m, 2H), 1.0 (d, J = 6.6 Hz, 6H); LC/MS: 90% 309 (M+1).

REFERENCE 21

(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid:

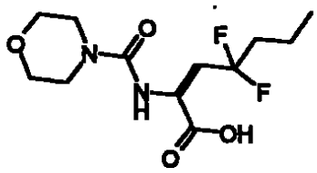


By proceeding in a similar manner to Reference Example 20 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid methyl ester there was prepared (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid

^{1}H NMR ($CDCl_3$): δ 5.9 (b, 1H), 5.29 (d, J = 6.3 Hz, 1H), 4.6 (m, 1H), 3.71 (m, 4H), 3.4 (m, 4H), 2.38-2.65 (m, 2H), 1.70 (t, J = 18.9 Hz, 3H); LC/MS: 100% 267 (M+ 1).

REFERENCE 22

(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid

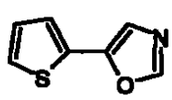


By proceeding in a similar manner to Reference Example 20 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester there was prepared (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid

^{1}H NMR ($CDCl_3$): δ 5.3 (b, 1H), 5.25 (d, J = 5.4 Hz, 1H), 4.6 (m, 1H), 3.71 (m, 4H), 3.4 (m, 4H), 2.6-2.3 (m, 2H), 1.9 (m, 2H), 1.55 (m, 2H), 1.0 (t, J = 7.3 Hz, 3H); LC/MS: 83% 295 (M+1).

REFERENCE 23

5-Thiophen-2-yl-oxazole



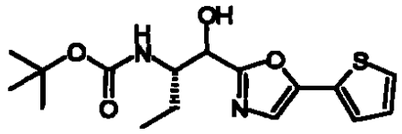
To a solution of p-toluenesulfonylmethyl isocyanide (3.0 g, 15.36 mmol) and Thiophene-2-carboxaldehyde (1.72 g, 15.36 mmol) in methanol (45 mL) under N_2 was added potassium carbonate

(2.12 g, 15.36 mmol). The mixture was heated to reflux for 5 hr, then cooled and concentrated in vacuum (cold water bath). The residue was partitioned between ether (100 mL) and water (100 mL). The organic layer was washed with water (100 mL), dried over magnesium sulfate and then concentrated in vacuum. The residue was purified over 35 g silica gel, eluted with ethyl acetate: heptane (1:5) to afford 5-thiophen-2-yl-oxazole (0.852 g, 37%).

^{1}H NMR ($CDCl_3$): δ 7.9 (s, 1H), 7.3 (m, 2H), 7.2 (s, 1H), 7.1 (dd, J = 5, 3.8 Hz, 1H); LC/MS: 100% 152 (M+1).

REFERENCE 24

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

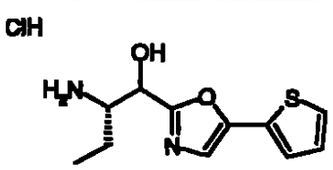


To a solution of 5-thiophen-2-yl-oxazole (0.85 g, 5.62 mmol) in dry THF (4 mL) was added triethylborane (1.0 M in THF, 5.62 mmol, 5.62 mL). The mixture was stirred at room temperature for 45 min, then cooled to –78°C and n-butyl lithium (1.6 M in hexane, 5.62 mmol, 3.51 mL) was added drop wise. The mixture was stirred at –78°C for 45 min then a solution of (1-Formyl-propyl)-carbamic acid tert-butyl ester (2.81 mmol, 0.526 g) in dry THF (3 mL) was added slowly. The mixture was stirred at –78°C for 4 h, then warmed to 0°C and quenched by adding 30 mL of 10% (vol) HOAc in ethanol. The mixture was stirred at room temperature for 18 hr and then concentrated in vacuum. The residue was purified over 90 g of silica gel, eluted with ethyl acetate: heptane (1:2 then 1:1) to afford {(S)-1-[hydroxy-(5-thiophen-2-yl-oxazol-2-yl)-methyl]-propyl}-carbamic acid tert-butyl ester (363 mg, 38%) as yellow oil.

^{1}H NMR ($CDCl_3$): δ (mixture of isomers) 7.35 (m, 2H), 7.1 (m, 2H), 4.9 (m, 2H), 4.0 (b, 1H), 3.6 (m, 1H), 1.8-1.55 (m, 2H), 1.4 and 1.3 (2s, 9H), 1.0 and 0.9 (2t, J = 7.4 Hz, 3H); LC/MS: 100 339 (M+1).

REFERENCE 25

(S)-2-Amino-1-(5-thiophen-2-yl-oxazol-2-yl)-butan-1-ol hydrochloride



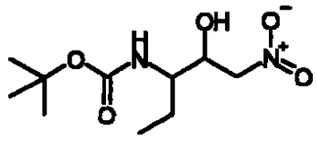
To a solution of {(S)-1-[hydroxy-(5-thiophen-2-yl-oxazol-2-yl)-methyl]-propyl}-carbamic acid tert-butyl ester (361 mg, 1.07 mmol) in dry dichloromethane (3 mL) was added 4N HCl in dioxane (3.0

mL, XS). The mixture was stirred at room temperature for 16 h, then concentrated in vacuum to afford (S)-2-Amino-1-(5-thiophen-2-yl-oxazol-2-yl)-butan-1-ol hydrochloride as a tan solid (quant.).

^{1}H NMR ($CDCl_3$): δ 7.5 (dd, J = 5.2, 1.2 Hz, 1H), 7.4 (dd, J = 3.6, 1.1 Hz, 1H), 7.3 (s, 1H), 7.1 (dd, J = 5, 3.6 Hz, 1H), 4.8 (m, 3H), 3.6 (m, 2H), 3.3 (b, 1H), 1.75 (m, 2H), 1.0 (t, J = 7.5 Hz, 3H); LC/MS: 100% 239 (M+1).

REFERENCE 26

(1-Ethyl-2-hydroxy-3-nitro-propyl)-carbamic acid tert-butyl ester

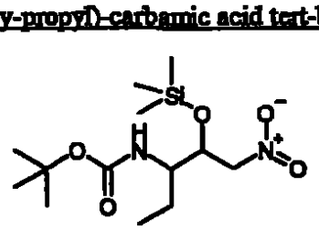


To a solution of (1-formyl-propyl)-carbamic acid tert-butyl ester (1.0 g, 5.34 mmol) in dry THF (10 mL) and ethanol was added nitromethane (3.91 g, 64.09 mmol) followed by triethylamine (2.70 g, 26.7 mmol). The mixture was stirred at room temperature for 22 h, and then concentrated in vacuum. The residue was diluted with ether (50 mL) and washed with concentrated NH_4Cl (60 mL). The ether layer was dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 35 g silica gel, eluted with ethyl acetate: heptane (1:3) to afford the desired alcohol (1.09 g, 82%) as a light yellow oily solid.

^{1}H NMR ($CDCl_3$): δ 4.2-4.8 (m, 4H), 3.15-3.8 (m, 2H), 1.69-1.6 (m, 2H), 1.47 (2xs, 9H), 1.02 and 1.0 (2xt, J = 7.1 Hz, 3H) LC/MS: 2 isomers, total 100% 149 (M-BOC+1).

REFERENCE 27

(1-Ethyl-3-nitro-2-trimethylsilanyloxy-propyl)-carbamic acid tert-butyl ester

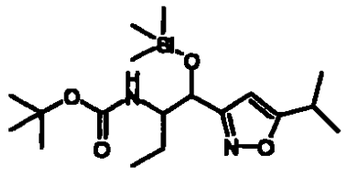


To a mixture of (1-ethyl-2-hydroxy-3-nitro-propyl)-carbamic acid tert-butyl ester (1.83 g, 7.37 mmol) and triethylamine (1.49 g, 14.75 mmol) in dry dichloromethane (25 mL) under N_2 was added trimethylsilyl chloride (1.20 g, 11.05 mmol). The mixture was stirred at room temperature for 24 h, then diluted with 40 mL of dichloromethane and washed with water (40 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 110 g silica gel, eluted with ethyl acetate: heptane (1:4) to afford (1-ethyl-3-nitro-2-trimethylsilanyloxy-propyl)-carbamic acid tert-butyl ester (1.505 g, 86%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 4.4-4.65 (m, 4H); 3.55 (m, 1H), 1.2-1.7 (m, 11H), 0.98 (2xt, J = 7.4 Hz, 3H), 0.13 (2s, 9H); LC/MS: 2 isomers, total 100% 221 (M-BOC+1).

REFERENCE 28

{1-[(5-Isopropyl-isoxazol-3-yl)-trimethylsilanyloxy-methyl]-propyl}-carbamic acid tert-butyl ester

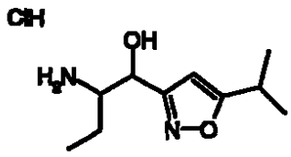


To a solution of (1-Ethyl-3-nitro-2-trimethylsilanyloxy-propyl)-carbamic acid tert-butyl ester (918 mg, 2.86 mmol), 1,4-Phenylene diisocyanate (1.38 g, 8.5 mmol) and 3-methyl-1-butyne (586 mg, 8.5 mmol) in dry toluene (15 mL) under N_2 was added triethylamine (10 drops). The mixture was heated to 50°C in a sealed vial for 28 h, and then cooled to room temperature Water (1 mL) was added and the mixture was stirred for an additional 2 h, then filtered. The filtrate was concentrated in vacuum and the residue was purified over 35 g silica gel, eluted with ethyl acetate: heptane (1:5) to afford {1-[(5-Isopropyl-isoxazol-3-yl)-trimethylsilanyloxy-methyl]-propyl}-carbamic acid tert-butyl ester (764 mg, 72%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 6.0 (2s 1H), 4.4-4.9 (m, 2H), 3.7 (m, 1H), 3.0 (m, 1H), 1.2-1.6 (m, 17H), 1.0 (m, 3H), 0.11 and 0.1 (2xs, 9H); LC/MS: 2 isomers, total 67% 271 (M-BOC+1).

REFERENCE 29

2-Amino-1-(5-isopropyl-isoxazol-3-yl)-butan-1-ol hydrochloride

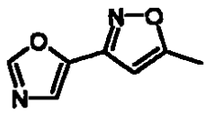


To a solution of {1-[(5-Isopropyl-isoxazol-3-yl)-trimethylsilanyloxy-methyl]-propyl}-carbamic acid tert-butyl ester in dry dichloromethane (5 mL) under N_2 was added a 4M solution of HCl in dioxane (5.0 mL, XS). The mixture was stirred at room temperature for 22 h, then concentrated in vacuum to afford the amine salt (475 mg, 99%) as a tan solid.

^{1}H NMR ($CDCl_3$): δ 6.25 (2xs, 1H), 5.0 (d, J = 3.9 Hz, 1H), 4.8 (d, J = 6.8 Hz, 1H), 3.4 (m, 1H), 3.1 (m, 1H), 1.5-1.7 (m, 2H), 1.3 (d, J = 6.8 Hz, 6H); 1.0 (t, J = 6.7 Hz, 3H); LC/MS: 100% 199 (M+1).

REFERENCE 30

5-Methyl-3-oxazol-5-yl-isoxazole

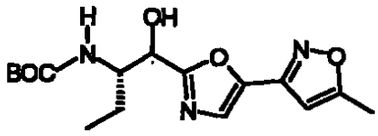


Diisobutylaluminum hydride (1.0M in DCM, 25.5ml, 25.5 mmol) was added drop wise over 20 minutes to a solution of methyl-5-methylisoxazole-3-carboxylate (3.0 gm, 21.3 mmol) in 35 ml of dry methylene chloride, with stirring at -78°C, and the reaction mixture was stirred at -78°C for 5.5 hours. The reaction was warmed to -40°C and quenched with ice (60 gm). After the biphasic mixture was allowed to warm to room temperature, potassium sodium tartrate tetrahydrate (100 ml saturated aqueous solution) was added. The bilayer were separated, the aqueous was extracted with methylene chloride. The organic extracts were dried over sodium sulfate and concentrated under reduced pressure to give 5-Methyl-isoxazole-3-carbaldehyde as white solid (1.3 gm).

P–Toluenesulfonyl methyl isocyanide (1.75 gm, 8.97 mmol) and Potassium carbonate (1.24 gm, 8.97 mmol) were added to a solution of 5-Methyl-isoxazole-3-carbaldehyde (1.0 gm, 8.97 mmol) in 35 ml of dry methanol and the reaction mixture was refluxed (90°C) for 5 hours. The reaction was cooled to room temperature and concentrated under reduce pressure. The residue was partitioned in diethyl ether (100 ml) and water (200 ml). The organic layer was separated and the aqueous extracted with diethyl ether. The organic extracts were washed with brine and water, dried over sodium sulfate and concentrated under reduced pressure to give the title compound as yellowish solid (1.25gm).
LC/MS: 87%, 238 (M+1)

REFERENCE 31

((S)-1-{Hydroxy-[5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester



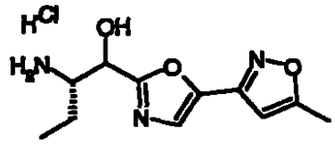
Triethylborane (1M in THF, 12 ml, 12 mmol) was added to a solution of 5-Methyl-3-oxazol-5-yl-isoxazole (1.8 gm, 12 mmol) in 40 ml of dry Tetrahydrofuran and the mixture was stirred at room temperature for 15 minutes. The mixture was cooled to -78°C, nBuLi (2.5M in Hexanes, 4.8 ml, 12 mmol) was added drop wise and the mixture was stirred at -78°C for 15 minutes. A solution of (S)-1-Formyl-propyl)-carbamic acid tert-butyl ester (898.7 mg, 4.8 mmol) in 15 ml of dry tetrahydrofuran was added drop wise and the reaction mixture was stirred at -78°C for 3 hours, then let warm to -30°C and quenched with acetic acid in ethanol (4%, 250 ml), stirring continued for 2 hours, while warming to room temperature. The reaction was concentrated under reduced pressure; the residue was dissolved in diethyl ether (250 ml) and stirred for 1.5 hours at room temperature. The precipitate was filtered; the

filtrate was concentrated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave the title compound as pale yellow solid (830 mg).

LC/MS 100%, 338 (M+1)

REFERENCE 32

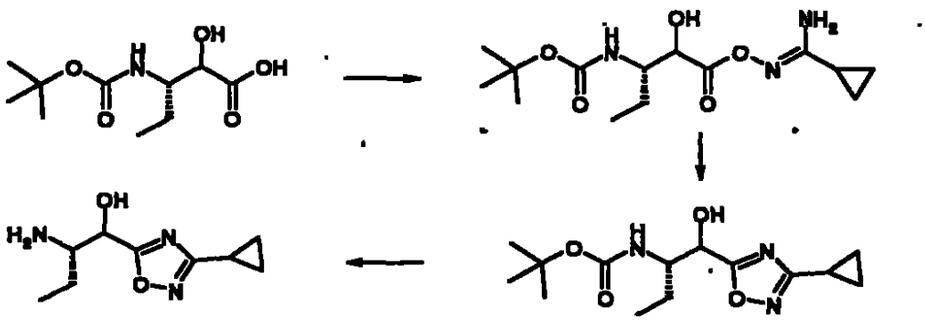
(S)-2-Amino-1-[5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl]-butan-1-ol: hydrochloride



Hydrogen chloride (4M in 1,4-dioxane, 3.3 ml) was added dropwise to a solution of ((S)-1-{Hydroxy-[5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester (0.75 gm, 2.22 mmol) in 10 ml of methylene chloride an the reaction mixture was stirred at room temperature for 2.5 hours. The reaction was diluted with diethyl ether (50 ml) and stirred for another hour at room temperature, concentrated in reduced pressure to give the title compound as yellowish solid (0.75 gm). ^{1}H NMR [(CD)$_3$SO]: δ 8.18 (m, 3H), 7.84 (s, 1H), 6.70 (s, 1H), 4.90 (m, 1H), 3.58 (m, 2H), 2.50 (s, 3H), 1.60 (m, 2H), 0.90 (t, 3H), LC/MS 100%, 238 (M+1)

REFERENCE 33

(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)].

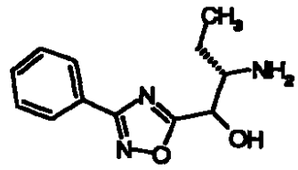
The residue was dissolved in tetrahydrofuran (20mL) and heated in a microwave reactor (Smith Creator) at 160°C for three minutes, cooled to room temperature and evaporated under vacuum to dryness. [LC/MS m/z=320 (M+H+Na)]. The residue was dissolved in dichloromethane (50mL) and

stirred at room temperature as a 50mL solution of 50% trifluoroacetic acid in dichloromethane was added drop wise. 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)]

Alternatively, deprotection of the BOC protecting group was carried out with HCl in dioxane to give (S) -2- amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride.

REFERENCE 34

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



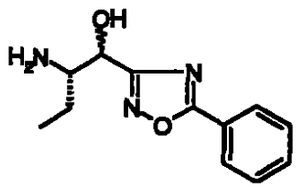
A solution of (S)-3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (2.00g, 8.57mmol) and N-hydroxy-benzamidine (1.3g, 9.5mmol) in dichloromethane (40mL) was stirred at 0°C. N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.90mmol/g, 6g, 11.4mmol) was added in portions. The reaction mixture was stirred 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)].

The product 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 (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 (S)-2-Amino-1-(3-phenyl-1,2,4-oxadiazol-5-yl)-butan-1-ol (775mg, 38%) as a white solid.

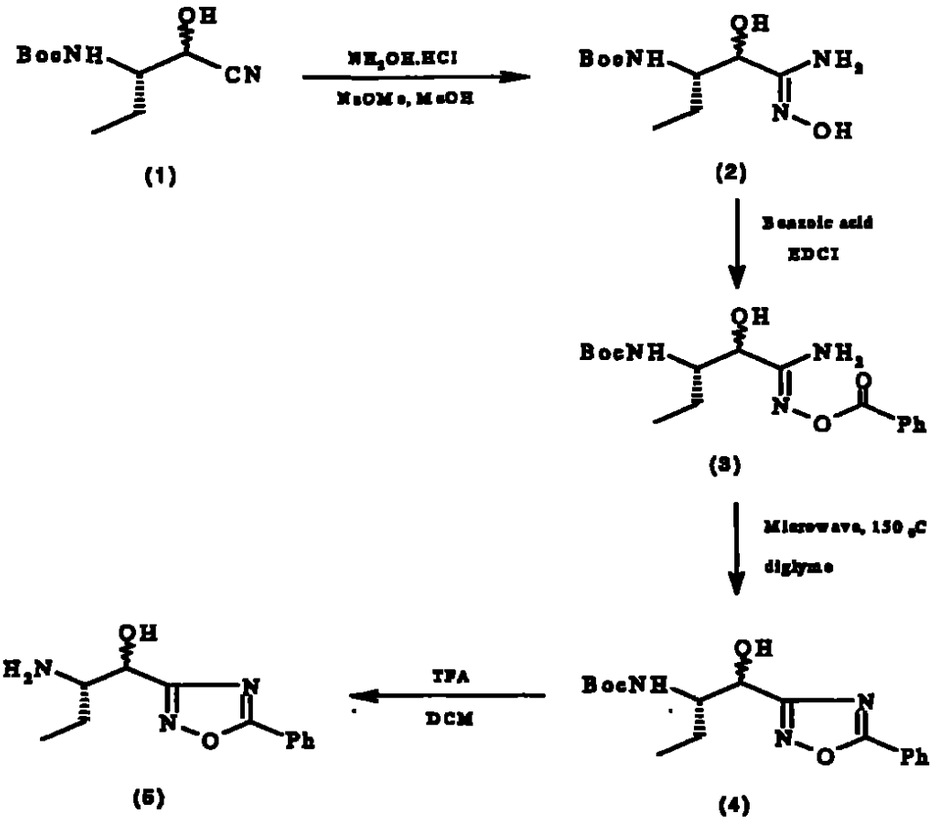
^1H NMR ($CDCl_3$):δ 8.12-8.06 (m, 2H), 7.54-7.45 (m, 3H), 4.93 & 4.75 (2xd, J= 5Hz & 3.5Hz, 1H), 3.25 &3.11 (2xm, 1H), 1.78-1.42 (2xm, 2H), 1.04 & 1.01 (2x t, J= 7.5Hz, 3H). [LC/MS m/z=234 (M+H)].

REFERENCE 35

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



Synthesized as described in the following reaction scheme:



{(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 over magnesium sulfate and then evaporated under reduced pressure. The residual yellow oil was subjected to mplc, 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: MH^+ 248.

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

A solution of {1-[hydroxy-(*N*-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (2) (2.5g, 10mmol) in dichloromethane (125ml) was treated with benzoic acid (1.36g, 11mmol), EDCI

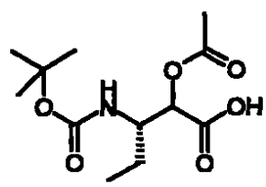
(2.14 g, 11mmol), HOBT (1.37g, 10mmol) and triethylamine (1.35mL, 11mmol) and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate solution, then water, then dried over Na_2SO_4 and then evaporated under reduced pressure. The residue was subjected to mplc eluting with 1% triethylamine in 2:3 v/v ethyl acetate and heptane mixture to give (1-[hydroxy-(N-benzoyloxycarbamimidoyl)-methyl]-propyl)-carbamicacid 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 Na_2SO_4 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. ^{1}HNMR ($CDCl_3$): δ 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 36

(S)-2-Acetoxy-3-tert-butoxycarbonylamino-pentanoic acid



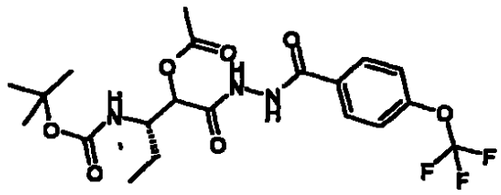
Pyridine (5 ml), 4-(dimethylamino)pyridine (0.01 g) and acetic anhydride (11 mmol, 1.12 g) were dissolved in dichloromethane (150 ml) and the resulting solution cooled to 0°C. (S)-3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (10 mmol, 2.33 g, A) was added at once and the resulting reaction mixture was stirred for 5 hours.

1M hydrochloric acid (250 ml) was added and the mixture transferred into a separating funnel. The phases were separated and the aqueous phase extracted three times with ethyl acetate (200 ml). The combined organic phases were washed twice with water (200 ml) and with brine (100 ml). The organic phase was dried with magnesium sulfate and the solvents evaporated under reduced pressure to give (S)-2-acetoxy-3-tert-butoxycarbonylamino-pentanoic acid (2.535 g, 92 %)..

MS: m/z=298 ($M+Na^+$), 276 ($M+H^+$)

REFERENCE 37

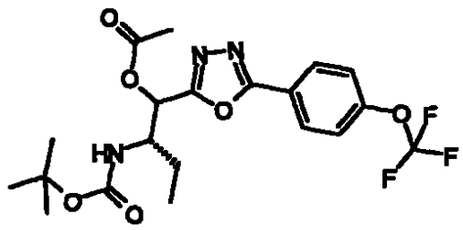
Acetic acid (S)-2-tert-butoxycarbonylamino-1-[N'-(4-trifluoromethoxy-benzoyl)hydrazinocarbonyl]-butyl ester



(S)-2-acetoxy-3-tert-butoxycarbonylamino-pentanoic acid (1.82 mmol, 0.5 g, A) was dissolved in 30 ml dichloromethane. N-Cyclohexylcarbodiimide-N'-methylpolystyrene (3.64 mmol, 1.92 g, B) was added and the resulting reaction mixture stirred for 2 min. 4-(trifluoromethoxy)benzoic acid hydrazide (1.65 mmol, 0.363 g, C) was added and the reaction mixture stirred over night. After 16 hours LC/MS analysis still showed hydrazide. Polystyrene methyl isocyanate (1.65 mmol, 1.15 g) was added and stirring continued for eight hours. The reaction mixture was filtered under suction and the filtrate concentrated under reduced pressure. To give acetic acid (S)-2-tert-butoxycarbonylamino-1-[N'-(4-trifluoromethoxy-benzoyl)hydrazinocarbonyl]-butyl ester as yellow foam (0.5 g, 64 %). According to LC/MS still some hydrazide present. MS: m/z= 500 ($M+Na^+$), 478 ($M+H^+$)

REFERENCE 38

Acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester



The acetic acid (S)-2-tert-butoxycarbonylamino-1-[N'-(4-trifluoromethoxy-benzoyl)-hydrazinocarbonyl]-butyl ester obtained above was split into 5 portions, which were separately reacted as follows:

acetic acid (S)-2-tert-butoxycarbonylamino-1-[N'-(4-trifluoromethoxy-benzoyl)-hydrazinocarbonyl]-butyl ester (0.21 mmol, 0.1 g) was dissolved in THF (5 ml) and the solution filled into a Smith Microwave synthesizer reaction vessel. 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-diazaphosphorine on polystyrene (1.05 mmol, 0.456 g, 2.3 mmol/g loading) and the p-Toluenesulfonic chloride (0.25 mmol, 0.048 g) were added and the reaction mixture heated at 150°C for 10 min (fixed hold time) in the microwave synthesizer.

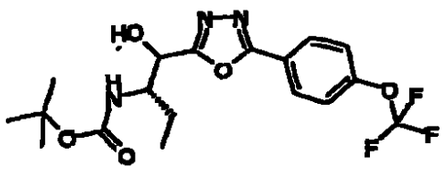
The combined reaction mixtures were filtered under suction and the resin washed with 300 ml ethyl acetate. The combined filtrates were concentrated under reduced pressure.

The crude product purified via flash chromatography (Biotage Horizon, 25M column, crude product loaded on caplet, 17 ml/min flow rate, 12 ml/fraction, 120 ml gradient from 0% ethyl acetate in heptane to 30 % ethyl acetate in heptane, 240 ml 30 % ethyl acetate in heptane, 60 ml gradient 30-50 % ethyl acetate in heptane, 300 ml 50 % ethyl acetate in heptane) to give acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester (0.28 g, 58)

MS: m/z= 460 ($M+H^+$)

REFERENCE 39

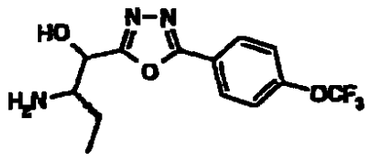
((S)-1-{Hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester



Acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester (0.61 mmol, 0.28 g) was dissolved in a mixture of THF (10 ml) and water (10 ml). Lithium hydroxide hydrate (1.22 mmol, 0.051 g) was added and the reaction mixture stirred for 2 h. The solvents were evaporated under reduced pressure and the residue transferred into a separating funnel with 300 ml ethyl acetate and 50 ml water. The phases were separated and the organic phase washed with brine (100 ml). The organic phase was then dried with magnesium sulfate. The solvent was evaporated under reduced pressure and dried under high vacuum to yield ((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester as yellow oil (0.225 g , 89 %) MS: m/z= 440 ($M+Na^+$), 418 ($M+H^+$)

REFERENCE 40

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

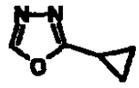


((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester (0.54 mmol, 0.225 g) was dissolved in dichloromethane (9 ml) and treated with trifluoroacetic acid (1 ml). The reaction mixture was stirred for four hours. The solvents were

evaporated under reduced pressure. The residue was re-dissolved in dichloromethane (20 ml) and Silicycle Trisamine (5.4 mmol, 1.47 g) was added. The reaction mixture was stirred for 60 h (over the weekend). The reaction mixtures were filtered under suction and the solvents evaporated to give (S)-2-Amino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butan-1-ol (0.164 g, 96 %). MS: m/z= 318 ($M+H^+$)

REFERENCE 41

2-Cyclopropyl-[1,3,4]oxadiazole



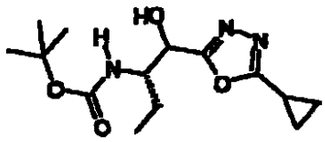
A mixture of cyclopropanecarboxylic acid methyl ester (10g, 0.1 mol) and hydrazine hydrate (7.3 mL, 0.15 mol) was refluxed for 28 hr and cooled to room temperature. The mixture was evaporated under reduced pressure and then dried by azeotropic removal of the solvent with toluene. The residue was dissolved in dichloromethane and washed with saturated NaCl. The organic phase was dried over anhydrous $MgSO_4$, solvent evaporated under reduced pressure to give cyclopropanecarboxylic acid hydrazide (4.36g, 44%)

A mixture of the Cyclopropanecarboxylic acid hydrazide (31.35g, 0.31 mol), trimethyl orthoformate (300 mL) and p-toluenesulfonic acid monohydrate (200 mg) was heated under reflux overnight. Excess trimethyl orthoformate and methanol were removed by distillation. Vacuum distillation of the residue afforded 2-Cyclopropyl-[1,3,4]oxadiazole (22g, 64%).

^1H NMR ($CDCl_3$): δ 8.24(s, 1H), 2.2 (m, 1H), 1.15 (m, 4H). LCMS: 100%, 111 (MH^+).

REFERENCE 42

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

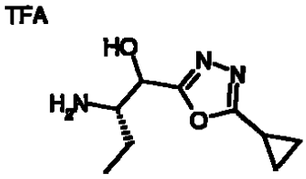


A solution of 2-cyclopropyl-[1,3,4]oxadiazole (2.16g, 19.6 mmol) in dry THF (100 mL) was cooled to –78°C. ^nBuLi (1.6M in hexanes, 12.3 mL, 19.6 mmol) was added dropwise. The reaction mixture was stirred at –78°C for 40 min. $MgBr_2.OEt_2$ (5.0692g, 19.6 mmol) was added. The reaction mixture was allowed to warm up to –45°C and stirred at that temperature for 1.5 hr. A solution of (1-formyl-propyl)-carbamic acid tert-butyl ester (3.7g, 19.6 mmol) in THF (40 mL) was added. The reaction mixture was allowed to warm up to –20°C and stirred at that temperature for 3.5 hrs. The reaction mixture was quenched with a solution of saturated NH_4Cl solution and extracted with ethyl acetate. Combined organic extracts was washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified by column chromatography

eluting with ethyl acetate and heptane mixture to give {1-[(5-cyclopropyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester (2.83g, 49%).
LCMS: 298 (MH^+).

REFERENCE 43

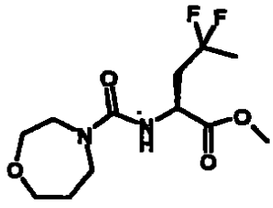
(S)-2-Amino-1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-butan-1-ol; compound with trifluoro-acetic acid



A mixture of {1-[(5-cyclopropyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester (2.83g, 9.95 mmol), trifluoro acetic acid (5 mL) in dichloromethane (20 mL) was stirred at room temperature for 2 hrs and concentrated to dryness under reduced pressure to give (S)-2-amino-1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-butan-1-ol; compound with trifluoro-acetic acid.
LCMS: 100% 198 (MH^+).

REFERENCE 44

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid methyl ester.

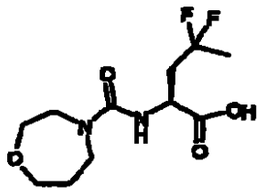


Triphosgene was dissolved in dichloromethane (10 mL) and to this was added, via syringe pump, a mixture of S-2-Amino-4, 4-difluoro-pentanoic acid hydrochloride (1.00g, 4.90 mmol) (see reference example 15), diisopropylethyl amine (1.88 mL, 10.80 mmol) dissolved in dichloromethane (10 mL) over the period of 1h. After stirring for an additional 15 minutes a solution of homomorpholine hydrochloride (0.67g, 4.90 mmol) and diisopropylethyl amine (1.90 mL, 10.90 mmol) in dichloromethane (10 mL) was added to the solution. The resulting solution was stirred at RT for 2h. The solvent was evaporated and the residue diluted with ethyl acetate (100 mL) then washed with 1M $KHSO_3$ (2x 10 mL), saturated $NaHCO_3$ and brine. The organics were dried (Na_2SO_4), filtered and concentrated to yield a pale yellow oil. The crude material was purified on 20 g silica gel eluting with ethyl acetate:heptane gradient 50-100%. (S)-4,4-Difluoro-2-[(perhydro-1, 4-oxazepine-4-carbonyl)-amino]-pentanoic acid methyl ester was obtained as a white solid (0.40g, 28%).
^1H NMR ($CDCl_3$) δ 5.12 (d, J=7.5Hz, 1H), 4.72 (dd, J = 12.0, 7.2 Hz, 1H), 3.75 (m, 7H), 3.55 (m, 4H), 2.45 (m, 2H), 1.98 (m, 2H), 1.66 (t, J = 18.7 Hz, 3H).

LC/MS: 295, 100%, (M+H), 317 (M+Na)

REFERENCE 45

(S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid



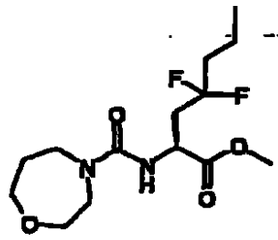
(S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid methyl ester (0.38g, 1.29mmol) was dissolved in tetrahydrofuran/methanol (15mL/10mL) and lithium hydroxide (35mg, 1.40mmol) dissolved in water (5mL) added. The reaction was stirred at RT for 18h, and then the methanol/tetrahydrofuran was removed in vacuo. The residue was acidified with 6M hydrochloric acid (0.25mL) and extracted with dichloromethane (3x 20 mL), dried (Na_2SO_4), and concentrated to yield (S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid as a white solid (0.36g, 99%).

^{1}H NMR (DMSO-d6) δ 12.6 (bs, 1H), 6.60 (d, 8.3 Hz, 1H), 4.30 (dd, J = 14.5, 7.0 Hz, 1H), 3.57 (m, 4H), 3.43 (m, 4H), 2.38 (m, 2H), 1.77 (m, 2H), 1.61 (t, J = 19.2Hz, 3H).

LC/MS: 100% 281 (M+H)

REFERENCE 46

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester



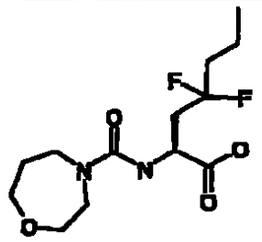
To a mixture of Sodium bicarbonate (5.25g), p-nitro chloroformate (5.03g, 25 mmol) in acetonitrile (130 ml) under nitrogen was added (S)-2-Amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride (5.79g, 0.025 mol) and stirred at room temperature for 5hr. Homomorpholine hydrochloride (3.61g, 26.25 mmol) and triethyl amine (12.5 ml) were added and the reaction stirred overnight at room temperature. Solvent evaporated off under reduced pressure, crude partitioned

between water (150 ml) and ethyl acetate (200 ml). Organic layer separated, washed with K_2CO_3 solution (150 ml), HCl (150 ml) and brine (150 ml). Organic layer separated, dried ($MgSO_4$) and evaporated under reduced pressure. Crude purified by column chromatography eluting with v/v 1:1 to 8:2 ethyl acetate heptane followed by ethyl acetate to give (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester (4.8g) as pale yellow oil.

LC/MS: 323 (M+H)

REFERENCE 47

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid

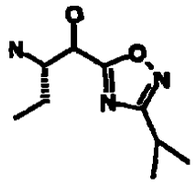


By proceeding in a similar manner to Reference Example 45 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester there was prepared (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid.

LC/MS: 309 (M+H)

REFERENCE 48

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

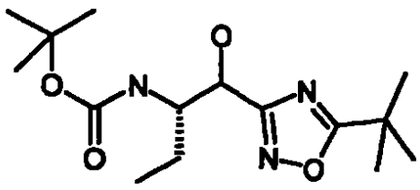


Similarly prepared according to the procedure for Reference Example 33.

LCMS: 200 (M+H)

REFERENCE 49

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



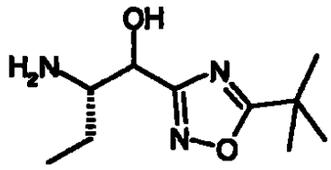
{(S)-1-[Hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (235mg, 0.95 mmol) in diglyme (2 ml) was treated with trimethyl acetic anhydride (0.212 ml, 1.04 mmol) and the reaction mixture heated at 170 °C for 5 minutes in a Emrys Optimizer microwave from Personal Chemistry. The solvent was evaporated under high vacuum. The crude obtained was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane (1:4) 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 (100 mg) (mixture of diastereoisomers).

^{1}H NMR ($CDCl_3$) δ: 4.92-4.69 (m, 2H), 4.05-3.85 (m, 1H), 3.57-3.41 & 3.32-3.15 (2xbs, 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 (M+H).

REFERENCE 50

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



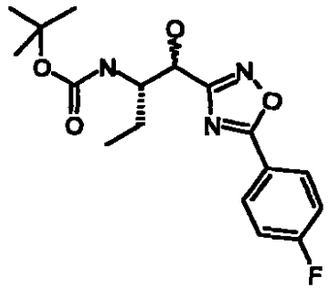
A solution of {(S)-1-[(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert butyl ester (2.11 g, 6.72 mmol) in methylene chloride (20 ml) was treated with trifluoroacetic acid (5.18 ml, 67.25 mmol) and stirred at room temperature for 3h. The solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride (100 ml) and treated with PS-trisamine from Argonaut Technologies (5.38g, 20.18 mmol, 3.75 mmol/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).

^{1}H NMR ($CDCl_3$) δ : 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 (M+H).

REFERENCE 51

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



A suspention of 4-fluoro benzoic acid (1.70g, 0.012mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.12g, 0.011mol) in methylene chloride (80ml) was treated with (S)-1-[Hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (3g, 0.012mol) and triethylamine (1.54ml, 0.011mol). The reaction was stirred at room temperature overnight. Then, it was diluted with 40ml of methylene chloride, washed with saturated aqueous bicarbonate solution (30ml), water (30ml), brine (30ml), dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane (2:1) to give an off white solid (2.20g)

^{1}H NMR ($CDCl_3$) δ : 8.10-7.95 (m, 2H), 7.16-7.00 (m, 2H), 5.43-5.24 (m, 2H), 5.22-5.05 (m, 1H), 5.01-4.85 (m, 1H), 4.50-4.39 (m, 1H), 3.80-3.60 (m, 1H), 1.90-1.78 (m, 2H), 1.40 (s, 9H), 0.98 (t, J=7.5Hz, 3H).

MS : 370 (M+H).

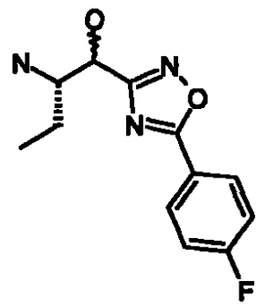
240 mg of the solid (0.65 mmol) compound obtained above was taken in diglyme (5ml) and heated at 160 °C in a microwave (Smith Creator, S00219) for 18 minutes. The solvent was evaporated under high vacuum. The crude obtained was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane (1:4) to give (S)-1-{[5-(4-Fluoro-phenyl)-1,2,4-oxadiazol-3-yl]-hydroxy-methyl}-propyl)-carbamic acid tert-butyl ester as a white solid (148mg).

^{1}H NMR ($CDCl_3$) δ: 8.16-8.09 (m, 2H), 7.25-7.12 (m, 2H), 4.98-4.73 (m, 2H), 4.13-3.87 (m, 1H), 3.82-3.35 (m, 1H), 1.80-1.52 (m, 2H), 1.46 & 1.34 (2xs, 9H), 1.02 & 0.99 (2xt, J=7.5Hz, 3H).

MS : 352 (M+H).

REFERENCE 52

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



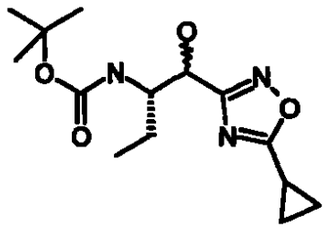
Similarly prepared according to Reference Example 50 above but using (S)-1-{[5-(4-Fluoro-phenyl)-1,2,4-oxadiazol-3-yl]-hydroxy-methyl}-propyl)-carbamic acid tert-butyl ester.

^{1}H NMR ($CDCl_3$) δ : 8.18-8.05 (m, 2H), 7.26-7.12 (m, 2H), 4.92 & 4.73 (2xd, J=5Hz, 1H), 3.27-3.05 (m, 1H), 1.75-1.62 (m, 1H), 1.59-1.41 (m, 1H), 1.02 & 1.00 (2xt, J=7.5Hz, 3H).

MS : 252 (M+H).

REFERENCE 53

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



A suspention of (S)-1-[Hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (6.12g, 24.78mmol) in methylene chloride (150ml) was treated with triethylamine (3.46ml, 24.82mmol) and then cooled to 0 °C. Then cyclopropyl carbonyl chloride (2.25ml, 24.79mmol) was added dropwise. The reaction was stirred at room temperature for 1h 45min. and diluted with 150ml of methylene chloride, washed with water (40ml), saturated aqueous bicarbonate (20ml), water (20ml), dried over Na_2SO_4 and solvent evaporated under reduced pressure to give a white solid (7.16g).

MS : 338 (M+Na).

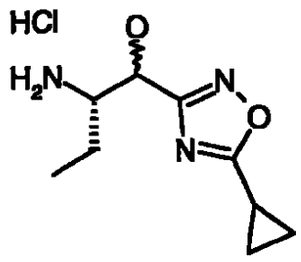
A solution of the compound obtained above (7.45g, 0.024mol) in dioxane (150ml) was heated at reflux for 15h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane to give (S)-1-[(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester as a pale yellow solid (5g).

^{1}H NMR ($CDCl_3$) δ : 4.94-4.74 (m, 2H), 3.97 & 3.85 (2xm, 1H), 3.62 & 3.48 (2xbs, 1H), 2.19 (m, 1H), 1.72-1.42 (m, 2H), 1.44 & 1.39 (2xs, 9H), 1.26-1.18 (m, 4H), 0.98 & 0.95 (2xt, J=7.4Hz, 3H).

MS : 298 (M+H).

REFERENCE 54

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



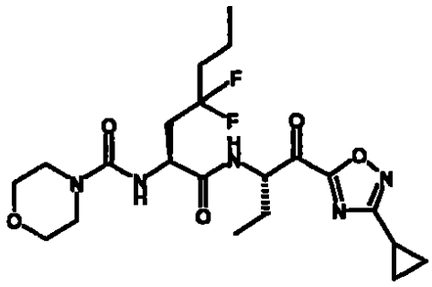
A solution of {(S)-1-[(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester (3.41g, 0.011mmol) in 4N HCl in dioxane (43ml, 0.172mmol) was stirred at room temperature for 2h. Solvent evaporated under reduced pressure. Residue triturated with a mixture of ethyl acetate and ether. It was then filtered to give (S)-2-Amino-1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-butan-1-ol HCl salt as a brown solid (2.47g).

^{1}H NMR ($CDCl_3$) δ: 8.21 (bs, 2H), 5.37 & 5.14 (2xd, 1H), 3.88 & 3.73 (2xm, 1H), 2.21 (m, 1H), 1.92-1.50 (m, 2H), 1.24 (m, 4H), 1.08 & 1.06 (2xt, J=7.4Hz, 3H).

MS : 198 (M+H).

EXAMPLE 1

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



To a mixture of (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (104 mg, 0.35 mmol), (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride (86.7 mg, 0.37 mmol) and diisopropyl amine (219 mg, 0.42 mmol) in dry dichloromethane (5 mL) was added PyBOP (113 mg, 0.87 mmol). The mixture was stirred at room temperature for 16 hr and the evaporated in vacuum. The residue was diluted with ethyl acetate (25 mL) and washed with saturated $NaHCO_3$ (30 mL), dilute HCl (30 mL), then saturated $NaHCO_3$ (30 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 12 g silica gel, eluting with ethyl acetate: heptane (2:1 then 1:0) to afford morpholine-4-carboxylic acid {1-[1-[(3-

cyclopropyl-[1,2,4]oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide (146 mg, 88%) as a white solid. LC/MS shows 2 isomers, total 100% M+1 474.

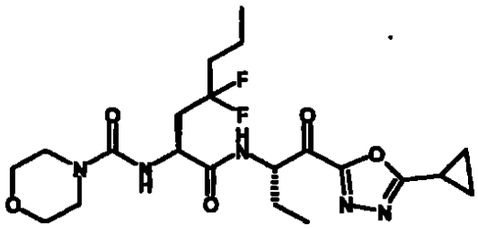
To a solution of morpholine-4-carboxylic acid (1-{1-[(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide (145 mg, 0.31 mmol) in dry dichloromethane (3 mL) under N2 was added Dess-Martin periodinane (15% wt solution in dichloromethane, 1.73 g, .061 mmol). The reaction was stirred at room temperature for 2 hr, then quenched with a solution of $Na_2S_2O_3$ 193 mg, 1.22 mmol) in saturated $NaHCO_3$ (30 mL). The aqueous layer was extracted with dichloromethane (2x30 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 12 g silica gel, eluted with ethyl acetate: heptane (1:1 then 2:1) to afford the desired ketone (119 mg, 81%) as a tan solid.

^1H NMR ($CDCl_3$): δ 7.4 (d, 7.0 Hz, 1H), 5.27 (m, 1H), 5.13 (d, J = 6.9 Hz, 1H), 4.65 (dd, J = 13.1, 6.9 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.8 (m, 3H), 1.55 (m, 2H), 1.15 (m, 4H), 0.98 (t, J = 7.4 Hz, 6H);

LC/MS: 28% 512 ($M+H_2O+Na$) and 68% 494 (M+Na).

EXAMPLE 2

Morpholine-4-carboxylic acid [(S)-1-[(S)-1-(5-cyclopropyl-1,3,4-oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl]-amide



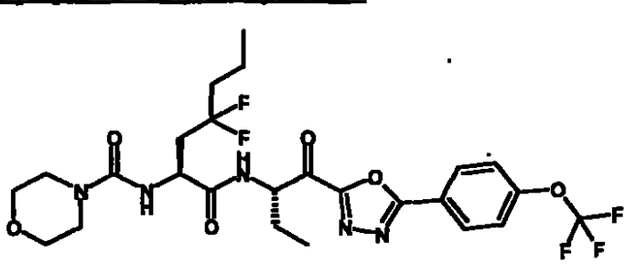
PyBOP (171.73 mg, 0.33 mmol), diisopropylethylamine (0.0575 ml, 0.33mmol) and (S)-2-amino-1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-butan-1-ol; compound with trifluoro-acetic acid (0.30 mmol) were added to a solution of (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (88.29 mg, 0.30 mmol) in dry methylene chloride (4 ml) and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with aqueous sodium bicarbonate, extracted twice with methylene chloride, the organic extracts were dried over sodium sulfate and evaporated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide as white solid (87 mg). LC/MS 97%, 474 (M+1).

Dess-Martin Periodinane (15wt% in DCM, 0.79 gm, 0.28 mmol) was added to a solution of morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide (67 mg, 0.14 mmol) in dry methylene chloride (10 ml) and stirred at room temperature for 2.5 hours. The reaction was quenched with a solution of $Na_2S_2O_3$ (110.68 mg, 0.70 mmol) in aqueous $NaHCO_3$. The organic layer was separated and the aqueous extracted with dichloromethane. The organic extracts were dried over sodium sulfate and concentrated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave morpholine-4-carboxylic acid {(S)-1-[(S)-1-(5-cyclopropyl-1,3,4-oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide as white powder (48 mg).

^1H NMR ($CDCl_3$): δ 7.52 (d, J=7.5Hz, 1H), 5.34 (m, 1H), 5.18 (d, J=7.5Hz, 1H), 4.65 (m, 1H), 3.72 (m, 4H), 3.40 (m, 4H), 2.50-2.22 (m, 3H), 2.18-2.08 (m, 1H), 1.96-1.78 (m, 3H), 1.60-1.45 (m, 2H), 1.30 (m, 4H), 0.98 (t+t, 6H).
LC/MS 95%, 472 (M+1).

EXAMPLE 3

Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide.



PyBOP (68.69 mg, 0.13 mmol), diisopropylethylamine (0.023 ml, 0.13mmol) and (S)-2-Amino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butan-1-ol (38.0 mg, 0.12 mmol) were added to a solution of (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (34 mg, 0.12 mmol) in dry methylene chloride (4 ml) and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with aqueous $NaHCO_3$, extracted twice with methylene chloride, the organic extracts were dried over $Na2SO_4$ and evaporated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propylcarbamoyl)-hexyl]-amide as white solid (61 mg). LC/MS 71%, M+1= 594

Dess-Martin Periodinane (15wt% in DCM, 0.58 gm, 0.21 mmol) was added to a solution of morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-

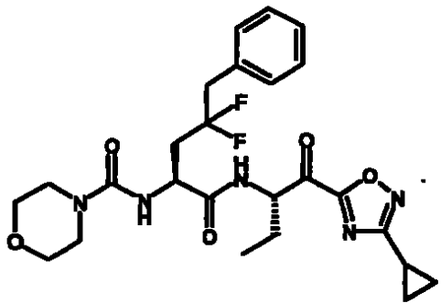
1,3,4-oxadiazol-2-yl]-methyl}-propylcarbamoyl)-hexyl]-amide (61 mg, 0.10 mmol) in dry methylene chloride (8 ml) and stirred at room temperature for 3 hrs. The reaction was quenched with a solution of $Na_2S_2O_3$ (81.43 mg, 0.50 mmol) in aqueous $NaHCO_3$. The organic layer was separated and the aqueous extracted with dichloromethane. The organic extracts were dried over sodium sulfate and concentrated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide as white powder (39 mg).

^1H NMR ($CDCl_3$): δ 8.25 (d, J=7.5Hz, 2H), 7.60 (d, J=7.5Hz, 1H), 7.42 (d, J=7.5Hz, 2H), 5.36 (m, 1H), 5.16 (d, J=7.5Hz, 1H), 4.70 (m, 1H), 3.74 (m, 4H), 3.42 (m, 4H), 2.54-2.32 (m, 2H), 2.28-2.14 (m, 1H), 2.02-1.80 (m, 3H), 1.60-1.45 (m, 2H), 1.06 (t, J=7Hz, 3H), 0.96 (t, J=7Hz, 3H).

LC/MS: 96%, 592 (M+1).

EXAMPLE 4

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide



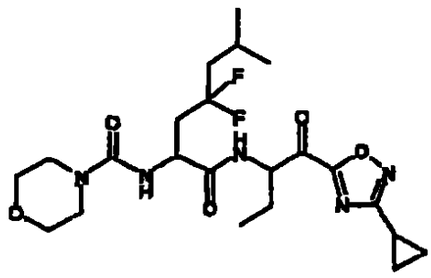
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide.

^1H NMR ($CDCl_3$): δ 7.3 (m, 6H), 5.25 (m, 1H), 5.08 (d, J = 6.9 Hz, 1H), 4.7 (dd, J = 12.8, 7.4 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, 16.8 Hz, 2H), 2.4-2.1 (m, 3H), 2.05 (m, 1H), 1.8 (m, 1H), 1.1 (m, 4H), 0.95 (t, J = 7.5 Hz, 3H);

LC/MS: 35% 560 ($M+H_2O+Na$) and 65% 542 (M+Na).

EXAMPLE 5

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



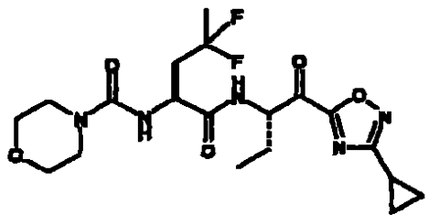
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared morpholine-4-carboxylic acid [1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-5-methyl-hexyl]-amide

^{1}H NMR ($CDCl_3$): δ 7.6 (d, J = 6.8 Hz, 1H), 5.2 (m, 2H), 4.66 (dd, J = 13, 7.2 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.3 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.8 (m, 3H), 1.1 (m, 4H), 0.97 (d, J = 6.6 Hz, 6H), 0.96 (t, J = 7.4 Hz, 3H);

LC/MS: 26%, 526 ($M+H_2O+Na$) and 74%, 508 ($M+Na$).

EXAMPLE 6

Morpholine-4-carboxylic acid [(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl]-amide



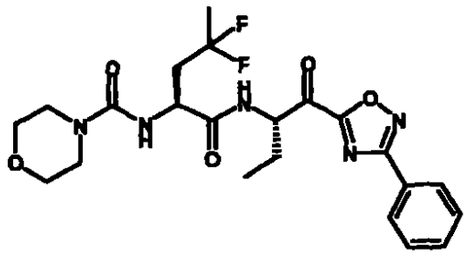
By proceeding in a similar manner to Example 1 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid [(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl]-amide

^{1}H NMR ($CDCl_3$): δ 7.47 (d, J = 6.8 Hz, 1H), 5.3 (m, 1H), 5.16 (d, J = 6.9 Hz, 1H), 4.65 (dd, J = 13, 7.4 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.8 (m, 1H), 1.67 (t, 18.7 Hz, 3H), 1.1 (m, 4H), 0.97 (t, J = 7.5 Hz, 3H);

LC/MS: 37% 484 ($M+H_2O+Na$) and 63% 484 ($M+CH_3CN$).

EXAMPLE 7

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



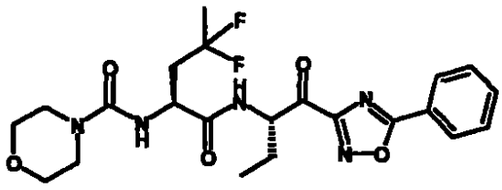
By proceeding in a similar manner to Example 1 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-(3-phenyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide as light tan solid.

^{1}H NMR ($CDCl_3$): δ 8.15 (dd, J = 7.7, 1.5 Hz, 2H), 7.61 (d, J = 6.4 Hz, 1H), 7.5 (m, 3H), 5.35 (m, 1H), 5.2 (d, J = 6.9 Hz, 1H), 4.68 (dd, J = 13.2, 7.8 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.2 (m, 1H), 1.95 (m, 1H), 1.66 (t, 18.7 Hz, 3H), 1.03 (t, J = 7.5 Hz, 3H);

LC/MS: 37% 520 ($M+H_2O+Na$) and 63% 502 (M+Na).

EXAMPLE 8

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



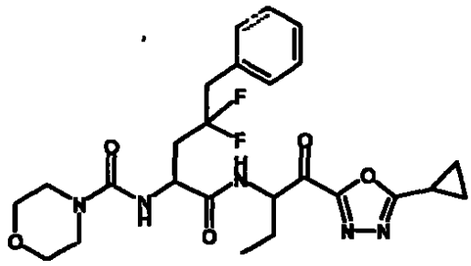
By proceeding in a similar manner to Example 1 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-butyl}-amide

^{1}H NMR ($CDCl_3$): δ 8.2 (d, J = 7.1 Hz, 2H), 7.65 (d, J = 7.4 Hz, 1H), 7.55 (m, 3H), 5.4 (dd, J = 12.2, 7 Hz, 1H), 5.3 (d, J = 7.4 Hz, 1H), 4.7 (dd, J = 13, 7.3 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.1 (m, 1H), 1.9 (m, 1H), 1.67 (t, 18.7 Hz, 3H), 1.0 (t, J = 7.4 Hz, 3H);

LC/MS: 6% 520 ($M+H_2O+Na$) and 94% 502 (M+Na).

EXAMPLE 9

Morpholine-4-carboxylic acid {1-[1-(5-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide:



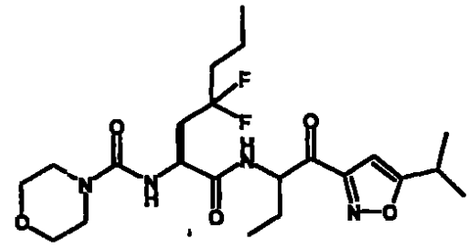
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-butan-1-ol Trifluoro acetic acid salt, there was prepared morpholine-4-carboxylic acid {1-[1-(5-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide.

^{1}H NMR ($CDCl_3$): δ 7.3 (m, 6H), 5.27 (m, 1H), 5.0 (d, J = 7.0 Hz, 1H major), 4.95 (d, J = 7.3 Hz, 1H minor), 4.7 (m, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, 16.3 Hz, 2H), 2.4-2.2 (m, 3H), 2.05 (m, 1H), 1.8 (m, 1H), 1.2 (m, 4H), 0.95 (t, J = 7.5 Hz, 3H);

LC/MS: 12% 560 (M+H_2O+Na) and 83% 542 (M+Na).

EXAMPLE 10

Morpholine-4-carboxylic acid {3,3-difluoro-1-[1-(5-isopropyl-isoxazole-3-carbonyl)-propylcarbamoyl]-hexyl}-amide:



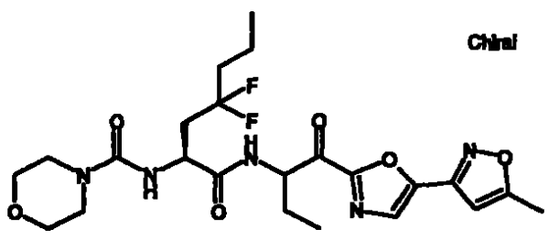
By proceeding in a similar manner to Example 1 above but using 2-amino-1-(5-isopropyl-isoxazol-3-yl)-butan-1-ol hydrochloride instead of (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride there was prepared morpholine-4-carboxylic acid {3,3-difluoro-1-[1-(5-isopropyl-isoxazole-3-carbonyl)-propylcarbamoyl]-hexyl}-amide as white solid.

^{1}H NMR ($CDCl_3$): δ ca 2:1 mixture of isomers 7.4 (b, 1H), 6.37 (s, 1H), 5.4 (m, 1H), 5.26 (d, J = 6.9 Hz, 1H major), 5.2 (d, J = 7.2 Hz, 1H minor), 4.7 (m, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.15 (m, 1H), 2.4 (m, 2H), 2.1 (m, 1H), 1.8 (m, 4H), 1.5 (m, 1H), 1.35 (d, J = 7.0 Hz, 6H), 0.95 (m, 6H);

LC/MS: 100% 473 (M+1).

EXAMPLE 11

Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(5-methyl-isoxazol-3-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide



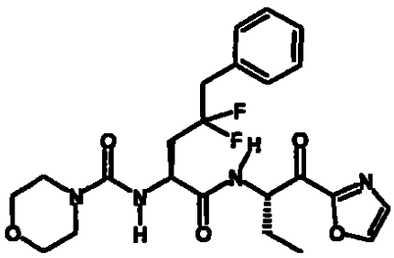
By proceeding in a similar manner to Example 3 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and (S)-2-amino-1-[5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl]-butan-1-ol; hydrochloride there was prepared Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(5-methyl-isoxazol-3-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide as white solid.

^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.40 (m, 1H), 6.44 (s, 1H), 5.48 (m, 1H), 5.22-5.10 (m, 1H), 4.68 (m, 1H), 3.72 (m, 4H), 3.40 (m, 4H), 2.54 (s, 3H), 2.50-2.30 (m, 2H), 2.22-2.08 (m, 1H), 1.94-1.78 (m, 3H), 1.60-1.46 (m, 2H), 1.08-0.94 (2xt, 6H).

LC/MS: 99%, 512 (M+1).

EXAMPLE 12

Morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(oxazole-2-carbonyl)-propylcarbamoyl]-4-phenyl-butyl}-amide

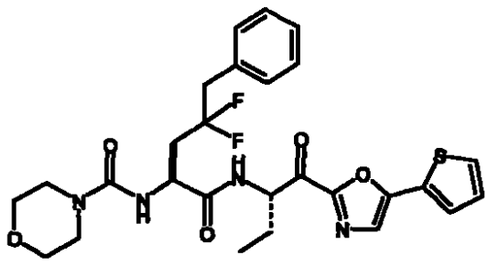


By proceeding in a similar manner to Example 2 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-oxazol-2-yl-butan-1-ol hydrochloride there was prepared morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(oxazole-2-carbonyl)-propylcarbamoyl]-4-phenyl-butyl}-amide

^{1}H NMR ($CDCl_3$): δ 7.86 (s, 1H), 7.37 (s, 1H), 7.30 (m, 5H), 7.24 (m, 1H), 5.45 (m, 1H), 5.08 (d, J = 9Hz, 1H), 4.70 (m, 1H), 3.72 (m, 4H), 3.38 (m, 4H), 3.22 (t, J= 17Hz, 2H), 2.35 (m, 2H), 2.12 (m, 1H), 1.85 (m, 1H), 0.95 (t, J= 9Hz, 3H);
LC/MS: 97%, 479 (M+1).

EXAMPLE 13

Morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-thiophen-2-yl-oxazole-2-carbonyl)-propylcarbamoyl]-butyl}-amide

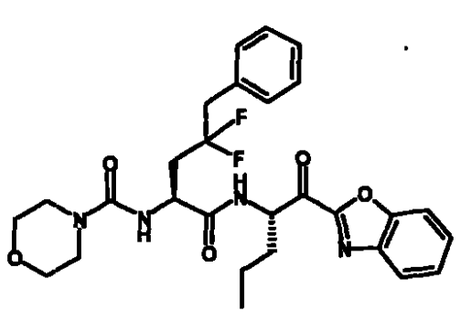


By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-(5-thiophen-2-yl-oxazol-2-yl)-butan-1-ol hydrochloride there was prepared morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-thiophen-2-yl-oxazole-2-carbonyl)-propylcarbamoyl]-butyl}-amide

^{1}H NMR ($CDCl_3$): δ 7.53 (dd, J = 3.6, 1 Hz, 1H), 7.48 (dd, J = 5, 1 Hz, 1H), 7.4 (s, 1H), 7.3 (m, 6H), 7.15 (dd, J = 5, 3.6 Hz, 1H), 5.4 (m, 1H), 5.15 (d, J = 7.1 Hz, 1H), 4.7 (dd, J = 13, 7.4 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, 16.7 Hz, 2H), 2.4 (m, 2H), 2.1 (m, 1H), 1.8 (m, 1H), 0.96 (t, J = 7.5 Hz, 3H);
LC/MS: 100% 561 (M+1).

EXAMPLE 14

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide

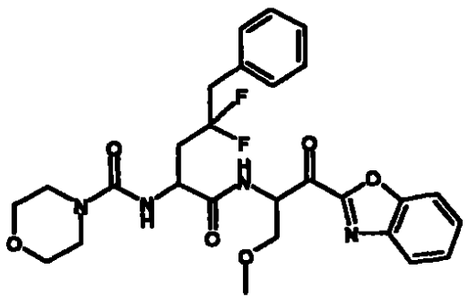


By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol there was prepared morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide.

^{1}H NMR ($CDCl_3$): δ 7.9 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.2 (m, 6H), 5.6 (m, 1H), 5.05 (d, J = 7Hz, 1H), 4.71 (dd, J = 12.8, 7.4 Hz, 1H), 3.7 (m, 4H), 3.35 (m, 4H), 3.18 (t, J= 16.8 Hz, 2H), 2.3 (m, 2H), 2.1 (m, 1H), 1.8 (m, 1H), 1.4 (m, 2H), 0.94 (t, J= 7.3 Hz, 3H);
LC/MS: 100% 543 (M+1).

EXAMPLE 15

Morpholine-4-carboxylic acid [1-(2-benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide

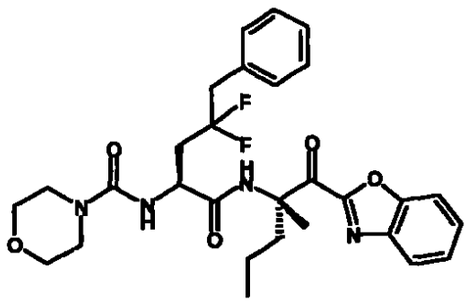


By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-benzooxazol-2-yl-3-methoxy-propan-1-ol there was prepared morpholine-4-carboxylic acid [1-(2-benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide.

^{1}H NMR ($CDCl_3$): δ 7.9 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.48 (t, J = 8 Hz, 1H), 7.2 (m, 6H), 5.7 (m, 1H), 5.1 (d, J = 7 Hz, 1H major), 5.05 (d, J = 7.3 Hz, 1H minor), 4.8 (m, 1H), 4.26 (dd, J = 9.7, 3.5 Hz, 1H), 3.8 (m, 1H), 3.7 (m, 4H), 3.35 (m, 4H), 3.27 (s, 3H), 3.22 (t, J= 16.2 Hz, 2H), 2.4 (m, 2H);
LC/MS: 94% 545 (M+1).

EXAMPLE 16

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-1-methyl-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide



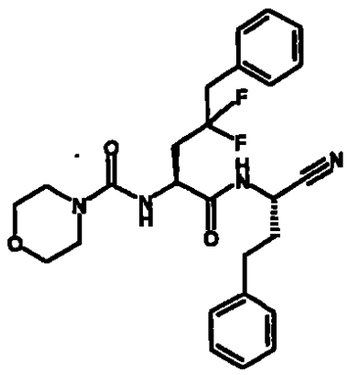
A mixture of (S)-2-amino-1-benzoxazol-2-yl-2-methyl-pentan-1-one hydrochloride (80.6 mg, 0.3 mmol), (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid (0.102 mg, 0.3 mmol), EDCI (69 mg, 0.36 mmol), HOBT (48.6 mg, 0.36 mmol) and Diisopropyl ethylamine (0.2 mL) in DMF was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with cold 1N HCl, saturated $NaHCO_3$ and then saturated NaCl solution. The organic phase was dried over magnesium sulfate and solvent evaporated under reduced pressure to give the crude product. Purification by Silica gel column chromatography, eluting with ethyl acetate and heptane mixture gave morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-1-methyl-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide (82%).

^1H NMR ($CDCl_3$): δ 7.8 (d, J = 7.8.0 Hz, 1H), 7.64 (d, J =7.8 Hz, 1H), 7.53 (dt, J = 7.2, 1.2 Hz, 1H), 7.43 (dt, J = 8, 1.2 Hz, 1H), 7.2 (m, 6H), 4.9 (d, J = 7.3 Hz, 1H), 4.65 (m, 1H), 3.7 (m, 4H), 3.3 (m, 4H), 3.1 (t, J= 16.8 Hz, 2H), 2.2 (m, 3H), 2.1 (m, 1H), 1.74 (s, 3H), 1.25 (m, 2H), 0.9 (t, J= 7.3 Hz, 3H);

LC/MS: 100% 557 (M+1).

EXAMPLE 17

Morpholine-4-carboxylic acid [(S)-1-((S)-1-cyano-3-phenyl-propylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide



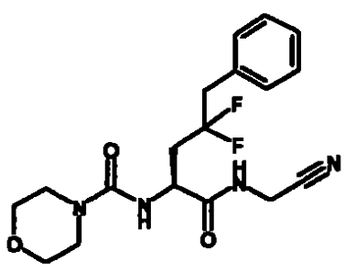
Proceeding according to the PyBOP coupling method given for example 1, but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-4-phenyl-butyronitrile

hydrochloride, there was prepared, morpholine-4-carboxylic acid [(S)-1-((S)-1-cyano-3-phenyl-propylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide.

^{1}H NMR ($CDCl_3$): δ 7.9 (d, J = 7.6 Hz, 1H), 7.2 (m, 10H), 5.1 (d, J = 7.3 Hz, 1H), 4.6 (m, 2H), 3.6 (m, 4H), 3.3 (m, 4H), 3.2 (t, J = 16.5 Hz, 2H), 2.74 (t, J = 7.2 H, 2H), 2.3 (m, 2H), 2.1 (m, 2H); LC/MS: 100 % 485 (M+1).

EXAMPLE 18

Morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide

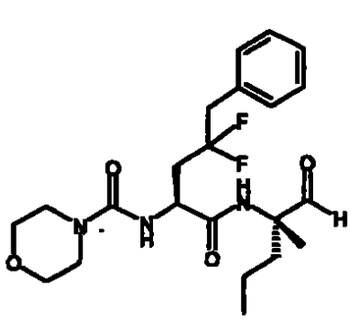


Proceeding according to the PyBOP coupling method given for Example 1, but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and amino-acetonitrile hydrochloride, there was prepared, morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide.

^{1}H NMR ($CDCl_3$): δ 7.95 (b, 1H), 7.3 (m, 5H), 5.25 (d, J = 7.0 Hz, 1H), 4.7 (dd, J = 12.7, 7.2 Hz, 1H), 4.1 (m, 2H), 3.7 (m, 4H), 3.35 (m, 4H), 3.2 (t, J = 16.3 Hz, 2H), 2.4 (m, 2H); LC/MS: 83 % 403 (M+Na).

EXAMPLE 19

Morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-formyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide



A mixture of (S)-2 amino-2-methyl-pentan-1-ol hydrochloride (104.4 mg, 0.67 mmol), (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid (231 mg, 0.67 mmol), EDCI (154 mg, 0.8 mmol), HOBT (108 mg, 0.8 mmol) and Diisopropyl ethylamine (0.23 mL) in DMF (2mL) was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with cold 1N HCl, saturated $NaHCO_3$ and then saturated NaCl solution. The organic phase was

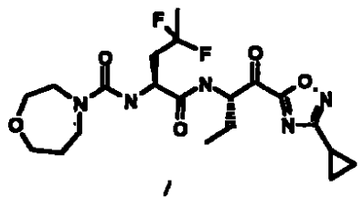
dried over $MgSO_4$ and solvent evaporated under reduced pressure to give the crude product. Purification by Silica gel column chromatography, eluting with ethyl acetate and heptane mixture gave morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-hydroxymethyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide (223 mg, 75%).

A mixture of Morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-hydroxymethyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide (217 mg) and Dess-Martin Periodinane (15% in DCM, 2 eq.) in DCM (5 mL) was stirred at room temperature for 3hrs and quenched with a solution of sodium thiosulfate in saturated $NaHCO_3$. The product was extracted with ethyl acetate and washed with saturated NaCl solution. Organic phase was dried over anhydrous $MgSO_4$, solvent evaporated under reduced pressure. Purification by silica gel chromatography eluting with ethyl acetate-heptane mixture gave Morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-formyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide (83 mg, 38%).

^1H NMR ($CDCl_3$): δ 9.3 (s, 1H), 7.2 (m, 5H), 7.0 (s, 1H), 5.0 (d, J = 7 Hz, 1H), 4.64 (dd, J = 13, 7.3 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, J= 16.5 Hz, 2H), 2.3 (m, 2H), 1.9 (m, 1H), 1.65 (m, 1H), 1.35 (s, 3H), 1.2 (m, 2H), 0.9 (t, J= 7.3 Hz, 3H);
LC/MS: 100% 440. (M+1)

EXAMPLE 20

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide



I

To a mixture of (S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid (97 mg, 0.35 mmol), (S)-2-Amino-1- (3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride (83 mg, 0.36 mmol) and diisopropylethyl amine (121 µL, 0.70 mmol) in dry dichloromethane (12 mL) was added 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (66 mg, 0.35 mmol) and 1-hydroxybenzotriazole hydrate (47 mg, 0.35 mmol). The mixture was stirred at room temperature for 16 hr then was diluted with dichloromethane (20 mL) and washed with dilute HCl (30 mL), then saturated $NaHCO_3$ (30 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuum. The residue was purified over 12 g silica gel, eluting with ethyl acetate: heptane (gradient 50 - 100 %) to afford Perhydro-1, 4-oxazepine-4-carboxylic acid ((S)-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-

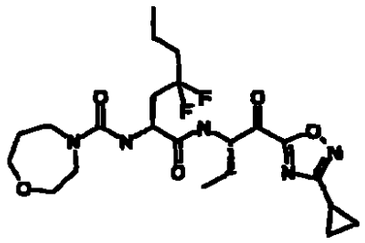
hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-butyl)-amide (120 mg, 75 %) as a colorless glassy solid. LC/MS 100% 460 (M+H).

To a solution of Perhydro-1, 4-oxazepine-4-carboxylic acid ((S)-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-butyl)-amide (110 mg, 0.24 mmol) in dry dichloromethane (20 mL) under N_2 was added Dess-Martin periodinane (143 mg, 0.34 mmol). The reaction was stirred at RT for 2 hr, and then dichloromethane (20 mL) was added. The reaction was quenched with a solution of $Na_2S_2O_3$ (0.26M, 2 mL) and washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuum. The residue was purified over 12 g silica gel, eluted with ethyl acetate: heptane (gradient 50-100%) to afford Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide (82 mg, 75%) as a white solid.

^{1}H NMR ($CDCl_3$) δ 7.52 (d, 6.2H), 5.28 (m, 1H), 5.05 (d, J = 7 Hz, 1H), 4.66 (m, 1H), 3.78 (m, 4H), 3.59 (m, 4H), 2.42 (m, 2H), 2.23 (m, 1H), 2.07 (m, 1H). 1.98 (m, 1H0, 1.85 (m, 1H), 1.69 (t, J = 18.8 Hz, 3H), 1.15 (m, 4H), 0.98 (t, J = 7.5Hz, 3H); LC/MS: 97% 458 (M+H).

EXAMPLE 21

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



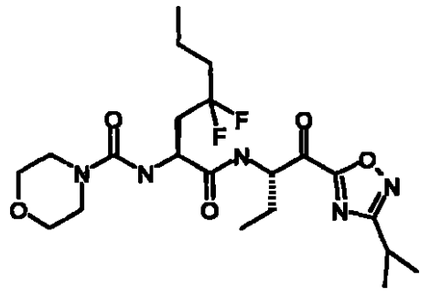
By proceeding in a similar manner Example 20 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid and (S) -2- amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide (98mg, 65%) as a white solid.

^{1}H NMR (CDCl3) δ 7.6 (d, J=7.5 Hz, 1H), 5.25 (m, 1H), 5.10 (d, J=7.5 Hz, 1H), 4.65 (dd, J=14, J=7.5 Hz, 1H), 3.75 (m, 6H), 3.55 (m, 4H), 2.4 (m, 2H), 2.2 (m, 2H), 1.95 (m, 1H), 1.8 (m, 3H), 1.55 (m, 2H), 1.10 (m, 4H), 0.95 (t, J=7.5 Hz, 6H);

LC/MS: 70% 486 (M+1) and 30% 504 (M+1+H2O).

EXAMPLE 22

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-isopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide

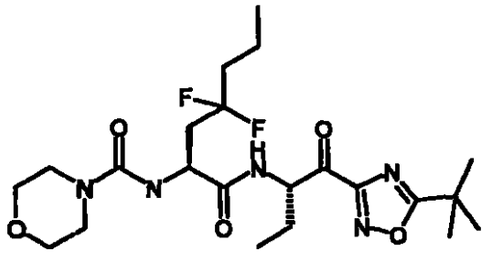


By proceeding in a similar manner to Example 20 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and (S)-2-amino-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared, Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-isopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide (122mg, 71%) as white solid.

1H NMR (CDCl3) δ 7.5 (d, J=7.0 Hz, 1H), 5.3 (m,1H), 5.25 (d, J=7.0 Hz, 1H), 4.65 (dd, J=13, 7.0 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (m, 1H), 2.35 (m, 2H), 2.1 (m, 1H), 1.8 (m, 3H), 1.55 (m, 2H), 1.40 (d, J=7 Hz, 6H), 0.9 (t, J=7.0 Hz, 6H); LC/MS: 72% 474 (M+1) and 28% 492 (M+1+H2O).

EXAMPLE 23

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

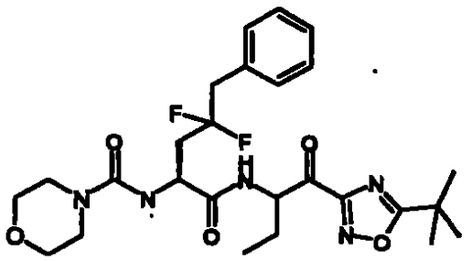


A solution of (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (175 mg, 0.60 mmol) in dimethylformamide (6 ml) was treated successively with (S)-2-Amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol (240 mg, 1.13 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (226 mg, 0.59 mmol) and diisopropylethylamine (0.104 ml, 0.60 mmol). Reaction stirred at room temperature overnight. Solvent evaporated under high vacuum. Residue taken up in ethyl acetate and washed with 1N hydrochloric acid, saturated aqueous bicarbonate solution and water, dried over Na_2SO_4 and solvent evaporated under reduced pressure.

Crude purified on flash silica (10g column) eluting with a mixture of ethyl acetate and heptane (2:1) to give Morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide as a brown oil (60 mg).
MS : 490 (M+H).

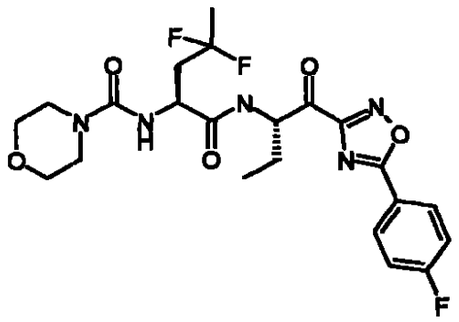
A solution of Morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide (57 mg, 0.117 mmol) in methylene chloride (3 ml) was treated with Dess-Martin periodinane (59 mg, 0.139 mmol) and stirred at room temperature for 90 minutes. The reaction mixture was washed with a solution of $Na_2S_2O_3$ in water (0.26M), saturated aqueous bicarbonate solution and water, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane (1:1) to give Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide as an off white solid (41 mg).
MS : 488 (M+H).

EXAMPLE 24
Morpholine-4-carboxylic acid {(S)-1-[1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide



By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-Amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-1-[1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide as 7:3 mixture of diastereoisomers.
^{1}H NMR ($CDCl_3$) δ: 7.36-7.19 (m, 5H), 7.15 (d, J=7.1Hz, 1H), 5.31 (m, 1H), 5.03 & 4.96 (2xd, J=7Hz, 1H), 4.68 (m, 1H), 3.76-3.59 (m, 4H), 3.45-3.26 (m, 4H), 3.18 (t, J=16.8Hz, 2H), 2.52-2.18 (m, 2H), 2.17-1.94 (m, 1H), 1.88-1.70 (m, 1H), 1.47 (s, 9H), 0.93 (t, J=7.4Hz, 3H).
MS : 536 (M+H).

EXAMPLE 25
Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide



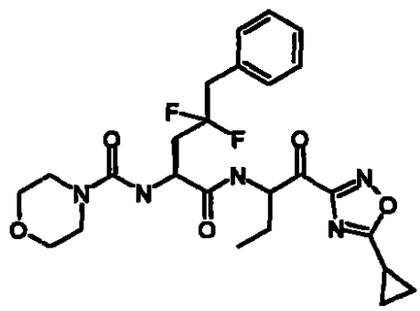
By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazol-3-yl]-butan-1-ol there was prepared Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide

^{1}H NMR ($CDCl_3$) δ: 8.21 (m, 2H), 7.31 (d, J=6.8Hz, 1H), 7.30-7.20 (m, 2H), 5.38 (m, 1H), 5.07 (d, J=6.8Hz, 1H), 4.63 (m, 1H), 3.75-3.64 (m, 4H), 3.44-3.33 (m, 4H), 2.58-2.28 (m, 2H), 2.22-2.04 (m, 1H), 1.96-1.79 (m, 1H), 1.66 (t, J=18.8Hz, 3H), 0.97 (t, J=7.4Hz, 3H).

MS : 498 (M+H).

EXAMPLE 26

Morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide



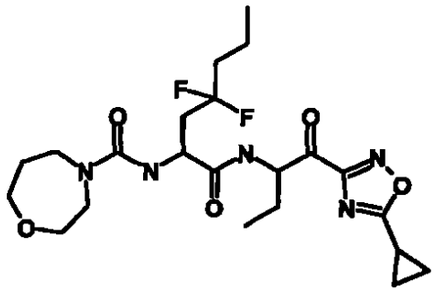
By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-Amino-1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide as 3:1 mixture of diastereoisomers.

^{1}H NMR ($CDCl_3$) δ: 7.36-7.20 (m, 5H), 7.14 (d, J=7.1Hz, 1H), 5.26 (m, 1H), 5.02 & 4.96 (2xd, J=7Hz, 1H), 4.70 (m, 1H), 3.73-3.61 (m, 4H), 3.43-3.28 (m, 4H), 3.18 (t, J=16.5Hz, 2H), 2.48-2.21 (m, 3H), 2.14-1.98 (m, 1H), 1.85-1.70 (m, 1H), 1.38-1.21 (m, 4H), 0.91 (t, J=7.5Hz, 3H).

MS : 520 (M+H).

EXAMPLE 27

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



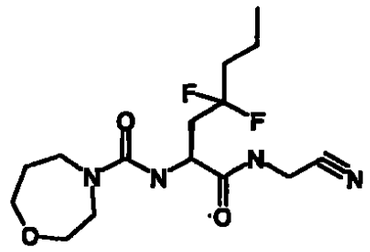
By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid and (S)-2-Amino-1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-butan-1-ol there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide as 5:1 mixture of diastereoisomers.

^{1}H NMR ($CDCl_3$) : 7.44 & 7.39 (2xd, J=7.3Hz, 1H), 5.30 (m, 1H), 5.05 & 4.98 (2xd, J=6.5Hz, 1H), 4.63 (m, 1H), 3.79-3.73 (m, 4H), 3.59-3.53 (m, 4H), 2.47-2.23 (m, 3H), 2.15-1.76 (m, 6H), 1.57-1.43 (m, 2H), 1.38-1.26 (m, 4H), 0.95 (t, J=7.3Hz, 3H), 0.93 (t, J=7.2Hz, 3H).

MS : 486 (M+H).

EXAMPLE 28

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide



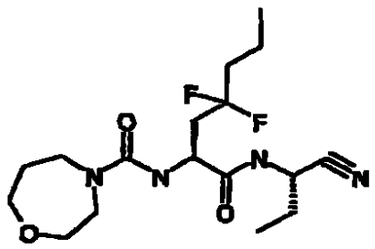
A suspension of Polystyrene bound carbodiimide (570mg, 0.73 mmol) and (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid (135 mg) in DCM (10 ml) stirred for 10 min. HOBT (60mg) added, stirred for 10 min. A suspension of amino acetonitrile hydrochloride (34 mg) and triethyl amine (52 uL) in DCM (5ml) added and stirred overnight at room temperature. PS-Trisamine (493 mg) added and stirred at room temperature for 2h 30 min. After filtration, filtrate

diluted with DCM, washed with water, evaporated under reduced pressure and purified by column chromatography eluting with ethyl acetate heptane mixture to give Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide as white solid.

LCMS : 100% 347 (M+H)

EXAMPLE 29

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide

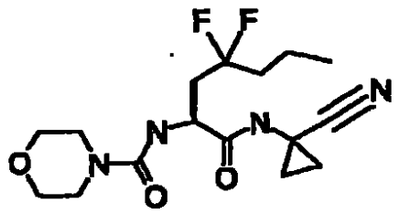


By proceeding in a similar manner to Example 28 above but using 4,4-Difluoro-2-[([1,4]oxazepane-4-carbonyl)-amino]-heptanoic acid and (S)-2-Amino-butyronitrile hydrochloride there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide.

LCMS : 100% 375 (M+H).

EXAMPLE 30

Morpholine-4-carboxylic acid [(S)-1-(1-cyano-cyclopropylcarbamoyl)-3,3-difluoro-hexyl]-amide



Prepared by reacting (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and 1-Amino-cyclopropanecarbonitrile hydrochloride, using TOTU as the coupling agent and diisopropyl ethylamine as the base.

LCMS : 359 (M+H)

EXAMPLE 31

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM, 0.5 mM DTT, 0.01% triton X-100).

Human cathepsin S (final concentration in the well is 1.74 nM) 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 (final concentration in the well is 0.08 mM) 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 32

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (comprising: MES 50 mM (pH 6); 2.5 mM EDTA , 2% DMSO and dithiothreitol (DTT), 2.5 mM).

Human cathepsin B (final concentration of 0.3 ng/μl) 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-pNa (final concentration of 100 μM) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 405nm) for 60 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 33

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μL 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 μL 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 34

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (10 μL of 0.2 ng/μL, final concentration of 0.02 ng/μl) 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 (10 μL of 0.1 mM, final concentration of 10 μM) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 30 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. The apparent inhibition constants (K_i) for compounds of the invention, against Cathepsin S, were in the range from about 10^{-10} M to about 10^{-7}M.

EXAMPLE 35

Representative Pharmaceutical Formulations Containing a Compound of Formula (I):

ORAL FORMULATION

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

INTRAVENOUS FORMULATION

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

TABLET FORMULATION

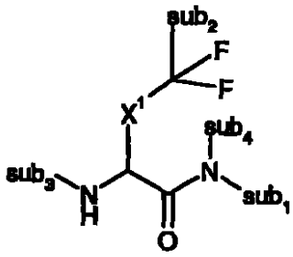
Compound of Formula I,	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.

While there have been described and pointed out fundamental novel features of the invention as applied to a preferred embodiment thereof, it will be understood that various omissions and substitutions and changes, in the form and details of the composition and methods illustrated, may be made by those skilled in the art *without* departing from the spirit of the invention. For example, it is expressly intended that chemical radical substitutions and/or method steps, which perform substantially the same function in substantially the same way to achieve the same results are within the scope of the invention.

The invention is not limited by the embodiments described above which are presented as examples only but can be modified in various ways within the scope of protection defined by the appended patent claims.

WE CLAIM:

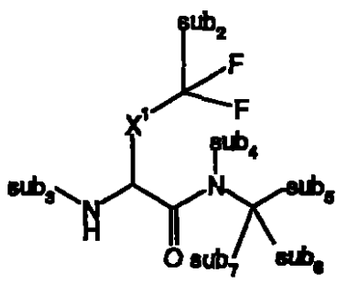
1. A compound having a backbone structure of a formula II:



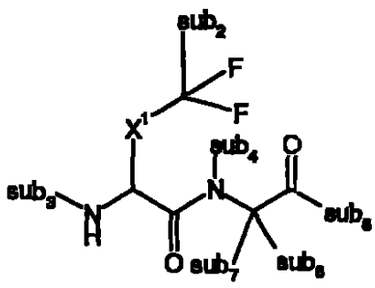
II

wherein X^1 is methylene, ethylene or a bond and sub_1-sub_4 are general substituents.

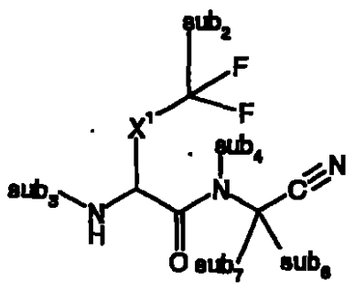
2. A compound of claim 1, have a backbone structure selected from the group consisting of Formulae III, IV and V:



III



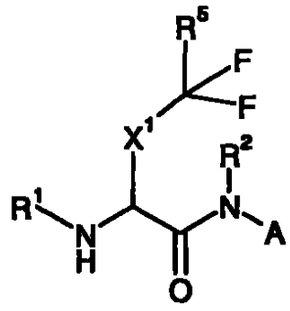
IV



V

wherein X^1 is methylene, ethylene or a bond and sub_1-sub_8 are general substituents.

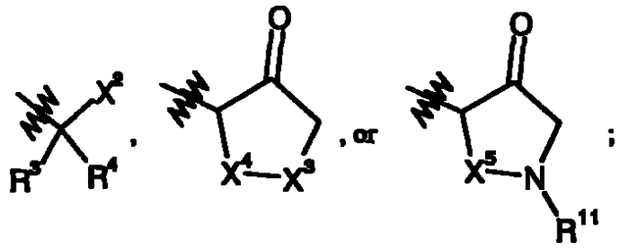
3. A compound having a structure of formula (I):



(I)

wherein

A is



X^1 is methylene, ethylene or a bond;

X^2 is CN, CHO, $C(O)R^6$, $C(O)C(O)NR^7R^7$, $C(O)C(O)NR^7R^8$, $C(O)C(O)R^{13}$, $C(O)C(O)OR^{13}$, $C(O)CH_2X^3R^{13}$;

X^3 is selected from the group consisting of O, $S(O)_n$, CO, CONH, NHCO, $NHSO_2$ and SO_2NH;

X^4 is $CH(R^{12})$ or $CH(R^{12})$-CH_2;

X^5 is methylene, ethylene, propylene or a bond;

X^6 is a bond or (C_{1-2})alkylene;

R^1 is H, $R^{13}C(O)$-, $R^{13}S(O)_2$-, $R^{13}OC(O)$-, $R^8R^7NC(O)$-, $R^8R^7NS(O)_2$-; $R^{13}S(O)_2NC(O)$- or $R^{13}C(O)NS(O)_2$-; or R^1 is selected from the group consisting of (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl and hetero(C_{5-13})aryl(C_{0-6})alkyl , each of which is 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, $-X^6NR^9R^9$,

$-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-12})aryl(C_{0-6})alkyl;

R^3 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-13})aryl(C_{0-6})alkyl optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^4 is H or (C_{1-6})alkyl; or R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^5 is H, F, or R^5 is (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl each 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, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^6 is (C_{6-12})aryl, hetero(C_{5-13})aryl and halo substituted (C_{1-6}) alkyl; wherein R^6 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, cyano, halo, halo-substituted (C_{1-6})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^7 is H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl; wherein R^7 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$,

$-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^8 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, and hetero(C_{5-13})aryl(C_{0-6})alkyl, or R^7 and R^8 together with the atom attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^9 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl;

R^{10} is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl;

R^{11} is selected from the group consisting of hydrogen, (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-3})alkyl, hetero(C_{8-12})-bicycloaryl(C_{0-3})alkyl, $-C(O)R^{13}$, $-C(S)R^{13}$, $-S(O)_2R^{13}$, $-C(O)OR^{13}$, $-C(O)N(R^7)R^8$, $-C(S)N(R^7)R^8$ and $-S(O)_2N(R^7)R^8$;

R^{12} is H or C_{1-6}alkyl optionally substituted by amido, (C_{6-12})aryl, hetero(C_{5-12})aryl, hetero(C_{5-12})cycloalkyl or hydroxy;

R^{13} is (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl; wherein R^{13} is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$; and

n is zero or an integer 1 or 2;

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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

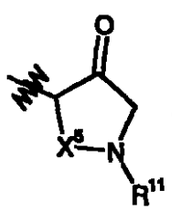
4. A compound according to claim 3 in which A is  .

5. A compound according to claim 4 in which R^3 is H, (C_{6-12})aryl(C_{2-6})alkyl or (C_{1-6})alkyl

optionally substituted by $-X^6OR^9$ wherein X^6 is a bond and R^9 is (C_{1-6})alkyl.

6. A compound according to claim 4 or 5 in which R^4 is H or (C_{1-6})alkyl.

7. A compound according to any one of claims 4-6 in which X^2 is CHO, CN or $C(O)R^6$ wherein R^6 is hetero(C_{5-13})aryl optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl.

8. A compound according to claim 3 in which A is  .

9. A compound according to claim 8 in which X^5 is propylene.

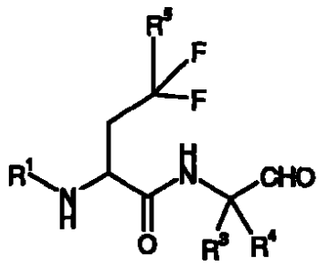
10. A compound according to claim 8 or 9 in which R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$ wherein R^{13} is alkyl or (C_{6-12})aryl.

11. A compound according to any one of claims 2-10 in which R^1 is (i) $R^{13}C(O)-$ wherein R^{13} is hetero(C_{5-12})cycloalkyl; (ii) $R^{13}OC(O)-$ wherein R^{13} is (C_{6-12})aryl(C_{1-6})alkyl; (iii) (C_{1-9})alkyl; or (iv) hetero(C_{5-12})cycloalkyl.

12. A compound according to any one of claims 2-11 in which R^2 is H.

13. A compound according to any one of claims 2-12 in which R^5 is (C_{1-9})alkyl or (C_{6-12})aryl(C_{1-6})alkyl.

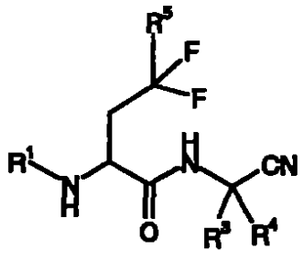
14. A compound of formula (Ia):



(Ia)

wherein R^1, R^3, R^4 and R^5 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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

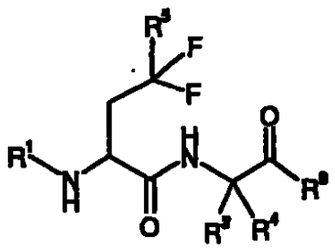
15. A compound of Formula (Ib):



(Ib)

wherein R^1, R^3, R^4 and R^5 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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

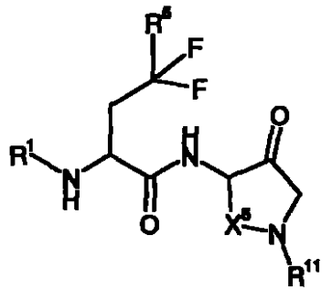
16. A compound of Formula (Ic):



(Ic)

wherein R^1, R^3, R^4, R^5 and R^6 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 (Ic) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

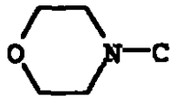
17. A compound of Formula (Id):



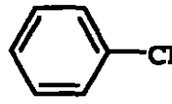
(Id)

wherein R^1, R^5, R^{11} and X^5 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 (Id) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

18. A compound according to any one of claims 14-17 in which R^1 is $R^{13}C(O)$- wherein R^{13} is hetero(C_{5-12})cycloalkyl.

19. A compound according to claim 18 in which R^1 is  .

20. A compound according to any one of claims 14, 15, 18 or 19 in which R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl or (C_{1-6})alkyl.

21. A compound according to claim 20 in which R^3 is H,  or

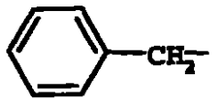
$CH_3CH_2CH_2$-.

22. A compound according to any one of claims 16, 18 or 19 in which R^3 is (C_{1-6})alkyl optionally substituted by $-X^6OR^9$ wherein X^6 is a bond and R^9 is (C_{1-6})alkyl.

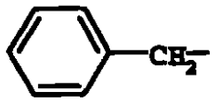
23. A compound according to claim 22 in which R^3 is CH_3-CH_2- , $CH_3-CH_2-CH_2-$ or CH_3-O-CH_2- .

24. A compound according to any one of claims 14-16 and 18-23 in which R^4 is H or methyl.

25. A compound according to any one of claims 14, 15, 17, 18-21 and 24 in which R^5 is (C_{6-12})aryl(C_{1-6})alkyl.

26. A compound according to claim 25 in which R^5 is  .

27. A compound according to any one of claims 16, 18, 19 and 24 in which R^5 (C_{1-9})alkyl or (C_{6-12})aryl(C_{1-6})alkyl.

28. A compound according to claim 25 in which R^5 is $CH_3CH_2CH_2$ or CH_3 CH_2 or CH_3 or  .

29. A compound according to claim 16, 18, 19, 24, 27 and 28 in which R^6 is hetero(C_{5-13})aryl, optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl.

30. A compound according to claim 29 in which R^6 is benzoxazolyl, oxadiazolyl, isoxazolyl, or oxazolyl each optionally substituted by one or more aryl or alkyl group substituents.

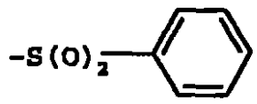
31. A compound according to claim 30 in which R^6 is benzoxazol-2-yl, 5-tert-butyl-[1,2,4]oxadiazol-3-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, 5-cyclopropyl-1,2,4-oxadiazol-3-yl, 5-cyclopropyl-1,3,4-oxadiazol-2-yl , 5-ethyl-1,3,4-oxadiazol-2-yl, 5-(4-fluoro-phenyl)-1,2,4-oxadiazol-

3-yl, 5-isopropyl-isoxazol-3-yl, 5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl, 5-(5-methyl-thien-2-yl)-oxazol-2-yl, oxazol-2-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 5-phenyl-1,2,4-oxadiazol-3-yl, 5-thiophen-2-yl-oxazol-2-yl, 5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl.

32. A compound according to claim 31 in which R^6 is benzoxazol-2-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, oxazol-2-yl, 5-cyclopropyl-1,2,4-oxadiazol-3-yl.

33. A compound according to claim 17 in which R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$ wherein R^{13} is alkyl or (C_{6-12})aryl.

34. A compound according to claim 28 in which R^{11} is $-C(O)OC(CH_3)_3$ or



.

35. A compound according to claim 3 selected from the group consisting of:

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

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

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

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

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

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

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

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

morpholine-4-carboxylic acid {3,3-difluoro-1-[1-(5-isopropyl-isoxazole-3-carbonyl)-propylcarbamoyl]-hexyl}-amide;

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(5-methyl-isoxazol-3-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;

morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(oxazole-2-carbonyl)-propylcarbamoyl]-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-thiophen-2-yl-oxazole-2-carbonyl)-propylcarbamoyl]-butyl}-amide;

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid [1-(2-benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-1-methyl-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid [(S)-1-((S)-1-cyano-3-phenyl-propylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;

morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;

morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-formyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide;

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

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

morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propylcarbamoyl]-butyl}-amide;

[(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-carbamic acid benzyl ester;

(S)-4,4-difluoro-5-phenyl-2-(tetrahydro-pyran-4-ylamino)-pentanoic acid cyanomethyl-amide;

(S)-4,4-difluoro-2-isobutylamino-5-phenyl-pentanoic acid cyanomethyl-amide;

morpholine-4-carboxylic acid [(S)-1-((S)-1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;

(S)-4-{(S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoylamino}-3-oxo-azepane-1-carboxylic acid tert-butyl ester;

morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-ethyl-1,3,4-oxadiazol-2-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide;

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

morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;
morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

36. A pharmaceutical composition comprising a compound of claim 2 and a pharmaceutically acceptable excipient.

37 A method of inhibiting cathepsin S in a patient wherein elevation of the enzymatic activity of cathepsin S contributes to said patient's pathological conditions by administering to said patient a therapeutically effective amount of a compound of claim 2.

38. Use of a compound according to claim 3, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin S.

39. Use of a compound according to claim 35, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin S.

40. Use of a compound according to claim 3, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin B.

41. Use of a compound according to claim 3, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin K.

42. The use according to any one of claims 38 to 41 of one of the following compounds:
morpholine-4-carboxylic acid {(*S*)-1-[(*S*)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide,
morpholine-4-carboxylic acid {(*S*)-1-[(*S*)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide,
morpholine-4-carboxylic acid {(*S*)-1-[(*S*)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide or
morpholine-4-carboxylic acid {(*S*)-3,3-difluoro-1-[(*S*)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide
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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof
for the production of pharmaceuticals that inhibit the enzymatic activity of Cathepsin S, K, or B.

43. The use according to claim 42 for treating pain, osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer or skin cancer.

44. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin S, such disease or medical condition being selected from arthritis, atherosclerosis, emphysema, osteoporosis, pain, muscular dystrophy, inflammation, multiple sclerosis, irritable bowel disease, rheumatoid arthritis, asthma, autoimmune responses, chronic obstructive pulmonary disease, and bronchiolitis, comprising administering to said patient an effective cathepsin S inhibiting amount of a compound according to claim 3.

45. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin K or B, such disease or medical condition being selected from

osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer, and skin cancer, comprising administering to said patient an effective cathepsin K or B inhibiting amount of a compound according to claim 3.

46. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cysteine protease, such disease or medical condition being selected from arthritis, atherosclerosis, emphysema, osteoporosis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, periodontal disease, metachromatic leukodystrophy, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, irritable bowel disease, rheumatoid arthritis and Hashimoto's thyroiditis, asthma, autoimmune responses, chronic obstructive pulmonary disease, and bronchiolitis, comprising administering to said patient an effective cysteine protease inhibiting amount of a compound according to claim 3.

47. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin K or B, such disease or medical condition being selected from pain, osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer, and skin cancer, comprising administering to said patient an effective cathepsin K or B inhibiting amount of a compound according to claim 35.

48. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cysteine protease, such disease or medical condition being selected from pain, osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer, and skin cancer, comprising administering to said patient an effective cysteine protease inhibiting amount of a compound according to claim 42.

49. A method of selectively inhibiting cathepsin K activity in a patient with elevated levels of cathepsin K which comprises administering to a patient in need thereof an effective cathepsin K inhibiting amount of a compound according to claim 3.

50. A method of selectively inhibiting cathepsin K activity in a patient with elevated levels of cathepsin K which comprises administering to a patient in need thereof an effective cathepsin K inhibiting amount of a compound according to claim 42.

51. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 3.

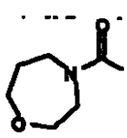
52. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 35.

51. A method of selectively inhibiting cathepsin B activity in a patient with elevated levels of cathepsin B which comprises administering to a patient in need thereof an effective cathepsin B inhibiting amount of a compound according to claim 3.

52. A method of selectively inhibiting cathepsin B activity in a patient with elevated levels of cathepsin B which comprises administering to a patient in need thereof an effective cathepsin B inhibiting amount of a compound according to claim 42.

53. A method of treating osteoarthritis in a mammal comprising administering to said mammal an effective amount of a compound according to claim 42.

54. A compound according to any one of claims 3-10, 12-18, or 20-30 wherein R^1 is



55. A compound according to claim 3 selected from the group consisting of:

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-isopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide,

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

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

Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide,

Morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide, and

Morpholine-4-carboxylic acid [(S)-1-(1-cyano-cyclopropylcarbamoyl)-3,3-difluoro-hexyl]-amide.

56. The use according to any one of claims 41 to 42 of one of the following compounds:

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-isopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide,

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

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

Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide,

Morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide, and

Morpholine-4-carboxylic acid [(S)-1-(1-cyano-cyclopropylcarbamoyl)-3,3-difluoro-hexyl]-amide.

57. A method of selectively inhibiting cathepsin K activity in a patient with elevated levels of cathepsin K which comprises administering to a patient in need thereof an effective cathepsin K inhibiting amount of a compound according to claim 55.

58. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 55.

59. A method of selectively inhibiting cathepsin B activity in a patient with elevated levels of cathepsin B which comprises administering to a patient in need thereof an effective cathepsin B inhibiting amount of a compound according to claim 55.

60. A method of treating osteoarthritis in a mammal comprising administering to said mammal an effective amount of a compound according to claim 55.

INTERNATI NAL SEARCH REPORT

I · ·tional Application No	
PCT/	US2004/035282

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D271/06 A61K31/5377 A61P35/00 C07D271/10 C07D261/08
C07D413/04 C07D263/32 C07D263/56 C07D295/18 A61P29/00
A61P37/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/55144 A (AXYS PHARMACEUTICALS, INC; LINK, JOHN, O; MARTELLI, ARNOLD, J; MARTICH) 21 September 2000 (2000-09-21) Claims 1-53; Formula (I); Table I, Formulae B23-B28; examples 28-31	1-60

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[X] Further documents are listed in the continuation of box C. [X] 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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 2005	31/03/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kirsch, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/035282

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/075836 A (MERCK FROSST CANADA & CO; AXYS PHARMACEUTICALS, INC; BAYLY, CHRISTOPHE) 18 September 2003 (2003-09-18) Claims 1-28; Formula (I); p. 11, l. 29-33; Table I: p. 28, l. 24-25; p. 29, l. 11-12, 16; Table II: p. 30, l. 13, p. 32, l. 8-9, 15; p. 65, l. 25-26; p. 68, l. 30-34; p. 69, l. 7-23, p. 73, l. 25-32; p. 74, l. 17-24; p. 75, l. 16-17, 31-35; p. 77, l. 29-33; p. 78, l. 1-2, 27-28; p. 79, l. 8-12; p. 83, l. 5-p. 84, l. 5; examples 16, 18, 38; p. 212, compounds 8-12; p. 213, compounds 1-2; p. 214, compounds 2-3; p. 219, compounds 3-4; p. 221, compound 2; p. 224, compound 9; p. 225, compound 1; p. 225-226	1-60
X	WO 00/55125 A (AXYS PHARMACEUTICALS, INC; BRYANT, CLIFFORD, M; BUNIN, BARRY, A; KRAYN) 21 September 2000 (2000-09-21) Claims 1-35; Formulae (I)	1-60
X	WO 02/069901 A (MERCK FROSST CANADA & CO; PE CORPORATION ; PRASIT, PETPIBOON; BAYLY, C) 12 September 2002 (2002-09-12) Claims 1-29; Formula (I)	1-60
X	WO 02/098850 A (AXYS PHARMACEUTICALS, INC; AVENTIS PHARMACEUTICALS INC; GRAUPE, MICHAE) 12 December 2002 (2002-12-12) Claims 1-20; Formula (I); Table II, Formulae B89 and B92	1-60
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International Application No
PCT/US2004/035282

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	CHEN J ET AL: "alpha-Aminoamides from a carbamoylsilane and aldehyde imines" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 44, no. 43, 20 October 2003 (2003-10-20), pages 8025-8027, XP004458767 ISSN: 0040-4039 Compound (1), entry 4	1
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	PATENT ABSTRACTS OF JAPAN vol. 1996, no. 10, 31 October 1996 (1996-10-31) -& JP 08 165274 A (SHIONOGI & CO LTD), 25 June 1996 (1996-06-25) Formula (Ia); compounds 25a, 26a; example 1 abstract	1
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X	T. ARAI ET AL.: "The Conformation of de Novo Designed Amphiphilic Peptides with Six or Nine L-2-(2,2,2-Trifluoroethyl)glycines as the Hydrophobic Amino Acid" BULL. CHEM. SOC. JPN, vol. 73, 2000, pages 439-445, XP002320762 Figure 1	1

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/035282

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

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 37, 44-60 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/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 III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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(71) Solicitante (para todos los Estados designados excepto US: **AVENTIS PHARMACEUTICALS INC.** (US/US); 300 Somerset Corporate Boulevard, Bridgewater, NJ 08807 (US).

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

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

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Ver Gaceta No. 23/2005 de Junio 9, 2005, Section II

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(54)Título: **NUEVOS DERIVADOS DE CETO-OXADIAZOL COMO INHIBIDORES DE LAS CATEPSINAS.**

(57) Resumen: Nuevos inhibidores de las catepsinas S, K, y L, las sales y N-óxidos farmacéuticamente aceptables de los mismos, sus usos como agentes terapéuticos y los métodos para su preparación.

PATENT COOPERATION TREATY

66 68

From the INTERNATIONAL BUREAU

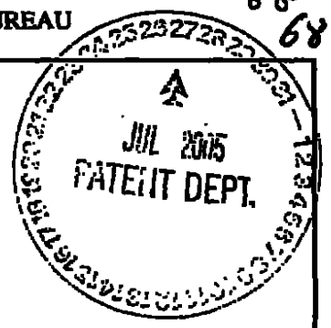
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14 July 2005 (14.07.2005)	
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PCT/US2004/035282	22 October 2004 (22.10.2004)	24 October 2003 (24.10.2003)

Applicant

AVENTIS PHARMACEUTICALS INC. et al

The International Bureau transmits herewith the following documents:

☐ copy of the international application as published by the International Bureau on under No. WO

☑ copy of international application as republished by the International Bureau on 14 July 2005 (14.07.2005) under No. WO 2005/040142
For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48) or (88) (*as the case may be*) on the front page of the attached document.

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(71) Applicant (*for all designated States except US*): AVENTIS PHARMACEUTICALS INC. [US/US]; 300 Somerset Corporate Boulevard, Bridgewater, New Jersey 08807-2854 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): THURAIRATNAM, Sukanthini [GB/US]; 6 Smoke Rise Lane, Bedminster, NJ 07921 (US). ALDOUS, David, John [US/US]; 268 Gates Avenue, Gillette, NJ 07933 (US). LEROY, Vincent [FR/US]; 1 JFK Boulevard, Franklin Greens Apt #36K, Somerset, NJ 08873 (US). TIMM, Andreas, Paul [DE/US]; 97 Bonney Court, Bridgewater, New Jersey 08807 (US).

(74) Agents: LIN, Jiang et al.; Aventis Pharmaceuticals Inc., Route 202-206, Bridgewater, NJ 08807 (US).

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

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

Declarations under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

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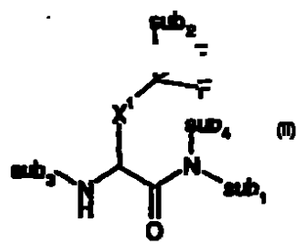
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WO 2005/040142 A1

(54) Title: NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS



(II)

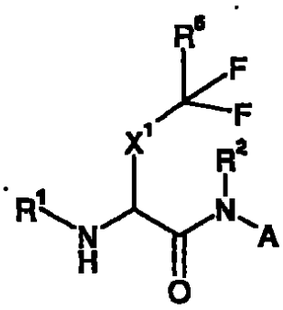
(57) Abstract: Novel difluorinated amide derivatives of Formula (II) as inhibitors of cathepsin S, K, B, and L, the pharmaceutically acceptable salts and *N*-oxides thereof, their uses as therapeutic agents and the methods of their making.

AMENDED CLAIMS

[received by the International Bureau on 31 May 2005 (31.05.05);
original claims 1-60 replaced by amended claims 1-62)]
+statement

WE CLAIM:

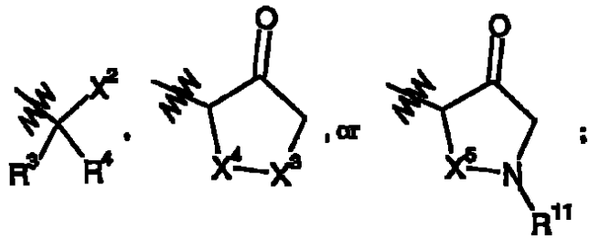
3. A compound having a structure of formula (I):



(I)

wherein

A is



X^1 is methylene, ethylene or a bond;

X^2 is CN, CHO, $C(O)R^6$, $C(O)C(O)NR^7R^7$, $C(O)C(O)NR^7R^8$, $C(O)C(O)R^{13}$, $C(O)C(O)OR^{13}$, $C(O)CH_2X^3R^{13}$;

X^3 is selected from the group consisting of O, $S(O)_n$, CO, CONH, NHCO, $NHSO_2$ and SO_2NH;

X^4 is $CH(R^{12})$ or $CH(R^{12})$-CH_2;

X^5 is methylene, ethylene, propylene or a bond;

X^6 is a bond or (C_{1-2})alkylene;

R^1 is $R^{13}C(O)$-, $R^{13}S(O)_2$-, $R^{13}OC(O)$-, $R^8R^7NC(O)$-, $R^8R^7NS(O)_2$-, $R^{13}S(O)_2NC(O)$- or $R^{13}C(O)NS(O)_2$-;

R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-12})aryl(C_{0-6})alkyl;

R^3 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-13})aryl(C_{0-6})alkyl optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^4 is H or (C_{1-6})alkyl; or R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^5 is H, F, or R^5 is (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl each 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, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

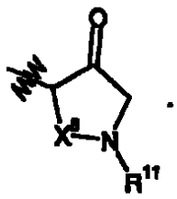
R^6 is (C_{6-12})aryl, hetero(C_{5-13})aryl and halo substituted (C_{1-6}) alkyl; wherein R^6 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, cyano, halo, halo-substituted (C_{1-6})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^7 is H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl; wherein R^7 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$,

optionally substituted by $-X^6OR^9$ wherein X^6 is a bond and R^9 is (C_{1-6})alkyl.

6. A compound according to claim 4 or 5 in which R^4 is H or (C_{1-6})alkyl.

7. A compound according to any one of claims 4-6 in which X^2 is CHO, CN or $C(O)R^6$ wherein R^6 is hetero(C_{5-13})aryl optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl.

8. A compound according to claim 3 in which A is  .

9. A compound according to claim 8 in which X^5 is propylene.

10. A compound according to claim 8 or 9 in which R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$ wherein R^{13} is alkyl or (C_{6-12})aryl.

11. A compound according to any one of claims 3-10 in which R^1 is (i) $R^{13}C(O)$- wherein R^{13} is hetero(C_{5-12})cycloalkyl; (ii) $R^{13}OC(O)$- wherein R^{13} is (C_{6-12})aryl(C_{1-6})alkyl; (iii) (C_{1-9})alkyl; or (iv) hetero(C_{5-12})cycloalkyl.

12. A compound according to any one of claims 3-11 in which R^2 is H.

13. A compound according to any one of claims 3-12 in which R^5 is (C_{1-9})alkyl or (C_{6-12})aryl(C_{1-6})alkyl.

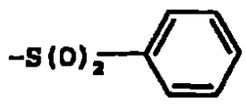
14. A compound of formula (Ia):

3-yl, 5-isopropyl-isoxazol-3-yl, 5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl, 5-(5-methyl-thien-2-yl)-oxazol-2-yl, oxazol-2-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 5-phenyl-1,2,4-oxadiazol-3-yl, 5-thiophen-2-yl-oxazol-2-yl, or 5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl.

32. A compound according to claim 31 in which R^6 is benzoxazol-2-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, oxazol-2-yl, or 5-cyclopropyl-1,2,4-oxadiazol-3-yl.

33. A compound according to claim 17 in which R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$ wherein R^{13} is alkyl or (C_{6-12})aryl.

34. A compound according to claim 28 in which R^{11} is $-C(O)OC(CH_3)_3$ or



35. A compound according to claim 3 selected from the group consisting of:
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(5-cyclopropyl-1,3,4-oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;
morpholine-4-carboxylic acid {1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-5-methyl-hexyl}-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;
morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide;
morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-butyl}-amide;
morpholine-4-carboxylic acid {1-[1-(5-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;
morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

36. A pharmaceutical composition comprising a compound of claim 3 and a pharmaceutically acceptable excipient.

37 A method of inhibiting cathepsin S in a patient wherein elevation of the enzymatic activity of cathepsin S contributes to said patient's pathological conditions by administering to said patient a therapeutically effective amount of a compound of claim 3.

38. Use of a compound according to claim 3, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin S.

39. Use of a compound according to claim 35, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin S.

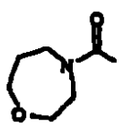
50. A method of selectively inhibiting cathepsin K activity in a patient with elevated levels of cathepsin K which comprises administering to a patient in need thereof an effective cathepsin K inhibiting amount of a compound according to claim 42.

51. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 3.

52. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 35.

53. A method of treating osteoarthritis in a mammal comprising administering to said mammal an effective amount of a compound according to claim 42.

54. A compound according to any one of claims 3-10, 12-18, or 20-30 wherein R^1 is



55. A compound according to claim 3 selected from the group consisting of:

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-isopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide,

57. A method of selectively inhibiting cathepsin K activity in a patient with elevated levels of cathepsin K which comprises administering to a patient in need thereof an effective cathepsin K inhibiting amount of a compound according to claim 55.

58. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 55.

59. A method of selectively inhibiting cathepsin B activity in a patient with elevated levels of cathepsin B which comprises administering to a patient in need thereof an effective cathepsin B inhibiting amount of a compound according to claim 55.

60. A method of treating osteoarthritis in a mammal comprising administering to said mammal an effective amount of a compound according to claim 55.

61. A method of selectively inhibiting cathepsin B activity in a patient with elevated levels of cathepsin B which comprises administering to a patient in need thereof an effective cathepsin B inhibiting amount of a compound according to claim 3.

62. A method of selectively inhibiting cathepsin B activity in a patient with elevated levels of cathepsin B which comprises administering to a patient in need thereof an effective cathepsin B inhibiting amount of a compound according to claim 42.

Statement Under Article 19(1)

Claims 1 and 2 have been canceled, resulting in the cancellation of page 75. Since page 75 is the first page of Applicants' claims, Applicants request that the phrase "WE CLAIM:" be added before claim 3 on page 76.

Claims 3, 11-13, 31-32, and 35-37 have been amended as detailed above. Claim 51 (second occurrence) and claim 52 (second occurrence) have been re-written as claims 61 and 62, respectively. Entry of replacement pages 76-77, 79, 83, 85, 88, and 90 is, therefore, respectfully requested.

Applicants request entry of the foregoing amendments preliminary to publication and examination of the above-identified patent application.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2004/035282	International filing date *(day/month/year)* 22.10.2004
Priority date *(day/month/year)* 24.10.2003	
International Patent Classification (IPC) or both national classification and IPC C07D271/06, A61K31/5377, A61P35/00, C07D271/10, C07D261/08, C07D413/04, C07D263/32, C07D263/56,	
Applicant AVENTIS PHARMACEUTICALS INC.	

1. This opinion contains indications relating to the following items:

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

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

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

For further options, see Form PCT/ISA/220.

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

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Kirsch, C Telephone No. +49 89 2399-2191

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/035282

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

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

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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

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

☐ the entire international application,

☒ claims Nos. 1-7, 37, 44-60

because:

☒ the said international application, or the said claims Nos. 37, 44-60 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

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

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

☒ no international search report has been established for the whole application or for said claims Nos. 1-7

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

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

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

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/035282

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-11, 14, 16-19, 21-23, 25-26, 28-35, 39, 42-43, 47-48, 50, 52, 52(bis), 53-60
	No:	Claims	1-7, 12-13, 15, 20, 24, 27, 36-38, 40-41, 44-46, 49, 51, 51(bis)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-60
Industrial applicability (IA)	Yes:	Claims	1-36,38-43
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

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

see separate sheet

Box No. VIII Certain observations on the international application

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

see separate sheet

Reference is made to the following documents :

D1: WO 00/55144
D2: WO 03/075836
D3: WO 00/55125
D4: WO 02/069901
D5: WO 02/098850
D6: WO 02/100849
D7: WO 03/097617 (P-Document)
D8: Orvieto F. et al., Bioorg. Med. Chem. Lett., 13(16), 18-08-2003, p. 2745-2748
D9: Bennett et al., Bioorg. Med. Chem. Lett., 11(3), 2001, p. 355-357
D10: Chen J. et al, Tetrahedron Lett., 44(43), 20 October 2003, p. 8025-8027
D11: DE 28 06 833
D12: FR 2 605 009
D13: JP 04 049298
D14: Patent Abstracts of Japan, 1996, 10 -& JP 08 165274
D15: WO 03/087069
D16: WO 99/64442
D17: WO 99/02549
D18: WO 02/079234
D19: WO 90/09162
D20: T. Arai et al., Bull. Chem. Soc. Jpn, 73, 2000, p. 439-445
D21: K. Burger et al., J. Fluorine Chem., 66, 1994, p. 87-90
D22: I. Ojima et al., Bioorg. Med. Chem. Lett., 2(3), 1992, p. 219-222
D23: R.M. Babb et al., J. Org. Chem., 35(5), 1970, p. 1438-1440
D24: S. Colarusso et al., J. Med. Chem., 46(3), 2003, p. 345-348

Document D7 has been found in a search of the state of the art in accordance with Art. 33(2) and (3) and rule 64.3 PCT. These documents will not be taken into account in international phase, however, the attention of the applicant is drawn to the fact that they may be relevant when assessing novelty and inventive step in the regional phases.

The present application describes difluorinated 2-aminoethylamide derivatives as cathepsin B, K or S inhibitors for the treatment of cancer, inflammatory disorders or autoimmune

diseases.

Re Item III

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

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a complete search over the whol breadth of the claim(s) was impossible. Consequently, the search has been restricted. The subject-matter mentioned in claims 7-60 has been searched completely.

Claims 37, 44-60 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-2 is not new in the sense of Article 33(2) PCT.

Documents D8 to D24 refer to various difluorinated 2-aminoethylamide derivatives (see specific passages in the ISR) which fall within the definition of claim 1 and 2. In this context the attention of the applicant is drawn to the fact that the examples as well as the whole technical teaching described in the prior art should be excluded in ord r to established novelty.

1.2. Document D1 deals with amine derivatives as cathepsin B, K, L or S inhibitors for the treatment of cancer, inflammatory disorders or bone diseases. Formula (I) of D1

overlaps with the present subject-matter. The fragments B23-B28 on p. 146-147 reveals the same structural features as in the present application. The subject-matter of claim 1 also lacks novelty with regard to document D1 (Art. 33(2) PCT).

Document D2 describes N-(cyanomethyl)-2-aminoethylamide derivatives useful as cathepsin inhibitors for the treatment of bone disorders, autoimmune diseases or inflammatory disorders. Formula (I) of D2 also overlaps with the present claimed subject-matter. Specific compounds comprising the same structural features as the present invention are disclosed in examples 16, 18 and 38 as well as in the rest of the description (see citations in the ISR). The subject-matter of claims 1-7, 12-13, 15, 20, 24, 27, 36-38, 40-41, 44-46, 49, 51, 51(bis) lacks novelty with regard to document D2 of the prior art (Art. 33(2) PCT).

1.3. Document D3 discloses aminomethylcarbonitrile derivatives as cathepsin B, K, L or S inhibitors for the treatment of tumors, inflammatory disorders, bone disorders or autoimmune diseases. There is an overlap between the subject-matter claimed in the present invention and formula (I) of D3. The combination of a 2-aminoethylamide core structure with a fluorinated alkyl substituent is not specifically disclosed in D3 and represents a new structural element which provide a contribution over the prior art. The present claimed subject-matter consists therefore in a new selection over D3. Novelty is established vis-à-vis D3 (Art. 33(2) PCT).

Document D4 deals with cyanomethylamide derivatives as cathepsin B, K, L and S inhibitors for the treatment of bone disorders. Formula (I) of D4 also overlaps with the present claimed subject-matter and the compounds on p. 10, l. 33-34 and p. 11, l. 16-1 describe difluorinated compounds. However, the present compounds refer to molecule wherein the amino part is disubstituted, i.e. one hydrogen atom is present on the nitrogen atom. The combination of a 2-(NHR)ethylamide core structure with a fluorinated alkyl substituent is therefore not specifically disclosed in document D4 and the subject-matter of claims 1-60 can be considered novel in the light of D4 (Art. 33(2) PCT).

Document D5 describes amide derivatives as cathepsin inhibitors for the treatment of cancer, inflammatory disorders, arthritis. Formula (I) of D5 is very broad and also encompass the compounds according to the present invention. Fragments B89 and B92

on p. 38 disclose difluorinated compounds. However, the combination of such fragments linked to an A-fragment via a nitrogen atom (A1, A59 or A60) is not described and represent a new piece of knowledged which provide a contribution over the prior art D5. Novelty is acknowledged with regard to document D5 (Art. 33(2) PCT).

Document D6 discloses N-(cyanomethyl)-2-carbonyloxyethylamide derivatives as cathepsin B, K, F, L or S inhibitors for the treatment of bone diseases, inflammatory disorders or autoimmune diseases. Amongst others, D6 also describes difluorinated compounds (p. 89, two last compounds). However, D6 deals with oxyethylamide instead of aminoethylamide and differ therefore from the present claimed subject-matter. Novelty of claims 1-60 is also established with regard to document D6 (Art. 33(2) PCT).

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-2, 4-40 does not involve an inventive step in the sense of Article 33(3) PCT.

Documents D1 to D5 are regarded as being the most relevant state of the art to the present claimed subject-matter and disclose amide derivatives as cathepsin B, K, L and S inhibitors.

The problem to be solved by the present invention may therefore be regarded as the provision of further amide derivatives which may be useful in the treatment of diseases involving cathepsin B, K, L or S.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons. The claimed-subject-matter is not new with regard to the documents D1 and D2 Therefore, it cannot provide any contribution to the art as required in Art. 33(3) PCT. Furthermore, the present invention represents solely a selection with regard to documents D3 to D5. The mere selection of specific features within a range known for its physiological properties cannot involve an inventive step in the sense of Art. 33(3) PCT because there is a clear incentive for the skilled man to seek in this direction.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 3, 14-17, 36-41, 44-53, 57-60, which therefore are also considered not inventive.

Dependent claims 4-13, 18-35, 42-43, 54-56 also represent a selection over all or some of documents D1 to D5 and do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

3. For the assessment of the present claims 37, 44-60 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII
Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents is not mentioned in the description, nor are these documents identified therein.

Re Item VIII
Certain observations on the international application

The application does not meet the requirements of Article 6 PCT, because claims 1-60 are not clear.

Claims 1-60 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable

the skilled person to determine which technical features are necessary to perform the stated functions: "general substituents", "prodrugs", "protected derivatives". These relative terms have no well-recognised meaning and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of the claims unclear, Article 6 PCT.

NUEVOS DERIVADOS DE CETO-OXADIAZOL COMO INHIBIDORES DE LAS CATEPSINAS

CAMPO DE LA INVENCIÓN

Esta invención se refiere al uso de nuevos derivados de ceto-oxadiazol para tratar enfermedades asociadas con la cisteína y, particularmente, enfermedades asociadas con la actividad de las catepsinas S, K, y B. Esta invención se refiere también a procedimientos para preparar dichos compuestos.

ANTECEDENTES DE LA INVENCIÓN

Las cisteína-proteasas representan una clase de peptidasas caracterizadas por la presencia de un resto de cisteína en el sitio catalítico de la enzima. Las cisteína-proteasas se asocian con la degradación y procesado normal de las proteínas. La actividad aberrante de las cisteína-proteasas, por ejemplo, como resultado del aumento de la expresión o de la mejora de la activación, sin embargo, puede tener consecuencias patológicas. A este respecto, ciertas cisteína-proteasas se asocian con una serie de enfermedades, incluyendo artritis, ateroesclerosis, enfisema, osteoporosis, distrofia muscular, inflamación, invasión tumoral, glomerulonefritis, enfermedad periodontal, leucodistrofia metacromática y otras.

Un incremento en la actividad de las catepsinas tal como, por ejemplo, la catepsina S, contribuye a la patología y/o sintomatología de una serie de enfermedades tales como, por ejemplo, trastornos autoinmunes, incluyendo, pero sin limitarse a ellos, diabetes de aparición juvenil, esclerosis múltiple, pénfigo vulgar, enfermedad de Graves, miastenia grave, lupus eritematoso sistémico, enfermedad del intestino irritable, artritis reumatoide y tiroiditis de Hashimoto, trastornos alérgicos incluyendo pero sin limitarse a ellos, asma, y respuestas inmunes alogénicas, incluyendo, pero sin limitarse a ellos, transplantes de órganos o injertos de tejidos. La catepsina S está también implicada en trastornos que incluyen elastolisis excesiva, tales como la enfermedad pulmonar obstructiva crónica (por ejemplo, enfisema), bronquiolitis, elastolisis excesiva de las vías respiratorias en el asma y bronquitis, neumonías y enfermedad cardiovascular tal como ruptura de placas y ateroma. La catepsina S está implicada en la formación fibrilar y, por tanto, los inhibidores de la catepsina S se pueden utilizar en el tratamiento de la amiloidosis sistémica.

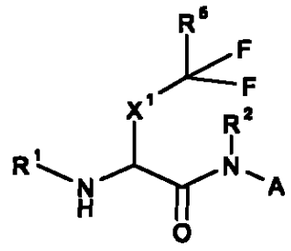
La actividad, por ejemplo, de la catepsina B en el fluido sinovial es significativamente elevada en los modelos de osteoartritis (F. Mehraban Ann. Rheum. Dis. 1997; *56*, 108-115). Similarmente, la catepsina K es una proteasa crítica en la degradación del colágeno mediada por el fibroblasto sinovial (W.-S. Hou (*et al.*) Am. J. Pathol. 2001, 159, 2167-2177). Por tanto, la

inhibición de las catepsinas B y K, por ejemplo, es un método útil para el tratamiento de enfermedades degenerativas de las articulaciones tales como, por ejemplo, la osteoartritis. La inhibición de la catepsina K, por ejemplo, lleva a la inhibición de la resorción ósea (G. B. Stroup (*et al.*) J. Bone Mineral Res. 2001, 16, 1739-1746). Los inhibidores de la catepsina K son, por tanto, útiles para el tratamiento de la osteoporosis.

Es conocido en la técnica que las catepsinas desempeñan un importante papel en la degradación de tejidos conjuntivos, en la generación de proteínas bioactivas y en el procesado de antígenos. Ellas han sido implicadas en la osteoporosis, distrofia muscular, bronquitis, enfisema, infección viral, metástasis cancerosa y enfermedades neurodegenerativas, tales como la enfermedad de Alzheimer y la enfermedad de Huntington. Recientemente, se ha generado un interés creciente sobre los inhibidores de catepsina con potenciales dianas terapéuticas, tales como la catepsina K o la catepsina L para la osteoporosis y la catepsina S para la modulación inmune (W. Kim., K. Kang. Expert Opin. Ther. Pat. 2002, 12, 419-432). Un aumento de la actividad de la catepsina K o B contribuye a la patología y/o sintomatología de una serie de enfermedades. Por consiguiente, las moléculas que inhiben la actividad de la catepsina-proteasa son útiles como agentes terapéuticos en el tratamiento de dichas enfermedades.

SUMARIO DE LA INVENCIÓN

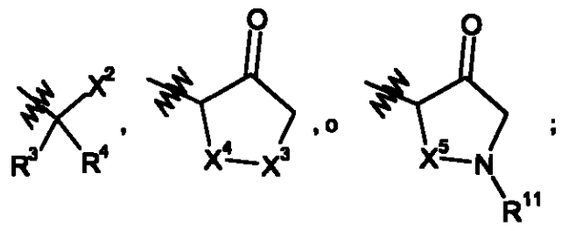
En un aspecto de la presente invención, se proporcionan compuestos que inhiben la actividad enzimática de las catepsinas S, B, y K y tienen la estructura de la fórmula (I):



(I)

en la que

A es



X^1 es metileno, etileno o un enlace;

X^2 es CN, CHO, $C(O)R^6$, $C(O)C(O)NR^7R^7$, $C(O)C(O)NR^7R^8$, $C(O)C(O)R^{13}$, $C(O)C(O)OR^{13}$, $C(O)CH_2X^3R^{13}$;

X^3 se selecciona del grupo que consiste en O, $S(O)_n$, CO, CONH, NHCO, $NHSO_2$ y SO_2NH;

X^4 es $CH(R^{12})$ o $CH(R^{12})$-CH_2;

X^5 es metileno, etileno, propileno o un enlace;

X^6 es un enlace o alquileno (C_{1-2});

R^1 es H, $R^{13}C(O)$-, $R^{13}S(O)_2$-, $R^{13}OC(O)$- , $R^8R^7NC(O)$-, $R^8R^7NS(O)_2$-; $R^{13}S(O)_2NC(O)$- o $R^{13}C(O)NS(O)_2$-; o R^1 se selecciona del grupo que consiste en alquilo (C_{1-9}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}) y heteroaril (C_{5-13})-alquilo (C_{0-6}), cada uno de los cuales está opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^2 se selecciona del grupo que consiste en hidrógeno, alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}) o heteroaril (C_{5-12})-alquilo (C_{0-6});

R^3 se selecciona del grupo que consiste en H, alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}) o heteroaril (C_{5-13})-alquilo (C_{0-6}) opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^4 es H o alquilo (C_{1-6}); o R^3 y R^4 considerados junto con el átomo de carbono al cual ambos R^3 y R^4 están unidos, forman cicloalquileno (C_{3-8}) o heterocicloalquileno (C_{3-8});

R^5 es H, F, o R^5 es alquilo (C_{1-9}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{3-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}) cada uno opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que

consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^6 es arilo (C_{6-12}), heteroarilo (C_{5-13}) y alquilo (C_{1-6}) sustituido con halo; donde R^6 está opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-9}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}), ciano, halo, alquilo (C_{1-6}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^7 es H, alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{3-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}), y alquilo (C_{1-6}) sustituido con halo; donde R^7 está opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^8 se selecciona del grupo que consiste en H, alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{3-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), y heteroaril (C_{5-13})-alquilo (C_{0-6}), o R^7 y R^8 junto con el átomo unido, forman cicloalquileno (C_{3-8}) o heterocicloalquileno (C_{3-8});

R^9 en cada aparición es independientemente hidrógeno, alquilo (C_{1-6}) o alquilo (C_{1-6}) sustituido con halo;

R^{10} es alquilo (C_{1-6}) o alquilo (C_{1-6}) sustituido con halo;

R^{11} se selecciona del grupo que consiste en hidrógeno, alquilo (C_{1-9}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}), bicicloaril (C_{9-12})-alquilo (C_{0-3}), heterobicicloaril (C_{8-12})-alquilo (C_{0-3}), $-C(O)R^{13}$, $-C(S)R^{13}$, $-S(O)_2R^{13}$, $-C(O)OR^{13}$, $-C(O)N(R^7)R^8$, $-C(S)N(R^7)R^8$ y $-S(O)_2N(R^7)R^8$;

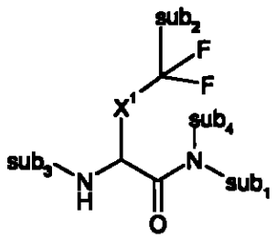
R^{12} es H o alquilo C_{1-6} opcionalmente sustituido con amido, arilo (C_{6-12}), heteroarilo (C_{5-12}), heterocicloalquilo (C_{5-12}) o hidroxi;

R^{13} es alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{3-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}), y alquilo (C_{1-6}) sustituido con halo; donde R^{13} está opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$; y

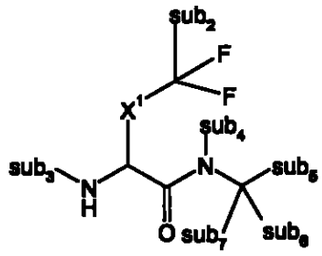
n es cero o un número entero 1 ó 2;

y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ia) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

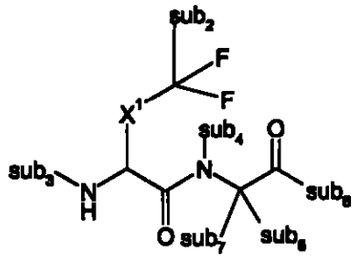
En otro aspecto de la presente invención, el objeto de la invención son las estructuras de la cadena principal de las fórmulas II, III, IV o V, en las que sub_1-sub_8 son sustituyentes generales. Los sustituyentes específicos en sub_1- sub_8 no son parte de este aspecto de la invención y pueden ser todos los grupos químicos o radicales que pueden estar sustituidos en aquellas posiciones (denominados como "sustituyentes generales" de aquí en adelante), incluyendo aquellas sustituciones que se hacen posibles por cualquier medio convencional o por cualquiera de las nuevas tecnologías desarrolladas en el futuro. Por tanto, para el propósito de esta solicitud, los "sustituyentes generales" no sirven como un elemento de reivindicación o limitación de la reivindicación y ellos mismos pueden ser nuevos y no obvios, o desconocidos en el momento de la invención.



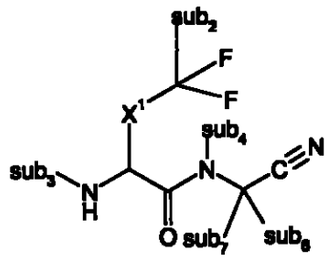
II



III



IV



V

En otro aspecto más de la invención, el objeto de la invención incluye la estructura de cadena principal de las fórmulas II, III, IV o V junto con los sustituyentes populares en sub_1-sub_8. Para el propósito de esta solicitud, "un sustituyente popular" significa un grupo químico o un radical que, en el momento de la presente invención, las personas con experiencia normal en la técnica, usando las sustituciones específicas descritas de aquí en adelante como guía, podrían considerar práctico para ser un sustituyente en sub_1-sub_8 sin experimentación excesiva practicando la presente invención.

En otro aspecto más de la invención, el objeto de la invención incluye las estructuras de la cadena principal de las fórmulas II, III, IV o V y los sustituyentes específicos descritos más adelante en sub_1-sub_8. El específico sustituyente descrito en la presente solicitud se denomina un "sustituyente particular." Para el propósito de la presente solicitud, un sustituyente particular, si se enumera en las reivindicaciones, sirve como una limitación de la reivindicación y puede conferir patentabilidad a la reivindicación por sí mismo o en combinación con la estructura de cadena principal junto con otros sustituyentes de la misma.

Definiciones:

A menos 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.

"Una entidad química relacionada" de un compuesto, significa un derivado N-óxido, un derivado profármaco, un derivado protegido, un isómero individual, una mezcla de isómeros, o una sal o solvato farmacéuticamente aceptable, de dicho compuesto, que pueden ser preparados sin experimentación excesiva por las personas con experiencia normal en el campo.

"Acilo" significa un grupo H-CO- o alquil-CO-, donde el grupo alquilo es como se describe en esta memoria.

"Acilamino" es un grupo acil-NH, donde acilo es como se define en esta memoria.

"Alcoxi" significa un grupo alquil-O, donde el grupo alquilo es como se describe en esta memoria. Los ejemplos de grupos alcoxi incluyen aliloxi, difluorometoxi, metoxi, trifluorometoxi, etoxi, *n*-propoxi, *i*-propoxi, *n*-butoxi y heptoxi.

"Alcoxicarbonilo" significa un grupo alquil-O-CO-, donde el grupo alquilo es como se describe en esta memoria. Los ejemplos de grupos alcoxicarbonilo incluyen metoxi- y etoxicarbonilo.

"Alquilo" representado por sí mismo significa un radical alifático lineal o ramificado, saturado o insaturado, que tiene el número de átomos de carbonos indicado (por ejemplo, alquilo (C_{1-6}) 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). 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 se indican átomos significa un enlace (por ejemplo, aril (C_{6-12})-alquilo (C_{0-6}) incluye fenilo, bencilo, fenetilo, 1-feniletilo, 3-fenilpropilo, y similares). Se podrá apreciar por los expertos en la técnica que cuando alquilo representa un radical alifático insaturado, tales radicales no pueden estar unidos directamente a un átomo de oxígeno, nitrógeno o azufre por medio de enlaces múltiples carbono-carbono de dicho radical alifático insaturado.

"Alquileno", a menos 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, alquileno (C_{1-2}) incluye metileno (-CH_2-) y etileno (-CH_2CH_2-). Se podrá apreciar por los expertos en la técnica que cuando alquileno representa un radical divalente alifático, insaturado, tales radicales no pueden estar unidos directamente a un átomo de oxígeno, nitrógeno o azufre por medio de enlaces múltiples carbono-carbono de dicho radical divalente, alifático, insaturado.

"Alquilendioxi" significa un grupo -O-alquilen-O-, donde alquileno es como se ha definido antes. Los ejemplos de grupos alquilendioxi incluyen metilendioxi y etilendioxi.

"Alquilsulfinilo" significa un grupo alquil-SO- donde el grupo alquilo es como se ha descrito previamente. Los grupos alquilsulfinilo preferidos son aquellos en los que el grupo alquilo es alquilo C_{1-4}.

"Alquilsulfonilo" significa un grupo alquil-SO_2- donde el grupo alquilo es como se ha descrito previamente. Los grupos alquilsulfonilo preferidos son aquellos en los que el grupo alquilo es alquilo C_{1-4}.

"Alquiltio" significa un grupo alquil-S-, donde el grupo alquilo es como se ha descrito previamente. Los ejemplos de grupos alquiltio incluyen metiltio, etiltio, isopropiltio y heptiltio.

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

"Aroílo" significa un grupo aril-CO, donde el grupo arilo es como se ha descrito en esta memoria. Los ejemplos de grupos aroílo incluyen benzoílo y 1- y 2-naftoílo.

"Aroilamino" es un grupo aroil-NH-, donde aroílo es como se ha definido previamente.

"Arilo", como un grupo o parte de un grupo, significa: (i) un resto carbocíclico aromático monocíclico o multicíclico opcionalmente sustituido, de 6 a 12 átomos de carbono, tal como fenilo o naftilo; o (ii) un resto carbocíclico aromático, multicíclico, opcionalmente sustituido y parcialmente saturado, en el que un arilo y un grupo cicloalquilo o cicloalquenilo se condensan juntos para formar una estructura cíclica, tal como un anillo tetrahidronaftilo, indenilo o indanilo. Excepto cuando se defina otra cosa, los grupos arilo pueden estar sustituidos con uno o más sustituyentes de grupo arilo, que pueden ser los mismos o diferentes, donde "sustituyente de grupo arilo" incluye, por ejemplo, acilo, acilamino, alcoxi, alcoxicarbonilo, alquilendioxi, alquilsulfinilo, alquilsulfonilo, alquiltio, aroílo, aroilamino, arilo, arilalquiloxi, arilalquiloxicarbonilo, arilalquiltio, ariloxi, ariloxicarbonilo, arilsulfinilo, arilsulfonilo, ariltio, carboxi (o un ácido bioisóstero), ciano, cicloalquilo, halo, heteroaroílo, heteroarilo, heteroarilalquiloxi, heteroaroilamino, heteroariloxi, heterocicloalquilo, hidroxi, nitro, trifluorometilo, $-NY^3Y^4$, $-CONY^3Y^4$, $-SO_2NY^3Y^4$, $-NY^3$-C(=O)alquilo, $-NY^3SO_2$alquilo o alquilo opcionalmente sustituido con arilo, heteroarilo, hidroxi, o $-NY^3Y^4$ (donde Y^3 y Y^4 son independientemente hidrógeno, alquilo, arilo, arilalquilo, cicloalquilo, heteroarilo o heteroarilalquilo; o el grupo $-NY^3Y^4$ puede formar una amina cíclica). Los ejemplos de arilo (C_{6-12}) opcionalmente sustituido incluyen, pero sin limitarse a ellos, bifenilo, bromofenilo, clorofenilo, diclorofenilo, difluorometoxifenilo, dimetilfenilo, etoxicarbonilfenilo, fluorofenilo, isopropilfenilo, metoxifenilo, metilfenilo, metilsulfonilfenilo, naftilo, pentafluorofenilo, fenilo, trifluorometoxifenilo, trifluorometilfenilo, y similares. Arilo (C_{6-12}) opcionalmente sustituido como se usa en esta solicitud para definir un radical sustituyente unido al grupo R^6 incluye trifluorometoxifenilo, difluorometoxifenilo, 4-fluorofenilo, y similares.

"Arilalquiloxi" significa un grupo arilalquilo-O-, donde los grupos arilalquilo son como se han descrito previamente. Los ejemplos de grupos arilalquiloxi incluyen benciloxi y 1- o 2-naftalenmetoxi.

"Arilalquiloxicarbonilo" significa un grupo arilalquilo-O-CO-, donde los grupos arilalquilo son como se han descrito previamente. Un ejemplo de un grupo arilalquiloxicarbonilo es benciloxicarbonilo.

"Arilalquiltio" significa un grupo arilalquil-S-, donde el grupo arilalquilo es como se ha descrito previamente. Un ejemplo de un grupo arilalquiltio es benciltio.

"Ariloxi" significa un grupo aril-O-, donde el grupo arilo es como se ha descrito previamente. Los ejemplos de grupos ariloxi incluyen fenoxi y naftoxi, cada uno opcionalmente sustituido.

"Ariloxicarbonilo" significa un grupo aril-O-C(=O)-, donde el grupo arilo es como se ha descrito previamente. Los ejemplos de grupos ariloxicarbonilo incluyen fenoxicarbonilo y naftoxicarbonilo.

"Arilsulfinilo" significa un grupo aril-SO- donde el grupo arilo es como se ha descrito previamente.

"Arilsulfonilo" significa un grupo aril-SO_2- donde el grupo arilo es como se ha descrito previamente.

"Ariltio" significa un grupo aril-S, donde el grupo arilo es como se ha descrito previamente. Los ejemplos de grupos ariltio incluyen feniltio y naftiltio.

"Cicloalquilo" significa un conjunto anular saturado o parcialmente insaturado, monocíclico, bicíclico condensado o policíclico puente, que contiene el número indicado de átomos de carbono en el anillo, y cualquiera de sus derivados carbocíclicos cetona, tiocetona o iminocetona (por ejemplo, cicloalquilo (C_{3-12}) incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclohexenilo, 2,5-ciclohexadienilo, biciclo[2,2,2]octilo, adamantan-1-ilo, decahidronaftilo, oxociclohexilo, dioxociclohexilo, tiociclohexilo, 2-oxobiciclo[2,2,1]hept-1-ilo, y similares). Se podrá apreciar por los expertos en la técnica que cuando cicloalquilo representa un conjunto anular cíclico insaturado, los anillos no pueden estar directamente unidos por medio de enlaces múltiples carbono-carbono a un átomo de oxígeno, nitrógeno o azufre.

"Cicloalquileno" significa un conjunto anular monocíclico o policíclico puente, divalente saturado o parcialmente insaturado, que contiene el número indicado de átomos de carbono en el anillo, y cualquiera de sus derivados carbocíclicos cetona, tiocetona o iminocetona.

"Heteroaroílo" significa un grupo heteroaril-C(=O)-, donde el grupo heteroarilo es como se ha descrito en esta memoria. Los ejemplos de grupos heteroarilo incluyen piridilcarbonilo.

"Heteroaroilamino" significa un grupo heteroaroil-NH- donde el resto heteroarilo es como se ha descrito previamente.

"Heteroarilo", como un grupo o parte de un grupo, indica: (i) un resto orgánico aromático monocíclico o multicíclico opcionalmente sustituido, de aproximadamente 5 a aproximadamente 13 miembros en el anillo en el cual uno o más de los miembros del anillo es/son elemento(s) distintos de carbono, por ejemplo nitrógeno, oxígeno o azufre (ejemplos de tales grupos incluyen grupos bencimidazolilo, benzoxazolilo, benzotiazolilo, furilo, imidazolilo, indolilo, indolizinilo, isoxazolilo, isoquinolinilo, isotiazolilo, oxadiazolilo, oxazolilo, pirazinilo, piridazinilo, pirazolilo, piridilo, pirimidinilo, pirrolilo, quinazolinilo, quinolinilo, 1,3,4-tiadiazolilo, tiazolilo, tienilo y triazolilo, opcionalmente sustituidos con uno o más sustituyentes de grupo arilo como se han definido antes, excepto cuando se defina otra cosa); (ii) un resto heterocarbocíclico multicíclico parcialmente saturado opcionalmente sustituido en el cual un heteroarilo y un grupo cicloalquilo o cicloalquenilo se condensan juntos para formar una estructura cíclica (ejemplos de tales grupos incluyen los grupos pirindanilo, opcionalmente sustituidos con uno o más "sustituyentes de grupo arilo " como se han definido antes excepto cuando se defina otra cosa). Los sustituyentes opcionales incluyen uno o más "sustituyentes de grupo arilo" como se han definido antes excepto cuando se defina otra cosa. Heteroarilo (C_{5-13}) opcionalmente sustituido como se usa en esta solicitud para definir R^6 incluye benzoxazol-2-ilo, 5-*terc*-butil-[1,2,4]oxadiazol-3-ilo, 3-ciclopropil-1,2,4-oxadiazol-5-ilo, 5-ciclopropil-1,2,4-oxadiazol-5-ilo, 5-ciclopropil-1,3,4-oxadiazol-2-ilo, 5-etil-[1,3,4]oxadiazol-2-ilo, 5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-ilo, 5-isopropil-isoxazol-3-ilo, 5-(5-metil-isoxazol-3-il)-oxazol-2-ilo, oxazol-2-ilo, 3-fenil-1,2,4-oxadiazol-5-ilo, 5-fenil-1,2,4-oxadiazol-3-ilo, 3-(tetrahidro-piran-4-il)-1,2,4-oxadiazol-5-ilo, 5-tiofen-2-il-oxazol-2-ilo, 5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-ilo, y similares.

"Heteroarilalquiloxi" significa un grupo heteroarilalquil-O, donde el grupo heteroarilalquilo es como se ha descrito previamente. Los ejemplos de grupos heteroariloxi incluyen piridilmetoxi opcionalmente sustituido.

"Heteroariloxi" significa un grupo heteroaril-O-, donde el grupo heteroarilo es como se ha descrito previamente. Los ejemplos de grupos heteroariloxi incluyen piridiloxi opcionalmente sustituido.

"Heterocicloalquilo" significa cicloalquilo, como se define en esta solicitud, con la condición de que uno o más de los átomos de carbono del anillo indicados están reemplazados por un resto heteroátomo seleccionado de -N=, -NR-, -O- o -S-, donde R es hidrógeno, alquilo (C_{1-6}), un grupo protector o representa la valencia libre que sirve como punto de unión a un nitrógeno del anillo, y cualquiera de sus derivados carbocíclicos cetona, tiocetona o iminocetona (por ejemplo, el término heterocicloalquilo (C_{5-12}) incluye imidazolidinilo, morfolinilo, piperazinilo, piperidilo, pirrolidinilo, pirrolinilo, quinuclidinilo, y similares). Los grupos protectores

adecuados incluyen *terc*-butoxicarbonilo, benciloxicarbonilo, bencilo, 4-metoxibencilo, 2-nitrobencilo, y similares. Tanto los derivados no protegidos como los protegidos están dentro del alcance de la invención.

"Heterocicloalquileno" significa cicloalquileno, como se define en esta solicitud, con la condición de que uno o más de los átomos de carbono miembros del anillo indicados, está reemplazado por un resto heteroátomo seleccionado de -N=, -NR-, -O-, -S- o $-S(O)_2-$, donde R es hidrógeno, alquilo (C_{1-6}) o un grupo protector.

"Isómeros", como se usa en esta descripción, significa los compuestos de la presente invención que tienen fórmulas moleculares idénticas pero difieren en la naturaleza o secuencia de unión de sus átomos o en el ordenamiento de sus átomos en el espacio. Los isómeros que difieren en el ordenamiento de sus átomos en el espacio se denominan "estereoisómeros". Los estereoisómeros que no son imagen en el espejo uno de otro se denominan "diastereoisómeros" y los estereoisómeros que no son imágenes superponibles en el espejo se denominan "enantiómeros" o a veces "isómeros ópticos". Un átomo de carbono con enlaces a cuatro sustituyentes no idénticos se denomina un "centro quiral". Un compuesto, que tiene un centro quiral tiene dos formas enantiómeras de quiralidad opuesta. Una "mezcla racémica" contiene ambos enantiómeros en una proporción 1: 1. Sin embargo, en los términos de esta solicitud, se ha empleado mezcla racémica cuando han estado presentes ambos enantiómeros sin tener en cuenta sus proporciones. Un compuesto que tiene más de un centro quiral tiene 2^{n-1} pares enantiómeros, donde *n* es el número de centros quirales. Los compuestos con más de un centro quiral pueden existir o como un diastereoisómero individual o como una mezcla de diastereoisómeros, denominada una "mezcla diastereoisómera". Cuando está presente un centro quiral se puede caracterizar un estereoisómero por la configuración absoluta de ese centro quiral. La configuración absoluta se refiere al ordenamiento en el espacio de los sustituyentes unidos al centro quiral. Los enantiómeros se caracterizan por la configuración absoluta de sus centros quirales y se describen por las reglas de secuencia *R*- y *S*- de Cahn, Ingold y Prelog. Las convenciones para la nomenclatura estereoquímica, los métodos para la determinación de la estereoquímica y la separación de estereoisómeros son bien conocidos en la técnica (por ejemplo, véase "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). Se debe entender que el objetivo de los nombres e ilustraciones usados en esta memoria, para describir los compuestos de la presente invención es englobar todos los posibles estereoisómeros. Así, por ejemplo, [el objetivo del nombre {1-[1-(3-ciclopropil-[1,2,4]oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico es' incluir la {(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico y la {(R)-1-[(R)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-

propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico y cualquier mezcla, racémica o de otro tipo, de las mismas.]

"Derivados *N*-óxido" significa derivados de compuestos de la presente invención en los cuales los nitrógenos están en estado oxidado (esto es, N-O) y que poseen la actividad farmacológica deseada.

"Farmacéuticamente aceptable" significa aquello que es útil para preparar una composición farmacéutica que en general es segura, no tóxica y que no es biológicamente ni de ninguna otra forma indeseable e incluye aquello que es aceptable para uso veterinario así como para uso farmacéutico humano.

"Sales farmacéuticamente aceptables " significa las sales de compuestos de la presente invención que son farmacéuticamente aceptables, como se ha definido antes, y que poseen la actividad farmacológica deseada. Dichas sales incluyen las sales de adición de ácido 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 ciclopentano-propiónico, 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 metilsulfónico, 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-en-1-carboxílico, ácido glucoheptónico, ácido 4,4'-metilenobis(3-hidroxi-2-en-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 incluyen también sales de adición de base que se pueden formar cuando los protones ácidos presentes son capaces de reaccionar con bases inorgánicas u orgánicas. Las bases inorgánicas aceptables incluyen hidróxido de sodio, carbonato de sodio, hidróxido de potasio, hidróxido de aluminio e hidróxido de calcio. Las bases orgánicas aceptables incluyen etanolamina, dietanolamina, trietanolamina, trometamina, *N*-metilglucamina y similares.

"Profármaco" significa un compuesto, que es convertible *in vivo* por medios metabólicos en un compuesto de la presente invención. Por ejemplo un éster de un compuesto de la presente invención que contiene un grupo hidroxi puede ser convertible por hidrólisis *in vivo* en la molécula original. Alternativamente un éster de un compuesto de la presente invención que contiene un grupo carboxi puede ser convertible por hidrólisis *in vivo* en la molécula original. Los

ésteres adecuados de los compuestos de la presente invención que contienen un grupo hidroxi, son por ejemplo acetatos, citratos, lactatos, tartratos, malonatos, oxalatos, salicilatos, propionatos, succinatos, fumaratos, maleatos, metileno-bis-b-hidroxinaftoatos, gentisatos, isetionatos, di-*p*-toluoiltartratos, metilsulfonatos, etanosulfonatos, bencenosulfonatos, *p*-toluenosulfonatos, ciclohexilsulfamatos y quinatos. Los ésteres adecuados de los compuestos de la presente invención que contienen un grupo carboxi son, por ejemplo, los descritos por F.J.Leinweber, Drug Metab. Res., 1987, 18, page 379, Una clase especialmente útil de los ésteres de los compuestos de la presente invención que contienen un grupo hidroxi, se puede formar a partir de restos ácidos seleccionados de los descritos por Bundgaard *et al.*, J. Med. Chem., 1989, 32, page 2503-2507, e incluyen (aminometil)-benzoatos sustituidos, por ejemplo, dialquilaminometilbenzoatos en los que los dos grupos alquilo puede estar unidos entre sí y/o pueden estar interrumpidos por un átomo de oxígeno o por un átomo de nitrógeno opcionalmente sustituido, por ejemplo, un átomo de nitrógeno alquilado, más especialmente (morfolino-metil)benzoatos, por ejemplo, 3- o 4-(morfolinometil)-benzoatos, y (4-alquilpiperazin-1-il)benzoatos, por ejemplo, 3- o 4-(4-alquilpiperazin-1-il)benzoatos.

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

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

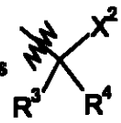
"Tratamiento" o "tratar" significa cualquier administración de un compuesto de la presente invención e incluye:

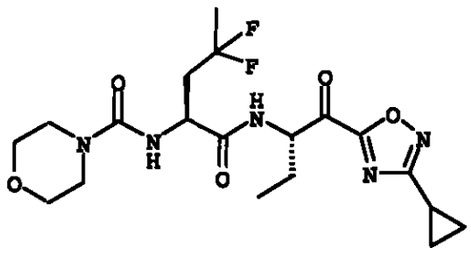
(1) prevenir que la enfermedad aparezca en un animal que puede estar predispuesto a la enfermedad pero que todavía no experimenta ni manifiesta la patología o sintomatología de la enfermedad,

(2) inhibir la enfermedad en un animal que está experimentando o manifestando la patología o sintomatología de la enfermedad (esto es, detener el futuro desarrollo de la patología y/o sintomatología), o

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

Nomenclatura:

Los compuestos de la presente invención y los intermedios y materiales de partida usados en su preparación se nombran de acuerdo con las reglas de nomenclatura de la IUPAC donde los grupos característicos tienen prioridad decreciente de mención según el grupo principal que se indica a continuación: ácidos, ésteres, amidas, etc. Como alternativa, los compuestos se nombran mediante AutoNom 4,0 (Beilstein Information Systems, Inc.). [Por ejemplo, un compuesto de la fórmula (I) en el que R^1 es morfolin-4-carbonilo, X^1 es metileno, R^5 es metilo, R^2 es H y A es  , donde R^3 es etilo, R^4 es H y X^2 es $C(O)R^6$ donde R^6 es 3-ciclopropil-1,2,4-oxadiazol-5-ilo; es decir, un compuesto que tiene la siguiente estructura:



se denomina {(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico

Sin embargo, se entiende que, para un compuesto particular del que se indican tanto la fórmula estructural como un nombre de nomenclatura, si la fórmula estructural y el nombre de nomenclatura son inconsistentes uno con otro, la fórmula estructural tiene prioridad sobre el nombre de nomenclatura.

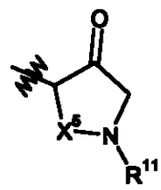
Se señalan las diferentes propiedades de novedad que caracterizan a la invención particularmente en las reivindicaciones anexas y formando parte de esta descripción. Para un mejor entendimiento de la invención, de sus ventajas de operación, y de los objetivos específicos logrados por su uso, se debe hacer referencia a la siguiente descripción en la que se ilustran y describen las realizaciones preferidas de la invención.

DESCRIPCIÓN DETALLADA DE LAS REALIZACIONES PREFERIDAS

Con referencia a la fórmula (I) anterior, los siguientes son grupos particulares:

X^1 puede representar particularmente metileno.

A puede representar particularmente  donde: R^3 es H, aril (C_{6-12})-alquilo (C_{2-6}) o alquilo (C_{1-6}) opcionalmente sustituido con $-X^6OR^9$ [donde X^6 es un enlace y R^9 es alquilo (C_{1-6})]; R^4 es H o alquilo (C_{1-6}); y X^2 es CHO, CN o $C(O)R^6$ [donde R^6 es heteroarilo (C_{5-13}) opcionalmente sustituido con alquilo (C_{1-9}), cicloalquilo (C_{3-12}), arilo (C_{6-12}) o heteroarilo (C_{5-13})].

A puede representar particularmente también  donde X^5 es propileno y R^{11} es $-C(O)OR^{13}$ o $-S(O)_2R^{13}$, donde R^{13} es alquilo o arilo (C_{6-12}).

R^1 puede representar particularmente $R^{13}C(O)-$ donde R^{13} es heterocicloalquilo (C_{5-12}).

R^1 puede representar particularmente también $R^{13}OC(O)-$ donde R^{13} es aril (C_{6-12})-alquilo (C_{1-6}).

R^1 puede representar particularmente también alquilo (C_{1-9}).

R^1 puede representar particularmente también heterocicloalquilo (C_{5-12}).

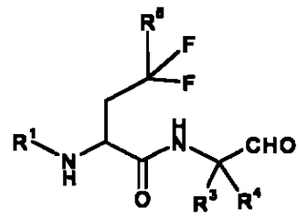
R^2 puede representar particularmente H.

R^5 puede representar particularmente alquilo (C_{1-9}).

R^5 puede representar particularmente también aril (C_{6-12})-alquilo (C_{1-6}).

Géneros particulares:

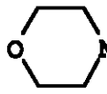
Un grupo particular de compuestos de la invención son los compuestos de la fórmula (Ia):



(Ia)

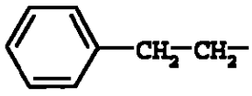
en la que R^1, R^3, R^4 y R^5 son como se han descrito antes en esta memoria, y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ia) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

Los compuestos de la fórmula (Ia) en los que R^1 es $R^{13}C(O)$- y R^{13} es heterocicloalquilo (C_{5-12}) son ejemplos. Los compuestos de la fórmula (Ia) en los que R^1 es



- son ejemplos particulares.

Los compuestos de la fórmula (Ia) en los que R^3 es H, aril (C_{6-12})-alquilo (C_{1-6}) o alquilo (C_{1-6}) son ejemplos. Los compuestos de la fórmula (Ia) en los que R^3 es H,

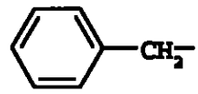


o $CH_3-CH_2-CH_2-$ son ejemplos particulares.

Los compuestos de la fórmula (Ia) en los que R^4 es H o metilo son ejemplos.

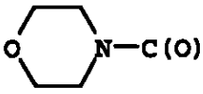
Los compuestos de la fórmula (Ia) en los que R^5 es aril (C_{6-12})-alquilo (C_{1-6}) son ejemplos.

Los compuestos de la fórmula (Ia) en los que R^5 representa

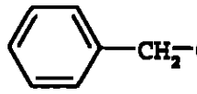


son ejemplos particulares.

Un grupo particular de compuestos de la invención son los compuestos de la fórmula (Ia) en los que: R^1 es $R^{13}C(O)$- (especialmente



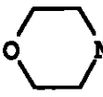
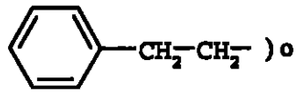
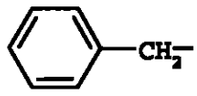
-); R^3 es H, aril (C_{6-12})-alquilo (C_{1-6}) (especialmente



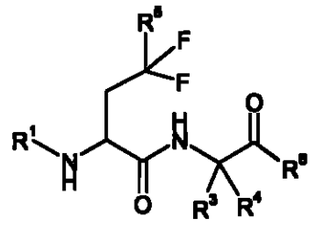
) o alquilo (C_{1-6}) (especialmente $CH_3-CH_2-CH_2-$); R^4 es H o metilo y R^5 es aril (C_{6-12})-alquilo (C_{1-6}) (especialmente



).

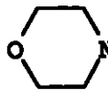
Un grupo particular de compuestos de la invención son los compuestos de la fórmula (Ib) en los que: R^1 es $R^{13}C(O)$- (especialmente ); R^3 es H, aril (C_{6-12})-alquilo (C_{1-6}) (especialmente ) o alquilo (C_{1-6}) (especialmente CH_3-CH_2-); R^4 es H o metilo y R^5 es aril (C_{6-12})-alquilo (C_{1-6}) (especialmente ).

Otro grupo particular de compuestos de la invención son los compuestos de la fórmula (Ic):



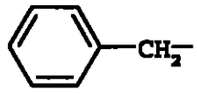
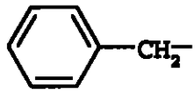
(Ic)

en la que R^1, R^3, R^4, R^5 y R^6 son como se han descrito antes en esta memoria, y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ic) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

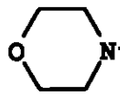
Los compuestos de la fórmula (Ic) en los que R^1 es $R^{13}C(O)$- y R^{13} es heterocicloalquilo (C_{5-12}) son ejemplos. Los compuestos de la fórmula (Ic) en los que R^1 es  son ejemplos particulares.

Los compuestos de la fórmula (Ic) en los que R^3 es alquilo (C_{1-6}) opcionalmente sustituido con $-X^6OR^9$ [donde X^6 es un enlace y R^9 es alquilo (C_{1-6})] son ejemplos. Los compuestos de la fórmula (Ic) en los que R^3 es CH_3-CH_2-, $CH_3-CH_2-CH_2-$ o CH_3-O-CH_2- son ejemplos particulares.

Los compuestos de la fórmula (Ic) en los que R^4 es H o metilo son ejemplos. Los compuestos de la fórmula (Ic) en los que R^4 es H son ejemplos.

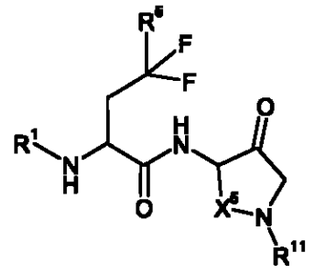
Los compuestos de la fórmula (Ic) en los que R^5 es alquilo (C_{1-9}) o aril (C_{6-12})-alquilo (C_{1-6}) son ejemplos. Los compuestos de la fórmula (Ic) en los que R^5 representa $CH_3CH_2CH_2$ o CH_3 CH_2 o CH_3 o  son ejemplos particulares. Los compuestos de la fórmula (Ic) en los que R^5 representa  son ejemplos particulares.

Los compuestos de la fórmula (Ic) en los que R^6 es heteroarilo (C_{5-13}), opcionalmente sustituido con alquilo (C_{1-9}), cicloalquilo (C_{3-12}), arilo (C_{6-12}) o heteroarilo (C_{5-13}), son ejemplos. Los ejemplos de grupos heteroarilo (C_{5-13}) opcionalmente sustituidos incluyen benzoxazolilo, oxadiazolilo, isoxazolilo, u oxazolilo, opcionalmente sustituidos. Los compuestos de la fórmula (Ic) en los que R^6 es benzoxazol-2-ilo, 5-*terc*-butil-[1,2,4]oxadiazol-3-ilo, 3-ciclopropil-1,2,4-oxadiazol-5-ilo, 5-ciclopropil-1,2,4-oxadiazol-2-ilo, 5-ciclopropil-1,3,4-oxadiazol-2-ilo, 5-etil-1,3,4-oxadiazol-2-ilo, 5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-ilo, 5-isopropil-isoxazol-3-ilo, 5-(5-metil-isoxazol-3-il)-oxazol-2-ilo, 5-(5-metil-tien-2-il)-oxazol-2-ilo, oxazol-2-ilo, 3-fenil-1,2,4-oxadiazol-5-ilo, 5-fenil-1,2,4-oxadiazol-3-ilo, 5-tiofen-2-il-oxazol-2-ilo, 5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-ilo y similares, son ejemplos. Los compuestos de la fórmula (Ic) en los que R^6 es benzoxazol-2-ilo, 3-ciclopropil-1,2,4-oxadiazol-5-ilo, oxazol-2-ilo, son ejemplos particulares.

Un grupo particular de compuestos de la invención son los compuestos de la fórmula (Ic) en los que: R^1 es $R^{13}C(O)$- (especialmente ); R^3 es alquilo (C_{1-6}) opcionalmente sustituido con $-X^6OR^9$ (especialmente CH_3-CH_2- , $CH_3-CH_2-CH_2-$ o CH_3-O-CH_2-); R^4 es H y R^5 es alquilo (C_{1-9}) o aril (C_{6-12})-alquilo (C_{1-6}) (especialmente ); R^6 es heteroarilo (C_{5-13}), opcionalmente sustituido con alquilo (C_{1-9}), cicloalquilo (C_{3-12}), heterocicloalquilo (C_{5-12}), arilo (C_{6-12}) o heteroarilo(C_{5-13}) (especial-

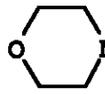
mente benzoxazol-2-ilo, 3-ciclopropil-1,2,4-oxadiazol-5-ilo, oxazol-2-ilo y 5-metil-isoxazol-3-il)-oxazol-2-ilo).

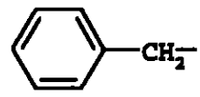
Otro grupo particular de compuestos de la invención son los compuestos de la fórmula (Id):

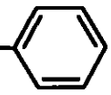


(Id)

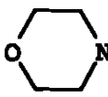
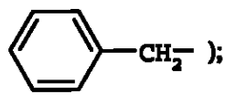
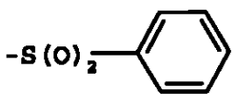
en la que R^1, R^5, R^{11} y X^5 son como se han descrito antes en esta memoria, y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Id) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

Los compuestos de la fórmula (Id) en los que R^1 es $R^{13}C(O)$- y R^{13} es heterocicloalquilo (C_{5-12}) son ejemplos. Los compuestos de la fórmula (Id) en los que R^1 es  son ejemplos particulares.

Los compuestos de la fórmula (Id) en los que R^5 es aril (C_{6-12})-alquilo (C_{1-6}) son ejemplos. Los compuestos de la fórmula (Id) en los que R^5 representa  son ejemplos particulares.

Los compuestos de la fórmula (Id) en los que R^{11} es $-C(O)OR^{13}$ o $-S(O)_2R^{13}$, donde R^{13} es alquilo o arilo (C_{6-12}) son ejemplos. Los compuestos de la fórmula (Id) en los que R^{11} representa $-C(O)OC(CH_3)_3$ o  son ejemplos particulares.

Los compuestos de la fórmula (Id) en los que X^1 es propileno son ejemplos.

Un grupo particular de compuestos de la invención son los compuestos de la fórmula (Id) en los que: R^1 es $R^{13}C(O)$- (especialmente ); R^5 es aril (C_{6-12})-alquilo (C_{1-6}) (especialmente ); R^{11} es $-C(O)OR^{13}$ [especialmente $-C(O)OC(CH_3)_3$] o $-S(O)_2R^{13}$ (especialmente ) y X^1 es propileno son ejemplos.

Los compuestos particulares de la presente invención incluyen:

{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(5-ciclopropil-1,3,4-oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

{1-[1-(3-ciclopropil-[1,2,4]oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-5-metil-hexil}-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-1-[(S)-1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-1-[(S)-1-(5-fenil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico;

{1-[1-(5-ciclopropil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

{3,3-difluoro-1-[1-(5-isopropil-isoxazol-3-carbonil)-propilcarbamoil]-hexil}-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{1-[5-(5-metil-isoxazol-3-il)-oxazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-1-[(S)-1-(oxazol-2-carbonil)-propilcarbamoil]-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-4-fenil-1-[(S)-1-(5-tiofen-2-il-oxazol-2-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(benzoxazol-2-carbonil)-butilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

[1-(2-benzoxazol-2-il-1-metoximetil-2-oxo-etilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(benzoxazol-2-carbonil)-1-metil-butilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

[(S)-1-((S)-1-ciano-3-fenil-propilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

[(S)-1-(cianometil-carbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

[(S)-3,3-difluoro-1-((S)-1-formil-1-metil-butilcarbamoil)-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

{(S)-1-[1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-1-[1-(5-*terc*-butil-[1,2,4]oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-4-fenil-1-[(S)-1-(5-fenil-[1,2,4]oxadiazol-3-il)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico;

éster bencílico del ácido [(S)-1-(cianometil-carbamoil)-3,3-difluoro-4-fenil-butil]-carbámico;

cianometil-amida del ácido (S)-4,4-difluoro-5-fenil-2-(tetrahidro-piran-4-ilamino)-pentanoico;

cianometil-amida del ácido (S)-4,4-difluoro-2-isobutilamino-5-fenil-pentanoico;

[(S)-1-((S)-1-bencenosulfonil-3-oxo-azepan-4-ilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

éster *terc*-butílico del ácido (S)-4-{(S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoilamino}-3-oxo-azepan-1-carboxílico;

((S)-1-{(S)-1-[(5-etil-1,3,4-oxadiazol-2-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-hexil)-amida del ácido morfolin-4-carboxílico;

{(S)-1-[1-(5-ciclopropil-1,3,4-oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-1-[1-(5-ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(R)-1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(benzoxazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico;

[(S)-1-(cianometil-carbamoil)-3,3-difluoro-hexil]-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(R)-1-[5-(5-metil-tiofen-2-il)-oxazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(S)-1-[5-(5-metil-tiofen-2-il)-oxazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico;

y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ia) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

Farmacología y servicio público:

Los compuestos de la invención son inhibidores de la catepsina S y, como tales, son útiles para tratar enfermedades en las que la actividad de la catepsina S contribuye a la patología y/o sintomatología de la enfermedad. Por ejemplo, los compuestos de la invención pueden ser útiles para tratar trastornos autoinmunes, incluyendo, pero sin limitarse a ellos, diabetes de aparición juvenil, esclerosis múltiple, pénfigo vulgar, enfermedad de Graves, miastenia grave, lupus eritematoso sistémico, enfermedad del intestino irritable, artritis reumatoide y tiroiditis de Hashimoto, trastornos alérgicos incluyendo pero sin limitarse a ellos, asma, y respuestas inmunes alogénicas, incluyendo, pero sin limitarse a ellos, transplantes de órganos o injertos de tejidos.

La catepsina S está implicada también en trastornos que incluyen elastolisis excesiva, tales como la enfermedad pulmonar obstructiva crónica (por ejemplo, enfisema), bronquiolitis, elastolisis excesiva de las vías respiratorias en el asma y bronquitis, neumonías y enfermedad cardiovascular tal como ruptura de placas y ateroma. La catepsina S está implicada en la formación fibrilar y, por tanto, los inhibidores de la catepsina S se pueden utilizar en el tratamiento de la amiloidosis sistémica.

Las actividades inhibidoras de la cisteína-proteasa de los compuestos de la invención se puede determinar por métodos conocidos por las personas de experiencia normal en la técnica. Se conocen ensayos adecuados *in vitro* para medir la actividad de la proteasa y la inhibición de la misma por los compuestos de ensayo. Típicamente, el ensayo mide la hidrólisis inducida por

la proteasa de un sustrato con base peptídica. Detalles de ensayos para medir la actividad inhibidora de la proteasa se dan en los ejemplos 31, 32, 33, 34, *infra*.

Los compuestos de la invención son también inhibidores de las catepsinas K y B y, como tales, son útiles para tratar enfermedades en las que la actividad de las catepsinas K y B contribuye a la patología y/o sintomatología de la enfermedad. Por ejemplo, los compuestos de la invención pueden ser útiles para tratar el dolor, la osteoartritis, la osteoporosis o el cáncer tal como cáncer de pulmón, leucemia (células B- y T-, aguda), cáncer de ovario, sarcomas, sarcoma de kaposi, cáncer de intestino, cáncer de nódulos linfáticos, tumor cerebral, cáncer de mama, cáncer de páncreas, cáncer de próstata o cáncer de piel.

Administración y composiciones farmacéuticas:

En general, los compuestos de la presente invención serán administrados en cantidades terapéuticamente eficaces por cualquiera de los modos usuales y aceptables conocidos en la técnica, ya sea 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 salud relativa del sujeto, la potencia del compuesto usado y otros factores. Por ejemplo, las cantidades terapéuticamente eficaces de un compuesto de la invención pueden variar desde aproximadamente 1 microgramo por kilogramo de peso corporal (μg/kg) al día hasta aproximadamente 60 miligramos por kilogramo de peso corporal (mg/kg) al día, típicamente desde aproximadamente 1 μg/kg/día hasta aproximadamente 20 mg/kg/día. Por tanto, una cantidad terapéuticamente eficaz para un paciente humano de 80 kg puede variar desde aproximadamente 80 μg /día hasta aproximadamente 4,8 g/día, típicamente de aproximadamente 80 μg /día a aproximadamente 1,6 g/día. En general, un experto normal en la técnica, actuando según sus conocimientos personales y la descripción de esta solicitud, será capaz de encontrar una cantidad terapéuticamente eficaz de un compuesto de la invención para tratar una enfermedad dada.

Los compuestos de la invención se pueden administrar como composiciones farmacéuticas por una de las siguientes vías: oral, sistémica (por ejemplo, transdérmica, intranasal o por supositorios) o parenteral (por ejemplo, intramuscular, intravenosa o subcutánea). Las composiciones pueden tener la forma de comprimidos, píldoras, cápsulas, semisólidos, polvos, formulaciones de liberación sostenida, soluciones, suspensiones, elixires, aerosoles, o cualquier otra composición apropiada y comprenden, en general, un compuesto de la invención en combinación con al menos un excipiente farmacéuticamente aceptable. Los excipientes aceptables son no tóxicos, ayudan a la administración, y no afectan de modo adverso al beneficio terapéutico del ingrediente activo. Dichos excipientes pueden ser sólidos, líquidos, semisólidos o, en el caso de una composición en aerosol, un excipiente gaseoso que generalmente está disponible para un experto en la técnica.

Los excipientes farmacéuticos sólidos incluyen almidón, celulosa, talco, glucosa, lactosa, sacarosa, gelatina, malta, arroz, harina, creta, gel de sílice, estearato de magnesio, estearato de sodio, monoestearato de glicerol, cloruro de sodio, leche desnatada seca, y similares. Los excipientes líquidos y semisólidos se pueden seleccionar de agua, etanol, glicerol, propilenglicol y diferentes aceites, incluyendo los de petróleo, animales, vegetales o de origen sintético (por ejemplo, aceite de cacahuete, aceite de soja, aceite mineral, aceite de sésamo, y similares). Los vehículos líquidos preferidos, particularmente para soluciones inyectables, incluyen agua, solución salina, dextrosa acuosa y glicoles.

La cantidad de un compuesto de la invención en la composición puede variar ampliamente dependiendo del tipo de formulación, tamaño de la unidad de dosis, tipo de excipientes y otros factores conocidos por los expertos en la técnica de las ciencias farmacéuticas. En general, una composición de un compuesto de la invención 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 excipientes. Preferiblemente la composición farmacéutica se administra en una forma farmacéutica de dosis unitaria para tratamiento continuo o en una forma farmacéutica de dosis unitaria *ad libitum* cuando se requiere específicamente el alivio de los síntomas. En el ejemplo 35 se describen formulaciones farmacéuticas representativas que contienen un compuesto de la invención.

Química:

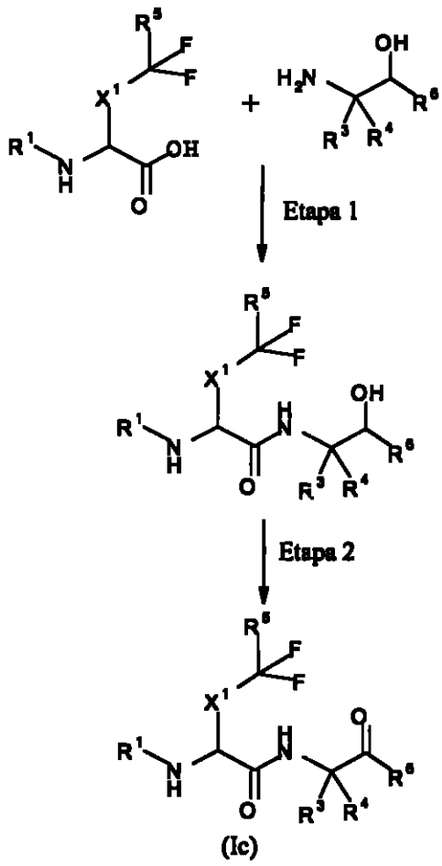
Procedimientos para preparar los compuestos de la invención:

Los compuestos de la invención se pueden preparar mediante la aplicación o adaptación de métodos conocidos, y esto significa los métodos utilizados hasta la fecha o descritos en la bibliografía, por ejemplo, los descritos por R.C. Larock en Comprehensive Organic Transformations, VCH publishers, 1989,

En las reacciones descritas más adelante puede ser necesario proteger los grupos funcionales reactivos, por ejemplo grupos hidroxi, amino, imino, tio o carboxi, cuando se desea que estén en el producto final, para evitar su participación indeseada en las reacciones. Los grupos protectores convencionales se pueden usar según la práctica estándar, para ejemplos véase T.W. Greene and P. G. M. Wuts en "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991,

Los compuestos de la invención se pueden preparar procediendo según el Esquema de reacción 1:

Esquema de reacción 1



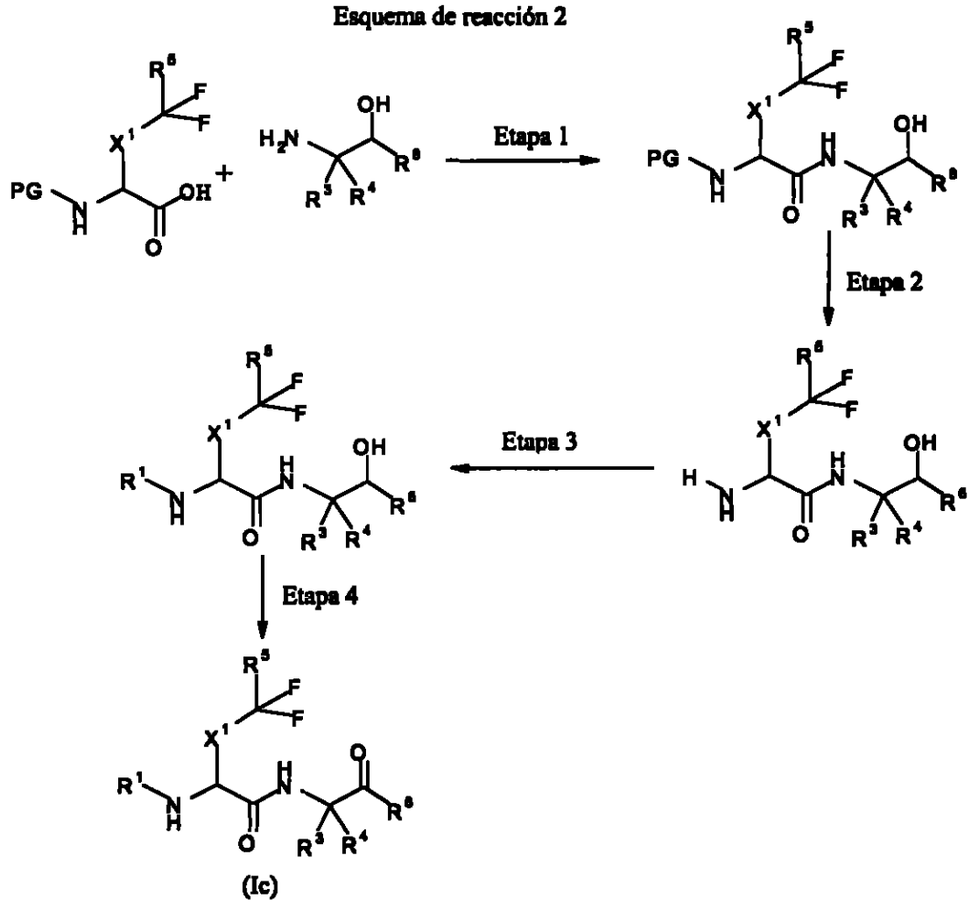
(Ic)

en el cual cada X^1, R^1, R^3, R^4, R^5, y R^6 son como se han definido en el Sumario de la invención. Así, en la etapa 1, se puede condensar un ácido con un compuesto amino de la fórmula para dar una β-hidroxi-amida. La reacción de condensación se puede efectuar con un agente de acoplamiento apropiado (por ejemplo, hexafluorofosfato de benzotriazol-1-iloxitrispirrolidinofosfonio (pyBOP®), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI), hexafluorofosfato de *O*-benzotriazol-1-il-*N*,*N*,*N*',*N*'-tetrametiluronio (HBTU), 1,3-diciclohexilcarbodiimida (DCC), o similares) y opcionalmente un catalizador apropiado (por ejemplo, 1-hidroxibenzotriazol (HOBt), 1-hidroxi-7-azabenzotriazol (HOAt), hexafluorofosfato de *O*-(7-azabenzotrizol-1-il)-1,1,3,3-tetrametiluronio (HATU), o similares) y una base no nucleófila (por ejemplo, trietilamina, *N*-metilmorfolina, y similares, o cualquier combinación adecuada de las mismas) a temperatura ambiente y requiere de 2 a 10 horas para completarse. La β-hidroxi-amida se puede oxidar entonces, en la etapa 2, para dar un compuesto de la fórmula (Ic). La reacción de oxidación se puede llevar a cabo convenientemente utilizando

peryodinano de Dess-Martin en un disolvente inerte, tal como diclorometano, y a una temperatura de aproximadamente 0 °C a aproximadamente temperatura ambiente.

Alternativamente los compuestos de esta invención se pueden preparar procediendo según el Esquema de reacción 2:

Esquema de reacción 2



(Ic)

en el cual cada X^1, R^1, R^3, R^4, R^5, y R^6 son como se han definido en el Sumario de la invención y PG es un grupo protector adecuado. Así, en la etapa 1, se puede condensar un ácido con un compuesto amino de la fórmula para dar una β-hidroxi-amida. La separación del grupo protector (etapa 2) seguida por la introducción del grupo R^1 (etapa 3) y oxidación (etapa 4) dará un compuesto de la fórmula (Ic).

Ejemplos:

La presente invención es aclarada adicionalmente, pero no limitada, por los siguientes ejemplos que ilustran la preparación de los compuestos de la fórmula (I) (Ejemplos) e intermedios (Referencias) según la invención.

Los espectros de ^1H resonancia magnética nuclear (NMR) se registraron en equipos Varian Mercury-300 o Unity-400 o UnityPlus-500 o Inova-500. En los espectros de resonancia magnética nuclear (NMR) los desplazamientos químicos (δ) se expresan en ppm en relación con tetrametilsilano. Las abreviaturas tienen los siguientes significados: s = singlete; d = doblete; t = triplete; m = multiplete; q = cuadruplete; dd = doblete de dobletes; ddd = doblete de dobles dobletes.

La cromatografía de líquidos de alta presión (HPLC) se realizó en columna Kromasil 10 micras, 100A Silica, 4,6 mm ID x 250 mm utilizando una mezcla de heptano/THF/1,2-dicloroetano como fase móvil.

Los espectros de masas se realizaron en Agilent 1100 series o MICROMASS LCT-TOF MS.

Los valores R_F de la cromatografía en capa fina (TLC) se determinaron utilizando placas de sílice de Merck.

Abreviaturas

CBZ- Benciloxi-carbonilo

DAST- Trifluoruro de (dietilamino)azufre

DCM- Diclorometano

DMF- Dimetilformamida

DMSO - Dimetilsulfóxido

DTT - Ditiotreitol

EDCI - Hidrocloruro de N-(3-dimetilaminopropil)-N¢-etilcarbodiimida

EDTA - Ácido etilendiaminotetraacético

EtOAc – Acetato de etilo

HOBT - Hidrato de 1-hidroxibenzotriazol

MeOH - Metanol

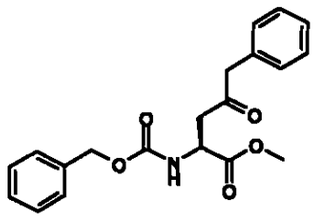
MES - Ácido 2-morfolinoetanosulfónico

pyBOP - Hexafluorofosfato de (benzotriazol-1-iloxi)tripirrolidinofosfonio

THF - Tetrahidrofurano

REFERENCIA 1

Éster metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-5-fenil-pentanoico :

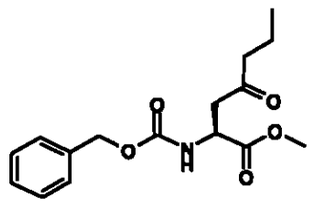


A una suspensión de bromuro de cobre (I) (4,26 mmol, 611,1 mg) en 3 ml de THF seco bajo N_2 se añadió una solución de bromuro de litio (8,52 mmol, 740 mg) en 5 ml de THF seco. Se agitó la mezcla a temperatura ambiente durante 20 min, y después se enfrió a –78 °C. Se añadió una solución de cloruro de bencilmagnesio (al 20 % en peso en THF, 4,26 mmol, 3,25 ml) seguido por una solución de éster metílico del ácido (S)-2-benciloxicarbonilamino-3-clorocarbonil-propiónico [Ref: Synth. Comm 1993, 23(18), 2511-2526] (3,59 mmol) en 7 ml de THF seco. Se agitó la mezcla a –78 °C durante 30 min y después se sofocó con NH_4Cl saturado (50 ml). Se extrajo la mezcla dos veces con acetato de etilo (30 ml). Las capas orgánicas se secaron sobre sulfato de magnesio y después se concentraron en vacío. Se purificó el residuo sobre 35 g de gel de sílice, eluyendo con EtOAc:heptano (1:1) para obtener el éster metílico del ácido (S)-2-benciloxicarbonil-amino-4-oxo-5-fenil-pentanoico (1,07 g, 84 %).

^{1}H NMR ($CDCl_3$): δ 7,4-7,17 (m, 10H), 5,73 (d, J = 8,2 Hz, 1H), 5,11 (s, 2H), 4,57 (m, 1H), 3,7 (2xs, 5H), 3,24 (dd, J = 18,5, 4,4 Hz, 1H), 3,0 (dd, J = 18,2, 4,1 Hz, 1H); LC/MS: 100 % 378 (M+Na).

REFERENCIA 2

Éster metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-heptanoico

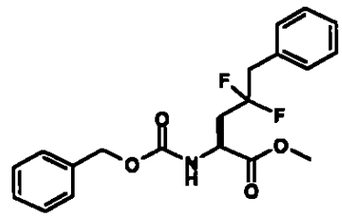


Procediendo de manera similar al Ejemplo de Referencia 1 anterior pero utilizando cloruro de propilmagnesio en lugar de cloruro de bencilmagnesio se preparó el éster metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-heptanoico.

^{1}H NMR ($CDCl_3$): δ 7,35 (m, 5H), 5,78 (d, J = 8,5 Hz, 1H), 5,13 (s, 2H), 4,58 (m, 1H), 3,75 (s, 3H), 3,2 (dd, J = 18,3, 4,2 Hz, 1H), 2,96 (dd, J = 18,3, 4,1 Hz, 1H), 2,4 (m, 2H), 1,6 (m, 2H), 0,92 (t, J = 7,4 Hz, 3H); LC/MS: 330 (M+Na).

REFERENCIA 3

Éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-5-fenil-pentanoico :

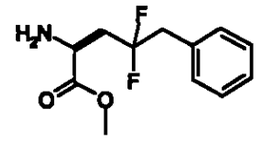


Se agitó a temperatura ambiente durante 3 días una mezcla de éster metílico del ácido 2-benciloxicarbonilamino-4-oxo-5-fenil-pentanoico (3,310 g, 9,31 mmol) y DAST (7 ml). Se diluyó la mezcla con diclorometano (100 ml) y se añadió cuidadosamente una solución 0,5 N de NaOH (150 ml). Se extrajo la capa acuosa con diclorometano (50 ml). Se secaron las capas orgánicas sobre sulfato de magnesio y después se concentraron en vacío. Se purificó el residuo sobre 110 g de gel de sílice, eluyendo con EtOAc:heptano (1:4 después 1:3) para obtener el éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-5-fenil-pentanoico (1,797 g, 51,1 %).

^{1}H NMR ($CDCl_3$) δ 7,3 (m, 10H), 5,43 (d, J = 7,6 Hz, 1H), 5,14 (s, 2H), 4,65 (m, 1H), 3,74 (s, 3H), 3,2 (t, J = 16,5 Hz, 2H), 2,4 (m, 2H); *LC/MS*: 97 % 400 (M+Na).

REFERENCIA 4

Hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-5-fenil-pentanoico:

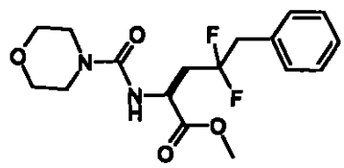


Una solución de éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-5-fenil-pentanoico (7,806 g, 20,68 mmol) en 120 ml de metanol y HCl 4 M en dioxano (41,4 mmol, 10,3 ml) se hidrogenó sobre Pd al 10 % /C (1,0 g) a 344,8 kPa. Después de 8 h, se añadió otra porción de Pd al 10 %/C (1,0 g). Después de 24 h, se separó el catalizador por filtración sobre un lecho de Celita, y se concentró el filtrado en vacío. El sólido amarillo claro resultante se disolvió en una cantidad mínima de metanol y se añadió lentamente a éter (150 ml). Se dejó envejecer la suspensión resultante durante 30 min y después se filtró. Se secó el sólido blanco con succión para obtener el hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-5-fenil-pentanoico (4,950 g, 85,5 %).

^{1}H NMR (DMSO-D_6): δ 8,6 (b, 3H), 7,3 (m, 5H), 4,26 (t, J = 6 Hz, 1H), 3,73 (s, 3H), 3,3 (t, J = 17,5 Hz, 2H), 2,55 (m, 2H); LC/MS: 100 % 244 (M+1).

REFERENCIA 5

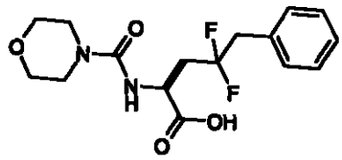
Éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico:



A una mezcla de hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-5-fenil-pentanoico (2,50 g, 8,94 mmol) y diisopropil-amina (22,3 mmol, 2,89 g) en diclorometano seco (40 ml) bajo N_2 se añadió gota a gota cloruro de morfolin-carbonilo (13,4 mmol, 2,0 g). Se agitó la mezcla a temperatura ambiente durante 15 horas, y después se diluyó con agua (50 ml). Se extrajo la capa acuosa con diclorometano (30 ml). Las capas orgánicas se secaron sobre sulfato de magnesio y después se concentraron en vacío. Por purificación sobre 110 g de gel de sílice, eluyendo con EtOAc:heptano (1:1, después 2:1) se obtuvo el éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico (2,82 g, 88,5 %). ^{1}H NMR ($CDCl_3$): δ 7,3 (m, 5H), 5,16 (d, J = 7,5 Hz, 1H), 4,75 (dd, J = 13, 6 Hz, 1H), 3,73 (s, 3H), 3,7 (m, 4H), 3,4 (m, 4H), 3,2 (t, J = 16,7 Hz, 2H), 2,4 (m, 2H). LC/MS: 100 % 357 (M+1).

REFERENCIA 6

Ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico :

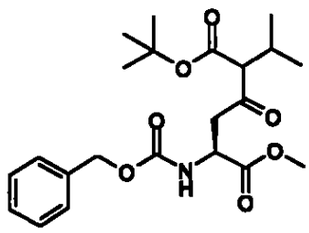


A una solución de éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico (2,81 g, 7,88 mmol) en MeOH:H_2O (2:1 vol, 40 ml) se añadió LiOH monohidrato (662 mg, 15,76 mmol). Se agitó la mezcla a temperatura ambiente durante 2,5 h, y después se diluyó con agua (30 ml). Se separó el metanol en vacío. Se ajustó el pH a pH 1 con HCl 6 N y se extrajo la capa acuosa con diclorometano (2x30 ml). Las capas orgánicas se secaron sobre sulfato de magnesio y se concentraron en vacío para obtener el ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico (2,509 g, 93 %).

^{1}H NMR ($CDCl_3$): δ 8,2 (b, 1H), 7,3 (m, 5H), 5,3 (m, 1H), 4,6 (m, 1H), 3,65 (m, 4H), 3,4 (m, 4H), 3,2 (t, J = 16,5 Hz, 2H), 2,4 (m, 2H); LC/MS: 94 % 343 (MH^+)

REFERENCIA 7

Éster 1-*terc*-butílico-éster 6-metílico del ácido (S)-5-benciloxicarbonilamino-2-isopropil-3-oxo-hexanodioico :



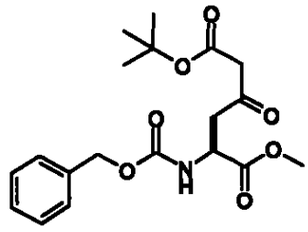
A una solución enfriada a –78 °C de diisopropil-amina (3,53 g, 34,88 mmol) en THF seco (20 ml) bajo N_2 se añadió gota a gota una solución de n-butil-litio (2,5 M en hexano, 34,88 mmol, 13,95 ml). Se agitó la mezcla a –78 °C durante 30 min, después se añadió una solución de éster *terc*-butílico del ácido 3-metil-butírico (34,88 mmol, 5,52 g) en THF (40 ml). Se agitó la mezcla a –78 °C durante 30 min, después se añadió gota a gota una solución de éster metílico del ácido (S)-2-benciloxicarbonilamino-3-clorocarbonil-propiónico (Ref: Synth. Comm 1993, 23(18), 2511-2526) (16,6 mmol) en 30 ml de THF seco. Después de agitar durante otras 2 h a –78 °C, se sofocó la reacción con 50 ml de HCl 1 N y se calentó a temperatura ambiente. Se ajustó el pH a pH 3 con NaOH 1 N y se separó el THF en vacío. Se extrajo la capa orgánica con EtOAc (2x60 ml). Las capas orgánicas se secaron sobre sulfato de magnesio y después se concentraron en vacío. Se purificó el residuo sobre 90 g de gel de sílice, se eluyó con EtOAc:heptano (1:3 después 1:2) y se obtuvo el éster 1-*terc*-butílico-éster 6-metílico del ácido (S)-5-benciloxicarbonilamino-2-isopropil-3-oxo-hexanodioico (2,417 g, 34,5 %).

^{1}H NMR ($CDCl_3$): δ 7,4 (m, 5H), 5,73 (d, J = 8,4 Hz, 1H), 5,12 (s, 2H), 4,6 (m, 1H), 3,74 (s, 3H), 3,39-3,06 (m, 3H), 2,4 (m, 1H), 1,45 (2s, 9H), 0,98 (d, J = 6,6 Hz, 3H), 0,88 (d, J = 6,7 Hz, 3H);

LC/MS: 100 % 422 (M+1).

REFERENCIA 8

Éster 6-*terc*-butílico-éster 1-metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-hexanodioico :



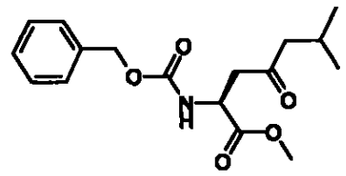
A una solución de éster 1-metílico del ácido N-CBZ- L-aspártico (1,00 g, 3,55 mmol) en tetrahidrofurano seco (17 ml) se añadió carbonil-diimidazol (634,1 mg, 3,91 mmol). Se agitó la mezcla a temperatura ambiente durante 6 h, después se añadió la sal de magnesio de mono-*terc*-butil-malonato (1,339 g, 3,91 mmol) (preparada según Angew. Chem. Int. Ed. Engl. 1979,

18(1), 72-74). Se agitó la mezcla a temperatura ambiente durante otras 20 h y después se concentró en vacío. El residuo se sometió a reparto entre éter (60 ml) y HCl 0,5 N (60 ml). La capa orgánica se lavó con solución saturada de $NaHCO_3$ (50 ml) después se secó sobre sulfato de magnesio y se concentró en vacío. Se purificó el residuo sobre 35 g de gel de sílice, se eluyó con EtOAc:heptano (1:1) para obtener el éster 6-*terc*-butílico-éster 1-metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-hexanodioico (1,17 g, 87 %).

^{1}H NMR ($CDCl_3$): δ 7,4 (m, 5H), 5,73 (d, J = 8,3 Hz, 1H), 5,1 (s, 2H), 4,6 (m, 1H), 3,75 (s, 3H), 3,37 (s, 2H), 3,32 (dd, J = 18,7, 4,3 Hz, 1H), 3,13 (dd, J = 18,5, 4,1 Hz, 1H), 1,47 (s, 9H); LC/MS: 93 % 402 (M+Na).

REFERENCIA 9

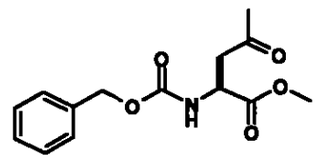
Éster metílico del ácido (S)-2-benciloxicarbonilamino-6-metil-4-oxo-heptanoico :



Una solución de éster 1-*terc*-butílico-éster 6-metílico del ácido 5-benciloxicarbonilamino-2-isopropil-3-oxo-hexanodioico (1,06 g, 2,51 mmol) y ácido *p*-toluenosulfónico monohidrato (35,8 mg, 0,19 mmol) en tolueno (20 ml) se calentó a reflujo bajo N_2 durante 6,5 h. Se enfrió la mezcla a temperatura ambiente, y se concentró en vacío. Se purificó el residuo sobre 35 g de gel de sílice, se eluyó con EtOAc:heptano (1:4) para obtener el éster metílico del ácido (S)-2-benciloxicarbonilamino-6-metil-4-oxo-heptanoico (727 mg, 90%). ^{1}H NMR ($CDCl_3$): δ 7,4 (m, 5H), 5,78 (d, J = 9,1 Hz, 1H), 5,13 (s, 2H), 4,6 (m, 1H), 3,74 (s, 3H), 3,2 (dd, J = 18,3, 4,4 Hz, 1H), 2,95 (dd, J = 18,2, 4,0 Hz, 1H), 2,3 (m, 2H), 2,1 (m, 1H), 0,92 (d, J = 6,7 Hz, 6H); LC/MS: 77 % 322 (MH^+).

REFERENCIA 10

Éster metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-pentanoico:



Procediendo de manera similar al Ejemplo de Referencia 9 anterior pero utilizando éster 6-*terc*-butílico-éster 1-metílico del ácido 2-benciloxicarbonilamino-4-oxo-hexanodioico se preparó el éster metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-pentanoico

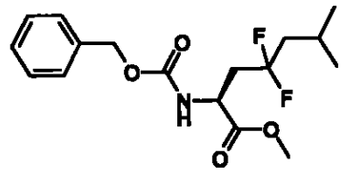
^{1}H NMR ($CDCl_3$): δ 7,4 (m, 5H), 5,76 (d, J = 8,1 Hz, 1H), 5,14 (s, 2H), 4,57 (m, 1H), 3,75 (s, 3H), 3,23 (dd, J = 18,4, 4,3 Hz, 1H), 3,0 (dd, J = 18,4, 4,3 Hz, 1H), 2,18 (s, 3H); LC/MS: >85 % 280 (MH^+).

Método alternativo

A una suspensión enfriada a 0°C de yoduro de cobre (I) en éter (20 ml) bajo N_2 se añadió lentamente metil-litio (solución 1,6 M en éter, 21,3 mmol, 13,3 ml). Se agitó la mezcla a 0 °C durante 10 min y después se enfrió a –78 °C. Se añadió gota a gota una solución de 3,55 mmol de éster metílico del ácido (S)-2-benciloxicarbonilamino-3-clorocarbonil-propiónico (Ref: Synth. Comm 1993, 23(18), 2511-2526) en 12 ml de THF seco. Se agitó la mezcla a -78 °C durante 30 min y después se sofocó añadiendo metanol (2 ml). Se vertió la mezcla sobre NH_4Cl saturado (80 ml) y se extrajo con éter (2x40 ml). Las capas orgánicas se secaron sobre sulfato de magnesio y se concentraron en vacío. Se purificó el residuo sobre 35 g de gel de sílice, se eluyó con EtOAc:heptano (1:1) para obtener el éster metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-pentanoico (261 mg, 26 %).

REFERENCIA 11

Éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-6-metil-heptanoico :

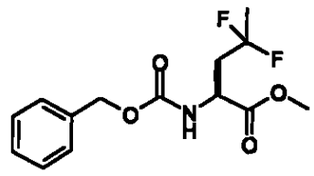


Se agitó a 35 °C durante 47 h una mezcla de éster metílico del ácido (S)-2-benciloxicarbonilamino-6-metil-4-oxo-heptanoico (915 mg, 2,85 mmol) y DAST (3 ml, XS). Se diluyó la mezcla con diclorometano (50 ml) y se añadió cuidadosamente a una solución saturada de $NaHCO_3$ (150 ml). Se extrajo la capa acuosa con diclorometano (30 ml). Las capas orgánicas se secaron sobre sulfato de magnesio y se concentraron en vacío. Se purificó el residuo sobre 35 g de gel de sílice, eluyendo con EtOAc:heptano (1:4) para obtener el éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-6-metil-heptanoico (156 mg, 16 %).

^{1}H NMR ($CDCl_3$): δ 7,4 (m, 5H), 5,48 (d, J = 7,9 Hz, 1H), 5,15 (s, 2H), 4,61 (q, J = 5,9 Hz, 1H), 3,78 (s, 3H), 2,4 (m, 2H), 1,95 (m, 1H), 1,8 (m, 2H), 0,98 (d, J = 6,6 Hz, 6H); LC/MS: 98 % 366 (M+Na).

REFERENCIA 12

Éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-pentanoico

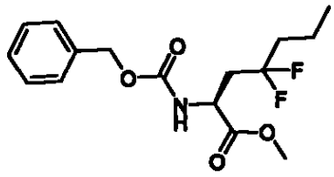


Procediendo de manera similar al Ejemplo de Referencia 11 anterior pero utilizando éster metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-pentanoico se preparó el éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-pentanoico

^{1}H NMR ($CDCl_3$): δ 7,4 (m, 5H), 5,46 (d, J = 7,1 Hz, 1H), 5,15 (s, 2H), 4,61 (q, J = 7,3 Hz, 1H), 3,78 (s, 3H), 2,45 (m, 2H), 1,67 (t, J = 18,8 Hz, 3H); LC/MS: 94 % 324 (M+Na).

REFERENCIA 13

Éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-heptanoico

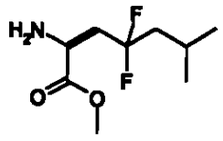


Procediendo de manera similar al Ejemplo de Referencia 11 anterior pero utilizando éster metílico del ácido (S)-2-benciloxicarbonilamino-4-oxo-heptanoico se preparó el éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-heptanoico.

LC/MS: 96 % 330 (MH^+), 352 (M+Na).

REFERENCIA 14

Hidrocloruro de éster metílico del ácido (S)-2-amino-4,4-difluoro-6-metil-heptanoico:



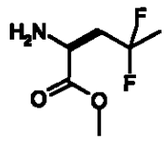
Una solución de éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-6-metil-heptanoico: (333 mg, 0,97 mmol) en metanol (10 ml) y HCl 4 M en dioxano (4 mmol, 1 ml) se hidrogenó sobre Pd al 10%/C (150 mg) a 344,8 kPa. Después de 7 h, se añadió otra porción de Pd al 10 %/C (200 mg) y se reanudó la hidrogenación. Después de 5,5 h, la reacción no progresó. Se filtró el catalizador y se concentró el filtrado en vacío y se sometió a las condiciones de hidrogenación. Después de 6,5 h, se separó el catalizador por filtración sobre un lecho de Celita, y el filtrado se concentró en vacío para obtener el hidrocloruro del éster metílico del ácido (S)-2-

amino-4,4-difluoro-6-metil-heptanoico como un sólido amarillo pegajoso (240 mg, cuantitativo).

^{1}H NMR ($CDCl_3$): δ 4,8 (b, 3H), 4,35 (b, 1H), 3,84 (s, 3H), 2,6 (m, 2H), 1,9 (m, 3H), 0,99 (d, J = 6,2 Hz, 6H); LC/MS: 90 % 210 (M+1).

REFERENCIA 15

Hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-pentanoico:



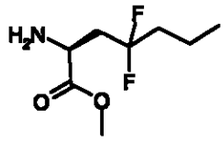
Procediendo de manera similar al Ejemplo de Referencia 14 anterior pero utilizando éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-pentanoico se preparó el hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-pentanoico.

^{1}H NMR ($CDCl_3$): δ 4,8 (s, 3H), 4,37 (m, 1H), 3,86 (s, 3H), 2,4-2,8 (m, 2H), 1,73 (t, J = 18,9 Hz, 3H);

LC/MS: 100 % 168 (M+1).

REFERENCIA 16

Hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-heptanoico

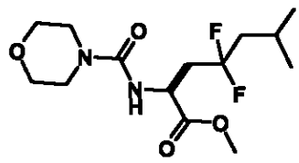


Procediendo de manera similar al Ejemplo de Referencia 14 anterior pero utilizando éster metílico del ácido (S)-2-benciloxicarbonilamino-4,4-difluoro-heptanoico se preparó el hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-heptanoico

LC/MS: 100 % 196 (MH^+).

REFERENCIA 17

Éster metílico del ácido (S)-4,4-difluoro-6-metil-2-[(morfolin-4-carbonil)-amino]-heptanoico:



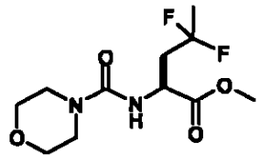
A una mezcla de hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-6-metil-heptanoico (238 mg, 0,97 mmol) y diisopropil-amina (2,42 mmol, 313 mg) en diclorome-

tano seco (5 ml) bajo N_2 se añadió gota a gota cloruro de morfolin-carbonilo (1,45 mmol, 218 mg). Se agitó la mezcla a temperatura ambiente durante 23 h, después se diluyó con diclorometano (25 ml) y se lavó con HCl diluido (30 ml), y $NaHCO_3$ saturado (30 ml). Las capas orgánicas se secaron sobre sulfato de magnesio y se concentraron en vacío. Por purificación sobre 12 g de gel de sílice, eluyendo con EtOAc:heptano (1:1, después 2:1) se obtuvo el éster metílico del ácido (S)-4,4-difluoro-6-metil-2-[(morfolin-4-carbonil)-amino]-heptanoico (206 mg, 66 %).

^{1}H NMR ($CDCl_3$): δ 5,2 (d, J = 7,4 Hz, 1H), 4,72 (dd, J = 13, 6 Hz, 1H), 3,78 (s, 3H), 3,7 (m, 4H), 3,4 (m, 4H), 2,4 (m, 2H), 1,95 (m, 1H), 1,8 (m, 2H), 0,99 (d, J = 6,4 Hz, 6H); LC/MS: 90 % 345 (M+Na).

REFERENCIA 18

Éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-pentanoico:

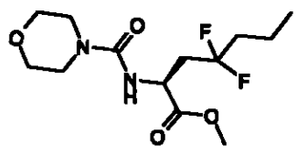


Procediendo de manera similar al Ejemplo de Referencia 17 anterior pero utilizando hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-pentanoico se preparó el éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-pentanoico.

^{1}H NMR ($CDCl_3$): δ 5,18 (d, J = 7,5 Hz, 1H), 4,71 (q, J = 7 Hz, 1H), 3,78 (s, 3H), 3,71 (m, 4H), 3,4 (m, 4H), 2,37-2,55 (m, 2H), 1,67 (t, J = 18,7 Hz, 3H); LC/MS: 100 % 303 (M+ Na).

REFERENCIA 19

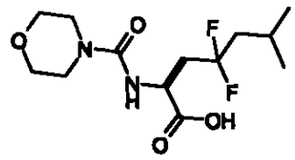
Éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico



Procediendo de manera similar al Ejemplo de Referencia 17 anterior pero utilizando hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-heptanoico se preparó el éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico; LC/MS: 100 % 309 (MH^+).

REFERENCIA 20

Ácido (S)-4,4-difluoro-6-metil-2-[(morfolin-4-carbonil)-amino]-heptanoico:

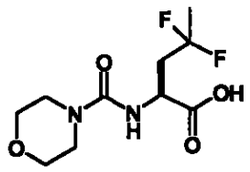


A una solución de éster metílico (205 mg, 0,63 mmol) en MeOH: H2O (2:1 vol, 4 ml) se añadió LiOH-monohidrato (80 mg, 1,9 mmol). Se agitó la mezcla a temperatura ambiente durante 21 h, después se diluyó con agua (15 ml) y se extrajo con éter (20 ml). Se ajustó el pH de la capa acuosa a pH 1 con HCl 1 N y se extrajo con diclorometano (2x20 ml). Las capas orgánicas se secaron sobre sulfato de magnesio y se concentraron en vacío para obtener el ácido (S)-4,4-difluoro-6-metil-2-[(morfolin-4-carbonil)-amino]-heptanoico (168 mg, 86 %).

^{1}H NMR ($CDCl_3$): δ 6,4 (b, 1H), 5,3 (d, J = 6,2 Hz, 1H), 4,6 (m, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 2,5 (m, 2H), 2,0 (m, 1H), 1,8 (m, 2H), 1,0 (d, J = 6,6 Hz, 6H); LC/MS: 90 % 309 (M+1).

REFERENCIA 21

Ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-pentanoico:

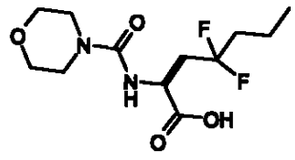


Procediendo de manera similar al Ejemplo de Referencia 20 anterior pero utilizando éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-pentanoico se preparó el ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-pentanoico

^{1}H NMR ($CDCl_3$): δ 5,9 (b, 1H), 5,29 (d, J = 6,3 Hz, 1H), 4,6 (m, 1H), 3,71 (m, 4H), 3,4 (m, 4H), 2,38-2,65 (m, 2H), 1,70 (t, J = 18,9 Hz, 3H); LC/MS: 100 % 267 (M+ 1).

REFERENCIA 22

Ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico

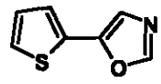


Procediendo de manera similar al Ejemplo de Referencia 20 anterior pero utilizando éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico se preparó el ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico

^{1}H NMR ($CDCl_3$): δ 5,3 (b, 1H), 5,25 (d, J = 5,4 Hz, 1H), 4,6 (m, 1H), 3,71 (m, 4H), 3,4 (m, 4H), 2,6-2,3 (m, 2H), 1,9 (m, 2H), 1,55 (m, 2H), 1,0 (t, J = 7,3 Hz, 3H); LC/MS: 83 % 295 (M+1).

REFERENCIA 23

5-Tiofen-2-il-oxazol

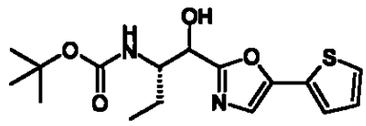


A una solución de isocianuro de *p*-toluenosulfonilmetilo (3,0 g, 15,36 mmol) y tiofen-2-carboxaldehído (1,72 g, 15,36 mmol) en metanol (45 ml) bajo N_2 se añadió carbonato de potasio (2,12 g, 15,36 mmol). Se calentó la mezcla a reflujo durante 5 h, después se enfrió y se concentró en vacío (baño de agua fría). El residuo se sometió a reparto entre éter (100 ml) y agua (100 ml). Se lavó la capa orgánica con agua (100 ml), se secó sobre sulfato de magnesio y después se concentró en vacío. Se purificó el residuo sobre 35 g de gel de sílice, se eluyó con acetato de etilo: heptano (1:5) para obtener el 5-tiofen-2-il-oxazol (0,852 g, 37 %).

^{1}H NMR ($CDCl_3$): δ 7,9 (s, 1H), 7,3 (m, 2H), 7,2 (s, 1H), 7,1 (dd, J = 5, 3,8 Hz, 1H); LC/MS: 100 % 152 (M+1).

REFERENCIA 24

Éster *terc*-butílico del ácido {(S)-1-[hidroxi-(5-tiofen-2-il-oxazol-2-il)-metil]-propil}-carbámico

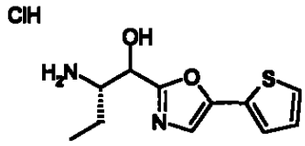


A una solución de 5-tiofen-2-il-oxazol (0,85 g, 5,62 mmol) en THF seco (4 ml) se añadió trietilborano (1,0 M en THF, 5,62 mmol, 5,62 ml). Se agitó la mezcla a temperatura ambiente durante 45 min, después se enfrió a –78 °C y se añadió gota a gota n-butil-litio (1,6 M en hexano, 5,62 mmol, 3,51 ml). Se agitó la mezcla a –78 °C durante 45 min y después se añadió lentamente una solución de éster *terc*-butílico del ácido (1-formil-propil)-carbámico (2,81 mmol, 0,526 g) en THF seco (3 ml). Se agitó la mezcla a –78 °C durante 4 h, después se calentó a 0 °C y se sofocó añadiendo 30 ml de HOAc al 10 % (vol) en etanol. Se agitó la mezcla a temperatura ambiente durante 18 h y después se concentró en vacío. Se purificó el residuo sobre 90 g de gel de sílice, se eluyó con acetato de etilo: heptano (1:2 después 1:1) para obtener el éster *terc*-butílico del ácido {(S)-1-[hidroxi-(5-tiofen-2-il-oxazol-2-il)-metil]-propil}-carbámico (363 mg, 38%) como un aceite amarillo.

^{1}H NMR ($CDCl_3$): δ (mezcla de isómeros) 7,35 (m, 2H), 7,1 (m, 2H), 4,9 (m, 2H), 4,0 (b, 1H), 3,6 (m, 1H), 1,8-1,55 (m, 2H), 1,4 y 1,3 (2s, 9H), 1,0 y 0,9 (2t, J = 7,4 Hz, 3H); LC/MS: 100 339 (M+1).

REFERENCIA 25

Hidrocloruro de (S)-2-amino-1-(5-tiofen-2-il-oxazol-2-il)-butan-1-ol



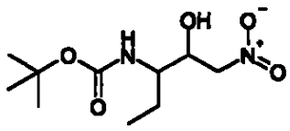
A una solución de éster *terc*-butílico del ácido {(S)-1-[hidroxi-(5-tiofen-2-il-oxazol-2-il)-metil]-propil}-carbámico (361 mg, 1,07 mmol) en diclorometano seco (3 ml) se añadió HCl 4 N en dioxano (3,0 ml, XS). Se agitó la mezcla a temperatura ambiente durante 16 h, después se concentró en vacío para obtener el hidrocloruro de (S)-2-amino-1-(5-tiofen-2-il-oxazol-2-il)-butan-1-ol como un sólido ocre (cuantitativo).

^{1}H NMR ($CDCl_3$): δ 7,5 (dd, J = 5,2, 1,2 Hz, 1H), 7,4 (dd, J = 3,6, 1,1 Hz, 1H), 7,3 (s, 1H), 7,1 (dd, J = 5, 3,6 Hz, 1H), 4,8 (m, 3H), 3,6 (m, 2H), 3,3 (b, 1H), 1,75 (m, 2H), 1,0 (t, J = 7,5 Hz, 3H);

LC/MS: 100 % 239 (M+1).

REFERENCIA 26

Éster *terc*-butílico del ácido 1-etil-2-hidroxi-3-nitro-propil)-carbámico

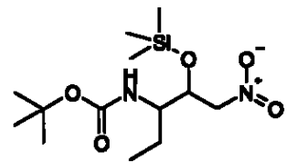


A una solución de éster *terc*-butílico del ácido (1-formil-propil)-carbámico (1,0 g, 5,34 mmol) en THF seco (10 ml) y etanol se añadió nitrometano (3,91 g, 64,09 mmol) seguido por trietilamina (2,70 g, 26,7 mmol). Se agitó la mezcla a temperatura ambiente durante 22 h, y después se concentró en vacío. Se diluyó el residuo con éter (50 ml) y se lavó con NH_4Cl concentrado (60 ml). La capa etérea se secó sobre sulfato de magnesio y se concentró en vacío. Se purificó el residuo sobre 35 g de gel de sílice, se eluyó con acetato de etilo: heptano (1:3) para obtener el alcohol deseado (1,09 g, 82 %) como un sólido oleoso amarillo claro.

^{1}H NMR ($CDCl_3$): δ 4,2-4,8 (m, 4H), 3,15-3,8 (m, 2H), 1,69-1,6 (m, 2H), 1,47 (2xs, 9H), 1,02 y 1,0 (2xt, J = 7,1 Hz, 3H); LC/MS: 2 isómeros, total 100 % 149 (M-BOC+1).

REFERENCIA 27

Éster *terc*-butílico del ácido (1-etil-3-nitro-2-trimetilsilaniloxi-propil)-carbámico

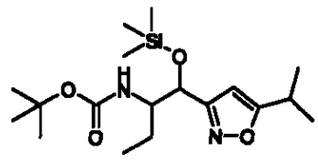


A una mezcla de éster *terc*-butílico del ácido (1-etil-2-hidroxi-3-nitro-propil)-carbámico (1,83 g, 7,37 mmol) y trietilamina (1,49 g, 14,75 mmol) en diclorometano seco (25 ml) bajo N_2 se añadió cloruro de trimetilsililo (1,20 g, 11,05 mmol). Se agitó la mezcla a temperatura ambiente durante 24 h, después se diluyó con 40 ml de diclorometano y se lavó con agua (40 ml). Se secó la capa orgánica sobre sulfato de magnesio y se concentró en vacío. Se purificó el residuo sobre 110 g de gel de sílice, se eluyó con acetato de etilo: heptano (1:4) para obtener el éster *terc*-butílico del ácido (1-etil-3-nitro-2-trimetilsilaniloxi-propil)-carbámico (1,505 g, 86%) como un aceite incoloro.

^{1}H NMR ($CDCl_3$): δ4,4 - 1,16 (m, 4H), 3,55 (m, 1H), 1,2-1,7 (m, 11H), 0,98 (2xt, J = 7,4 Hz, 3H), 0,13 (2s, 9H); LC/MS: 2 isómeros, total 100 % 221 (M-BOC+1).

REFERENCIA 28

Éster *terc*-butílico del ácido {1-[(5-isopropil-isoxazol-3-il)-trimetilsilaniloxi-metil]-propil}-carbámico

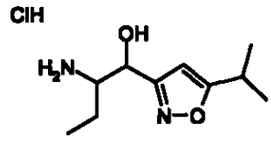


A una solución de éster *terc*-butílico del ácido (1-etil-3-nitro-2-trimetilsilaniloxi-propil)-carbámico (918 mg, 2,86 mmol), diisocianato de 1,4-fenileno (1,38 g, 8,5 mmol) y 3-metil-1-butino (586 mg, 8,5 mmol) en tolueno seco (15 ml) bajo N_2 se añadió trietilamina (10 gotas). Se calentó la mezcla a 50 °C en un vial sellado durante 28 h, y después se enfrió a temperatura ambiente. Se añadió agua (1 ml) y se agitó la mezcla durante 2 h más y después se filtró. Se concentró el filtrado en vacío y se purificó el residuo sobre 35 g de gel de sílice, se eluyó con acetato de etilo: heptano (1:5) para obtener el éster *terc*-butílico del ácido {1-[(5-isopropil-isoxazol-3-il)-trimetilsilaniloxi-metil]-propil}-carbámico (764 mg, 72 %) como un aceite incoloro.

^{1}H NMR ($CDCl_3$): δ 6,0 (2s 1H), 4,4-4,9 (m, 2H), 3,7 (m, 1H), 3,0 (m, 1H), 1,2-1,6 (m, 17H), 1,0 (m, 3H), 0,11 y 0,1 (2xs, 9H); LC/MS: 2 isómeros, total 67 % 271 (M-BOC+1).

REFERENCIA 29

Hidrocloruro de 2-amino-1-(5-isopropil-isoxazol-3-il)-butan-1-ol

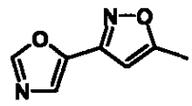


A una solución de éster *terc*-butílico del ácido {1-[(5-isopropil-isoxazol-3-il)-trimetilsilaniloxi-metil]-propil}-carbámico en diclorometano seco (5 ml) bajo N_2 se añadió una solución 4 M de HCl en dioxano (5,0 ml, XS). Se agitó la mezcla a temperatura ambiente durante 22 h y después se concentró en vacío para obtener la sal amina (475 mg, 99%) como un sólido ocre.

^{1}H NMR ($CDCl_3$): δ 6,25 (2xs, 1H), 5,0 (d, J = 3,9 Hz, 1H), 4,8 (d, J = 6,8 Hz, 1H), 3,4 (m, 1H), 3,1 (m, 1H), 1,5-1,7 (m, 2H), 1,3 (d, J = 6,8 Hz, 6H); 1,0 (t, J = 6,7 Hz, 3H); LC/MS: 100 % 199 (M+1).

REFERENCIA 30

5-Metil-3-oxazol-5-il-isoxazol



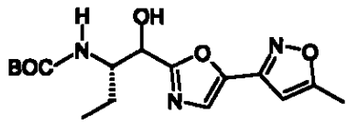
Se añadió gota a gota hidruro de diisobutilaluminio (1,0 M en DCM, 25,5ml, 25,5 mmol) a lo largo de 20 minutos a una solución de metil-5-metilisoxazol-3-carboxilato (3,0 g, 21,3 mmol) en 35 ml de cloruro de metileno seco, con agitación a –78 °C, y se agitó la mezcla de reacción a –78 °C durante 5,5 horas. Se calentó la reacción a –40 °C y se sofocó con hielo (60 g). Después que la mezcla bifásica se dejó calentar a temperatura ambiente, se añadió tartrato de potasio y sodio tetrahidratado (100 ml de solución acuosa saturada). Se separaron las dos capas y se extrajo la capa acuosa con cloruro de metileno. Los extractos orgánicos se secaron sobre sulfato de sodio y se concentraron a presión reducida para dar 5-metil-isoxazol-3-carbaldehído como un sólido blanco (1,3 g).

Se añadieron isocianuro de *p*-toluenosulfonil-metilo (1,75 g, 8,97 mmol) y carbonato de potasio (1,24 g, 8,97 mmol) a una solución de 5-metil-isoxazol-3-carbaldehído (1,0 g, 8,97 mmol) en 35 ml de metanol seco y la mezcla de reacción se mantuvo a reflujo (90 °C) durante 5 horas. Se enfrió la reacción a temperatura ambiente y se concentró a presión reducida. El residuo se sometió a reparto en éter dietílico (100 ml) y agua (200 ml). Se separó la capa orgánica y la capa acuosa se extrajo con éter dietílico. Los extractos orgánicos se lavaron con salmuera y agua, se secaron sobre sulfato de sodio y se concentraron a presión reducida para dar el compuesto del epígrafe como un sólido amarillento (1,25 g).

LC/MS: 87 %, 238 (M+1)

REFERENCIA 31

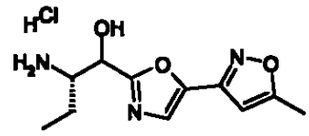
Éster *terc*-butílico del ácido ((S)-1-{hidroxi-[5-(5-metil-isoxazol-3-il)-oxazol-2-il]-metil}-propil)-carbámico



Se añadió trietilborano (1 M en THF, 12 ml, 12 mmol) a una solución de 5-metil-3-oxazol-5-il-isoxazol (1,8 g, 12 mmol) en 40 ml de tetrahidrofurano seco y se agitó la mezcla a temperatura ambiente durante 15 minutos. Se enfrió la mezcla a –78 °C, se añadió gota a gota nBuLi (2,5 M en hexano, 4,8 ml, 12 mmol) y se agitó la mezcla a –78 °C durante 15 minutos. Se añadió gota a gota una solución de éster *terc*-butílico del ácido (S)-1-formil-propil)-carbámico (898,7 mg, 4,8 mmol) en 15 ml de tetrahidrofurano seco y se agitó la mezcla de reacción a –78 °C durante 3 horas, después se dejó calentar a –30 °C y se sofocó con acético ácido en etanol (4 %, 250 ml), y se continuó agitando durante 2 horas, mientras se calentaba a temperatura ambiente. Se concentró la reacción a presión reducida; se disolvió el residuo en éter dietílico (250 ml) y se agitó durante 1,5 horas a temperatura ambiente. Se filtró el precipitado; se concentró el filtrado a presión reducida. Por cromatografía en columna sobre sílice eluyendo con una mezcla de cloruro de metileno y acetato de etilo se obtuvo el compuesto del epígrafe como un sólido amarillo pálido (830 mg); LC/MS 100 %, 338 (M+1)

REFERENCIA 32

(S)-2-Amino-1-[5-(5-metil-isoxazol-3-il)-oxazol-2-il]-butan-1-ol; hidrocloruro

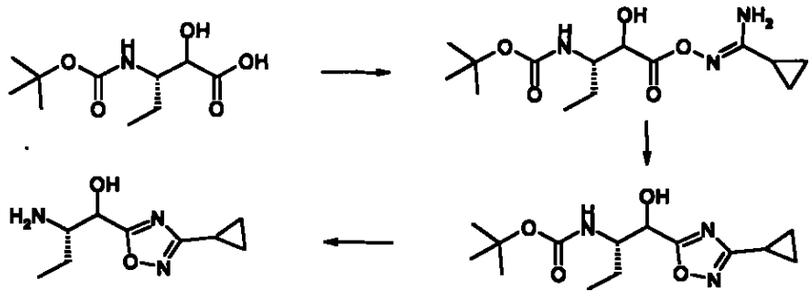


Se añadió gota a gota cloruro de hidrógeno (4 M en 1,4-dioxano, 3,3 ml) a una solución de éster *terc*-butílico del ácido ((S)-1-{hidroxi-[5-(5-metil-isoxazol-3-il)-oxazol-2-il]-metil}-propil)-carbámico (0,75 g, 2,22 mmol) en 10 ml de cloruro de metileno y se agitó la mezcla de reacción a temperatura ambiente durante 2,5 horas. Se diluyó la reacción con éter dietílico (50 ml) y se agitó durante otra hora a temperatura ambiente, se concentró a presión reducida para dar el compuesto del epígrafe como un sólido amarillento (0,75 g).

^{1}H NMR [$(CD)_3SO$]: δ 8,18 (m, 3H), 7,84 (s, 1H), 6,70 (s, 1H), 4,90 (m, 1H), 3,58 (m, 2H), 2,50 (s, 3H), 1,60 (m, 2H), 0,90 (t, 3H), LC/MS 100%, 238 (M+1)

REFERENCIA 33

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



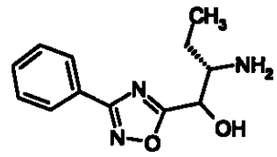
Se agitó a 0 °C una solución de ácido (S)-3-*terc*-butoxicarbonilamino-2-hidroxi-pentanoico (2,00 g, 8,57 mmol) y N-hidroxi-ciclopropanocarboxamidina (1,03 g, 10,29 mmol) en diclorometano (20 ml) y se añadieron en porciones 1,25 equivalentes de N-ciclohexilcarbodiimida-N'-metil-poliestireno (1,70 mmol/g, 6,30 g, 10,72 mmol). Se agitó la mezcla de reacción bajo nitrógeno durante tres horas mientras se calentaba a 15 °C. Se filtró la mezcla de reacción, se lavó la resina con diclorometano y se evaporó a sequedad el filtrado bajo vacío. [LC/MS m/z=338 (M+H+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 a temperatura ambiente y se evaporó bajo vacío a sequedad. [LC/MS m/z=320 (M+H+Na)]. El residuo se disolvió en diclorometano (50 ml) y se agitó a temperatura ambiente mientras se añadían gota a gota 50 ml de solución de ácido trifluoroacético al 50 % en diclorometano. Después de tres horas se evaporó la reacción bajo vacío a sequedad y se disolvió de nuevo en 50 ml de diclorometano. Se añadieron tres equivalentes de triamina-3 Silicycle y se agitó la mezcla a temperatura ambiente durante la noche. Se filtró la mezcla y se lavó con diclorometano. Se evaporó bajo vacío para dar 1,04 g (61 % global). [LC/MS m/z=198 (M+H)]

Alternativamente, la desprotección del grupo protector BOC se realizó con HCl en dioxano para dar hidrocloruro de (S) -2- amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol.

REFERENCIA 34

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



Se agitó a 0 °C una solución de ácido (S)-3-*terc*-butoxicarbonilamino-2-hidroxi-pentanoico (2,00 g, 8,57 mmol) y N-hidroxi-benzamidina (1,3 g, 9,5 mmol) en diclorometano (40 ml). Se añadió en porciones N-ciclohexilcarbodiimida-N'-metil-poliestireno (1,90 mmol/g,

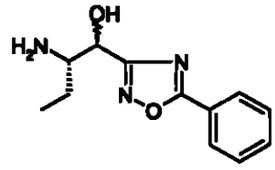
6 g, 11,4 mmol). Se agitó la mezcla de reacción bajo nitrógeno durante una hora. Se filtró la mezcla de reacción, se lavó la resina con diclorometano y se evaporó a sequedad el filtrado bajo vacío. [LC/MS m/z=352 ($M+H^+$), 296($M+H^+$-isobuteno)]. El residuo se disolvió en tetrahidrofurano (20 ml) y se calentó en un reactor de microondas (Smith Creator) a 180 °C durante tres minutos, se enfrió a temperatura ambiente y se evaporó bajo vacío a sequedad. Se purificó el residuo por cromatografía rápida (se eluyó 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)].

Se disolvió el producto en diclorometano (45 ml) y se añadió ácido trifluoroacético (5 ml). Después de dos horas se evaporó la reacción bajo vacío a sequedad. El residuo se redisolvió en 50 ml de diclorometano. Se añadió triamina-3 Silicycle (9,9 g, 39 mmol) y se agitó la mezcla a temperatura ambiente durante la noche. Se filtró la mezcla y se lavó con diclorometano. Se concentró el filtrado bajo vacío para dar (S)-2-amino-1-(3-fenil-1,2,4-oxadiazol-5-il)-butan-1-ol (775 mg, 38 %) como un sólido blanco.

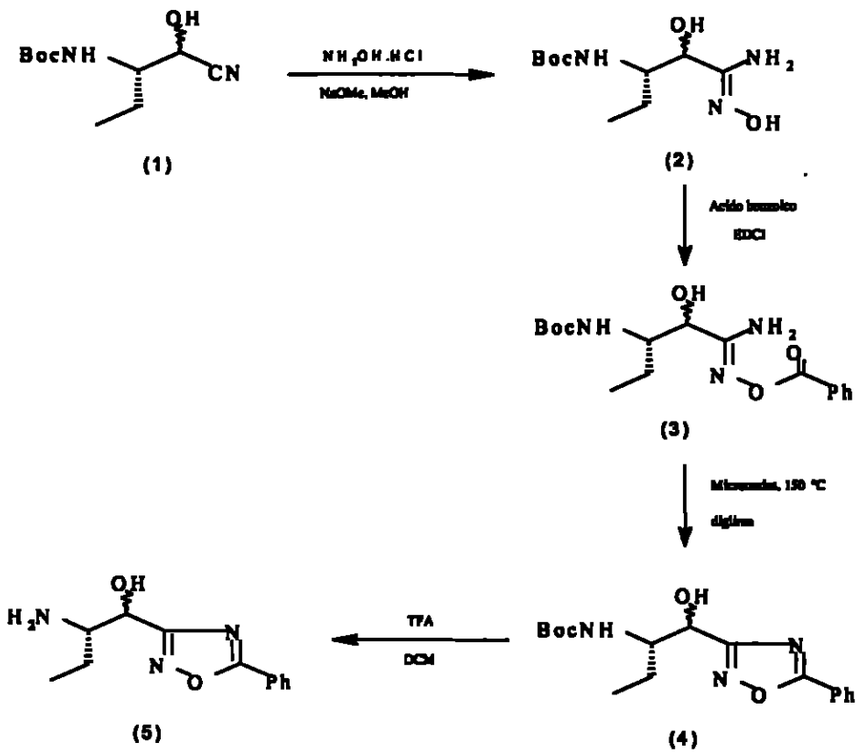
^{1}H NMR ($CDCl_3$):δ 8,12-8,06 (m, 2H), 7,54-7,45 (m, 3H), 4,93 & 4,75 (2xd, J= 5Hz & 3,5Hz, 1H), 3,25 &3,11 (2xm, 1H), 1,78-1,42 (2xm, 2H), 1,04 & 1,01 (2x t, J= 7,5Hz, 3H). [LC/MS m/z=234 (M+H)].

REFERENCIA 35

(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 del ácido {(S)-1-[hidroxi-(N-hidroxicarbamimidoil)-metil]-propil}-carbámico (2)

Una solución de éster *terc*-butílico del ácido (2-ciano-1-etil-2-hidroxi-etil)-carbámico (9,53 g, 44 mmol) en metanol (80 ml) se enfrió a 0 °C y se trató sucesivamente con hidrocloruro de hidroxilamina (3,05 g, 44 mmol) en metanol (80 ml) y solución de metóxido de sodio al 25 % en metanol (10,2 ml). Después de agitar a 0 °C durante 5 minutos se agitó la mezcla de reacción a temperatura ambiente durante 5 horas y después se evaporó. El residuo se sometió a reparto entre acetato de etilo y agua. Se separó la capa orgánica, se secó sobre sulfato de magnesio y después se evaporó a presión reducida. El aceite amarillo residual se sometió a cromatografía líquida de media presión (mplc), eluyendo con una mezcla de acetato de etilo y heptano para dar el éster *terc*-butílico del ácido {(S)-1-[hidroxi-(N-hidroxicarbamimidoil)-metil]-propil}-carbámico (3,5 g) como un sólido blanco. MS: MH^+ 248.

Éster *terc*-butílico del ácido {1-[hidroxi-(N-benzoiloxicarbamimidoil)-metil]-propil}-carbámico (3)

Una solución de éster *terc*-butílico del ácido {1-[hidroxi-(*N*-hidroxicarbamimidoil)-metil]-propil}-carbámico (2) (2,5 g, 10 mmol) en diclorometano (125 ml) se trató con ácido benzoico (1,36 g, 11 mmol), EDCI (2,14 g, 11 mmol), HOBT (1,37 g, 10 mmol) y trietilamina

(1,35 ml, 11 mmol) y se agitó a temperatura ambiente durante la noche. Se lavó la mezcla de reacción con solución saturada de bicarbonato de sodio, después agua, después se secó sobre Na_2SO_4 y después se evaporó a 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 el éster *terc*-butílico del ácido {1-[hidroxi-(N-benzoiloxicarbamimidoil)-metil]-propil}-carbámico (850mg) como un sólido amarillo. MS: MH^+ 352.

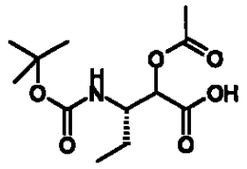
2-Amino-1-(5-fenil-[1,2,4]oxadiazol-3-il)-butan-1-ol (5)

Una solución de (3) (1,5 g, 4,3 mmol) en diglima se calentó a 150 °C en un reactor de microondas (Smith Creator, S00219) durante 40 minutos. Se evaporó el disolvente bajo vacío en Genevac Evaporator a 80 °C durante 3 horas para dar un sólido marrón. Se recogió éste en diclorometano (40 ml) y se trató con ácido trifluoroacético a temperatura ambiente durante 2 horas. Se evaporó el disolvente a sequedad a presión reducida, se recogió el crudo en agua, se lavó con DCM, la capa acuosa se alcalinizó con solución 1 M de NaOH y se extrajo con diclorometano. La capa orgánica se secó sobre Na_2SO_4 y se evaporó a presión reducida para dar 2-amino-1-(5-fenil-[1,2,4]oxadiazol-3-il)-butan-1-ol (300mg) como un sólido marrón pálido.

^1H NMR ($CDCl_3$): δ 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).

REFERENCIA 36

Ácido (S)-2-acetoxi-3-*terc*-butoxicarbonilamino-pentanoico



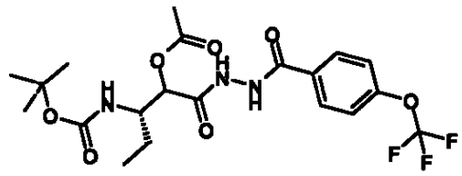
Se disolvieron piridina (5 ml), 4-(dimetilamino)piridina (0,01 g) y anhidrido acético (11 mmol, 1,12 g) en diclorometano (150 ml) y la solución resultante se enfrió a 0 °C. Se añadió de una vez ácido (S)-3-*terc*-butoxicarbonilamino-2-hidroxi-pentanoico (10 mmol, 2,33 g, A) y la mezcla de reacción resultante se agitó durante 5 horas.

Se añadió ácido clorhídrico 1 M (250 ml) y la mezcla se transfirió a un embudo de separación. Se separaron las fases y la fase acuosa se extrajo tres veces con acetato de etilo (200 ml). Las fases orgánicas reunidas se lavaron dos veces con agua (200 ml) y con salmuera (100 ml). La fase orgánica se secó con sulfato de magnesio y los disolventes se evaporaron a presión reducida para dar el ácido (S)-2-acetoxi-3-*terc*-butoxicarbonilamino-pentanoico (2,535 g, 92 %).

MS: m/z=298 ($M+Na^+$), 276 ($M+H^+$)

REFERENCIA 37

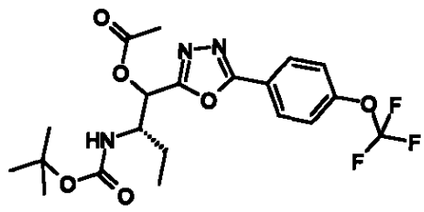
Éster de ácido acético y (S)-2-*terc*-butoxicarbonilamino-1-[N'-(4-trifluorometoxi-benzoil)hidrazinocarbonil]-butilo



Se disolvió ácido (S)-2-acetoxi-3-*terc*-butoxicarbonilamino-pentanoico (1,82 mmol, 0,5 g, A) en 30 ml de diclorometano. Se añadió N-ciclohexilcarbodiimida-N'-metilpoliestireno (3,64 mmol, 1,92 g, B) y la mezcla de reacción resultante se agitó durante 2 min. Se añadió hidrazida del ácido 4-(trifluorometoxi)benzoico (1,65 mmol, 0,363 g, C) y se agitó la mezcla de reacción durante la noche. Después de 16 horas el análisis por LC/MS todavía mostraba hidrazida. Se añadió metilisocianato de poliestireno (1,65 mmol, 1,15 g) y se continuó agitando durante ocho horas. Se filtró la mezcla de reacción con succión y se concentró el filtrado a presión reducida, para dar el éster de ácido acético y (S)-2-*terc*-butoxicarbonilamino-1-[N'-(4-trifluorometoxi-benzoil)hidrazinocarbonil]-butilo como una espuma amarilla (0,5 g, 64 %). Según LC/MS todavía quedaba algo de hidrazida. MS: m/z= 500 ($M+Na^+$), 478 ($M+H^+$)

REFERENCIA 38

Éster de ácido acético y (S)-2-*terc*-butoxicarbonilamino-1-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-il]-butilo



El éster de ácido acético y (S)-2-*terc*-butoxicarbonilamino-1-[N'-(4-trifluorometoxi-benzoil)-hidrazinocarbonil]-butilo obtenido anteriormente se dividió en 5 porciones, que se hicieron reaccionar separadamente como sigue:

el éster de ácido acético y (S)-2-*terc*-butoxicarbonilamino-1-[N'-(4-trifluorometoxi-benzoil)-hidrazinocarbonil]-butilo (0,21 mmol, 0,1 g) se disolvió en THF (5 ml) y la solución se llenó en un vaso de reacción de un sintetizador Smith Microwave. Se añadieron 2-*terc*-butilimino-2-dietilamino-1,3-dimetilperhidro-1,2,3-diazafosforina en poliestireno (1,05 mmol, 0,456 g, 2,3 mmol/g de carga) y cloruro de *p*-toluenosulfónico (0,25 mmol, 0,048 g) y la mezcla de reacción

se calentó a 150 °C durante 10 min (tiempo de retención fijado) en el sintetizador de microondas.

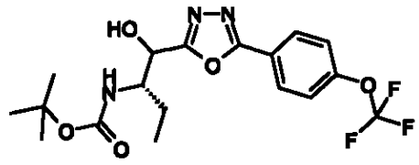
Las mezclas de reacción reunidas se filtraron con succión y se lavó la resina con 300 ml de acetato de etilo. Los filtrados reunidos se concentraron a presión reducida.

El producto crudo se purificó por cromatografía rápida (Biotage Horizon, columna 25 M, el producto crudo se cargó en caplet, caudal 17 ml/min, 12 ml/fracción, 120 ml en gradiente desde acetato de etilo 0 % en heptano hasta acetato de etilo al 30 % en heptano, 240 ml de acetato de etilo al 30 % en heptano, 60 ml en gradiente de acetato de etilo 30-50 % en heptano, 300 ml de acetato de etilo al 50 % en heptano) para dar el éster de ácido acético y (S)-2-*terc*-butoxicarbonilamino-1-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-il]-butilo (0,28 g, 58 %)

MS: m/z= 460 ($M+H^+$)

REFERENCIA 39

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

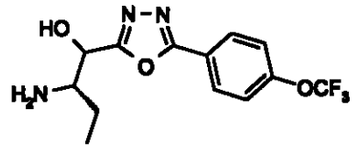


Se disolvió el éster de ácido acético y (S)-2-*terc*-butoxicarbonilamino-1-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-il]-butilo (0,61 mmol, 0,28 g) en una mezcla de THF (10 ml) y agua (10 ml). Se añadió hidróxido de litio hidratado (1,22 mmol, 0,051 g) y la mezcla de reacción se agitó durante 2 h. Se evaporaron los disolventes a presión reducida y se transfirió el residuo a un embudo de separación con 300 ml de acetato de etilo y 50 ml de agua. Se separaron las fases y la fase orgánica se lavó con salmuera (100 ml). Después se secó la fase orgánica con sulfato de magnesio. Se evaporó el disolvente a presión reducida y se secó bajo alto vacío para dar el éster *terc*-butílico del ácido ((S)-1-{hidroxi-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-il]-metil}-propil)-carbámico como un aceite amarillo (0,225 g, 89 %).

MS: m/z= 440 ($M+Na^+$), 418 ($M+H^+$)

REFERENCIA 40

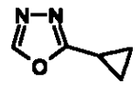
(S)-2-Amino-1-(5-p-tolil-1,3,4-oxadiazol-2-il)-butan-1-ol



Se disolvió éster *terc*-butílico del ácido ((S)-1-{hidroxi-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-il]-metil}-propil)-carbámico (0,54 mmol, 0,225 g) en diclorometano (9 ml) y se trató con ácido trifluoroacético (1 ml). Se agitó la mezcla de reacción durante cuatro horas. Se evaporaron los disolventes a presión reducida. El residuo se re-disolvió en diclorometano (20 ml) y se añadió triamina Silicycle (5,4 mmol, 1,47 g). Se agitó la mezcla de reacción durante 60 h (a lo largo del fin de semana). Se filtraron las mezclas de reacción con succión y se evaporaron los disolventes para dar el (S)-2-amino-1-(5-p-tolil-1,3,4-oxadiazol-2-il)-butan-1-ol (0,164 g, 96 %). MS: m/z= 318 ($M+H^+$)

REFERENCIA 41

2-Ciclopropil-[1,3,4]oxadiazol



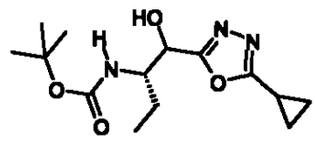
Se mantuvo a reflujo durante 28 h una mezcla de éster metílico del ácido ciclopropanocarboxílico (10 g, 0,1 mol) e hidrato de hidrazina (7,3 ml, 0,15 mol) y se enfrió a temperatura ambiente. Se evaporó la mezcla a presión reducida y después se secó por separación azeotrópica del disolvente con tolueno. El residuo se disolvió en diclorometano y se lavó con NaCl saturado. La fase orgánica se secó sobre $MgSO_4$ anhidro, se evaporó el disolvente a presión reducida para dar la hidrazida del ácido ciclopropanocarboxílico (4,36 g, 44 %)

Una mezcla de la hidrazida del ácido ciclopropanocarboxílico (31,35 g, 0,31 mol), ortoformiato de trimetilo (300 ml) y ácido *p*-toluenosulfónico monohidratado (200 mg) se calentó a reflujo durante la noche. El exceso de ortoformiato de trimetilo y metanol se separó por destilación. Por destilación en vacío del residuo se obtuvo el 2-ciclopropil-[1,3,4]oxadiazol (22 g, 64 %).

^1H NMR ($CDCl_3$): δ 8,24(s, 1H), 2,2 (m, 1H), 1,15 (m, 4H). LCMS: 100 %, 111 (MH^+).

REFERENCIA 42

Éster *terc*-butílico del ácido {1-[(5-ciclopropil-[1,3,4]oxadiazol-2-il)-hidroxi-metil]-propil}-carbámico



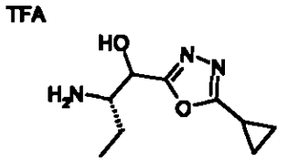
Se enfrió a –78 °C una solución de 2-ciclopropil-[1,3,4]oxadiazol (2,16 g, 19,6 mmol) en THF seco (100 ml). Se añadió gota a gota ^{n}BuLi (1,6 M en hexano, 12,3 ml, 19,6 mmol). Se agitó la mezcla de reacción a –78 °C durante 40 min. Se añadió $MgBr_2.OEt_2$ (5,0692 g, 19,6 mmol). Se dejó que la mezcla de reacción se calentara hasta –45 °C y se agitó a esta temperatura durante 1,5 h. Se añadió una solución de éster *terc*-butílico del ácido (1-formil-propil)-

carbámico (3,7 g, 19,6 mmol) en THF (40 ml). Se dejó que la mezcla de reacción se calentara hasta –20 °C y se agitó a esta temperatura durante 3,5 h. Se sofocó la mezcla de reacción con una solución saturada de NH_4Cl y se extrajo con acetato de etilo. Los extractos orgánicos reunidos se lavaron con solución saturada de NaCl y se secaron sobre $MgSO_4$. Se evaporó el disolvente a presión reducida y se purificó el crudo por cromatografía en columna eluyendo con mezcla de acetato de etilo y heptano para dar el éster *terc*-butílico del ácido {1-[(5-ciclopropil-[1,3,4]oxadiazol-2-il)-hidroxi-metil]-propil}-carbámico (2,83 g, 49 %).

LCMS: 298 (MH^+).

REFERENCIA 43

(S)-2-Amino-1-(5-ciclopropil-1,3,4-oxadiazol-2-il)-butan-1-ol; compuesto con ácido trifluoro-acético

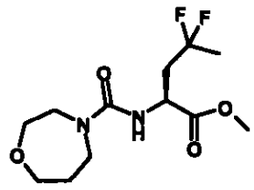


Se agitó a temperatura ambiente durante 2 horas una mezcla de éster *terc*-butílico del ácido {1-[(5-ciclopropil-[1,3,4]oxadiazol-2-il)-hidroxi-metil]-propil}-carbámico (2,83 g, 9,95 mmol), ácido trifluoro-acético (5 ml) en diclorometano (20 ml) y se concentró a sequedad a presión reducida para dar el (S)-2-amino-1-(5-ciclopropil-1,3,4-oxadiazol-2-il)-butan-1-ol; compuesto con ácido trifluoro-acético.

LCMS: 100 % 198 (MH^+).

REFERENCIA 44

Éster metílico del ácido (S)-4,4-difluoro-2-[(perhidro-1,4-oxazepin-4-carbonil)-amino]-pentanoico.



Se disolvió trifosgeno en diclorometano (10 ml) y se añadió a esto, con una bomba de jeringa, una mezcla de hidrocloruro de ácido S-2-amino-4,4-difluoro-pentanoico (1,00 g, 4,90 mmol) (véase el ejemplo de referencia 15), diisopropiletil-amina (1,88 ml, 10,80 mmol) disuelta en diclorometano (10 ml) a lo largo de un periodo de 1 h. Después de agitar durante 15 minutos adicionales se añadió a la solución una solución de hidrocloruro de homomorfolina (0,67 g, 4,90

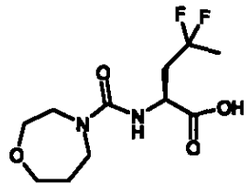
mmol) y diisopropiletil-amina (1,90 ml, 10,90 mmol) en diclorometano (10 ml). La solución resultante se agitó a temperatura ambiente durante 2 h. Se evaporó el disolvente y se diluyó el residuo con acetato de etilo (100 ml) y después se lavó con $KHSO_3$ 1 M (2x 10 ml), $NaHCO_3$ saturado, y salmuera. Las capas orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron para dar un aceite amarillo pálido. El material crudo se purificó sobre 20 g de gel de sílice eluyendo con acetato de etilo:heptano con gradiente de 50-100 %. Se obtuvo el éster metílico del ácido (S)-4,4-difluoro-2- [(perhidro-1,4-oxazepin-4-carbonil)-amino]-pentanoico como un sólido blanco (0,40 g, 28 %).

^{1}H NMR ($CDCl_3$) δ 5,12 (d, J=7,5Hz, 1H), 4,72 (dd, J = 12,0, 7,2 Hz, 1H), 3,75 (m, 7H), 3,55 (m, 4H), 2,45 (m, 2H), 1,98 (m, 2H), 1,66 (t, J = 18,7 Hz, 3H).

LC/MS: 295, 100 %, (M+H), 317 (M+Na)

REFERENCIA 45

Ácido (S)-4,4-difluoro-2- [(perhidro-1,4-oxazepin-4-carbonil)-amino]-pentanoico



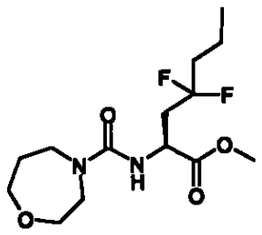
Se disolvió el éster metílico del ácido (S)-4,4-difluoro-2-[(perhidro-1,4-oxazepin-4-carbonil)-amino]-pentanoico (0,38 g, 1,29 mmol) en tetrahidrofurano/metanol (15ml/10 ml) y se añadió hidróxido de litio (35 mg, 1,40 mmol) disuelto en agua (5 ml). Se agitó la reacción a temperatura ambiente durante 18 h, y después se separó el metanol/tetrahidrofurano en vacío. Se acidificó el residuo con ácido clorhídrico 6 M (0,25 ml) y se extrajo con diclorometano (3x 20 ml), se secó (Na_2SO_4), y se concentró para dar el ácido (S)-4,4-difluoro-2-[(perhidro-1,4-oxazepin-4-carbonil)-amino]-pentanoico como un sólido blanco (0,36 g, 99 %).

^{1}H NMR (DMSO-d6) δ 12,6 (bs, 1H), 6,60 (d, 8,3 Hz, 1H), 4,30 (dd, J = 14,5, 7,0 Hz, 1H), 3,57 (m, 4H), 3,43 (m, 4H), 2,38 (m, 2H), 1,77 (m, 2H), 1,61 (t, J = 19,2Hz, 3H).

LC/MS: 100 % 281 (M+H)

REFERENCIA 46

Éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico

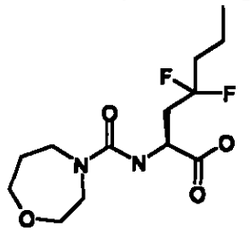


A una mezcla de bicarbonato de sodio (5,25 g), *p*-nitro-cloroformiato (5,03 g, 25 mmol) en acetonitrilo (130 ml) bajo nitrógeno se añadió hidrocloruro del éster metílico del ácido (S)-2-amino-4,4-difluoro-heptanoico (5,79 g, 0,025 mol) y se agitó a temperatura ambiente durante 5 horas. Se añadieron hidrocloruro de homomorfolina (3,61 g, 26,25 mmol) y trietil-amina (12,5 ml) y se agitó la reacción durante la noche a temperatura ambiente. Se separó el disolvente por evaporación a presión reducida, se sometió el crudo a reparto entre agua (150 ml) y acetato de etilo (200 ml). Se separó la capa orgánica, se lavó con solución de K_2CO_3 (150 ml), HCl (150 ml) y salmuera (150 ml). Se separó la capa orgánica, se secó ($MgSO_4$) y se evaporó a presión reducida. Se purificó el crudo por cromatografía en columna eluyendo con acetato de etilo: heptano 1:1 a 8:2 v/v, seguido por acetato de etilo para dar el éster metílico del ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico (4,8g) como un aceite amarillo pálido.

LC/MS: 323 (M+H).

REFERENCIA 47

Ácido 4,4-difluoro-2-[([1,4]oxazepan-4-carbonil)-amino]-heptanoico

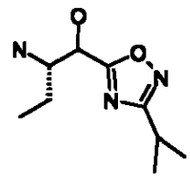


Procediendo de manera similar al Ejemplo de Referencia 45 anterior pero utilizando éster metílico del ácido 4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico se preparó el ácido 4,4-difluoro-2-[([1,4]oxazepan-4-carbonil)-amino]-heptanoico.

LC/MS: 309 (M+H).

REFERENCIA 48

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

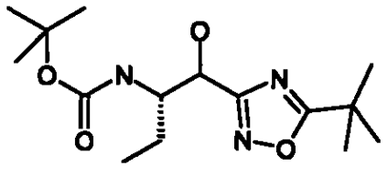


Se preparó similarmente según el procedimiento del Ejemplo de Referencia 33.

LCMS: 200 (M+H).

REFERENCIA 49

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



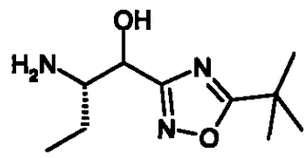
El éster *terc*-butílico del ácido {(S)-1-[hidroxi-(N-hidroxicarbamimidoil)-metil]-propil}-carbámico (235 mg, 0,95 mmol) en diglima (2 ml), se trató con anhidrido trimetil-acético (0,212 ml, 1,04 mmol) y se calentó la mezcla de reacción a 170 °C durante 5 minutos en un microondas Emrys Optimizer de Personal Chemistry. Se evaporó el disolvente bajo alto vacío. El crudo obtenido se purificó por cromatografía rápida eluyendo con una mezcla de acetato de etilo y heptano (1:4) para dar el éster *terc*-butílico del ácido {(S)-1-[(5-*terc*-butil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propil}-carbámico como un aceite marrón (100 mg) (mezcla de diastereoisómeros).

^{1}H NMR ($CDCl_3$)δ: 4,92-4,69 (m, 2H), 4,05-3,85 (m, 1H), 3,57-3,41 & 3,32-3,15 (2xbs, 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 (M+H).

REFERENCIA 50

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



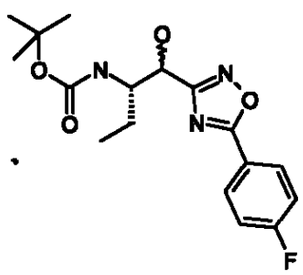
Una solución de éster *terc*-butílico del ácido {(S)-1-[(5-*terc*-butil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propil}-carbámico (2,11 g, 6,72 mmol) en cloruro de metileno (20 ml) se trató con ácido trifluoroacético (5,18 ml, 67,25 mmol) y se agitó a temperatura ambiente durante 3 h. Se evaporó el disolvente a presión reducida. Se disolvió el residuo en cloruro de metileno (100 ml) y se trató con PS-trisamina de Argonaut Technologies (5,38 g, 20,18 mmol, 3,75 mmol/g de carga) y se agitó la reacción a temperatura ambiente durante 4 h, se filtró y se evaporó el filtrado para dar el (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).

^{1}H NMR ($CDCl_3$)δ: 4,73 & 4,58 (2xd, J=5Hz, 1H), 3,12-3,00 (m, 1H), 2,64-2,31 (ba, 3H), 1,69-1,44 (m, 2H), 1,43 (s, 9H), 0,99 & 0,97 (2xt, J=7,5Hz, 3H).

MS: 214 (M+H).

REFERENCIA 51

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



Una suspensión de ácido 4-fluoro-benzoico (1,70 g, 0,012 mol) e hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (2,12 g, 0,011 mol) en cloruro de metileno (80 ml) se trató con éster *terc*-butílico del ácido (S)-1-[hidroxi-(N-hidroxicarbamimidoil)-metil]-propil}-carbámico (3 g, 0,012 mol) y trietilamina (1,54 ml, 0,011 mol). Se agitó la reacción a temperatura ambiente durante la noche. Después, se diluyó con 40 ml de cloruro de metileno, se lavó con solución acuosa saturada de bicarbonato (30 ml), agua (30 ml), salmuera (30 ml), se secó sobre Na_2SO_4 y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía

rápida eluyendo con una mezcla de acetato de etilo y heptano (2:1) para dar un sólido blanco-sucio (2,20 g)

^{1}H NMR ($CDCl_3$)δ: 8,10-7,95 (m, 2H), 7,16-7,00 (m, 2H), 5,43-5,24 (m, 2H), 5,22-5,05 (m, 1H), 5,01-4,85 (m, 1H), 4,50-4,39 (m, 1H), 3,80-3,60 (m, 1H), 1,90-1,78 (m, 2H), 1,40 (s, 9H), 0,98 (t, J=7,5Hz, 3H).

MS: 370 (M+H).

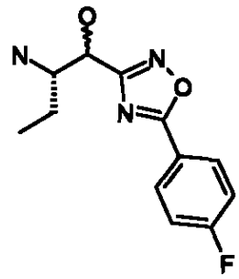
Se recogieron 240 mg del compuesto sólido (0,65 mmol) obtenido antes en diglima (5 ml) y se calentaron a 160 °C en un microondas (Smith Creator, S00219) durante 18 minutos. Se evaporó el disolvente bajo alto vacío. El crudo obtenido se purificó por cromatografía rápida eluyendo con una mezcla de acetato de etilo y heptano (1:4) para dar el éster *terc*-butílico del ácido (S)-1-{[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-il]-hidroxi-metil}-propil)-carbámico como un sólido blanco (148 mg).

^{1}H NMR ($CDCl_3$)δ: 8,16-8,09 (m, 2H), 7,25-7,12 (m, 2H), 4,98-4,73 (m, 2H), 4,13-3,87 (m, 1H), 3,82-3,35 (m, 1H), 1,80-1,52 (m, 2H), 1,46 & 1,34 (2xs, 9H), 1,02 & 0,99 (2xt, J=7,5Hz, 3H).

MS: 352 (M+H).

REFERENCIA 52

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



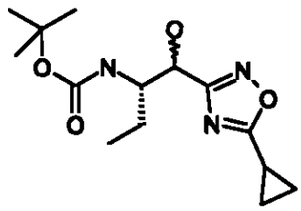
Se preparó similarmente según el Ejemplo de Referencia 50 anterior pero utilizando éster *terc*-butílico del ácido (S)-1-{[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-il]-hidroxi-metil}-propil)-carbámico.

^{1}H NMR ($CDCl_3$)δ: 8,18-8,05 (m, 2H), 7,26-7,12 (m, 2H), 4,92 & 4,73 (2xd, J=5Hz, 1H), 3,27-3,05 (m, 1H), 1,75-1,62 (m, 1H), 1,59-1,41 (m, 1H), 1,02 & 1,00 (2xt, J=7,5Hz, 3H).

MS: 252 (M+H).

REFERENCIA 53

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



Una suspensión de éster *terc*-butílico del ácido (S)-1-[hidroxi-(N-hidroxicarbamimidoil)-metil]-propil}-carbámico (6,12 g, 24,78 mmol) en cloruro de metileno (150 ml) se trató con trietilamina (3,46 ml, 24,82 mmol) y después se enfrió a 0 °C. Después se añadió gota a gota cloruro de ciclopropil-carbonilo (2,25 ml, 24,79 mmol). Se agitó la reacción a temperatura ambiente durante 1 h 45 min y se diluyó con 150 ml de cloruro de metileno, se lavó con agua (40 ml), bicarbonato acuoso saturado (20 ml), agua (20 ml), se secó sobre Na_2SO_4 y se evaporó el disolvente a presión reducida para dar un sólido blanco (7,16g).

MS: 338 (M+Na).

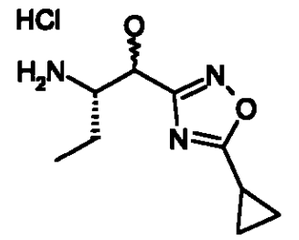
Se calentó a reflujo durante 15 h una solución del compuesto obtenido antes (7,45 g, 0,024 mol) en dioxano (150 ml). Se evaporó el disolvente a presión reducida y se purificó el residuo por cromatografía rápida eluyendo con una mezcla de acetato de etilo y heptano para dar el éster *terc*-butílico del ácido (S)-1-[(5-ciclopropil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propil}-carbámico como un sólido amarillo pálido (5 g).

^{1}H NMR ($CDCl_3$)δ: 4,94-4,74 (m, 2H), 3,97 & 3,85 (2xm, 1H), 3,62 & 3,48 (2xbs, 1H), 2,19 (m, 1H), 1,72-1,42 (m, 2H), 1,44 & 1,39 (2xs, 9H), 1,26-1,18 (m, 4H), 0,98 & 0,95 (2xt, J=7,4Hz, 3H).

MS: 298 (M+H).

REFERENCIA 54

Sal HCl de (S)-2-amino-1-(5-ciclopropil-1,2,4-oxadiazol-3-il)-butan-1-ol



Se agitó a temperatura ambiente durante 2 h una solución de éster *terc*-butílico del ácido {(S)-1-[(5-ciclopropil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propil}-carbámico (3,41 g, 0,011 mmol) en HCl 4 N en dioxano (43 ml, 0,172 mmol). Se evaporó el disolvente a presión reducida. Se trituró el residuo con una mezcla de acetato de etilo y éter. Después se filtró para dar la

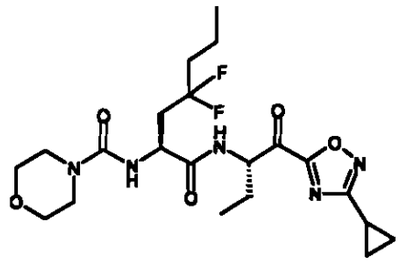
sal HCl de (S)-2-amino-1-(5-ciclopropil-1,2,4-oxadiazol-3-il)-butan-1-ol como un sólido marrón (2,47 g).

^{1}H NMR ($CDCl_3$)δ: 8,21 (bs, 2H), 5,37 & 5,14 (2xd, 1H), 3,88 & 3,73 (2xm, 1H), 2,21 (m, 1H), 1,92-1,50 (m, 2H), 1,24 (m, 4H), 1,08 & 1,06 (2xt, J=7,4Hz, 3H).

MS: 198 (M+H).

EJEMPLO 1

{(S)-1-[(S)-1-(3-Ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico



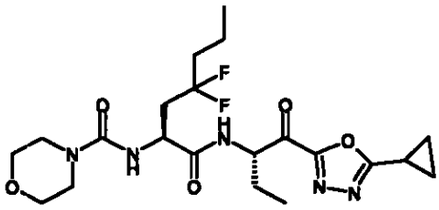
A una mezcla de ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico (104 mg, 0,35 mmol), hidrocloruro de (S)-2-amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol (86,7 mg, 0,37 mmol) y diisopropil-amina (219 mg, 0,42 mmol) en diclorometano seco (5 ml), se añadió pyBOP (113 mg, 0,87 mmol). Se agitó la mezcla a temperatura ambiente durante 16 h y se evaporó en vacío. Se diluyó el residuo con acetato de etilo (25 ml) y se lavó con $NaHCO_3$ saturado (30 ml), HCl diluido (30 ml), y después con $NaHCO_3$ saturado (30 ml). Se secó la capa orgánica sobre sulfato de magnesio y se concentró en vacío. Se purificó el residuo sobre 12 g de gel de sílice, eluyendo con acetato de etilo: heptano (2:1 después 1:0) para obtener la {1-{1-[(3-ciclopropil-[1,2,4]oxadiazol-5-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-hexil)-amida del ácido morfolin-4-carboxílico (146 mg, 88 %) como un sólido blanco. La LC/MS muestra 2 isómeros, total 100 % M+1 474.

A una solución de (1-{1-[(3-ciclopropil-[1,2,4]oxadiazol-5-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-hexil)-amida del ácido morfolin-4-carboxílico (145 mg, 0,31 mmol) en diclorometano seco (3 ml) bajo N2 se añadió peryodinano de Dess-Martin (solución al 15 % en peso en diclorometano, 1,73 g, .061 mmol). Se agitó la reacción a temperatura ambiente durante 2 h, después se sofocó con un solución de $Na_2S_2O_3$ (193 mg, 1,22 mmol) en $NaHCO_3$ saturado (30 ml). Se extrajo la capa acuosa con diclorometano (2x30 ml). Las capas orgánicas se secaron sobre sulfato de magnesio y se concentraron en vacío. Se purificó el residuo sobre 12 g de gel de sílice, y se eluyó con acetato de etilo: heptano (1:1 después 2:1) para obtener la cetona deseada (119 mg, 81 %) como un sólido ocre.

^{1}H NMR ($CDCl_3$): δ 7,4 (d, 7,0 Hz, 1H), 5,27 (m, 1H), 5,13 (d, J = 6,9 Hz, 1H), 4,65 (dd, J = 13,1, 6,9 Hz, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 2,4 (m, 2H), 2,2 (m, 1H), 2,05 (m, 1H), 1,8 (m, 3H), 1,55 (m, 2H), 1,15 (m, 4H), 0,98 (t, J = 7,4 Hz, 6H);
LC/MS: 28 % 512 (M+H_2O+Na) y 68 % 494 (M+Na).

EJEMPLO 2

{(S)-1-[(S)-1-(5-Ciclopropil-1,3,4-oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico



Se añadieron pyBOP (171,73 mg, 0,33 mmol), diisopropiletilamina (0,0575 ml, 0,33 mmol) y (S)-2-amino-1-(5-ciclopropil-1,3,4-oxadiazol-2-il)-butan-1-ol; compuesto con ácido trifluoro-acético (0,30 mmol), a una solución de ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico (88,29 mg, 0,30 mmol) en cloruro de metileno seco (4 ml) y se agitó la mezcla de reacción durante la noche a temperatura ambiente. Se sofocó la reacción con bicarbonato de sodio acuoso, se extrajo dos veces con cloruro de metileno, los extractos orgánicos se secaron sobre sulfato de sodio y se evaporaron a presión reducida. Por cromatografía en columna sobre sílice eluyendo con una mezcla de cloruro de metileno y acetato de etilo se obtuvo la {(S)-1-{(S)-1-[(5-ciclopropil-1,3,4-oxadiazol-2-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-hexil)-amida del ácido morfolin-4-carboxílico como un sólido blanco (87 mg). LC/MS 97 %, 474 (M+1).

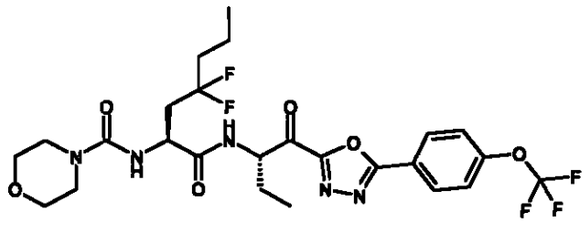
Se añadió peryodinano de Dess-Martin (15 % en peso en DCM, 0,79 g, 0,28 mmol) a una solución de ((S)-1-{(S)-1-[(5-ciclopropil-1,3,4-oxadiazol-2-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-hexil)-amida del ácido morfolin-4-carboxílico (67 mg, 0,14 mmol) en cloruro de metileno seco (10 ml) y se agitó a temperatura ambiente durante 2,5 horas. Se sofocó la reacción con una solución de $Na_2S_2O_3$ (110,68 mg, 0,70 mmol) en $NaHCO_3$ acuoso. Se separó la capa orgánica y se extrajo la capa acuosa con diclorometano. Los extractos orgánicos se secaron sobre sulfato de sodio y se concentraron a presión reducida. Por cromatografía en columna sobre sílice eluyendo con una mezcla de cloruro de metileno y acetato de etilo se obtuvo la {(S)-1-[(S)-1-(5-ciclopropil-1,3,4-oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico como un polvo blanco (48 mg).

^{1}H NMR ($CDCl_3$): δ 7,52 (d, J=7,5Hz, 1H), 5,34 (m, 1H), 5,18 (d, J=7,5Hz, 1H), 4,65 (m, 1H), 3,72 (m, 4H), 3,40 (m, 4H), 2,50-2,22 (m, 3H), 2,18-2,08 (m, 1H), 1,96-1,78 (m, 3H), 1,60-1,45 (m, 2H), 1,30 (m, 4H), 0,98 (t+t, 6H).

LC/MS 95 %, 472 (M+1).

EJEMPLO 3

((S)-3,3-Difluoro-1-{(S)-1-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico.



Se añadieron pyBOP (68,69 mg, 0,13 mmol), diisopropiletilamina (0,023 ml, 0,13 mmol) y (S)-2-amino-1-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-il]-butan-1-ol (38,0 mg, 0,12 mmol) a una solución de ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico (34 mg, 0,12 mmol) en cloruro de metileno seco (4 ml) y se agitó la mezcla de reacción durante la noche a temperatura ambiente. Se sofocó la reacción con $NaHCO_3$ acuoso, se extrajo dos veces con cloruro de metileno, los extractos orgánicos se secaron sobre $Na2SO_4$ y se evaporaron a presión reducida. Por cromatografía en columna sobre sílice eluyendo con una mezcla de cloruro de metileno y acetato de etilo se obtuvo la [(S)-3,3-difluoro-1-((S)-1-{hidroxi-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-il]-metil}-propilcarbamoil)-hexil]-amida del ácido morfolin-4-carboxílico como un sólido blanco (61 mg). LC/MS 71 %, M+1= 594

Se añadió peryodinano de Dess-Martin (15 % en peso en DCM, 0,58 g, 0,21 mmol) a una solución de [(S)-3,3-difluoro-1-((S)-1-{hidroxi-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-il]-metil}-propilcarbamoil)-hexil]-amida del ácido morfolin-4-carboxílico (61 mg, 0,10 mmol) en cloruro de metileno seco (8 ml) y se agitó a temperatura ambiente durante 3 horas. Se sofocó la reacción con una solución de $Na_2S_2O_3$ (81,43 mg, 0,50 mmol) en $NaHCO_3$ acuoso. Se separó la capa orgánica y se extrajo la capa acuosa con diclorometano. Los extractos orgánicos se secaron sobre sulfato de sodio y se concentraron a presión reducida. Por cromatografía en columna sobre sílice eluyendo con una mezcla de cloruro de metileno y acetato de etilo se obtuvo la ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico como un polvo blanco (39 mg).

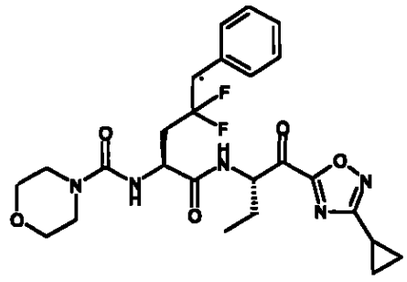
^{1}H NMR ($CDCl_3$): δ 8,25 (d, J=7,5Hz, 2H), 7,60 (d, J=7,5Hz, 1H), 7,42 (d, J=7,5Hz, 2H), 5,36 (m, 1H), 5,16 (d, J=7,5Hz, 1H), 4,70 (m, 1H), 3,74 (m, 4H), 3,42 (m, 4H), 2,54-2,32 (m, 2H),

2,28-2,14 (m, 1H), 2,02-1,80 (m, 3H), 1,60-1,45 (m, 2H), 1,06 (t, J=7Hz, 3H), 0,96 (t, J=7Hz, 3H).

LC/MS: 96 %, 592 (M+1).

EJEMPLO 4

{(S)-1-[(S)-1-(3-Ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico



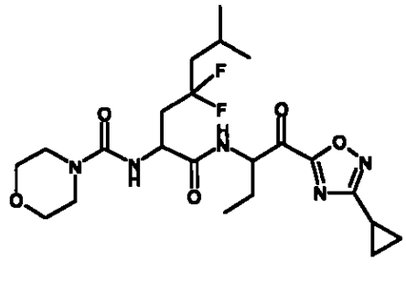
Procediendo de manera similar al Ejemplo 1 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico y (S)-2-amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol se preparó la {(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico.

^{1}H NMR ($CDCl_3$): δ 7,3 (m, 6H), 5,25 (m, 1H), 5,08 (d, J = 6,9 Hz, 1H), 4,7 (dd, J = 12,8, 7,4 Hz, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 3,2 (t, 16,8 Hz, 2H), 2,4-2,1 (m, 3H), 2,05 (m, 1H), 1,8 (m, 1H), 1,1 (m, 4H), 0,95 (t, J = 7,5 Hz, 3H);

LC/MS: 35 % 560 ($M+H_2O+Na$) y 65 % 542 (M+Na).

EJEMPLO 5

{1-[1-(3-Ciclopropil-[1,2,4]oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-5-metil-hexil}-amida del ácido morfolin-4-carboxílico

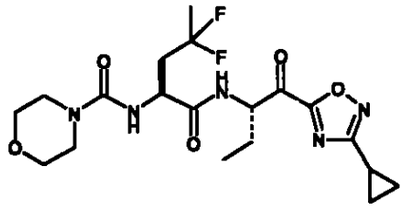


Procediendo de manera similar al Ejemplo 1 anterior pero utilizando ácido (S)-4,4-difluoro-6-metil-2-[(morfolin-4-carbonil)-amino]-heptanoico y (S)-2-amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol se preparó la {1-[1-(3-ciclopropil-[1,2,4]oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-5-metil-hexil}-amida del ácido morfolin-4-carboxílico

^{1}H NMR ($CDCl_3$): δ 7,6 (d, J = 6,8 Hz, 1H), 5,2 (m, 2H), 4,66 (dd, J = 13, 7,2 Hz, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 2,3 (m, 2H), 2,2 (m, 1H), 2,05 (m, 1H), 1,95 (m, 1H), 1,8 (m, 3H), 1,1 (m, 4H), 0,97 (d, J = 6,6 Hz, 6H), 0,96 (t, J = 7,4 Hz, 3H);
LC/MS: 26 %, 526 ($M+H_2O+Na$) y 74 %, 508 (M+Na).

EJEMPLO 6

{(S)-1-[(S)-1-(3-Ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico

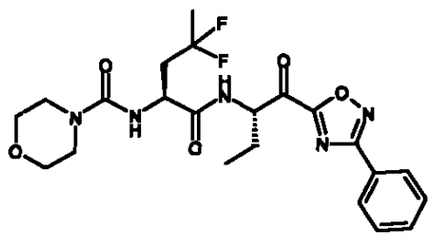


Procediendo de manera similar al Ejemplo 1 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-pentanoico y (S)-2-amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol se preparó la {(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico

^{1}H NMR ($CDCl_3$): δ 7,47 (d, J = 6,8 Hz, 1H), 5,3 (m, 1H), 5,16 (d, J = 6,9 Hz, 1H), 4,65 (dd, J = 13, 7,4 Hz, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 2,4 (m, 2H), 2,2 (m, 1H), 2,05 (m, 1H), 1,8 (m, 1H), 1,67 (t, 18,7 Hz, 3H), 1,1 (m, 4H), 0,97 (t, J = 7,5 Hz, 3H);
LC/MS: 37 % 484 ($M+H_2O+Na$) y 63 % 484 ($M+CH_3CN$).

EJEMPLO 7

{(S)-3,3-Difluoro-1-[(S)-1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico

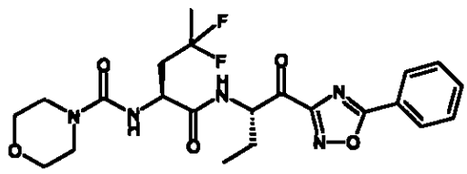


Procediendo de manera similar al Ejemplo 1 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-pentanoico y (S)-2-amino-1-(3-fenil-1,2,4-oxadiazol-5-il)-butan-1-ol se preparó la {(S)-3,3-difluoro-1-[(S)-1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico como un sólido ocre claro.

^{1}H NMR ($CDCl_3$): δ 8,15 (dd, J = 7,7, 1,5 Hz, 2H), 7,61 (d, J = 6,4 Hz, 1H), 7,5 (m, 3H), 5,35 (m, 1H), 5,2 (d, J = 6,9 Hz, 1H), 4,68 (dd, J = 13,2, 7,8 Hz, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 2,4 (m, 2H), 2,2 (m, 1H), 1,95 (m, 1H), 1,66 (t, 18,7 Hz, 3H), 1,03 (t, J = 7,5 Hz, 3H);
LC/MS: 37 % 520 ($M+H_2O+Na$) y 63 % 502 (M+Na).

EJEMPLO 8

{(S)-3,3-Difluoro-1-[(S)-1-(5-fenil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico

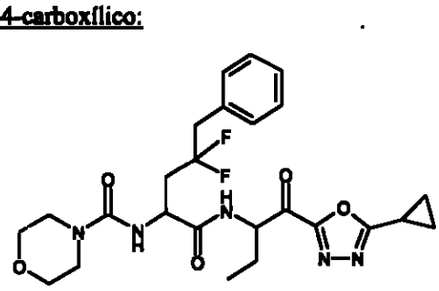


Procediendo de manera similar al Ejemplo 1 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-pentanoico y (S)-2-amino-1-(5-fenil-[1,2,4]oxadiazol-3-il)-butan-1-ol se preparó la {(S)-3,3-difluoro-1-[(S)-1-(5-fenil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico

^{1}H NMR ($CDCl_3$): δ 8,2 (d, J = 7,1 Hz, 2H), 7,65 (d, J = 7,4 Hz, 1H), 7,55 (m, 3H), 5,4 (dd, J = 12,2, 7 Hz, 1H), 5,3 (d, J = 7,4 Hz, 1H), 4,7 (dd, J = 13, 7,3 Hz, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 2,4 (m, 2H), 2,1 (m, 1H), 1,9 (m, 1H), 1,67 (t, 18,7 Hz, 3H), 1,0 (t, J = 7,4 Hz, 3H);
LC/MS: 6 % 520 ($M+H_2O+Na$) y 94 % 502 (M+Na).

EJEMPLO 9

{1-[1-(5-Ciclopropil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico:



Procediendo de manera similar al Ejemplo 1 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico y la sal de ácido trifluoro-acético

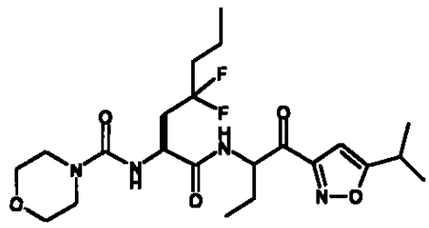
de (S)-2-amino-1-(5-ciclopropil-1,3,4-oxadiazol-2-il)-butan-1-ol, se preparó la {1-[1-(5-ciclopropil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico.

^{1}H NMR ($CDCl_3$): δ 7,3 (m, 6H), 5,27 (m, 1H), 5,0 (d, J = 7,0 Hz, 1H major), 4,95 (d, J = 7,3 Hz, 1H minor), 4,7 (m, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 3,2 (t, 16,3 Hz, 2H), 2,4-2,2 (m, 3H), 2,05 (m, 1H), 1,8 (m, 1H), 1,2 (m, 4H), 0,95 (t, J = 7,5 Hz, 3H);

LC/MS: 12 % 560 (M+H_2O+Na) y 83 % 542 (M+Na).

EJEMPLO 10

{3,3-Difluoro-1-[1-(5-isopropil-isoxazol-3-carbonil)-propilcarbamoil]-hexil}-amida del ácido morfolin-4-carboxílico:



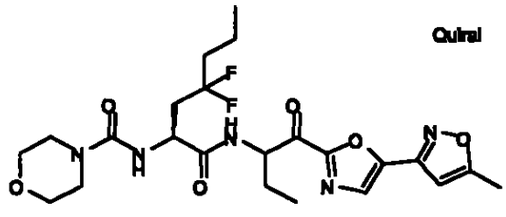
Procediendo de manera similar al Ejemplo 1 anterior pero utilizando hidrocloruro de 2-amino-1-(5-isopropil-isoxazol-3-il)-butan-1-ol en lugar de hidrocloruro de (S)-2-amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol se preparó la {3,3-difluoro-1-[1-(5-isopropil-isoxazol-3-carbonil)-propilcarbamoil]-hexil}-amida del ácido morfolin-4-carboxílico como un sólido blanco.

^{1}H NMR ($CDCl_3$): δ mezcla de isómeros aproximadamente 2:1 7,4 (b, 1H), 6,37 (s, 1H), 5,4 (m, 1H), 5,26 (d, J = 6,9 Hz, 1H major), 5,2 (d, J = 7,2 Hz, 1H minor), 4,7 (m, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 3,15 (m, 1H), 2,4 (m, 2H), 2,1 (m, 1H), 1,8 (m, 4H), 1,5 (m, 1H), 1,35 (d, J = 7,0 Hz, 6H), 0,95 (m, 6H);

LC/MS: 100 % 473 (M+1).

EJEMPLO 11

((S)-3,3-Difluoro-1-{1-[5-(5-metil-isoxazol-3-il)-oxazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico



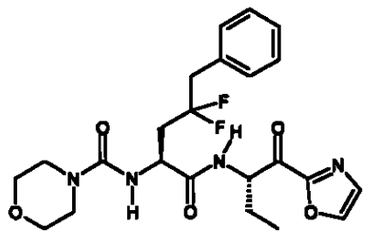
Procediendo de manera similar al Ejemplo 3 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico e hidrocloruro de (S)-2-amino-1-[5-(5-metil-isoxazol-3-il)-oxazol-2-il]-butan-1-ol, se preparó la {(S)-3,3-difluoro-1-{1-[5-(5-metil-isoxazol-3-il)-oxazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico como un sólido blanco.

^{1}H NMR ($CDCl_3$): δ 7,78 (s, 1H), 7,40 (m, 1H), 6,44 (s, 1H), 5,48 (m, 1H), 5,22-5,10 (m, 1H), 4,68 (m, 1H), 3,72 (m, 4H), 3,40 (m, 4H), 2,54 (s, 3H), 2,50-2,30 (m, 2H), 2,22-2,08 (m, 1H), 1,94-1,78 (m, 3H), 1,60-1,46 (m, 2H), 1,08-0,94 (2xt, 6H).

LC/MS: 99 %, 512 (M+1).

EJEMPLO 12

{(S)-3,3-Difluoro-1-[(S)-1-(oxazol-2-carbonil)-propilcarbamoil]-4-fenil-butil}-amida del ácido morfolin-4-carboxílico



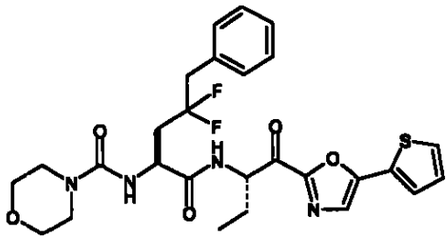
Procediendo de manera similar al Ejemplo 2 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico e hidrocloruro de (S)-2-amino-1-oxazol-2-il-butan-1-ol se preparó la {(S)-3,3-difluoro-1-[(S)-1-(oxazol-2-carbonil)-propicarbamoil]-4-fenil-butil}-amida del ácido morfolin-4-carboxílico

^{1}H NMR ($CDCl_3$): δ 7,86 (s, 1H), 7,37 (s, 1H), 7,30 (m, 5H), 7,24 (m, 1H), 5,45 (m, 1H), 5,08 (d, J = 9Hz, 1H), 4,70 (m, 1H), 3,72 (m, 4H), 3,38 (m, 4H), 3,22 (t, J= 17Hz, 2H), 2,35 (m, 2H), 2,12 (m, 1H), 1,85 (m, 1H), 0,95 (t, J= 9Hz, 3H);

LC/MS: 97 %, 479 (M+1).

EJEMPLO 13

{(S)-3,3-Difluoro-4-fenil-1-[(S)-1-(5-tiofen-2-il-oxazol-2-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico

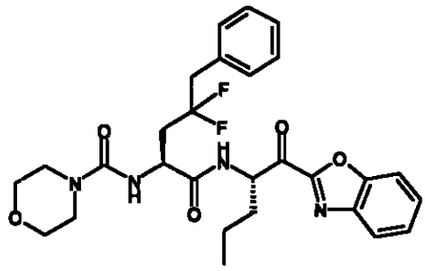


Procediendo de manera similar al Ejemplo 1 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico e hidrocloruro de (S)-2-amino-1-(5-tiofen-2-il-oxazol-2-il)-butan-1-ol se preparó la {(S)-3,3-difluoro-4-fenil-1-[(S)-1-(5-tiofen-2-il-oxazol-2-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico

^{1}H NMR ($CDCl_3$): δ 7,53 (dd, J = 3,6, 1 Hz, 1H), 7,48 (dd, J = 5, 1 Hz, 1H), 7,4 (s, 1H), 7,3 (m, 6H), 7,15 (dd, J = 5, 3,6 Hz, 1H), 5,4 (m, 1H), 5,15 (d, J = 7,1 Hz, 1H), 4,7 (dd, J = 13, 7,4 Hz, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 3,2 (t, 16,7 Hz, 2H), 2,4 (m, 2H), 2,1 (m, 1H), 1,8 (m, 1H), 0,96 (t, J = 7,5 Hz, 3H);
LC/MS: 100 % 561 (M+1).

EJEMPLO 14

{(S)-1-[(S)-1-(Benzoxazol-2-carbonil)-butilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico

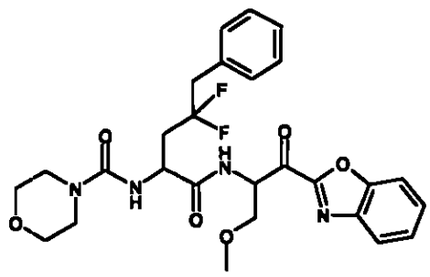


Procediendo de manera similar al Ejemplo 1 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico y (S)-2-amino-1-benzoxazol-2-il-pentan-1-ol se preparó la {(S)-1-[(S)-1-(benzoxazol-2-carbonil)-butilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico.

^{1}H NMR ($CDCl_3$): δ 7,9 (d, J = 8,0 Hz, 1H), 7,66 (d, J = 8 Hz, 1H), 7,56 (t, J = 7,2 Hz, 1H), 7,47 (t, J = 8 Hz, 1H), 7,2 (m, 6H), 5,6 (m, 1H), 5,05 (d, J = 7Hz, 1H), 4,71 (dd, J = 12,8, 7,4 Hz, 1H), 3,7 (m, 4H), 3,35 (m, 4H), 3,18 (t, J= 16,8 Hz, 2H), 2,3 (m, 2H), 2,1 (m, 1H), 1,8 (m, 1H), 1,4 (m, 2H), 0,94 (t, J= 7,3 Hz, 3H);
LC/MS: 100 % 543 (M+1).

EJEMPLO 15

[1-(2-Benzoxazol-2-il-1-metoximetil-2-oxo-etilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico



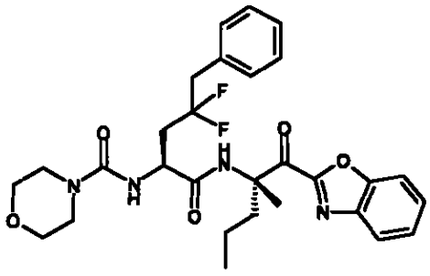
Procediendo de manera similar al Ejemplo 1 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico y (S)-2-amino-1-benzoxazol-2-il-3-metoxi-propan-1-ol se preparó la [1-(2-benzoxazol-2-il-1-metoximetil-2-oxo-etilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico.

^{1}H NMR ($CDCl_3$): δ 7,9 (d, J = 7,7 Hz, 1H), 7,67 (d, J = 8 Hz, 1H), 7,56 (t, J = 8 Hz, 1H), 7,48 (t, J = 8 Hz, 1H), 7,2 (m, 6H), 5,7 (m, 1H), 5,1 (d, J = 7 Hz, 1H major), 5,05 (d, J = 7,3 Hz, 1H minor), 4,8 (m, 1H), 4,26 (dd, J = 9,7, 3,5 Hz, 1H), 3,8 (m, 1H), 3,7 (m, 4H), 3,35 (m, 4H), 3,27 (s, 3H), 3,22 (t, J= 16,2 Hz, 2H), 2,4 (m, 2H);

LC/MS: 94 % 545 (M+1).

EJEMPLO 16

{(S)-1-[(S)-1-(Benzoxazol-2-carbonil)-1-metil-butilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico



Se agitó a temperatura ambiente durante la noche una mezcla de hidrocloruro de (S)-2-amino-1-benzoxazol-2-il-2-metil-pentan-1-ona (80,6 mg, 0,3 mmol), ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico (0,102 mg, 0,3 mmol), EDCI (69 mg, 0,36 mmol), HOBT (48,6 mg, 0,36 mmol) y diisopropil-etilamina (0,2 ml) en DMF. Se diluyó la mezcla de reacción con acetato de etilo, se lavó con HCl 1 N frío, $NaHCO_3$ saturado y después solución saturada de NaCl. Se secó la fase orgánica sobre sulfato de magnesio y se evaporó el disolvente a presión reducida para dar el producto crudo. Por purificación por cromatografía en columna de gel de sílice, eluyendo con mezcla de acetato de etilo y heptano se obtuvo la {(S)-1-

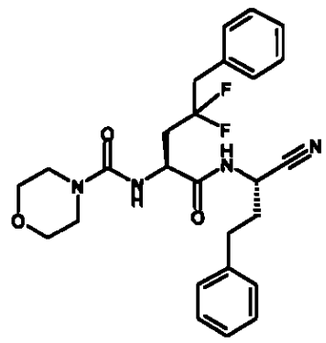
[(S)-1-(benzoxazol-2-carbonil)-1-metil-butilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico (82 %).

^{1}H NMR ($CDCl_3$): δ 7,8 (d, J = 7,8,0 Hz, 1H), 7,64 (d, J =7,8 Hz, 1H), 7,53 (dt, J = 7,2, 1,2 Hz, 1H), 7,43 (dt, J = 8, 1,2 Hz, 1H), 7,2 (m, 6H), 4,9 (d, J = 7,3 Hz, 1H), 4,65 (m, 1H), 3,7 (m, 4H), 3,3 (m, 4H), 3,1 (t, J= 16,8 Hz, 2H), 2,2 (m, 3H), 2,1 (m, 1H), 1,74 (s, 3H), 1,25 (m, 2H), 0,9 (t, J= 7,3 Hz, 3H);

LC/MS: 100 % 557 (M+1).

EJEMPLO 17

[(S)-1-((S)-1-Ciano-3-fenil-propilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico



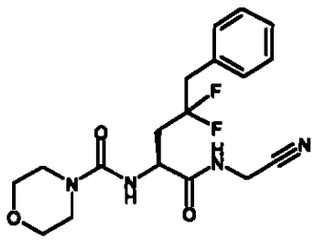
Procediendo según el método de acoplamiento de pyBOP dado en el Ejemplo 1, pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico e hidrocloruro de (S)-2-amino-4-fenil-butironitrilo, se preparó la [(S)-1-((S)-1-ciano-3-fenil-propilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico.

^{1}H NMR ($CDCl_3$): δ 7,9 (d, J = 7,6 Hz, 1H), 7,2 (m, 10H), 5,1 (d, J = 7,3 Hz, 1H), 4,6 (m, 2H), 3,6 (m, 4H), 3,3 (m, 4H), 3,2 (t, J = 16,5 Hz, 2H), 2,74 (t, J = 7,2 H, 2H), 2,3 (m, 2H), 2,1 (m, 2H);

LC/MS: 100 % 485 (M+1).

EJEMPLO 18

[(S)-1-(Cianometil-carbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico

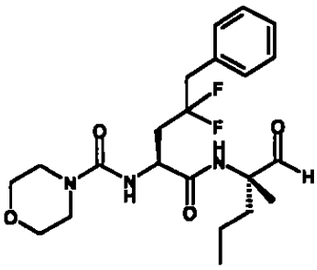


Procediendo según el método de acoplamiento de pyBOP dado en el Ejemplo 1, pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico e hidrocloruro de amino-acetonitrilo, se preparó la [(S)-1-(cianometil-carbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico.

^{1}H NMR ($CDCl_3$): δ 7,95 (b, 1H), 7,3 (m, 5H), 5,25 (d, J = 7,0 Hz, 1H), 4,7 (dd, J = 12,7, 7,2 Hz, 1H), 4,1 (m, 2H), 3,7 (m, 4H), 3,35 (m, 4H), 3,2 (t, J = 16,3 Hz, 2H), 2,4 (m, 2H); LC/MS: 83 % 403 (M+Na).

EJEMPLO 19

[(S)-3,3-Difluoro-1-((S)-1-formil-1-metil-butilcarbamoil)-4-fenil-butil]-amida del ácido morfolin-4-carboxílico



Se agitó a temperatura ambiente durante la noche una mezcla de hidrocloruro de (S)-2-amino-2-metil-pentan-1-ol (104,4 mg, 0,67 mmol), ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico (231 mg, 0,67 mmol), EDCI (154 mg, 0,8 mmol), HOBT (108 mg, 0,8 mmol) y diisopropil-etilamina (0,23 ml) en DMF (2 ml). Se diluyó la mezcla de reacción con acetato de etilo, se lavó con HCl 1 N frío, $NaHCO_3$ saturado y después solución saturada de NaCl. Se secó la fase orgánica sobre $MgSO_4$ y se evaporó el disolvente a presión reducida para dar el producto crudo. Por purificación por cromatografía en columna de gel de sílice, eluyendo con mezcla de acetato de etilo y heptano se obtuvo la [(S)-3,3-difluoro-1-((S)-1-hidroximetil-1-metil-butilcarbamoil)-4-fenil-butil]-amida del ácido morfolin-4-carboxílico (223 mg, 75 %).

Se agitó a temperatura ambiente durante 3 horas una mezcla de [(S)-3,3-difluoro-1-((S)-1-hidroximetil-1-metil-butilcarbamoil)-4-fenil-butil]-amida del ácido morfolin-4-carboxílico

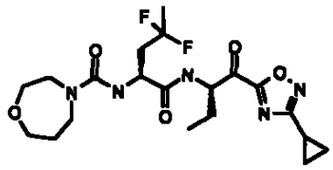
(217 mg) y peryodinano de Dess-Martin (al 15 % en DCM, 2 eq.) en DCM (5 ml) y se sofocó con una solución de tiosulfato de sodio en $NaHCO_3$ saturado. Se extrajo el producto con acetato de etilo y se lavó con solución saturada de NaCl. Se secó la fase orgánica sobre $MgSO_4$ anhidro, y se evaporó el disolvente a presión reducida. Por purificación por cromatografía en gel de sílice eluyendo con mezcla de acetato de etilo-heptano se obtuvo la [(S)-3,3-difluoro-1-((S)-1-formil-1-metil-butilcarbamoil)-4-fenil-butil]-amida del ácido morfolin-4-carboxílico (83 mg, 38 %).

^{1}H NMR ($CDCl_3$): δ 9,3 (s, 1H), 7,2 (m, 5H), 7,0 (s, 1H), 5,0 (d, J = 7 Hz, 1H), 4,64 (dd, J = 13, 7,3 Hz, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 3,2 (t, J= 16,5 Hz, 2H), 2,3 (m, 2H), 1,9 (m, 1H), 1,65 (m, 1H), 1,35 (s, 3H), 1,2 (m, 2H), 0,9 (t, J= 7,3 Hz, 3H);

LC/MS: 100 % 440, (M+1)

EJEMPLO 20

{(S)-1-[(S)-1-(3-Ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico



A una mezcla de ácido (S)-4,4-difluoro-2-[(perhidro-1,4-oxazepin-4-carbonil)-amino]-pentanoico (97 mg, 0,35 mmol), hidrocloruro de (S)-2-amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol (83 mg, 0,36 mmol) y diisopropiletil-amina (121 µL, 0,70 mmol) en diclorometano seco (12 ml) se añadió hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (66 mg, 0,35 mmol) e hidrato de 1-hidroxibenzotriazol (47 mg, 0,35 mmol). Se agitó la mezcla a temperatura ambiente durante 16 h después se diluyó con diclorometano (20 ml) y se lavó con HCl diluido (30 ml) y después con $NaHCO_3$ saturado (30 ml). Se secó (Na_2SO_4) la capa orgánica y se concentró en vacío. Se purificó el residuo sobre 12 g de gel de sílice, eluyendo con acetato de etilo: heptano (gradiente 50 - 100 %) para obtener la {(S)-1-{(S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-butil)-amida del ácido perhidro-1,4-oxazepin-4-carboxílico (120 mg, 75 %) como un sólido vítreo incoloro. LC/MS 100 % 460 (M+H).

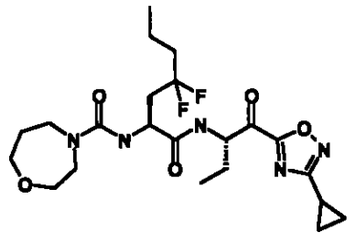
A una solución de ((S)-1-{(S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-butil)-amida del ácido perhidro-1,4-oxazepin-4-carboxílico (110 mg, 0,24 mmol) en diclorometano seco (20 ml) bajo N_2 se añadió peryodinano de Dess-Martin (143 mg, 0,34 mmol). Se agitó la reacción a temperatura ambiente durante 2 h, y después se añadió diclorometano (20 ml). Se sofocó la reacción con una solución de $Na_2S_2O_3$ (0,26 M, 2

ml) y se lavó con $NaHCO_3$ saturado (20 ml). Se extrajo la capa acuosa con diclorometano (2 x 30 ml). Las capas orgánicas se secaron (Na_2SO_4) y se concentraron en vacío. Se purificó el residuo sobre 12 g de gel de sílice, y se eluyó con acetato de etilo: heptano (gradiente 50-100 %) para obtener la {(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico (82 mg, 75 %) como un sólido blanco.

^{1}H NMR ($CDCl_3$) δ 7,52 (d, 6,2H), 5,28 (m, 1H), 5,05 (d, J = 7 Hz, 1H), 4,66 (m, 1H), 3,78 (m, 4H), 3,59 (m, 4H), 2,42 (m, 2H), 2,23 (m, 1H), 2,07 (m, 1H), 1,98 (m, 1H0, 1,85 (m, 1H), 1,69 (t, J = 18,8 Hz, 3H), 1,15 (m, 4H), 0,98 (t, J = 7,5Hz, 3H); LC/MS: 97 % 458 (M+H).

EJEMPLO 21

{(S)-1-[(S)-1-(3-Ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico



Procediendo de manera similar al Ejemplo 20 anterior pero utilizando ácido (S)-4,4-difluoro-2-{([1,4]oxazepan-4-carbonil)-amino}-heptanoico e hidrocloruro de (S)-2- amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol se preparó la {(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico (98 mg, 65 %) como un sólido blanco.

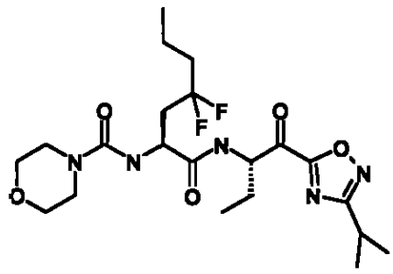
^{1}H NMR ($CDCl_3$) δ 7,6 (d, J=7,5 Hz, 1H), 5,25 (m, 1H), 5,10 (d, J=7,5 Hz, 1H), 4,65 (dd, J=14, J=7,5 Hz, 1H), 3,75 (m, 6H), 3,55 (m, 4H), 2,4 (m, 2H), 2,2 (m, 2H), 1,95 (m, 1H), 1,8 (m, 3H), 1,55 (m, 2H), 1,10 (m, 4H), 0,95 (t, J=7,5 Hz, 6H);

LC/MS: 70 % 486 (M+1) y 30 % 504 (M+1+H2O).

EJEMPLO 22

154

{(S)-1-[(S)-1-(3-Isopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico



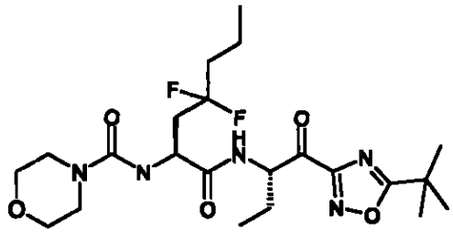
Procediendo de manera similar al Ejemplo 20 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico y (S)-2-amino-1-(3-isopropil-1,2,4-oxadiazol-5-il)-butan-1-ol se preparó la {(S)-1-[(S)-1-(3-isopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico (122 mg, 71 %) como un sólido blanco.

1H NMR (CDCl3) δ 7,5 (d, J=7,0 Hz, 1H), 5,3 (m,1H), 5,25 (d, J=7,0 Hz, 1H), 4,65 (dd, J=13, 7,0 Hz, 1H), 3,7 (m, 4H), 3,4 (m, 4H), 3,2 (m, 1H), 2,35 (m, 2H), 2,1 (m, 1H), 1,8 (m, 3H), 1,55 (m, 2H), 1,40 (d, J=7 Hz, 6H), 0,9 (t, J=7,0 Hz, 6H);

LC/MS: 72 % 474 (M+1) y 28 % 492 (M+1+H2O).

EJEMPLO 23

{(S)-1-[(S)-1-(5-*terc*-Butil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico



Una solución de ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico (175 mg, 0,60 mmol) en dimetilformamida (6 ml) se trató sucesivamente con (S)-2-amino-1-(5-*terc*-butil-1,2,4-oxadiazol-3-il)-butan-1-ol (240 mg, 1,13 mmol), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (226 mg, 0,59 mmol) y diisopropiletilamina (0,104 ml, 0,60 mmol). Se agitó la reacción a temperatura ambiente durante la noche. Se evaporó el disolvente bajo alto vacío. Se recogió el residuo en acetato de etilo y se lavó con ácido clorhídrico 1 N, solución acuosa saturada de bicarbonato y agua, se secó sobre Na_2SO_4 y se evaporó el disolvente a presión reducida. Se purificó el crudo sobre sílice rápida (columna de 10

g) eluyendo con una mezcla de acetato de etilo y heptano (2:1) para dar la ((S)-1-{(S)-1-[(5-*terc*-butil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-hexil)-amida del ácido morfolin-4-carboxílico como un aceite marrón (60 mg).

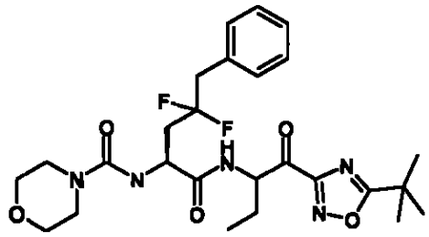
MS: 490 (M+H).

Una solución de ((S)-1-{(S)-1-[(5-*terc*-butil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-hexil)-amida del ácido morfolin-4-carboxílico (57 mg, 0,117 mmol) en cloruro de metileno (3 ml) se trató con peryodinano de Dess-Martin (59 mg, 0,139 mmol) y se agitó a temperatura ambiente durante 90 minutos. Se lavó la mezcla de reacción con una solución de $Na_2S_2O_3$ en agua (0,26 M), solución acuosa saturada de bicarbonato y agua, se secó sobre Na_2SO_4 y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía rápida eluyendo con una mezcla de acetato de etilo y heptano (1:1) para dar la {(S)-1-[(S)-1-(5-*terc*-butil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico como un sólido blanco-sucio (41 mg).

MS: 488 (M+H).

EJEMPLO 24

{(S)-1-[1-(5-*terc*-Butil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico



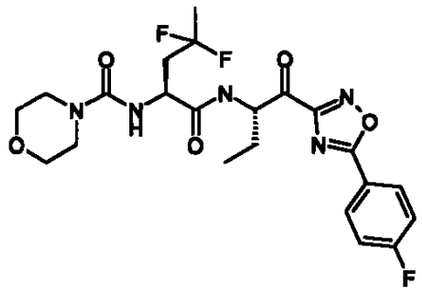
Procediendo de manera similar al Ejemplo 23 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico y (S)-2-amino-1-(5-*terc*-butil-1,2,4-oxadiazol-3-il)-butan-1-ol se preparó la {(S)-1-[1-(5-*terc*-butil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico como una mezcla 7:3 de diastereoisómeros.

^{1}H NMR ($CDCl_3$)δ: 7,36-7,19 (m, 5H), 7,15 (d, J=7,1Hz, 1H), 5,31 (m, 1H), 5,03 & 4,96 (2xd, J=7Hz, 1H), 4,68 (m, 1H), 3,76-3,59 (m, 4H), 3,45-3,26 (m, 4H), 3,18 (t, J=16,8Hz, 2H), 2,52-2,18 (m, 2H), 2,17-1,94 (m, 1H), 1,88-1,70 (m, 1H), 1,47 (s, 9H), 0,93 (t, J=7,4Hz, 3H).

MS: 536 (M+H).

EJEMPLO 25

((S)-3,3-Difluoro-1-{(S)-1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico



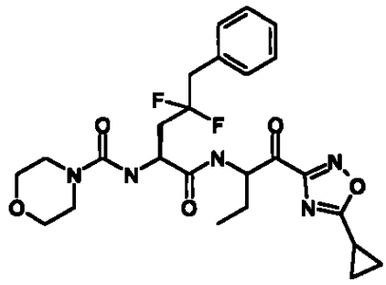
Procediendo de manera similar al Ejemplo 23 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-pentanoico y (S)-2-amino-1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-il]-butan-1-ol se preparó la {(S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico

^{1}H NMR ($CDCl_3$)δ: 8,21 (m, 2H), 7,31 (d, J=6,8Hz, 1H), 7,30-7,20 (m, 2H), 5,38 (m, 1H), 5,07 (d, J=6,8Hz, 1H), 4,63 (m, 1H), 3,75-3,64 (m, 4H), 3,44-3,33 (m, 4H), 2,58-2,28 (m, 2H), 2,22-2,04 (m, 1H), 1,96-1,79 (m, 1H), 1,66 (t, J=18,8Hz, 3H), 0,97 (t, J=7,4Hz, 3H).

MS: 498 (M+H).

EJEMPLO 26

{(S)-1-[1-(5-Ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico



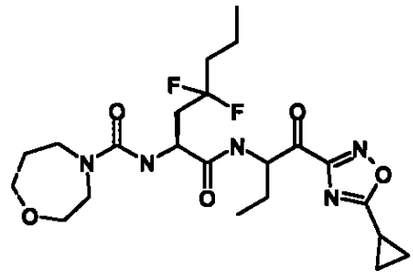
Procediendo de manera similar al Ejemplo 23 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoico y (S)-2-amino-1-(5-ciclopropil-1,2,4-oxadiazol-3-il)-butan-1-ol se preparó la {(S)-1-[1-(5-ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico como una mezcla 3:1 de diastereoisómeros.

^{1}H NMR ($CDCl_3$)δ: 7,36-7,20 (m, 5H), 7,14 (d, J=7,1Hz, 1H), 5,26 (m, 1H), 5,02 & 4,96 (2xd, J=7Hz, 1H), 4,70 (m, 1H), 3,73-3,61 (m, 4H), 3,43-3,28 (m, 4H), 3,18 (t, J=16,5Hz, 2H), 2,48-2,21 (m, 3H), 2,14-1,98 (m, 1H), 1,85-1,70 (m, 1H), 1,38-1,21 (m, 4H), 0,91 (t, J=7,5Hz, 3H).

MS: 520 (M+H).

EJEMPLO 27

{(S)-1-[1-(5-Ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico



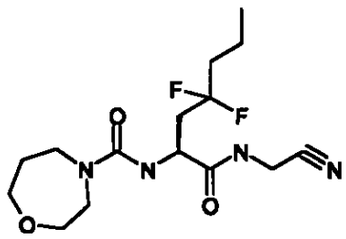
Procediendo de manera similar al Ejemplo 23 anterior pero utilizando ácido (S)-4,4-difluoro-2-[(perhidro-1,4-oxazepin-4-carbonil)-amino]-heptanoico y (S)-2-amino-1-(5-ciclopropil-1,2,4-oxadiazol-3-il)-butan-1-ol se preparó la {(S)-1-[1-(5-ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico como una mezcla 5:1 de diastereoisómeros.

^{1}H NMR ($CDCl_3$): 7,44 & 7,39 (2xd, J=7,3Hz, 1H), 5,30 (m, 1H), 5,05 & 4,98 (2xd, J=6,5Hz, 1H), 4,63 (m, 1H), 3,79-3,73 (m, 4H), 3,59-3,53 (m, 4H), 2,47-2,23 (m, 3H), 2,15-1,76 (m, 6H), 1,57-1,43 (m, 2H), 1,38-1,26 (m, 4H), 0,95 (t, J=7,3Hz, 3H), 0,93 (t, J=7,2Hz, 3H).

MS: 486 (M+H).

EJEMPLO 28

[(S)-1-(Cianometil-carbamoil)-3,3-difluoro-hexil]-amida de ácido perhidro-1,4-oxazepin-4-carboxílico



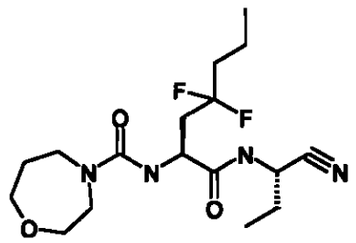
Se agitó durante 10 min una suspensión de carbodiimida unida a poliestireno (570 mg, 0,73 mmol) y ácido 4,4-difluoro-2-[([1,4]oxazepan-4-carbonil)-amino]-heptanoico (135 mg) en DCM (10 ml). Se añadió HOBT (60 mg) y se agitó durante 10 min. Se añadió una suspensión de hidrocloruro de amino-acetonitrilo (34 mg) y trietil-amina (52 µl) en DCM (5 ml) y se agitó durante la noche a temperatura ambiente. Se añadió PS-Trisamina (493 mg) y se agitó a temperatura ambiente durante 2 h 30 min. Después de filtración, se diluyó el filtrado con DCM, se lavó con agua, se evaporó a presión reducida y se purificó por cromatografía en columna eluyendo

con mezcla de acetato de etilo y heptano para dar la [(S)-1-(cianometil-carbamoil)-3,3-difluoro-hexil]-amida del ácido perhidro-1,4-oxazepin-4-carboxílico como un sólido blanco.

LCMS: 100 % 347 (M+H)

EJEMPLO 29

[(S)-1-((S)-1-Ciano-propilcarbamoil)-3,3-difluoro-hexil]-amida del ácido perhidro-1,4-oxazepin-4-carboxílico

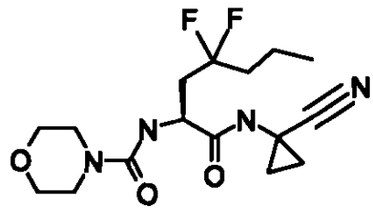


Procediendo de manera similar al Ejemplo 28 anterior pero utilizando ácido 4,4-difluoro-2-[([1,4]oxazepan-4-carbonil)-amino]-heptanoico e hidrocloruro de (S)-2-amino-butironitrilo se preparó la [(S)-1-((S)-1-ciano-propilcarbamoil)-3,3-difluoro-hexil]-amida del ácido perhidro-1,4-oxazepin-4-carboxílico.

LCMS: 100 % 375 (M+H).

EJEMPLO 30

[(S)-1-(1-Ciano-ciclopropilcarbamoil)-3,3-difluoro-hexil]-amida del ácido morfolin-4-carboxílico



Se preparó haciendo reaccionar ácido (S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-heptanoico e hidrocloruro de 1-amino-ciclopropanocarbonitrilo, utilizando TOTU como el agente de acoplamiento y diisopropil-etilamina como la base.

LCMS: 359 (M+H).

EJEMPLO 31

Ensayo de catepsina S

Se prepararon soluciones de los compuestos de ensayo con diferentes concentraciones en 10 µl de dimetilsulfóxido (DMSO) y después se diluyeron en tampón de ensayo (40 µl, que comprende: MES, 50 mM (pH 6,5); EDTA, 2,5 mM; y NaCl, 100 mM, DTT 0,5 mM, triton X-100 al 0,01 %).

Se añadió a las diluciones catepsina S humana (la concentración final en el pocillo es 1,74 nM). Se mezclaron las soluciones de ensayo durante 5-10 segundos en un plato agitador, se taparon y se incubaron durante 30 minutos a temperatura ambiente. Se añadió a las soluciones de ensayo Z-Val-Val-Arg-AMC (la concentración final en el pocillo es 0,08 mM) y la hidrólisis fue seguida espectrofotométricamente a (λ 460 nm) durante 5 minutos. Se calcularon las constantes de inhibición aparente (K_i) a partir de las curvas de progreso de la enzima utilizando modelos matemáticos estándar.

EJEMPLO 32

Ensayo de catepsina B

Se prepararon soluciones de los compuestos de ensayo con diferentes concentraciones en 10 ml de dimetilsulfóxido (DMSO) y después se diluyeron en tampón de ensayo (que comprende: MES 50 mM (pH 6); EDTA 2,5 mM, DMSO al 2 % y ditiotreitol (DTT), 2,5 mM).

Se añadió a las diluciones catepsina B humana (concentración final de 0,3 ng/µl). Se mezclaron las soluciones de ensayo durante 5-10 segundos en un plato agitador, se cubrieron y se incubaron durante 30 minutos a temperatura ambiente. Se añadió a las soluciones de ensayo Z-FR-pNa (concentración final de 100 µM) y la hidrólisis fue seguida espectrofotométricamente a (λ 405 nm) durante 60 minutos. Se calcularon las constantes de inhibición aparente (K_i) a partir de las curvas de progreso de la enzima utilizando modelos matemáticos estándar.

EJEMPLO 33

Ensayo de catepsina K

Se prepararon soluciones de los compuestos de ensayo con diferentes concentraciones en 10 µl de dimetilsulfóxido (DMSO) y después se diluyeron en tampón de ensayo (40 µl, que comprende: MES, 50 mM (pH 5,5); EDTA, 2,5 mM; y DTT, 2,5 mM). Se añadió a las diluciones catepsina K humana (0,0906 pmoles en 25 µl de tampón de ensayo). Se mezclaron las soluciones de ensayo durante 5-10 segundos en un plato agitador, se cubrieron y se incubaron durante 30 minutos a temperatura ambiente. Se añadió a las soluciones de ensayo Z-Phe-Arg-AMC (4 nmoles en 25 µl de tampón de ensayo) y la hidrólisis fue seguida espectrofotométricamente a (λ 460 nm) durante 5 minutos. Se calcularon las constantes de inhibición aparente (K_i) a partir de las curvas de progreso de la enzima utilizando modelos matemáticos estándar.

EJEMPLO 34

Ensayo de catepsina L

Se prepararon soluciones de los compuestos de ensayo con diferentes concentraciones en 10 µl de dimetilsulfóxido (DMSO) y después se diluyeron en tampón de ensayo (40 µl, que comprende: MES, 50 mM (pH 6); EDTA, 2,5 mM; y DTT, 2,5 mM). Se añadió a las diluciones catepsina L humana (10 µl de 0,2 ng/µl, concentración final de 0,02 ng/µl). Se mezclaron las

soluciones de ensayo durante 5-10 segundos en un plato agitador, se cubrieron y se incubaron durante 30 minutos a temperatura ambiente. Se añadió a las soluciones de ensayo Z-Phe-Arg-AMC (10 µl de 0,1 mM, concentración final de 10 µM) y la hidrólisis fue seguida espectrofotométricamente a (λ 460 nm) durante 30 minutos. Se calcularon las constantes de inhibición aparente (K_i) a partir de las curvas de progreso de la enzima utilizando modelos matemáticos estándar.

Los compuestos de la invención se analizaron según los ensayos descritos antes para la inhibición de la proteasa y se observó que presentaban una actividad inhibidora selectiva de la catepsina S. Las constantes de inhibición aparente (K_i) para los compuestos de la invención, frente a la catepsina S, estuvieron en el intervalo de aproximadamente 10^{-10} M a aproximadamente 10^{-7} M.

EJEMPLO 35

Formulaciones farmacéuticas representativas que contienen un compuesto de la fórmula (I):

FORMULACIÓN ORAL

Compuesto de la fórmula I,	10-100 mg
Ácido cítrico monohidratado	105 mg
Hidróxido de sodio	18 mg
Aromatizante	
Agua	c.s.p. 100 ml

FORMULACIÓN INTRAVENOSA

Compuesto de la fórmula I,	0,1-10 mg
Dextrosa monohidratada	c.s.p. hacer isotónica
Ácido cítrico monohidratado	1.05 mg
Hidróxido de sodio	0.18 mg
Agua para inyección	c.s. p. 1,0 ml

FORMULACIÓN EN COMPRIMIDOS

Compuesto de la fórmula I,	1 %
Celulosa microcristalina	73 %
Ácido esteárico	25 %
Sílice coloidal	1 %.

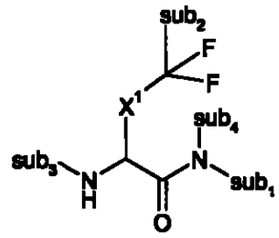
Aunque se han descrito y señalado nuevas características fundamentales de la invención aplicadas a una de sus realizaciones preferidas, se debe entender que se pueden hacer diferentes

omisiones y sustituciones y cambios, en la forma y detalles de la composición y métodos ilustrados, por los expertos en la técnica sin separarse del espíritu de la invención. Por ejemplo, se pretende expresamente que las sustituciones de radicales químicos y/o etapas del método, que realizan sustancialmente la misma función en sustancialmente la misma ruta para alcanzar los mismos resultados están dentro del alcance de la invención.

La invención no está limitada por las realizaciones descritas antes que se presentan solamente como ejemplos pero se pueden modificar de varias maneras dentro del alcance de protección definido por las reivindicaciones de patente anexas.

REIVINDICACIONES:

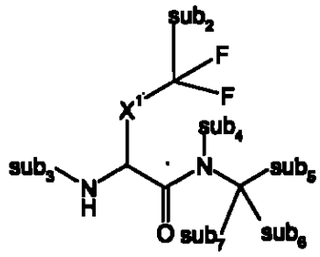
1. Un compuesto que tiene una estructura de cadena principal de la fórmula II:



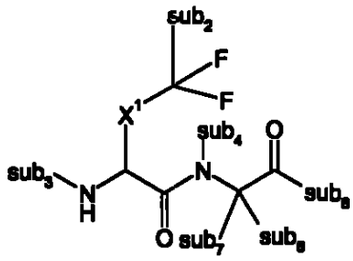
II

en la que X^1 es metileno, etileno o un enlace y sub_1-sub_4 son sustituyentes generales.

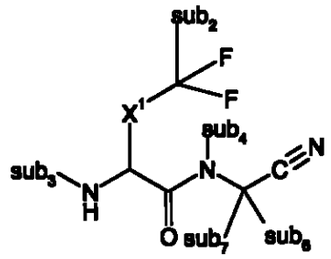
2. Un compuesto de la reivindicación 1, que tiene una estructura de cadena principal seleccionada del grupo que consiste en las fórmulas III, IV y V:



III



IV

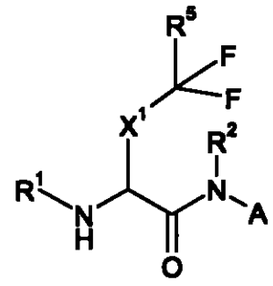


V

en las que X^1 es metileno, etileno o un enlace y sub_1-sub_8 son sustituyentes generales.

160
163

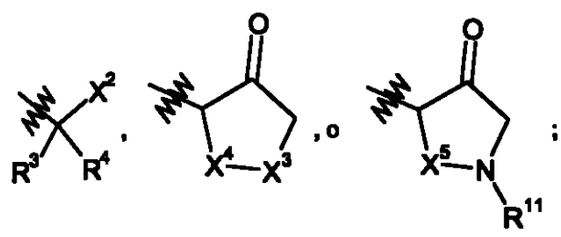
3. Un compuesto que tiene una estructura de la fórmula (I):



(I)

en la que

A es



X^1 es metileno, etileno o un enlace;

X^2 es CN, CHO, $C(O)R^6$, $C(O)C(O)NR^7R^7$, $C(O)C(O)NR^7R^8$, $C(O)C(O)R^{13}$, $C(O)C(O)OR^{13}$, $C(O)CH_2X^3R^{13}$;

X^3 se selecciona del grupo que consiste en O, $S(O)_n$, CO, CONH, NHCO, $NHSO_2$ y SO_2NH;

X^4 es $CH(R^{12})$ o $CH(R^{12})$-CH_2;

X^5 es metileno, etileno, propileno o un enlace;

X^6 es un enlace o alquileno (C_{1-2});

R^1 es H, $R^{13}C(O)$-, $R^{13}S(O)_2$-, $R^{13}OC(O)$- , $R^8R^7NC(O)$-, $R^8R^7NS(O)_2$-; $R^{13}S(O)_2NC(O)$- o $R^{13}C(O)NS(O)_2$-; o R^1 se selecciona del grupo que consiste en alquilo (C_{1-9}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}) y heteroaril (C_{5-13})-alquilo (C_{0-6}), cada uno de los cuales está opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$,

$-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^2 se selecciona del grupo que consiste en hidrógeno, alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}) o heteroaril (C_{5-12})-alquilo (C_{0-6});

R^3 se selecciona del grupo que consiste en H, alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}) o heteroaril (C_{5-13})-alquilo (C_{0-6}) opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^4 es H o alquilo (C_{1-6}); o R^3 y R^4 considerados junto con el átomo de carbono al cual ambos R^3 y R^4 están unidos, forman cicloalquileno (C_{3-8}) o heterocicloalquileno (C_{3-8});

R^5 es H, F, o R^5 es alquilo (C_{1-9}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{3-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}) cada uno opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^6 es arilo (C_{6-12}), heteroarilo (C_{5-13}) y alquilo (C_{1-6}) sustituido con halo; donde R^6 está opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-9}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}), ciano, halo, alquilo (C_{1-6}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^7 es H, alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{3-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}), y alquilo (C_{1-6}) sustituido con halo; donde R^7 está opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sus-

tituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$;

R^8 se selecciona del grupo que consiste en H, alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{3-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), y heteroaril (C_{5-13})-alquilo (C_{0-6}), o R^7 y R^8 junto con el átomo unido, forman cicloalquileno (C_{3-8}) o heterocicloalquileno (C_{3-8});

R^9 en cada aparición es independientemente hidrógeno, alquilo (C_{1-6}) o alquilo (C_{1-6}) sustituido con halo;

R^{10} es alquilo (C_{1-6}) o alquilo (C_{1-6}) sustituido con halo;

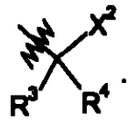
R^{11} se selecciona del grupo que consiste en hidrógeno, alquilo (C_{1-9}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{5-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}), bicicloaril (C_{9-12})-alquilo (C_{0-3}), heterobicicloaril (C_{8-12})-alquilo (C_{0-3}), $-C(O)R^{13}$, $-C(S)R^{13}$, $-S(O)_2R^{13}$, $-C(O)OR^{13}$, $-C(O)N(R^7)R^8$, $-C(S)N(R^7)R^8$ y $-S(O)_2N(R^7)R^8$;

R^{12} es H o alquilo C_{1-6} opcionalmente sustituido con amido, arilo (C_{6-12}), heteroarilo (C_{5-12}), heterocicloalquilo (C_{5-12}) o hidroxi;

R^{13} es alquilo (C_{1-6}), cicloalquil (C_{3-12})-alquilo (C_{0-6}), heterocicloalquil (C_{3-12})-alquilo (C_{0-6}), aril (C_{6-12})-alquilo (C_{0-6}), heteroaril (C_{5-13})-alquilo (C_{0-6}), y alquilo (C_{1-6}) sustituido con halo; donde R^{13} está opcionalmente sustituido con 1 a 5 radicales independientemente seleccionados de un grupo que consiste en alquilo (C_{1-4}), ciano, halo, alquilo (C_{1-4}) sustituido con halo, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ y $-X^6C(O)R^{10}$; y

n es cero o un número entero 1 ó 2;

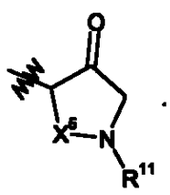
y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ia) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

4. Un compuesto según la reivindicación 3, en el cual A es  .

5. Un compuesto según la reivindicación 4, en el cual R^3 es H, aril (C_{6-12})-alquilo (C_{2-6}) o alquilo (C_{1-6}) opcionalmente sustituido con $-X^6OR^9$ donde X^6 es un enlace y R^9 es alquilo (C_{1-6}).

6. Un compuesto según las reivindicaciones 4 o 5, en el cual R^4 es H o alquilo (C_{1-6}).

7. Un compuesto según una cualquiera de las reivindicaciones 4-6, en el cual X^2 es CHO, CN o $C(O)R^6$ donde R^6 es heteroarilo (C_{5-13}) opcionalmente sustituido con alquilo (C_{1-9}), cicloalquilo (C_{3-12}), arilo (C_{6-12}) o heteroarilo (C_{5-13}).

8. Un compuesto según la reivindicación 3, en el cual A es  .

9. Un compuesto según la reivindicación 8, en el cual X^5 es propileno.

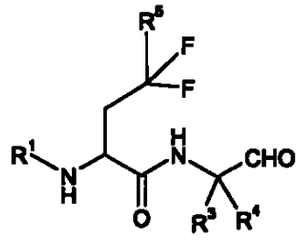
10. Un compuesto según las reivindicaciones 8 o 9, en el cual R^{11} es $-C(O)OR^{13}$ o $-S(O)_2R^{13}$ donde R^{13} es alquilo o arilo (C_{6-12}).

11. Un compuesto según una cualquiera de las reivindicaciones 2-10, en el cual R^1 es (i) $R^{13}C(O)$- donde R^{13} es heterocicloalquilo (C_{5-12}); (ii) $R^{13}OC(O)$- donde R^{13} es aril (C_{6-12})-alquilo (C_{1-6}); (iii) alquilo (C_{1-9}); o (iv) heterocicloalquilo (C_{5-12}).

12. Un compuesto según una cualquiera de las reivindicaciones 2-11, en el cual R^2 es H.

13. Un compuesto según una cualquiera de las reivindicaciones 2-12, en el cual R^5 es alquilo (C_{1-9}) o aril (C_{6-12})-alquilo (C_{1-6}).

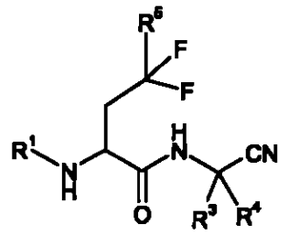
14. Un compuesto de la fórmula (Ia):



(Ia)

en la que R^1, R^3, R^4 y R^5 son como se han descrito antes en esta memoria, y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ia) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

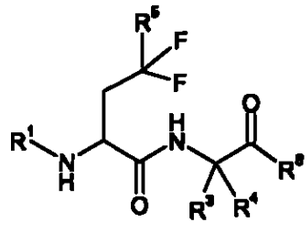
15. Un compuesto de la fórmula (Ib):



(Ib)

en la que R^1, R^3, R^4 y R^5 son como se han descrito antes en esta memoria, y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ib) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

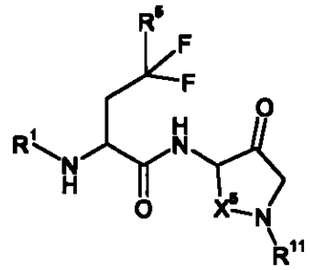
16. Un compuesto de la fórmula (Ic):



(Ic)

en la que R^1, R^3, R^4, R^5 y R^6 son como se han descrito antes en esta memoria, y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ic) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

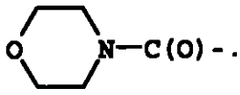
17. Un compuesto de la fórmula (Id):



(Id)

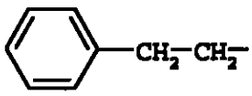
en la que R^1, R^5, R^{11} y X^5 son como se han descrito antes en esta memoria, y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Id) y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

18. Un compuesto según una cualquiera de las reivindicaciones 14-17, en el cual R^1 es $R^{13}C(O)$- donde R^{13} es heterocicloalquilo (C_{5-12}).

19. Un compuesto según la reivindicación 18, en el cual R^1 es  .

20. Un compuesto según una cualquiera de las reivindicaciones 14, 15, 18 o 19, en el cual R^3 es H, aril (C_{6-12})-alquilo (C_{1-6}) o alquilo (C_{1-6}).

21. Un compuesto según la reivindicación 20, en el cual R^3 es H,

 o $CH_3CH_2CH_2$-.

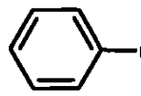
22. Un compuesto según una cualquiera de las reivindicaciones 16, 18 o 19, en el cual R^3 es alquilo (C_{1-6}) opcionalmente sustituido con $-X^6OR^9$ donde X^6 es un enlace y R^9 es alquilo (C_{1-6}).

23. Un compuesto según la reivindicación 22, en el cual R^3 es CH_3-CH_2-, $CH_3-CH_2-CH_2-$ o CH_3-O-CH_2-.

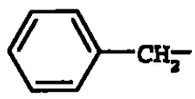
24. Un compuesto según una cualquiera de las reivindicaciones 14-16 y 18-23, en el cual R^4 es H o metilo.

25. Un compuesto según una cualquiera de las reivindicaciones 14, 15, 17, 18-21 y 24, en el cual R^5 es aril (C_{6-12})-alquilo (C_{1-6}).

165
159

26. Un compuesto según la reivindicación 25, en el cual R^5 es  .

27. Un compuesto según una cualquiera de las reivindicaciones 16, 18, 19 y 24, en el cual R^5 alquilo (C_{1-9}) o aril (C_{6-12})-alquilo (C_{1-6}).

28.Un compuesto según la reivindicación 25, en el cual R^5 es $CH_3CH_2CH_2$ o CH_3 CH_2 o CH_3 o  .

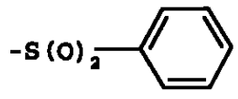
29. Un compuesto según las reivindicaciones 16, 18, 19, 24, 27 y 28, en el cual R^6 es heteroarilo (C_{5-13}), opcionalmente sustituido con alquilo (C_{1-9}), cicloalquilo (C_{3-12}), arilo (C_{6-12}) o heteroarilo (C_{5-13}).

30. Un compuesto según la reivindicación 29, en el cual R^6 es benzoxazolilo, oxadiazolilo, isoxazolilo, u oxazolilo cada uno opcionalmente sustituido con uno o más grupos sustituyentes arilo o alquilo.

31. Un compuesto según la reivindicación 30, en el cual R^6 es benzoxazol-2-ilo, 5-*terc*-butil-[1,2,4]oxadiazol-3-ilo, 3-ciclopropil-1,2,4-oxadiazol-5-ilo, 5-ciclopropil-1,2,4-oxadiazol-3-ilo, 5-ciclopropil-1,3,4-oxadiazol-2-ilo, 5-etil-1,3,4-oxadiazol-2-ilo, 5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-ilo, 5-isopropil-isoxazol-3-ilo, 5-(5-metil-isoxazol-3-il)-oxazol-2-ilo, 5-(5-metil-tien-2-il)-oxazol-2-ilo, oxazol-2-ilo, 3-fenil-1,2,4-oxadiazol-5-ilo, 5-fenil-1,2,4-oxadiazol-3-ilo, 5-tiofen-2-il-oxazol-2-ilo, 5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-ilo.

32. Un compuesto según la reivindicación 31, en el cual R^6 es benzoxazol-2-ilo, 3-ciclopropil-1,2,4-oxadiazol-5-ilo, oxazol-2-ilo, 5-ciclopropil-1,2,4-oxadiazol-3-ilo.

33. Un compuesto según la reivindicación 17, en el cual R^{11} es $-C(O)OR^{13}$ o $-S(O)_2R^{13}$ donde R^{13} es alquilo o arilo (C_{6-12}).

34. Un compuesto según la reivindicación 28, en el cual R^{11} es $-C(O)OC(CH_3)_3$ o  .

35. Un compuesto según la reivindicación 3, seleccionado del grupo que consiste en:
{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico;
{(S)-1-[(S)-1-(5-ciclopropil-1,3,4-oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluorometoxi-fenil)-1,3,4-oxadiazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

{1-[1-(3-ciclopropil-[1,2,4]oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-5-metil-hexil}-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-1-[(S)-1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-1-[(S)-1-(5-fenil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico;

{1-[1-(5-ciclopropil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

{3,3-difluoro-1-[1-(5-isopropil-isoxazol-3-carbonil)-propilcarbamoil]-hexil}-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{1-[5-(5-metil-isoxazol-3-il)-oxazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-1-[(S)-1-(oxazol-2-carbonil)-propilcarbamoil]-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-4-fenil-1-[(S)-1-(5-tiofen-2-il-oxazol-2-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(benzoxazol-2-carbonil)-butilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

[1-(2-benzoxazol-2-il-1-metoximetil-2-oxo-etilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(benzoxazol-2-carbonil)-1-metil-butilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

[(S)-1-((S)-1-ciano-3-fenil-propilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

[(S)-1-(cianometil-carbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

[(S)-3,3-difluoro-1-((S)-1-formil-1-metil-butilcarbamoil)-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

{(S)-1-[1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-

amida del ácido morfolin-4-carboxílico;

{(S)-1-[1-(5-*terc*-butil-[1,2,4]oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-3,3-difluoro-4-fenil-1-[(S)-1-(5-fenil-[1,2,4]oxadiazol-3-il)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico;

éster bencílico del ácido [(S)-1-(cianometil-carbamoil)-3,3-difluoro-4-fenil-butil]-carbámico;

cianometil-amida del ácido (S)-4,4-difluoro-5-fenil-2-(tetrahidro-piran-4-ilamino)-pentanoico;

cianometil-amida del ácido (S)-4,4-difluoro-2-isobutilamino-5-fenil-pentanoico;

[(S)-1-((S)-1-bencenosulfonil-3-oxo-azepan-4-ilcarbamoil)-3,3-difluoro-4-fenil-butil]-amida del ácido morfolin-4-carboxílico;

éster *terc*-butílico del ácido (S)-4-{(S)-4,4-difluoro-2-[(morfolin-4-carbonil)-amino]-5-fenil-pentanoilamino}-3-oxo-azepan-1-carboxílico;

((S)-1-{(S)-1-[(5-etil-1,3,4-oxadiazol-2-il)-hidroxi-metil]-propilcarbamoil}-3,3-difluoro-hexil)-amida del ácido morfolin-4-carboxílico;

{(S)-1-[1-(5-ciclopropil-1,3,4-oxadiazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico;

{(S)-1-[1-(5-ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(R)-1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico;

{(S)-1-[(S)-1-(benzoxazol-2-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico;

[(S)-1-(cianometil-carbamoil)-3,3-difluoro-hexil]-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(R)-1-[5-(5-metil-tiofen-2-il)-oxazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico;

((S)-3,3-difluoro-1-{(S)-1-[5-(5-metil-tiofen-2-il)-oxazol-2-carbonil]-propilcarbamoil}-hexil)-amida del ácido morfolin-4-carboxílico;

y sus correspondientes *N*-óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ia) y sus *N*-óxidos y sus

profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

36. Una composición farmacéutica que comprende un compuesto de la reivindicación 2 y un excipiente farmacéuticamente aceptable.

37. Un método para inhibir la catepsina S en un paciente en el que la elevación de la actividad enzimática de la catepsina S contribuye a las condiciones patológicas de dicho paciente, administrando a dicho paciente una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 2.

38. El uso de un compuesto según la reivindicación 3, en la fabricación de un medicamento para el tratamiento de un paciente que padece, o está sujeto a padecer, enfermedades que se pueden mejorar por la administración del compuesto como un inhibidor de la catepsina S.

39. El uso de un compuesto según la reivindicación 35, en la fabricación de un medicamento para el tratamiento de un paciente que padece, o está sujeto a padecer, enfermedades que se pueden mejorar por la administración del compuesto como un inhibidor de la catepsina S.

40. El uso de un compuesto según la reivindicación 3, en la fabricación de un medicamento para el tratamiento de un paciente que padece, o está sujeto a padecer, enfermedades que se pueden mejorar por la administración del compuesto como un inhibidor de la catepsina B.

41. El uso de un compuesto según la reivindicación 3, en la fabricación de un medicamento para el tratamiento de un paciente que padece, o está sujeto a padecer, enfermedades que se pueden mejorar por la administración del compuesto como un inhibidor de la catepsina K.

42. El uso según una cualquiera de las reivindicaciones 38 a 41, de uno de los siguientes compuestos:

{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico,

{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico,

{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido morfolin-4-carboxílico, o

{(S)-3,3-difluoro-1-[(S)-1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-butil}-amida del ácido morfolin-4-carboxílico,

y sus correspondientes N óxidos, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos; y las sales y solvatos (por ejemplo hidratos) farmacéuticamente aceptables de dichos compuestos de la fórmula (Ia) y sus N-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos.

para la producción de productos farmacéuticos que inhiben la actividad enzimática de las catepsinas S, K, o B.

43. El uso según la reivindicación 42, para tratar el dolor, la osteoartritis, la osteoporosis o el cáncer tal como cáncer de pulmón, leucemia (células B- y T-, aguda), cáncer de ovario, sarcomas, sarcoma de kaposi, cáncer de intestino, cáncer de nódulos linfáticos, tumor cerebral, cáncer de mama, cáncer de páncreas, cáncer de próstata o cáncer de piel.

44. Un método para tratar a un paciente que padece una enfermedad o condición médica que implica niveles elevados de catepsina S, siendo seleccionada dicha enfermedad o condición médica de artritis, ateroesclerosis, enfisema, osteoporosis, dolor, distrofia muscular, inflamación, esclerosis múltiple, enfermedad del intestino irritable, artritis reumatoide, asma, respuestas autoinmunes, enfermedad pulmonar obstructiva crónica, y bronquiolitis, que comprende administrar a dicho paciente una cantidad eficaz inhibidora de la catepsina S de un compuesto según la reivindicación 3.

45. Un método para tratar a un paciente que padece una enfermedad o condición médica que implica niveles elevados de catepsina K o B, siendo seleccionada dicha enfermedad o condición médica de osteoartritis, osteoporosis o cáncer tal como cáncer de pulmón, leucemia (células B- y T-, aguda), cáncer de ovario, sarcomas, sarcoma de kaposi, cáncer de intestino, cáncer de nódulos linfáticos, tumor cerebral, cáncer de mama, cáncer de páncreas, cáncer de próstata, y cáncer de piel, que comprende administrar a dicho paciente una cantidad eficaz inhibidora de la catepsina K o B de un compuesto según la reivindicación 3.

46. Un método para tratar a un paciente que padece una enfermedad o condición médica que implica niveles elevados de cisteína-proteasa, siendo seleccionada dicha enfermedad o condición médica de artritis, ateroesclerosis, enfisema, osteoporosis, distrofia muscular, inflamación, invasión tumoral, glomerulonefritis, enfermedad periodontal, leucodistrofia metacromática, diabetes de aparición juvenil, esclerosis múltiple, pénfigo vulgar, enfermedad de Graves, miastenia grave, lupus eritematoso sistémico, enfermedad del intestino irritable, artritis reumatoide y tiroiditis de Hashimoto, asma, respuestas autoinmunes, enfermedad pulmonar obstructiva crónica, y bronquiolitis, que comprende administrar a dicho paciente una cantidad eficaz inhibidora de la cisteína-proteasa de un compuesto según la reivindicación 3.

47. Un método para tratar a un paciente que padece una enfermedad o condición médica que implica niveles elevados de catepsina K o B, siendo seleccionada dicha enfermedad o condición médica de dolor, osteoartritis, osteoporosis o cáncer tal como cáncer de pulmón, leucemia (células B- y T-, agua), cáncer de ovario, sarcomas, sarcoma de kaposi, cáncer de intestino, cáncer de nódulos linfáticos, tumor cerebral, cáncer de mama, cáncer de páncreas, cáncer de

próstata, y cáncer de piel, que comprende administrar a dicho paciente una cantidad eficaz inhibidora de la catepsina K o B de un compuesto según la reivindicación 35.

48. Un método para tratar a un paciente que padece una enfermedad o condición médica que implica niveles elevados de cisteína-proteasa, siendo seleccionada dicha enfermedad o condición médica de dolor, osteoartritis, osteoporosis o cáncer tal como cáncer de pulmón, leucemia (células B- y T-, aguda), cáncer de ovario, sarcomas, sarcoma de kaposi, cáncer de intestino, cáncer de nódulos linfáticos, tumor cerebral, cáncer de mama, cáncer de páncreas, cáncer de próstata, y cáncer de piel, que comprende administrar a dicho paciente una cantidad eficaz inhibidora de la cisteína-proteasa de un compuesto según la reivindicación 42.

49. Un método para inhibir selectivamente la actividad de la catepsina K en un paciente con niveles elevados de catepsina K, que comprende administrar a un paciente que lo necesite una cantidad eficaz inhibidora de la catepsina K de un compuesto según la reivindicación 3.

50. Un método para inhibir selectivamente la actividad de la catepsina K en un paciente con niveles elevados de catepsina K, que comprende administrar a un paciente que lo necesite una cantidad eficaz inhibidora de la catepsina K de un compuesto según la reivindicación 42.

51. Un método para inhibir selectivamente la actividad de la catepsina S en un paciente con niveles elevados de catepsina S, que comprende administrar a un paciente que lo necesite una cantidad eficaz inhibidora de la catepsina S de un compuesto según la reivindicación 3.

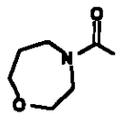
52. Un método para inhibir selectivamente la actividad de la catepsina S en un paciente con niveles elevados de catepsina S, que comprende administrar a un paciente que lo necesite una cantidad eficaz inhibidora de la catepsina S de un compuesto según la reivindicación 35.

51. Un método para inhibir selectivamente la actividad de la catepsina B en un paciente con niveles elevados de catepsina B, que comprende administrar a un paciente que lo necesite una cantidad eficaz inhibidora de la catepsina B de un compuesto según la reivindicación 3.

52. Un método para inhibir selectivamente la actividad de la catepsina B en un paciente con niveles elevados de catepsina B, que comprende administrar a un paciente que lo necesite una cantidad eficaz inhibidora de la catepsina B de un compuesto según la reivindicación 42.

53. Un método para tratar la osteoartritis en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto según la reivindicación 42.

54. Un compuesto según una cualquiera de las reivindicaciones 3-10, 12-18, o 20-30, en el que R^1 es



55. Un compuesto según la reivindicación 3, seleccionado del grupo que consiste en:
{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico,
{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida de ácido perhidro-1,4-oxazepin-4-carboxílicol;
{(S)-1-[(S)-1-(3-isopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico,
{(S)-1-[(S)-1-(5-*terc*-butil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico,
{(S)-1-[1-(5-*terc*-butil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico,
((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico,
{(S)-1-[1-(5-ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico,
{(S)-1-[1-(5-ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico,
[(S)-1-(cianometil-carbamoil)-3,3-difluoro-hexil]-amida del ácido perhidro-1,4-oxazepin-4-carboxílico,
[(S)-1-((S)-1-ciano-propilcarbamoil)-3,3-difluoro-hexil]-amida del ácido perhidro-1,4-oxazepin-4-carboxílico, y
[(S)-1-(1-ciano-ciclopropilcarbamoil)-3,3-difluoro-hexil]-amida del ácido morfolin-4-carboxílico.

56. El uso según una cualquiera de las reivindicaciones 41 a 42, de uno de los siguientes compuestos:
{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-butil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico,
{(S)-1-[(S)-1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida de ácido perhidro-1,4-oxazepin-4-carboxílicol;

{(S)-1-[(S)-1-(3-isopropil-1,2,4-oxadiazol-5-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico,

{(S)-1-[(S)-1-(5-*terc*-butil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido morfolin-4-carboxílico,

{(S)-1-[1-(5-*terc*-butil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico,

((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-fenil)-1,2,4-oxadiazol-3-carbonil]-propilcarbamoil}-butil)-amida del ácido morfolin-4-carboxílico,

{(S)-1-[1-(5-ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-4-fenil-butil}-amida del ácido morfolin-4-carboxílico,

{(S)-1-[1-(5-ciclopropil-1,2,4-oxadiazol-3-carbonil)-propilcarbamoil]-3,3-difluoro-hexil}-amida del ácido perhidro-1,4-oxazepin-4-carboxílico,

[(S)-1-(cianometil-carbamoil)-3,3-difluoro-hexil]-amida del ácido perhidro-1,4-oxazepin-4-carboxílico,

[(S)-1-((S)-1-ciano-propilcarbamoil)-3,3-difluoro-hexil]-amida del ácido perhidro-1,4-oxazepin-4-carboxílico, y

[(S)-1-(1-ciano-ciclopropilcarbamoil)-3,3-difluoro-hexil]-amida del ácido morfolin-4-carboxílico.

57. Un método para inhibir selectivamente la actividad de la catepsina K en un paciente con niveles elevados de catepsina K que comprende administrar a un paciente que lo necesite una cantidad eficaz inhibidora de la catepsina K de un compuesto según la reivindicación 55.

58. Un método para inhibir selectivamente la actividad de la catepsina S en un paciente con niveles elevados de catepsina S que comprende administrar a un paciente que lo necesite una cantidad eficaz inhibidora de la catepsina S de un compuesto según la reivindicación 55.

59. Un método para inhibir selectivamente la actividad de la catepsina B en un paciente con niveles elevados de catepsina B que comprende administrar a un paciente que lo necesite una cantidad eficaz inhibidora de la catepsina B de un compuesto según la reivindicación 55.

60. Un método para tratar la osteoartritis en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto según la reivindicación 55.

RESUMEN DE LA DESCRIPCIÓN

Nuevos inhibidores de las catepsinas S, K, B, y L, las sales y *N*-óxidos farmacéuticamente aceptables de los mismos, sus usos como agentes terapéuticos y los métodos para su preparación.

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PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)
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	US20030066WO
I	Title of invention	NOVEL KETO-OXADDIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	AVENTIS PHARMACEUTICALS INC.
II-5	Address	300 Somerset Corporate Boulevard Bridgewater, New Jersey 08807-2854 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	(908) 231-3800
II-9	Facsimile No.	(908) 231-2626
III-1	Applicant and/or inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	THURAIRATNAM, Sukanthini
III-1-5	Address	6 Smoke Rise Lane Bedminster, NJ 07921 United States of America
III-1-6	State of nationality	GB
III-1-7	State of residence	US

III-2	Applicant and/or inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	ALDOUS, David, John
III-2-5	Address	268 Gates Avenue Gillette, NJ 07933 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	LEROY, Vincent
III-3-5	Address	1 JFK Boulevard Franklin Greens Apt #36K Somerset, NJ 08873 United States of America
III-3-6	State of nationality	FR
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)	TIMM, Andreas, Paul
III-4-5	Address	97 Bonney Court Bridgewater, New Jersey 08807 United States of America
III-4-6	State of nationality	DE
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)	LIN, Jiang
IV-1-2	Address	Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
IV-1-3	Telephone No.	(908) 231-3582
IV-1-4	Facsimile No.	(908) 231-2626
IV-1-5	e-mail	jiang.lin@aventis.com
IV-1-6	Agent's registration No.	51065
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	BARNEY,Charlotte, L.(35060); BOLCSAK,James, W.(39912); COPPOLA,William, C.(41686); DAHLING,Gerald, V.(29632); DARKES,Paul, R.(33862); DOLAN,Peter, L.(46307); DUBBERLEY,F., Aaron(41001); GERMAN,Joel, B.(48676); GUPTA,Balaram(40009); KIRK,Joseph, P., Jr.(36844); KNIGHT,Julie, Anne(48867); KRUPEN,Karen, I.(34647); KURYS,Barbara, E.(34650); MARTIN,Lawrence, L.(46902); MOON,Carolyn, D.(33022); NELLIGAN,Mark, C.(36389); NEWMAN,Irving(22638); OEHLER,Ross, J.(33270); ORT,Ronald, G.(36969); PARKER,Raymond, S., III(34893); ROSSI,Joseph(47038); STRUPCZEWSKI,Joseph(50903)
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	24 October 2003 (24.10.2003)
VI-1-2	Number	60/514,373
VI-1-3	Country	US

VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	1	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

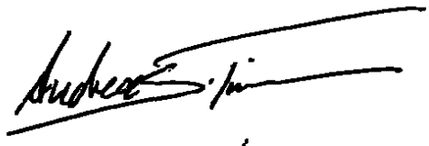
VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application AVENTIS PHARMACEUTICALS INC. is entitled to claim priority of earlier application No. 60/514,373 by virtue of the following:
VIII-3-1(iv)		an assignment from THURAIRATNAM, Sukanthini to AVENTIS PHARMACEUTICALS INC., dated 10 November 2003 (10.11.2003)
VIII-3-1(iv)		an assignment from ALDOUS, David, John to AVENTIS PHARMACEUTICALS INC., dated 07 November 2003 (07.11.2003)
VIII-3-1(iv)		an assignment from LEROY, Vincent to AVENTIS PHARMACEUTICALS INC., dated 10 November 2003 (10.11.2003)
VIII-3-1(iv)		an assignment from TIMM, Andreas, Paul to AVENTIS PHARMACEUTICALS INC., dated 10 November 2003 (10.11.2003)
VIII-3-1(ix)	This declaration is made for the purposes of:	all designations

VIII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) Declaration of inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to the international application of which it forms a part (if filing declaration with application). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	60/514,373, US, 24 October 2003 (24.10.2003)

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name (LAST, First)	THURAIRATNAM, Sukanthini
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Bedminster, United States of America
VIII-4-1-1-3	Mailing address:	6 Smoke Rise Lane Bedminster, NJ 07921 United States of America
VIII-4-1-1-4	Citizenship:	GB
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)	Sukanthini Thurairatnam
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)	6th December 2004

VIII-4-1-2-1	Name (LAST, First)	ALDOUS, David, John
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	Gillette,
VIII-4-1-2-3	Mailing address:	268 Gates Avenue Gillette, NJ 07933 United States of America
VIII-4-1-2-4	Citizenship:	US
VIII-4-1-2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	6th December 2004
VIII-4-1-3-1	Name (LAST, First)	LEROY, Vincent
VIII-4-1-3-2	Residence: (city and either US State, if applicable, or country)	Somerset,
VIII-4-1-3-3	Mailing address:	1 JFK Boulevard Franklin Greens Apt #36K Somerset, NJ 08873 United States of America
VIII-4-1-3-4	Citizenship:	FR
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)	

VIII-4-1-2-1	Name (LAST, First)	ALDOUS, David, John
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	Gillette,
VIII-4-1-2-3	Mailing address:	268 Gates Avenue Gillette, NJ 07933 United States of America
VIII-4-1-2-4	Citizenship:	US
VIII-4-1-2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-3-1	Name (LAST, First)	LEROY, Vincent
VIII-4-1-3-2	Residence: (city and either US State, if applicable, or country)	Somerset,
VIII-4-1-3-3	Mailing address:	1 JFK Boulevard Franklin Greens Apt #36K Somerset, NJ 08873 United States of America
VIII-4-1-3-4	Citizenship:	FR
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)	Dec. 13th, 2004

VIII-4-1-4-1	Name (LAST, First)	TIMM, Andreas, Paul
VIII-4-1-4-2	Residence: (city and either US State, if applicable, or country)	Bridgewater, New Jersey
VIII-4-1-4-3	Mailing address:	97 Bonney Court Bridgewater, NJ 08807 United States of America
VIII-4-1-4-4	Citizenship:	DE
VIII-4-1-4-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-4-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	6th December 2004

PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	10	✓
IX-2	Description	74	-
IX-3	Claims	16	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	101	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-SAFE physical media	-	✓
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)	LIN, Jiang	
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

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

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

US20030066WO

PCT POWER OF ATTORNEY

Paper Copy (NOT for submission)

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)

1	The undersigned applicant(s)	AVENTIS PHARMACEUTICALS INC.; THURAIRATNAM, Sukanthini; ALDOUS, David, John; LEROY, Vincent; TIMM, Andreas, Paul
1-1-1	hereby appoints (appoint) the following person	LIN, Jiang Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-2	hereby appoints (appoint) the following person	BARNEY, Charlotte, L. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-3	hereby appoints (appoint) the following person	BOLCSAK, James, W. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America.
1-1-4	hereby appoints (appoint) the following person	COPPOLA, William, C. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-5	hereby appoints (appoint) the following person	DAHLING, Gerald, V. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-6	hereby appoints (appoint) the following person	DARKES, Paul, R. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-7	hereby appoints (appoint) the following person	DOLAN, Peter, L. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-8	hereby appoints (appoint) the following person	DUBBERLEY, F., Aaron Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-9	hereby appoints (appoint) the following person	GERMAN, Joel, B. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-10	hereby appoints (appoint) the following person	GUPTA, Balaram Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America

PCT POWER OF ATTORNEY

Paper Copy (NOT for submission)

1-1-11	hereby appoints (appoint) the following person	KIRK, Joseph, P., Jr. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-12	hereby appoints (appoint) the following person	KNIGHT, Julie, Anne Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-13	hereby appoints (appoint) the following person	KRUPEN, Karen, I. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-14	hereby appoints (appoint) the following person	KURYS, Barbara, E. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-15	hereby appoints (appoint) the following person	MARTIN, Lawrence, L. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-16	hereby appoints (appoint) the following person	MOON, Carolyn, D. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-17	hereby appoints (appoint) the following person	NELLIGAN, Mark, C. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-18	hereby appoints (appoint) the following person	NEWMAN, Irving Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-19	hereby appoints (appoint) the following person	OEHLER, Ross, J. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-20	hereby appoints (appoint) the following person	ORT, Ronald, G. Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-21	hereby appoints (appoint) the following person	PARKER, Raymond, S., III Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America

PCT POWER OF ATTORNEY

Paper Copy (NOT for submission)

1-1-22	hereby appoints (appoint) the following person	ROSSI, Joseph Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-23	hereby appoints (appoint) the following person	STRUPCZEWSKI, Joseph Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	*Title of invention*	NOVEL KETO-OXADDIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS
1-4-2	Applicant's or agent's file reference	US20030066WO
1-4-3	International application number (if already available)	US04/35282
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned	

2-1	Signature of applicant, agent or common representative	
2-1-1	Name	AVENTIS PHARMACEUTICALS INC.
2-1-2	Name of signatory	Ross J. Oehler
2-1-3	Capacity	Vice President
2-2	Signature of applicant, agent or common representative	
2-2-1	Name (LAST, First)	THURAIRATNAM, Sukanthini
2-2-2	Name of signatory	
2-2-3	Capacity	
2-3	Signature of applicant, agent or common representative	
2-3-1	Name (LAST, First)	ALDOUS, David, John
2-3-2	Name of signatory	
2-3-3	Capacity	
2-4	Signature of applicant, agent or common representative	
2-4-1	Name (LAST, First)	LEROY, Vincent
2-4-2	Name of signatory	
2-4-3	Capacity	

PCT POWER OF ATTORNEY

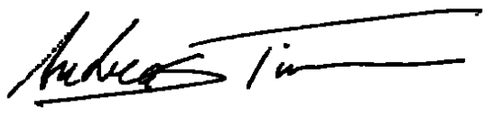
Paper Copy (NOT for submission)

1-1-22	hereby appoints (appoint) the following person	ROSSI, Joseph Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-1-23	hereby appoints (appoint) the following person	STRUPCZEWSKI, Joseph Aventis Pharmaceuticals Inc. Route 202-206 Bridgewater, NJ 08807 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of invention	NOVEL KETO-OXADDIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS
1-4-2	Applicant's or agent's file reference	US20030066WO
1-4-3	International application number (if already available)	US04/35282
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned	

2-1	Signature of applicant, agent or common representative	
2-1-1	Name	AVENTIS PHARMACEUTICALS INC.
2-1-2	Name of signatory	Ross J. Oehler
2-1-3	Capacity	Vice President
2-2	Signature of applicant, agent or common representative	
2-2-1	Name (LAST, First)	THURAIRATNAM, Sukanthini
2-2-2	Name of signatory	
2-2-3	Capacity	
2-3	Signature of applicant, agent or common representative	
2-3-1	Name (LAST, First)	ALDOUS, David, John
2-3-2	Name of signatory	
2-3-3	Capacity	
2-4	Signature of applicant, agent or common representative	Dec. 13th, 2004
2-4-1	Name (LAST, First)	LEROY, Vincent
2-4-2	Name of signatory	
2-4-3	Capacity	

PCT POWER OF ATTORNEY

Paper Copy (NOT for submission)

2-5	Signature of applicant, agent or common representative	
2-5-1	Name (LAST, First)	TIMM, Andreas, Paul
2-5-2	Name of signatory	
2-5-3	Capacity	
3	Date	22 October 2004 (22.10.2004)

PATENT COOPERATION TREAT

PCT

From the INTERNATIONAL BUREAU

To:

J. Rossi

195

LIN, Jiang
Aventis Pharmaceuticals Inc.
Route 202-206
Bridgewater, NJ 08807
ETATS-UNIS D'AMERIQUE

FIRST NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH DO NOT APPLY THE 30 MONTH/TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

Date of mailing *(day/month/year)* 26 May 2005 (26.05.2005)	
Applicant's or agent's file reference US20030066WO	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/035282	22 October 2004 (22.10.2004)	24 October 2003 (24.10.2003)

Applicant
AVENTIS PHARMACEUTICALS INC. et al

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does apply, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
06 May 2005 (06.05.2005)

   CH

   In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

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

   LU, SE, TZ, UG, ZM

   In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

   For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 20 MONTHS from the priority date.

   In practice, time limits other than the 20-month time limit will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

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

NO ACTION DUE file

DUE DATE —

DATED BY 06/2/05

AT J. Rossi

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Simin Baharlou
Facsimile No.+41 22 740 14 35	Facsimile No.+41 22 338 71 30

Form PCT/IB/308(First Notice) (January 2004)

PATENT CO PERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

AUG 2005
PATENT DEPT.

196

file

PCT

To:

ROSSI, Joseph
Aventis Pharmaceuticals Inc.
Route 202-206
Bridgewater, NJ 08807
ETATS-UNIS D'AMERIQUE

COMPUTER ENTERED
8/8/05

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)*	01-08-2005
Applicant's or agent's file reference: US20030066WO	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/035282	22/10/2004	24/10/2003

Applicant

AVENTIS PHARMACEUTICALS INC.

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

21/07/2005

2. This date of receipt is:

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

- [ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on: _____

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

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	CHURCHER G Tel. (+49-89) 2399-2545

Europäisches Patentamt · European Patent Office · Office européen des brevets

Form PCT/IPEA/402 (April 2002; reprint January 2004) (27/07/2005)

IN THE PCT
EUROPEAN PATENT OFFICE

In re the Application of:	Aventis Pharmaceuticals Inc.
International Appln. No.:	PCT/US2004/035282
International Filing Date:	22 October 2004 (22.10.2004)
Title:	NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS

TO: European Patent Office
Att: International Searching Authority (ISA/EP)
Erhardstr. 27
D-80331 Muenchen
Germany

REQUEST FOR THE RECTIFICATION OF OBVIOUS ERRORS
PURSUANT TO PCT RULE 91.1(b)

Applicants submit herewith replacement pages 1, 45, 46, 48, 49, 57, 66, 70, 71, 72, and 86 under Rule 91.1(b) prior to the expiration of 17 months from the filing date of the document from which the present patent application claims priority, *i.e.*, United States Provisional Patent Application Serial No. 60/514,373, filed 24 October 2003. An explanation of the amendment(s) found on each replacement page follows.

Applicants hereby submit a replacement sheet for page number 1 containing two amendments. The first is an amendment to the title wherein an obvious typographical error was corrected. In this regard, an extra "D" was removed from the word "OXADDIAZOLE" to yield the correctly spelled word --OXADIAZOLE--.

The second amendment to page number 1 is found at line 14, wherein the word --protease-- was added after the word "cysteine." This amendment is carried out to correct an obvious error. In this regard, Applicants respectfully submit that the skilled artisan would immediately realize that the word "cysteine" alone is incomplete and incorrect in the context in which it is used without the word "protease" to refer to the cysteine protease enzyme. Support for this amendment is also found at, for example, page 1, line 18. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 45 containing an amendment to line 26, wherein the chemical name "(S)-2-Amino-1-(5-p-tolyl-1,3,4-oxadiazol-

2-yl)-butan-1-ol" was replaced with the name --(S)-2-Amino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butan-1-ol--. This amendment was made to correct an obvious error in the name of the compound that is the subject of Reference 40 relative to its disclosed chemical structure. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 46 containing an amendment to lines 3-4, wherein the chemical name "(S)-2-Amino-1-(5-p-tolyl-1,3,4-oxadiazol-2-yl)-butan-1-ol" was replaced with the name --(S)-2-Amino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butan-1-ol--. This amendment was made to correct an obvious error in the name of the compound that is the subject of Reference 40 relative to its disclosed chemical structure. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 48 containing an amendment to line 21, wherein the chemical name "(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester" was replaced with the name --(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester--. This amendment was made to correct an obvious error in the name of the compound that is the subject of Reference 46 relative to its disclosed chemical structure. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 49 containing four (4) separate amendments. The first amendment is found on lines 4-5, wherein the chemical name "(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester" was replaced with the name --(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester--. This amendment was made to correct an obvious error in the name of the compound that is the subject of Reference 46 relative to its disclosed chemical structure. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

The second amendment made to the replacement sheet for page number 49 is found on line 7, wherein the chemical name "4,4-Difluoro-2-[([1,4]oxazepane-4-carbonyl)-amino]-heptanoic acid" was replaced with the name --(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid--. This amendment was made to correct an obvious error in the name of the compound that is the subject of Reference 47 relative to its disclosed chemical

structure. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

The third amendment made to the replacement sheet for page number 49 is found on lines 11-12, wherein the chemical name "4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester" was replaced with the name --(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester--. This amendment was made to correct an obvious error in the name of the compound that is the subject of Reference 47 relative to its disclosed chemical structure. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

The fourth amendment made to the replacement sheet for page number 49 is found on lines 12-13, wherein the chemical name "4,4-Difluoro-2-[([1,4]oxazepane-4-carbonyl)-amino]-heptanoic acid" was replaced with the name --(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid--. This amendment was made to correct an obvious error in the name of the compound that is the subject of Reference 47 relative to its disclosed chemical structure. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 57 containing an amendment to line 18, wherein the chemical name "(S)-4,4-dDifluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid" was replaced with the name --(S)-4,4-dDifluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid--. This amendment was made to correct an obvious typographical error in that there was an erroneous "d" before the "Difluoro" portion of the chemical name. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 66 containing an amendment to line 23, wherein the chemical name "(S)-4,4-difluoro-2-{([1,4]oxazepane-4-carbonyl)-amino}-heptanoic acid" was replaced with the name --(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid--. This amendment was made to correct an obvious error in the name of one of the starting materials used to make the compound that is the subject of Example 21 relative to the disclosed chemical structure of the compound. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 70 containing an amendment to lines 20-22, wherein the chemical name "4,4-Difluoro-2-[([1,4]oxazepane-4-

carbonyl)-amino]-heptanoic acid" was replaced with the name --(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid--. This amendment was made to correct an obvious error in the name of one of the starting materials used to make the compound that is the subject of Example 28 relative to the disclosed chemical structure of the compound. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 71 containing an amendment to line 13, wherein an obvious error was corrected. In this regard, the amendment was made to supply underlining that was obviously missing from the text. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 72 containing an amendment to line 16, wherein an obvious error resulting from a word processing program was corrected. In this regard, the amendment was made to replace the erroneous symbol "□" with the symbol --μ-- to correctly designate 10 microliters dimethyl sulfoxide (DMSO) used in the Example 32. This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants hereby submit a replacement sheet for page number 86 containing an amendment to line 30, wherein an obvious error was corrected. In this regard, the amendment was made to replace add the letter --m-- to the term "muscular dystrophy." This amendment has no effect on the description and does not go beyond the disclosure in the international application as filed.

Applicants request entry of the foregoing amendments preliminary to publication and examination of the above-identified patent application.

Respectfully submitted,

Dated: January 26, 2005

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Attorney for Applicants

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NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS

FIELD OF THE INVENTION

This invention relates to the use of novel keto-oxadiazole derivatives for treating diseases associated with cysteine protease and, particularly, diseases associated with activity of cathepsin S, K, and B. This invention also relates to processes of making such compounds.

BACKGROUND OF THE INVENTION

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, for example, as a result of increased 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, atherosclerosis, emphysema, osteoporosis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, periodontal disease, metachromatic leukodystrophy and others.

An increase in cathepsin activity such as, for example, cathepsin S, contributes to the pathology and/or symptomatology of a number of diseases such as, for example, autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, irritable bowel disease, rheumatoid arthritis and Hashimoto's 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 is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsin S may be of use in treatment of systemic amyloidosis.

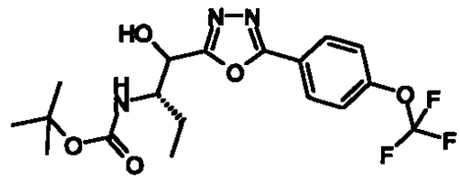
The combined reaction mixtures were filtered under suction and the resin washed with 300 ml ethyl acetate. The combined filtrates were concentrated under reduced pressure.

The crude product purified via flash chromatography (Biotage Horizon, 25M column, crude product loaded on caplet, 17 ml/min flow rate, 12 ml/fraction, 120 ml gradient from 0% ethyl acetate in heptane to 30 % ethyl acetate in heptane, 240 ml 30 % ethyl acetate in heptane, 60 ml gradient 30-50 % ethyl acetate in heptane, 300 ml 50 % ethyl acetate in heptane) to give acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester (0.28 g, 58 %)

MS: m/z= 460 ($M+H^+$)

REFERENCE 39

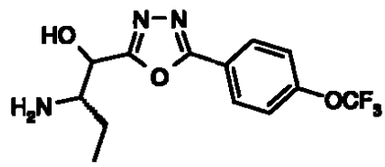
((S)-1-{Hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester



Acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester (0.61 mmol, 0.28 g) was dissolved in a mixture of THF (10 ml) and water (10 ml). Lithium hydroxide hydrate (1.22 mmol, 0.051 g) was added and the reaction mixture stirred for 2 h. The solvents were evaporated under reduced pressure and the residue transferred into a separating funnel with 300 ml ethyl acetate and 50 ml water. The phases were separated and the organic phase washed with brine (100 ml). The organic phase was then dried with magnesium sulfate. The solvent was evaporated under reduced pressure and dried under high vacuum to yield ((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester as yellow oil (0.225 g , 89 %) MS: m/z= 440 ($M+Na^+$), 418 ($M+H^+$)

REFERENCE 40

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

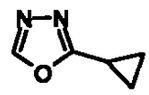


((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester (0.54 mmol, 0.225 g) was dissolved in dichloromethane (9 ml) and treated with trifluoroacetic acid (1 ml). The reaction mixture was stirred for four hours. The solvents were

evaporated under reduced pressure. The residue was re-dissolved in dichloromethane (20 ml) and Silicycle Triamine (5.4 mmol, 1.47 g) was added. The reaction mixture was stirred for 60 h (over the weekend). The reaction mixtures were filtered under suction and the solvents evaporated to give (S)-2-Amino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butan-1-ol (0.164 g, 96 %). MS: m/z= 318 ($M+H^+$)

REFERENCE 41

2-Cyclopropyl-[1,3,4]oxadiazole



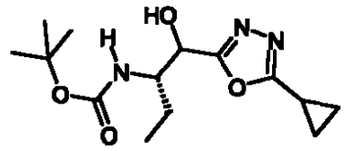
A mixture of cyclopropanecarboxylic acid methyl ester (10g, 0.1 mol) and hydrazine hydrate (7.3 mL, 0.15 mol) was refluxed for 28 hr and cooled to room temperature. The mixture was evaporated under reduced pressure and then dried by azeotropic removal of the solvent with toluene. The residue was dissolved in dichloromethane and washed with saturated NaCl. The organic phase was dried over anhydrous $MgSO_4$, solvent evaporated under reduced pressure to give cyclopropanecarboxylic acid hydrazide (4.36g, 44%)

A mixture of the Cyclopropanecarboxylic acid hydrazide (31.35g, 0.31 mol), trimethyl orthoformate (300 mL) and p-toluenesulfonic acid monohydrate (200 mg) was heated under reflux overnight. Excess trimethyl orthoformate and methanol were removed by distillation. Vacuum distillation of the residue afforded 2-Cyclopropyl-[1,3,4]oxadiazole (22g, 64%).

^1H NMR ($CDCl_3$): δ 8.24(s, 1H), 2.2 (m, 1H), 1.15 (m, 4H). LCMS: 100%, 111 (MH^+).

REFERENCE 42

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

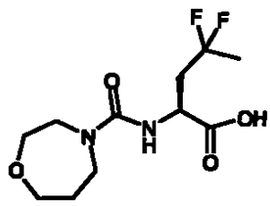


A solution of 2-cyclopropyl-[1,3,4]oxadiazole (2.16g, 19.6 mmol) in dry THF (100 mL) was cooled to –78°C. ^{n}BuLi (1.6M in hexanes, 12.3 mL, 19.6 mmol) was added dropwise. The reaction mixture was stirred at –78°C for 40 min. $MgBr_2.OEt_2$ (5.0692g, 19.6 mmol) was added: The reaction mixture was allowed to warm up to –45°C and stirred at that temperature for 1.5 hr. A solution of (1-formyl-propyl)-carbamic acid tert-butyl ester (3.7g, 19.6 mmol) in THF (40 mL) was added. The reaction mixture was allowed to warm up to –20°C and stirred at that temperature for 3.5 hrs. The reaction mixture was quenched with a solution of saturated NH_4Cl solution and extracted with ethyl acetate. Combined organic extracts was washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified by column chromatography

LC/MS: 295, 100%, (M+H), 317 (M+Na)

REFERENCE 45

(S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid



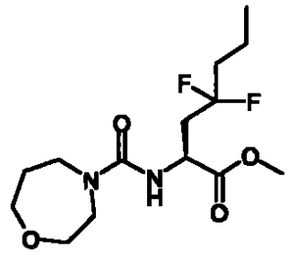
(S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid methyl ester (0.38g, 1.29mmol) was dissolved in tetrahydrofuran/methanol (15mL/10mL) and lithium hydroxide (35mg, 1.40mmol) dissolved in water (5mL) added. The reaction was stirred at RT for 18h, and then the methanol/tetrahydrofuran was removed in vacuo. The residue was acidified with 6M hydrochloric acid (0.25mL) and extracted with dichloromethane (3x 20 mL), dried (Na_2SO_4), and concentrated to yield (S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid as a white solid (0.36g, 99%).

^{1}H NMR (DMSO-d6) δ 12.6 (bs, 1H), 6.60 (d, 8.3 Hz, 1H), 4.30 (dd, J = 14.5, 7.0 Hz, 1H), 3.57 (m, 4H), 3.43 (m, 4H), 2.38 (m, 2H), 1.77 (m, 2H), 1.61 (t, J = 19.2Hz, 3H).

LC/MS: 100% 281 (M+H)

REFERENCE 46

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester



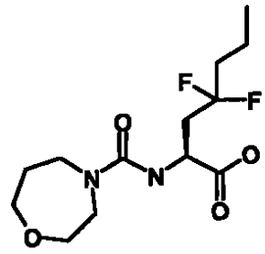
To a mixture of Sodium bicarbonate (5.25g), p-nitro chloroformate (5.03g, 25 mmol) in acetonitrile (130 ml) under nitrogen was added (S)-2-Amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride (5.79g, 0.025 mol) and stirred at room temperature for 5hr. Homomorpholine hydrochloride (3.61g, 26.25 mmol) and triethyl amine (12.5 ml) were added and the reaction stirred overnight at room temperature. Solvent evaporated off under reduced pressure, crude partitioned

between water (150 ml) and ethyl acetate (200 ml). Organic layer separated, washed with K_2CO_3 solution (150 ml), HCl (150 ml) and brine (150 ml). Organic layer separated, dried ($MgSO_4$) and evaporated under reduced pressure. Crude purified by column chromatography eluting with v/v 1:1 to 8:2 ethyl acetate heptane followed by ethyl acetate to give (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester (4.8g) as pale yellow oil.

LC/MS: 323 (M+H)

REFERENCE 47

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid

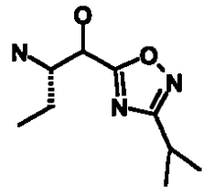


By proceeding in a similar manner to Reference Example 45 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester there was prepared (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid.

LC/MS: 309 (M+H)

REFERENCE 48

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



Similarly prepared according to the procedure for Reference Example 33.

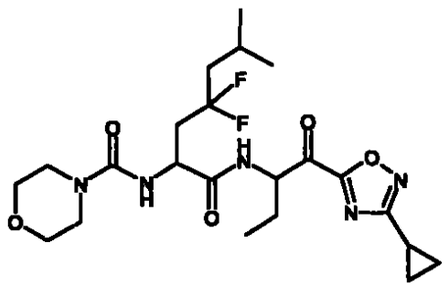
LCMS: 200 (M+H)

REFERENCE 49

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

EXAMPLE 5

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



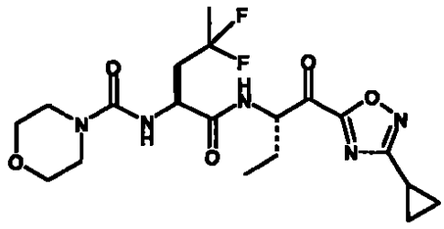
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared morpholine-4-carboxylic acid {1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-5-methyl-hexyl}-amide .

^{1}H NMR ($CDCl_3$): δ 7.6 (d, J = 6.8 Hz, 1H), 5.2 (m, 2H), 4.66 (dd, J = 13, 7.2 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.3 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.8 (m, 3H), 1.1 (m, 4H), 0.97 (d, J = 6.6 Hz, 6H), 0.96 (t, J = 7.4 Hz, 3H);

LC/MS: 26%, 526 (M+H_2O+Na) and 74%, 508 (M+Na).

EXAMPLE 6

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



By proceeding in a similar manner to Example 1 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide

^{1}H NMR ($CDCl_3$): δ 7.47 (d, J = 6.8 Hz, 1H), 5.3 (m, 1H), 5.16 (d, J = 6.9 Hz, 1H), 4.65 (dd, J = 13, 7.4 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.8 (m, 1H), 1.67 (t, 18.7 Hz, 3H), 1.1 (m, 4H), 0.97 (t, J = 7.5 Hz, 3H);

LC/MS: 37% 484 (M+H_2O+Na) and 63% 484 (M+CH_3CN).

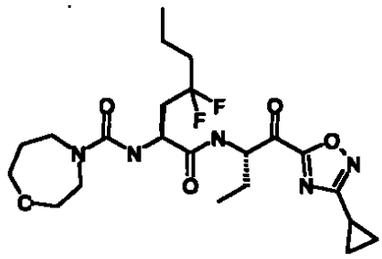
hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-butyl)-amide (120 mg, 75 %) as a colorless glassy solid. LC/MS 100% 460 (M+H).

To a solution of Perhydro-1, 4-oxazepine-4-carboxylic acid ((S)-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-butyl)-amide (110 mg, 0.24 mmol) in dry dichloromethane (20 mL) under N_2 was added Dess-Martin periodinane (143 mg, 0.34 mmol). The reaction was stirred at RT for 2 hr, and then dichloromethane (20 mL) was added. The reaction was quenched with a solution of $Na_2S_2O_3$ (0.26M, 2 mL) and washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuum. The residue was purified over 12 g silica gel, eluted with ethyl acetate: heptane (gradient 50-100%) to afford Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide (82 mg, 75%) as a white solid.

^{1}H NMR ($CDCl_3$) δ 7.52 (d, 6.2H), 5.28 (m, 1H), 5.05 (d, J = 7 Hz, 1H), 4.66 (m, 1H), 3.78 (m, 4H), 3.59 (m, 4H), 2.42 (m, 2H), 2.23 (m, 1H), 2.07 (m, 1H), 1.98 (m, 1H0, 1.85 (m, 1H), 1.69 (t, J = 18.8 Hz, 3H), 1.15 (m, 4H), 0.98 (t, J = 7.5Hz, 3H); LC/MS: 97% 458 (M+H).

EXAMPLE 21

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



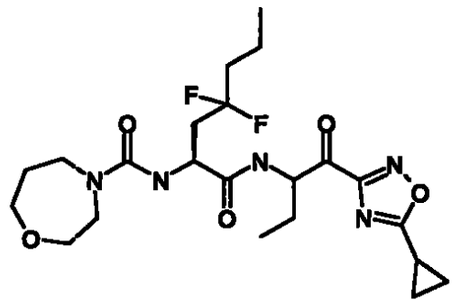
By proceeding in a similar manner Example 20 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid and (S) -2- amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide (98mg, 65%) as a white solid.

^{1}H NMR (CDCl3) δ 7.6 (d, J=7.5 Hz, 1H), 5.25 (m, 1H), 5.10 (d, J=7.5 Hz, 1H), 4.65 (dd, J=14, J=7.5 Hz, 1H), 3.75 (m, 6H), 3.55 (m, 4H), 2.4 (m, 2H), 2.2 (m, 2H), 1.95 (m, 1H), 1.8 (m, 3H), 1.55 (m, 2H), 1.10 (m, 4H), 0.95 (t, J=7.5 Hz, 6H);

LC/MS: 70% 486 (M+1) and 30% 504 (M+1+H2O).

EXAMPLE 27

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



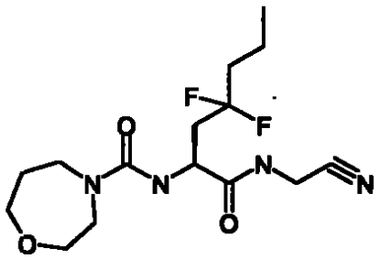
By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid and (S)-2-Amino-1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-butan-1-ol there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide as 5:1 mixture of diastereoisomers.

^{1}H NMR ($CDCl_3$) : 7.44 & 7.39 (2xd, J=7.3Hz, 1H), 5.30 (m, 1H), 5.05 & 4.98 (2xd, J=6.5Hz, 1H), 4.63 (m, 1H), 3.79-3.73 (m, 4H), 3.59-3.53 (m, 4H), 2.47-2.23 (m, 3H), 2.15-1.76 (m, 6H), 1.57-1.43 (m, 2H), 1.38-1.26 (m, 4H), 0.95 (t, J=7.3Hz, 3H), 0.93 (t, J=7.2Hz, 3H).

MS : 486 (M+H).

EXAMPLE 28

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide

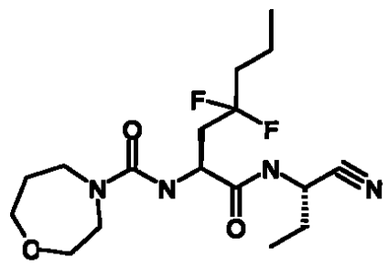


A suspension of Polystyrene bound carbodiimide (570mg, 0.73 mmol) and 4,4-Difluoro-2-[([1,4]oxazepane-4-carbonyl)-amino]-heptanoic acid (135 mg) in DCM (10 ml) stirred for 10 min. HOBT (60mg) added, stirred for 10 min. A suspension of amino acetonitrile hydrochloride (34 mg) and triethyl amine (52 uL) in DCM (5ml) added and stirred overnight at room temperature. PS-Trisamine (493 mg) added and stirred at room temperature for 2h 30 min. After filtration, filtrate

diluted with DCM, washed with water, evaporated under reduced pressure and purified by column chromatography eluting with ethyl acetate heptane mixture to give Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide as white solid.
LCMS : 100% 347 (M+H)

EXAMPLE 29

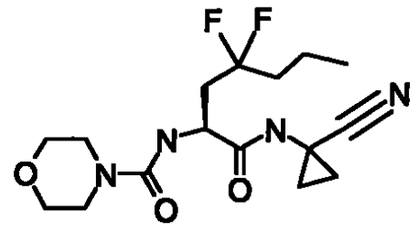
Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide



By proceeding in a similar manner to Example 28 above but using 4,4-Difluoro-2-[([1,4]oxazepane-4-carbonyl)-amino]-heptanoic acid and (S)-2-Amino-butyronitrile hydrochloride there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide.
LCMS : 100% 375 (M+H).

EXAMPLE 30

Morpholine-4-carboxylic acid [(S)-1-(1-cyano-cyclopropylcarbamoyl)-3,3-difluoro-hexyl]-amide



Prepared by reacting (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and 1-Amino-cyclopropanecarbonitrile hydrochloride, using TOTU as the coupling agent and diisopropyl ethylamine as the base.
LCMS : 359 (M+H)

EXAMPLE 31

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM, 0.5 mM DTT, 0.01% triton X-100).

Human cathepsin S (final concentration in the well is 1.74 nM) 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 (final concentration in the well is 0.08 mM) 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 32

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 □L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (comprising: MES 50 mM (pH 6); 2.5 mM EDTA , 2% DMSO and dithiothreitol (DTT), 2.5 mM).

Human cathepsin B (final concentration of 0.3 ng/μl) 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-pNa (final concentration of 100 μM) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 405nm) for 60 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 33

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μL 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 μL 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.

40. Use of a compound according to claim 3, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin B.

41. Use of a compound according to claim 3, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin K.

42. The use according to any one of claims 38 to 41 of one of the following compounds:
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide,
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide,
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide or
morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide
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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof
for the production of pharmaceuticals that inhibit the enzymatic activity of Cathepsin S, K, or B.

43. The use according to claim 42 for treating pain, osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer or skin cancer.

44. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin S, such disease or medical condition being selected from arthritis, atherosclerosis, emphysema, osteoporosis, pain, uscular dystrophy, inflammation, multiple sclerosis, irritable bowel disease, rheumatoid arthritis, asthma, autoimmune responses, chronic obstructive pulmonary disease, and bronchiolitis, comprising administering to said patient an effective cathepsin S inhibiting amount of a compound according to claim 3.

45. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin K or B, such disease or medical condition being selected from

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF DECISION CONCERNING
REQUEST FOR RECTIFICATION

(PCT Rule 91.1(f))

To:
AVENTIS PHARMACEUTICALS INC.
Attn. Lin, Jiang
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807
UNITED STATES OF AMERICA

Date of mailing (day/month/year): 08/02/2005

Applicant's or agent's file reference: US20030066WO

REPLY DUE: NONE
However, see last paragraph below

International application N°.: PCT/US2004/035282

International filing date (day/month/year): 22/10/2004

Applicant: AVENTIS PHARMACEUTICALS INC.

The applicant is hereby notified that this International Searching Authority has considered the request for rectification of obvious errors in the International application/in other papers submitted by the applicant to this Authority, and that it has decided:

1. [X] to authorize the rectification:
   - [X] as requested by the applicant.
   - [ ] to the extent set forth below*:
2. [ ] to refuse to authorize the rectification or part of it for the following reasons*:

NO ACTION DUE fil
DUE DATE —
DKTD BY Jes 2/15/05
ATTY J. Rossi

A copy of this notification, together with a copy of the applicant's request for rectification, has been sent to the receiving Office and to the International Bureau.

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Authorized officer: Stefan Brell

Form PCT/ISA/217 (July 1998)

NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS

FIELD OF THE INVENTION

This invention relates to the use of novel keto-oxadiazole derivatives for treating diseases associated with cysteine protease and, particularly, diseases associated with activity of cathepsin S, K, and B. This invention also relates to processes of making such compounds.

BACKGROUND OF THE INVENTION

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, for example, as a result of increased 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, atherosclerosis, emphysema, osteoporosis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, periodontal disease, metachromatic leukodystrophy and others.

An increase in cathepsin activity such as, for example, cathepsin S, contributes to the pathology and/or symptomatology of a number of diseases such as, for example, autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, irritable bowel disease, rheumatoid arthritis and Hashimoto's 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 is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsin S may be of use in treatment of systemic amyloidosis.

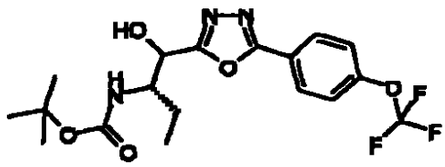
The combined reaction mixtures were filtered under suction and the resin washed with 300 ml ethyl acetate. The combined filtrates were concentrated under reduced pressure.

The crude product purified via flash chromatography (Biotage Horizon, 25M column, crude product loaded on caplet, 17 ml/min flow rate, 12 ml/fraction, 120 ml gradient from 0% ethyl acetate in heptane to 30 % ethyl acetate in heptane, 240 ml 30 % ethyl acetate in heptane, 60 ml gradient 30-50 % ethyl acetate in heptane, 300 ml 50 % ethyl acetate in heptane) to give acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester (0.28 g, 58 %)

MS: m/z= 460 ($M+H^+$)

REFERENCE 39

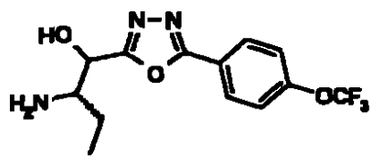
((S)-1-{Hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester



Acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester (0.61 mmol, 0.28 g) was dissolved in a mixture of THF (10 ml) and water (10 ml). Lithium hydroxide hydrate (1.22 mmol, 0.051 g) was added and the reaction mixture stirred for 2 h. The solvents were evaporated under reduced pressure and the residue transferred into a separating funnel with 300 ml ethyl acetate and 50 ml water. The phases were separated and the organic phase washed with brine (100 ml). The organic phase was then dried with magnesium sulfate. The solvent was evaporated under reduced pressure and dried under high vacuum to yield ((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester as yellow oil (0.225 g , 89 %) MS: m/z= 440 ($M+Na^+$), 418 ($M+H^+$)

REFERENCE 40

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

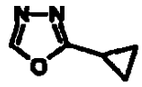


((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester (0.54 mmol, 0.225 g) was dissolved in dichloromethane (9 ml) and treated with trifluoroacetic acid (1 ml). The reaction mixture was stirred for four hours. The solvents were

evaporated under reduced pressure. The residue was re-dissolved in dichloromethane (20 ml) and Silicycle Triamine (5.4 mmol, 1.47 g) was added. The reaction mixture was stirred for 60 h (over the weekend). The reaction mixtures were filtered under suction and the solvents evaporated to give (S)-2-Amino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butan-1-ol (0.164 g, 96 %). MS: m/z= 318 ($M+H^+$)

REFERENCE 41

2-Cyclopropyl-[1,3,4]oxadiazole



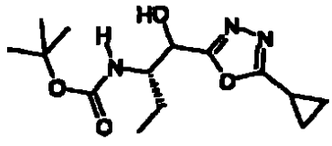
A mixture of cyclopropanecarboxylic acid methyl ester (10g, 0.1 mol) and hydrazine hydrate (7.3 mL, 0.15 mol) was refluxed for 28 hr and cooled to room temperature. The mixture was evaporated under reduced pressure and then dried by azeotropic removal of the solvent with toluene. The residue was dissolved in dichloromethane and washed with saturated NaCl. The organic phase was dried over anhydrous $MgSO_4$, solvent evaporated under reduced pressure to give cyclopropanecarboxylic acid hydrazide (4.36g, 44%)

A mixture of the Cyclopropanecarboxylic acid hydrazide (31.35g, 0.31 mol), trimethyl orthoformate (300 mL) and p-toluenesulfonic acid monohydrate (200 mg) was heated under reflux overnight. Excess trimethyl orthoformate and methanol were removed by distillation. Vacuum distillation of the residue afforded 2-Cyclopropyl-[1,3,4]oxadiazole (22g, 64%).

^1H NMR ($CDCl_3$): δ 8.24(s, 1H), 2.2 (m, 1H), 1.15 (m, 4H). LCMS: 100%, 111 (MH^+).

REFERENCE 42

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

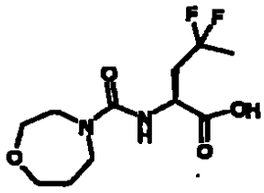


A solution of 2-cyclopropyl-[1,3,4]oxadiazole (2.16g, 19.6 mmol) in dry THF (100 mL) was cooled to –78°C. ^nBuLi (1.6M in hexanes, 12.3 mL, 19.6 mmol) was added dropwise. The reaction mixture was stirred at –78°C for 40 min. $MgBr_2.OEt_2$ (5.0692g, 19.6 mmol) was added. The reaction mixture was allowed to warm up to –45°C and stirred at that temperature for 1.5 hr. A solution of (1-formyl-propyl)-carbamic acid tert-butyl ester (3.7g, 19.6 mmol) in THF (40 mL) was added. The reaction mixture was allowed to warm up to –20°C and stirred at that temperature for 3.5 hrs. The reaction mixture was quenched with a solution of saturated NH_4Cl solution and extracted with ethyl acetate. Combined organic extracts was washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified by column chromatography

LC/MS: 295, 100%, (M+H), 317 (M+Na)

REFERENCE 45

(S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid



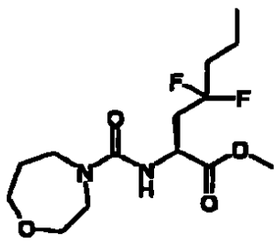
(S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid methyl ester (0.38g, 1.29mmol) was dissolved in tetrahydrofuran/methanol (15mL/10mL) and lithium hydroxide (35mg, 1.40mmol) dissolved in water (5mL) added. The reaction was stirred at RT for 18h, and then the methanol/tetrahydrofuran was removed in vacuo. The residue was acidified with 6M hydrochloric acid (0.25mL) and extracted with dichloromethane (3x 20 mL), dried (Na_2SO_4), and concentrated to yield (S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid as a white solid (0.36g, 99%).

^{1}H NMR (DMSO-d6) δ 12.6 (bs, 1H), 6.60 (d, 8.3 Hz, 1H), 4.30 (dd, J = 14.5, 7.0 Hz, 1H), 3.57 (m, 4H), 3.43 (m, 4H), 2.38 (m, 2H), 1.77 (m, 2H), 1.61 (t, J = 19.2Hz, 3H).

LC/MS: 100% 281 (M+H)

REFERENCE 46

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester



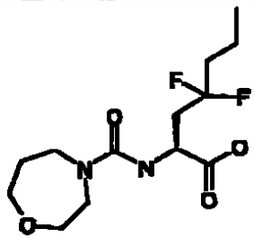
To a mixture of Sodium bicarbonate (5.25g), p-nitro chloroformate (5.03g, 25 mmol) in acetonitrile (130 ml) under nitrogen was added (S)-2-Amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride (5.79g, 0.025 mol) and stirred at room temperature for 5hr. Homomorpholine hydrochloride (3.61g, 26.25 mmol) and triethyl amine (12.5 ml) were added and the reaction stirred overnight at room temperature. Solvent evaporated off under reduced pressure, crude partitioned

between water (150 ml) and ethyl acetate (200 ml). Organic layer separated, washed with K_2CO_3 solution (150 ml), HCl (150 ml) and brine (150 ml). Organic layer separated, dried ($MgSO_4$) and evaporated under reduced pressure. Crude purified by column chromatography eluting with v/v 1:1 to 8:2 ethyl acetate heptane followed by ethyl acetate to give (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester (4.8g) as pale yellow oil.

LC/MS: 323 (M+H)

REFERENCE 47

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid

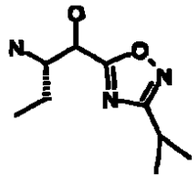


By proceeding in a similar manner to Reference Example 45 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester there was prepared (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid.

LC/MS: 309 (M+H)

REFERENCE 48

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



Similarly prepared according to the procedure for Reference Example 33.

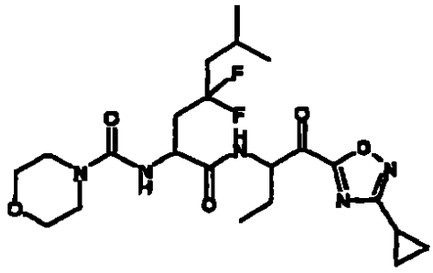
LCMS: 200 (M+H)

REFERENCE 49

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

EXAMPLE 5

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



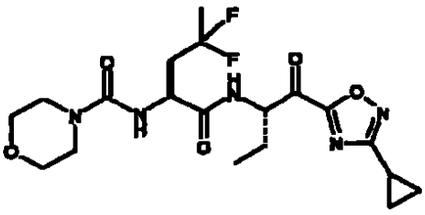
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared morpholine-4-carboxylic acid {1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-5-methyl-hexyl}-amide

^{1}H NMR ($CDCl_3$): δ 7.6 (d, J = 6.8 Hz, 1H), 5.2 (m, 2H), 4.66 (dd, J = 13, 7.2 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.3 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.8 (m, 3H), 1.1 (m, 4H), 0.97 (d, J = 6.6 Hz, 6H), 0.96 (t, J = 7.4 Hz, 3H);

LC/MS: 26%, 526 (M+H_2O+Na) and 74%, 508 (M+Na).

EXAMPLE 6

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



By proceeding in a similar manner to Example 1 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide

^{1}H NMR ($CDCl_3$): δ 7.47 (d, J = 6.8 Hz, 1H), 5.3 (m, 1H), 5.16 (d, J = 6.9 Hz, 1H), 4.65 (dd, J = 13, 7.4 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.8 (m, 1H), 1.67 (t, 18.7 Hz, 3H), 1.1 (m, 4H), 0.97 (t, J = 7.5 Hz, 3H);

LC/MS: 37% 484 (M+H_2O+Na) and 63% 484 (M+CH_3CN).

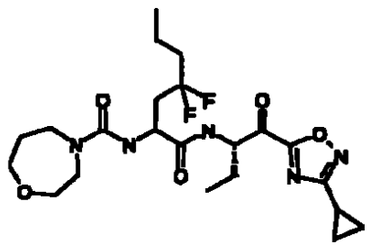
hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-butyl)-amide (120 mg, 75 %) as a colorless glassy solid. LC/MS 100% 460 (M+H).

To a solution of Perhydro-1, 4-oxazepine-4-carboxylic acid ((S)-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-butyl)-amide (110 mg, 0.24 mmol) in dry dichloromethane (20 mL) under N_2 was added Dess-Martin periodinane (143 mg, 0.34 mmol). The reaction was stirred at RT for 2 hr, and then dichloromethane (20 mL) was added. The reaction was quenched with a solution of $Na_2S_2O_3$ (0.26M, 2 mL) and washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuum. The residue was purified over 12 g silica gel, eluted with ethyl acetate: heptane (gradient 50-100%) to afford Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide (82 mg, 75%) as a white solid.

^{1}H NMR ($CDCl_3$) δ 7.52 (d, 6.2H), 5.28 (m, 1H), 5.05 (d, J = 7 Hz, 1H), 4.66 (m, 1H), 3.78 (m, 4H), 3.59 (m, 4H), 2.42 (m, 2H), 2.23 (m, 1H), 2.07 (m, 1H), 1.98 (m, 1H0, 1.85 (m, 1H), 1.69 (t, J = 18.8 Hz, 3H), 1.15 (m, 4H), 0.98 (t, J = 7.5Hz, 3H); LC/MS: 97% 458 (M+H).

EXAMPLE 21

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



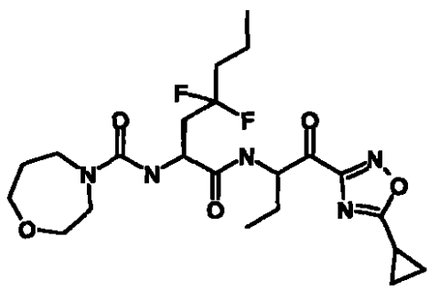
By proceeding in a similar manner Example 20 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid and (S) -2- amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide (98mg, 65%) as a white solid.

^{1}H NMR (CDCl3) δ 7.6 (d, J=7.5 Hz, 1H), 5.25 (m, 1H), 5.10 (d, J=7.5 Hz, 1H), 4.65 (dd, J=14, J=7.5 Hz, 1H), 3.75 (m, 6H), 3.55 (m, 4H), 2.4 (m, 2H), 2.2 (m, 2H), 1.95 (m, 1H), 1.8 (m, 3H), 1.55 (m, 2H), 1.10 (m, 4H), 0.95 (t, J=7.5 Hz, 6H);

LC/MS: 70% 486 (M+1) and 30% 504 (M+1+H2O).

EXAMPLE 27

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl]-amide



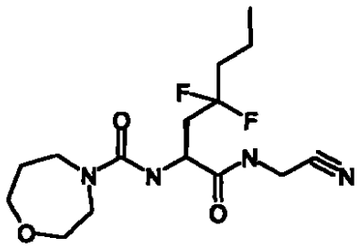
By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid and (S)-2-Amino-1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-butan-1-ol there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl]-amide as 5:1 mixture of diastereoisomers.

^{1}H NMR ($CDCl_3$) : 7.44 & 7.39 (2xd, J=7.3Hz, 1H), 5.30 (m, 1H), 5.05 & 4.98 (2xd, J=6.5Hz, 1H), 4.63 (m, 1H), 3.79-3.73 (m, 4H), 3.59-3.53 (m, 4H), 2.47-2.23 (m, 3H), 2.15-1.76 (m, 6H), 1.57-1.43 (m, 2H), 1.38-1.26 (m, 4H), 0.95 (t, J=7.3Hz, 3H), 0.93 (t, J=7.2Hz, 3H).

MS : 486 (M+H).

EXAMPLE 28

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide

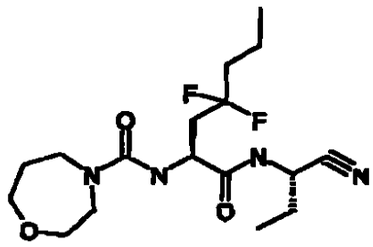


A suspension of Polystyrene bound carbodiimide (570mg, 0.73 mmol) and (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid (135 mg) in DCM (10 ml) stirred for 10 min. HOBT (60mg) added, stirred for 10 min. A suspension of amino acetonitrile hydrochloride (34 mg) and triethyl amine (52 uL) in DCM (5ml) added and stirred overnight at room temperature. PS-Trisamine (493 mg) added and stirred at room temperature for 2h 30 min. After filtration, filtrate

diluted with DCM, washed with water, evaporated under reduced pressure and purified by column chromatography eluting with ethyl acetate heptane mixture to give Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide as white solid.
LCMS : 100% 347 (M+H)

EXAMPLE 29

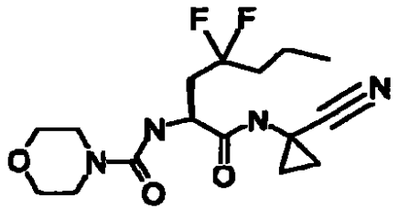
Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide



By proceeding in a similar manner to Example 28 above but using 4,4-Difluoro-2-[([1,4]oxazepane-4-carbonyl)-amino]-heptanoic acid and (S)-2-Amino-butyronitrile hydrochloride there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide.
LCMS : 100% 375 (M+H).

EXAMPLE 30

Morpholine-4-carboxylic acid [(S)-1-(1-cyano-cyclopropylcarbamoyl)-3,3-difluoro-hexyl]-amide



Prepared by reacting (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and 1-Amino-cyclopropanecarbonitrile hydrochloride, using TOTU as the coupling agent and diisopropyl ethylamine as the base.
LCMS : 359 (M+H)

EXAMPLE 31

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM, 0.5 mM DTT, 0.01% triton X-100).

Human cathepsin S (final concentration in the well is 1.74 nM) 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 (final concentration in the well is 0.08 mM) 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 32

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (comprising: MES 50 mM (pH 6); 2.5 mM EDTA , 2% DMSO and dithiothreitol (DTT), 2.5 mM).

Human cathepsin B (final concentration of 0.3 ng/μl) 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-pNa (final concentration of 100 μM) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 405nm) for 60 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 33

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μL 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 μL 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.

40. Use of a compound according to claim 3, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin B.

41. Use of a compound according to claim 3, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin K.

42. The use according to any one of claims 38 to 41 of one of the following compounds:
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide,
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide,
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide or
morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide
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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof
for the production of pharmaceuticals that inhibit the enzymatic activity of Cathepsin S, K, or B.

43. The use according to claim 42 for treating pain, osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer or skin cancer.

44. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin S, such disease or medical condition being selected from arthritis, atherosclerosis, emphysema, osteoporosis, pain, muscular dystrophy, inflammation, multiple sclerosis, irritable bowel disease, rheumatoid arthritis, asthma, autoimmune responses, chronic obstructive pulmonary disease, and bronchiolitis, comprising administering to said patient an effective cathepsin S inhibiting amount of a compound according to claim 3.

45. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin K or B, such disease or medical condition being selected from

224 999

PCT

In the European Patent Office

In re the Application of:	**Aventis Pharmaceuticals Inc.**
International Appln. No.:	**PCT/US2004/035282**
International Filing Date:	**22 October 2004 (22.10.2004)**
Title:	**NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS**

TO: **INTERNATIONAL PRELIMARY EXAMINATION AUTHORITY**
European Patent Office
27 Erhardstr. 27
D-80298 Munich, Germany

AMENDMENT PURSUANT TO PCT ARTICLE 34

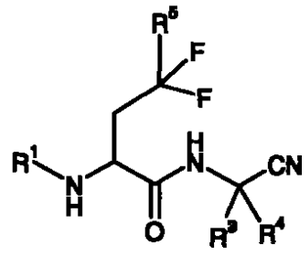
In response to the Written Opinion of the International Searching Authority of the European Patent Office dated March 31, 2005, Applicant respectfully submits the following amendments pursuant to Article 34, which are being filed with the Demand for Preliminary Examination. Replacement pages 1, 15, 15A, 21, 85, and 86 submitted herewith incorporate such amendments to the Specification and Claims as particularly set forth below.

At page 1, the Title was changed from "NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHESPIN INHIBITORS" to --NOVEL COMPOUNDS AND COMPOSITIONS AS CATHESPIN INHIBITORS--. This amendment was made to better characterize the compounds of the present invention.

At page 1, line 13, "novel keto-oxadiazole" was changed to --novel difluoro derivatives--. This amendment was made to better characterize the compounds of the present invention. Support for this amendment is found throughout Applicant's specification.

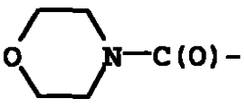
At page 15 to 15A, the following disclosure was added at page 15, line 10:

> --A further particular group of compounds of the invention are compounds of formula (Ib):

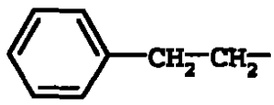


(Ib)

wherein R^1, R^3, R^4 and R^5 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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Compounds of Formula (Ib) in which R^1 is $R^{13}C(O)$- and R^{13} is hetero(C_{5-12})cycloalkyl are examples. Compounds of Formula (Ib) in which R^1 is  are particular examples.

Compounds of Formula (Ib) in which R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl or (C_{1-6})alkyl are examples.

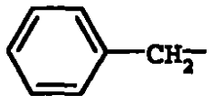
Compounds of Formula (Ib) in which R^3 is H ,  or $CH_3-CH_2-CH_2-$ are particular examples.

Compounds of Formula (Ib) in which R^4 is H or methyl are examples.

Compounds of Formula (Ib) in which R^5 is

(C_{6-12})aryl(C_{1-6})alkyl are examples.

Compounds of Formula (Ib) in which R^5 represents



are particular examples.–

This disclosure was added to correct an inadvertent transcription error relative to the disclosure of U.S. Provisional Patent Application No. 60/514,373, filed October 24, 2003 ("the 373 provisional priority application"), *i.e.*, the application from which the present application claims priority. Applicant submits respectfully that the omission of formula (Ib) and the accompanying disclosure was clearly in error as original page 15, lines 11-14, refer to "formula (Ib)" and provide additional disclosure with respect to particular species of formula (Ib). Thus, the above amendment merely corrects this inadvertent error. Support for this amendment can be found in, for example, other compounds disclosed in the present specification such as, for example, the compounds of Examples 17, 18, 28, 29, and 30, as well as in the 373 provisional priority application.

At page 21, line 20, "pain," was deleted. This word was inadvertently added to this portion of the disclosure. Support for this amendment can be found, for example, throughout the 373 provisional priority application.

At page 85,[1] line 3 of Claim 44 was amended to correct an obvious typographical error by the addition of an –m-- before the word "uscular."

At page 85, line 4 of claim 44, the term "autoimume responses" was amended to read –autoimume disorders–.

At page 85, line 7 of claim 46, the term "autoimume responses" was amended to read –autoimume disorders–.

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At page 86, line 2 of claim 47, the word "pain," was deleted.

Applicant submits that no new matter has been added to the present patent applications in connection with the above-identified amendments. Accordingly, entry of the amendments and replacement pages 1, 15, 15A, 21, 85, and 86 is, therefore, respectfully requested.

If, in the opinion of the Examiner, a favorable IPER cannot be issued on the basis of Applicant's Article 19 Amendment filed on May 31, 2005 and the above amendments, Applicants expressly request issuance of an additional written opinion under Rule 66.4 and/or institution of a telephone interview under Rule 66.6. It is submitted that such additional communication, if needed, will facilitate the issuance of a favorable IPER, and provide efficiencies in subsequent regional and national phase examination.

Respectfully submitted,

Dated: July 20, 2005

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[1] The page numbers referred to for pages within the Claims section of the present application are those of the Replacement Sheets for the Claims that were submitted with Applicant's Article 19 Amendment filed on May 31, 2005.

NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

FIELD OF THE INVENTION

This invention relates to the use of novel difluoro derivatives for treating diseases associated with cysteine protease and, particularly, diseases associated with activity of cathepsin S, K, and B. This invention also relates to processes of making such compounds.

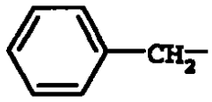
BACKGROUND OF THE INVENTION

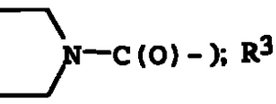
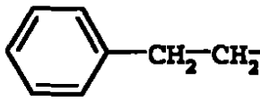
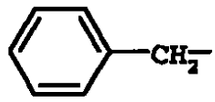
Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, for example, as a result of increased 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, atherosclerosis, emphysema, osteoporosis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, periodontal disease, metachromatic leukodystrophy and others.

An increase in cathepsin activity such as, for example, cathepsin S, contributes to the pathology and/or symptomatology of a number of diseases such as, for example, autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, irritable bowel disease, rheumatoid arthritis and Hashimoto's 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 is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsin S may be of use in treatment of systemic amyloidosis.

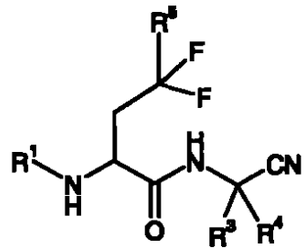
Compounds of Formula (Ia) in which R^4 is H or methyl are examples.

Compounds of Formula (Ia) in which R^5 is (C_{6-12})aryl(C_{1-6})alkyl are examples.

Compounds of Formula (Ia) in which R^5 represents  are particular examples.

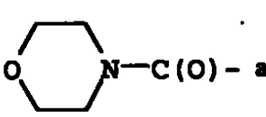
A particular group of compounds of the invention are compounds of formula (Ia) in which: R^1 is $R^{13}C(O)$- (especially ); R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl (especially ) or (C_{1-6})alkyl (especially $CH_3-CH_2-CH_2-$); R^4 is H or methyl and R^5 is (C_{6-12})aryl(C_{1-6})alkyl (especially ).

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

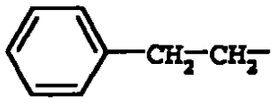


(Ib)

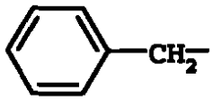
wherein R^1, R^3, R^4 and R^5 are as hereinbefore described, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ib) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

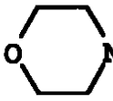
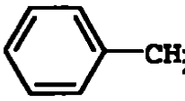
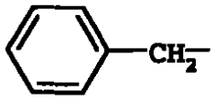
Compounds of Formula (Ib) in which R^1 is $R^{13}C(O)$- and R^{13} is hetero(C_{5-12})cycloalkyl are examples. Compounds of Formula (Ib) in which R^1 is  are particular examples.

Compounds of Formula (Ib) in which R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl or (C_{1-6})alkyl are examples.

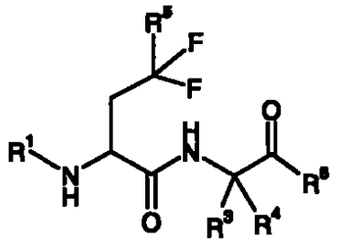
Compounds of Formula (Ib) in which R^3 is H,  or $CH_3-CH_2-CH_2-$ are particular examples.

Compounds of Formula (Ib) in which R^4 is H or methyl are examples.

Compounds of Formula (Ib) in which R^5 is (C_{6-12})aryl(C_{1-6})alkyl are examples. Compounds of Formula (Ib) in which R^5 represents  are particular examples.

A particular group of compounds of the invention are compounds of formula (Ib) in which: R^1 is $R^{13}C(O)$- (especially ); R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl (especially ) or (C_{1-6})alkyl (especially CH_3-CH_2-); R^4 is H or methyl and R^5 is (C_{6-12})aryl(C_{1-6})alkyl (especially ).

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



treating diseases in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention may be useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, irritable bowel disease, rheumatoid arthritis and Hashimoto's 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 is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsin S may be 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 31, 32, 33, 34, *infra*.

The compounds of the invention are also inhibitors of cathepsin K and B and, as such, are useful for treating diseases in which cathepsin K and B activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention may be useful in treating osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer or skin cancer.

Administration and Pharmaceutical Compositions:

In general, compounds of the present invention 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 the invention may range from about 1 micrograms per kilogram body weight (μg/kg) per day to about 60 milligram per kilogram body weight (mg/kg) per day, typically from about 1 μg/kg/day to about 20 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 80 μg /day to about 4.8 g/day, typically from about 80 μg /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

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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof·
for the production of pharmaceuticals that inhibit the enzymatic activity of Cathepsin S, K, or B.

43. The use according to claim 42 for treating pain, osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer or skin cancer.

44. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin S, such disease or medical condition being selected from arthritis, atherosclerosis, emphysema, osteoporosis, pain, uscular dystrophy, inflammation, multiple sclerosis, irritable bowel disease, rheumatoid arthritis, asthma, autoimmune disorders, chronic obstructive pulmonary disease, and bronchiolitis, comprising administering to said patient an effective cathepsin S inhibiting amount of a compound according to claim 3.

45. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin K or B, such disease or medical condition being selected from osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer, and skin cancer, comprising administering to said patient an effective cathepsin K or B inhibiting amount of a compound according to claim 3.

46. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cysteine protease, such disease or medical condition being selected from arthritis, atherosclerosis, emphysema, osteoporosis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, periodontal disease, metachromatic leukodystrophy, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, irritable bowel disease, rheumatoid arthritis and Hashimoto's thyroiditis, asthma, autoimmune disorders, chronic obstructive pulmonary disease, and bronchiolitis, comprising administering to said patient an effective cysteine protease inhibiting amount of a compound according to claim 3.

47. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cathepsin K or B, such disease or medical condition being selected from osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer, and skin cancer, comprising administering to said patient an effective cathepsin K or B inhibiting amount of a compound according to claim 35.

48. A method of treating a patient suffering from a disease or medical condition which involves elevated levels of cysteine protease, such disease or medical condition being selected from pain, osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer, and skin cancer, comprising administering to said patient an effective cysteine protease inhibiting amount of a compound according to claim 42.

49. A method of selectively inhibiting cathepsin K activity in a patient with elevated levels of cathepsin K which comprises administering to a patient in need thereof an effective cathepsin K inhibiting amount of a compound according to claim 3.

50. A method of selectively inhibiting cathepsin K activity in a patient with elevated levels of cathepsin K which comprises administering to a patient in need thereof an effective cathepsin K inhibiting amount of a compound according to claim 42.

51. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 3.

52. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 35.

53. A method of treating osteoarthritis in a mammal comprising administering to said mammal an effective amount of a compound according to claim 42.

IN THE INTERNATIONAL BUREAU OF WIPO

In re the Application of:	Aventis Pharmaceuticals Inc.
International Appln. No.:	PCT/US2004/035282
International Filing Date:	22 October 2004 (22.10.2004)
Title:	NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS

TO: INTERNATIONAL BUREAU OF WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

AMENDMENT PURSUANT TO PCT ARTICLE 19

In response to the Search Report prepared by the International Searching Authority, mailed on 31 March 2005, Applicants respectfully submit herewith replacement pages 76-77, 79, 83, 85, 88, and 90 which incorporates the following amendments to the Claims:

Claims 1 and 2 have been canceled.

In claim 12, line 1, "2-11" was amended to read --3-11--.

In claim 3, line 15, "H" has been deleted from the definition of R^1.

In claim 3, the alternate definition of R^1,

> "or R^1 is selected from the group consisting of (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl and hetero(C_{5-13})aryl(C_{0-6})alkyl , each of which is 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, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;" ,

was deleted.

In claim 11, line 1, "2-10" was amended to read --3-10--.

In claim 12, line 1, "2-11" was amended to read –3-11–.

In claim 13, line 1, "2-12" was amended to read –3-12–.

In claim 31, line 6, the word –or– was inserted between "5-thiophen-2-yl-oxazol-2-yl," and 5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl.

In claim 32, line 2, the word –or– was inserted between "oxazol-2-yl," and "5 cyclopropyl-1,2,4-oxadiazol-3-yl".

In claim 35, lines 9, 11, 13, 15, and 17, ":" was replaced with –;–.

In claim 36, line 1, "2" was replaced with –3–.

In claim 37, line 3, "2" was replaced with –3–.

Claim 51 (second occurrence) was replaced by new claim 61.

Claim 52 (second occurrence) was replaced by new claim 62.

In accordance with PCT Section 205(b), the following claims is/are:

(I) unchanged: claims 4-10, 14-30, 33-34, 38-50, 51 (first occurrence), 52 (first occurrence), and 53-60

(II) cancelled: 1-2, 51 (second occurrence), and 52 (second occurrence)

(III) new: 61-62

(IV) replacement of claims 3, 11-13, 31-32, 35-37, 51 (second occurrence), and 52 (second occurrence) as above

(V) result of division of one or more claims as filed: none.

Statement Under Article 19(1)

Claims 1 and 2 have been canceled, resulting in the cancellation of page 75. Since page 75 is the first page of Applicants' claims, Applicants request that the phrase "WE CLAIM:" be added before claim 3 on page 76.

Claims 3, 11-13, 31-32, and 35-37 have been amended as detailed above. Claim 51 (second occurrence) and claim 52 (second occurrence) have been re-written as claims 61 and 62, respectively. Entry of replacement pages 76-77, 79, 83, 85, 88, and 90 is, therefore, respectfully requested.

Applicants request entry of the foregoing amendments preliminary to publication and examination of the above-identified patent application.

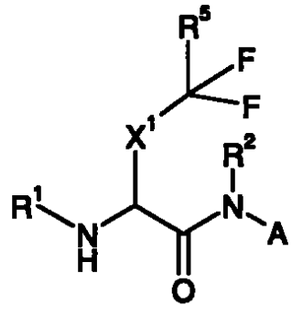
Respectfully submitted,

Dated: May 31, 2005

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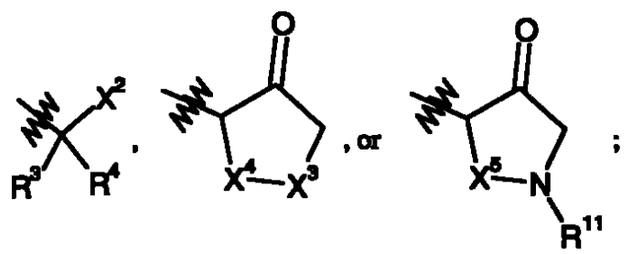
3. A compound having a structure of formula (I):



(I)

wherein

A is



X^1 is methylene, ethylene or a bond;

X^2 is CN, CHO, $C(O)R^6$, $C(O)C(O)NR^7R^7$, $C(O)C(O)NR^7R^8$, $C(O)C(O)R^{13}$, $C(O)C(O)OR^{13}$, $C(O)CH_2X^3R^{13}$;

X^3 is selected from the group consisting of O, $S(O)_n$, CO, CONH, NHCO, $NHSO_2$ and SO_2NH;

X^4 is $CH(R^{12})$ or $CH(R^{12})$-CH_2;

X^5 is methylene, ethylene, propylene or a bond;

X^6 is a bond or (C_{1-2})alkylene;

R^1 is $R^{13}C(O)$-, $R^{13}S(O)_2$-, $R^{13}OC(O)$-, $R^8R^7NC(O)$-, $R^8R^7NS(O)_2$-; $R^{13}S(O)_2NC(O)$- or $R^{13}C(O)NS(O)_2$-;

R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-12})aryl(C_{0-6})alkyl;

R^3 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-13})aryl(C_{0-6})alkyl optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^4 is H or (C_{1-6})alkyl; or R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^5 is H, F, or R^5 is (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl each 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, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

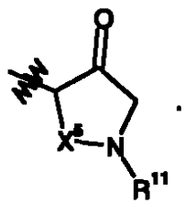
R^6 is (C_{6-12})aryl, hetero(C_{5-13})aryl and halo substituted (C_{1-6}) alkyl; wherein R^6 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, cyano, halo, halo-substituted (C_{1-6})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^7 is H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl; wherein R^7 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$,

optionally substituted by $-X^6OR^9$ wherein X^6 is a bond and R^9 is (C_{1-6})alkyl.

6. A compound according to claim 4 or 5 in which R^4 is H or (C_{1-6})alkyl.

7. A compound according to any one of claims 4-6 in which X^2 is CHO, CN or $C(O)R^6$ wherein R^6 is hetero(C_{5-13})aryl optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl.

8. A compound according to claim 3 in which A is 

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9. A compound according to claim 8 in which X^5 is propylene.

10. A compound according to claim 8 or 9 in which R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$ wherein R^{13} is alkyl or (C_{6-12})aryl.

11. A compound according to any one of claims 3-10 in which R^1 is (i) $R^{13}C(O)$- wherein R^{13} is hetero(C_{5-12})cycloalkyl; (ii) $R^{13}OC(O)$- wherein R^{13} is (C_{6-12})aryl(C_{1-6})alkyl; (iii) (C_{1-9})alkyl; or (iv) hetero(C_{5-12})cycloalkyl.

12. A compound according to any one of claims 3-11 in which R^2 is H.

13. A compound according to any one of claims 3-12 in which R^5 is (C_{1-9})alkyl or (C_{6-12})aryl(C_{1-6})alkyl.

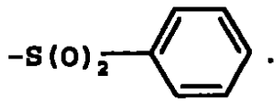
14. A compound of formula (Ia):

3-yl, 5-isopropyl-isoxazol-3-yl, 5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl, 5-(5-methyl-thien-2-yl)-oxazol-2-yl, oxazol-2-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 5-phenyl-1,2,4-oxadiazol-3-yl, 5-thiophen-2-yl-oxazol-2-yl, or 5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl.

32. A compound according to claim 31 in which R^6 is benzoxazol-2-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, oxazol-2-yl, or 5-cyclopropyl-1,2,4-oxadiazol-3-yl.

33. A compound according to claim 17 in which R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$ wherein R^{13} is alkyl or (C_{6-12})aryl.

34. A compound according to claim 28 in which R^{11} is $-C(O)OC(CH_3)_3$ or



.

35. A compound according to claim 3 selected from the group consisting of:
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(5-cyclopropyl-1,3,4-oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;
morpholine-4-carboxylic acid {1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-5-methyl-hexyl}-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;
morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide;
morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-butyl}-amide;
morpholine-4-carboxylic acid {1-[1-(5-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;
morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;
morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;
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 prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

36. A pharmaceutical composition comprising a compound of claim 3 and a pharmaceutically acceptable excipient.

37 A method of inhibiting cathepsin S in a patient wherein elevation of the enzymatic activity of cathepsin S contributes to said patient's pathological conditions by administering to said patient a therapeutically effective amount of a compound of claim 3.

38. Use of a compound according to claim 3, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin S.

39. Use of a compound according to claim 35, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions that can be ameliorated by the administration of the compound as an inhibitor of cathepsin S.

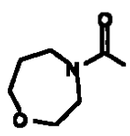
50. A method of selectively inhibiting cathepsin K activity in a patient with elevated levels of cathepsin K which comprises administering to a patient in need thereof an effective cathepsin K inhibiting amount of a compound according to claim 42.

51. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 3.

52. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 35.

53. A method of treating osteoarthritis in a mammal comprising administering to said mammal an effective amount of a compound according to claim 42.

54. A compound according to any one of claims 3-10, 12-18, or 20-30 wherein R^1 is



55. A compound according to claim 3 selected from the group consisting of:

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide,

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-isopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide,

57. A method of selectively inhibiting cathepsin K activity in a patient with elevated levels of cathepsin K which comprises administering to a patient in need thereof an effective cathepsin K inhibiting amount of a compound according to claim 55.

58. A method of selectively inhibiting cathepsin S activity in a patient with elevated levels of cathepsin S which comprises administering to a patient in need thereof an effective cathepsin S inhibiting amount of a compound according to claim 55.

59. A method of selectively inhibiting cathepsin B activity in a patient with elevated levels of cathepsin B which comprises administering to a patient in need thereof an effective cathepsin B inhibiting amount of a compound according to claim 55.

60. A method of treating osteoarthritis in a mammal comprising administering to said mammal an effective amount of a compound according to claim 55.

61. A method of selectively inhibiting cathepsin B activity in a patient with elevated levels of cathepsin B which comprises administering to a patient in need thereof an effective cathepsin B inhibiting amount of a compound according to claim 3.

62. A method of selectively inhibiting cathepsin B activity in a patient with elevated levels of cathepsin B which comprises administering to a patient in need thereof an effective cathepsin B inhibiting amount of a compound according to claim 42.

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PATENT C PERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
US20030066WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2004/035282	22/10/2004	24/10/2003
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 11 sheets.

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

1. **Basis of the report**
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [X] Certain claims were found unsearchable (See Box II).

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

4. With regard to the title,
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established by this Authority to read as follows:

   NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS

5. With regard to the abstract,
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

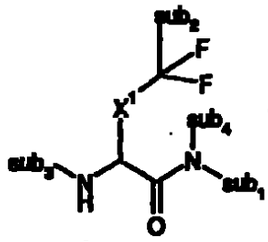
6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
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Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Novel difluorinated amide derivatives of formula II.



II

as inhibitors of cathepsin S, K, B, and L, the pharmaceutically acceptable salts and *N*-oxides thereof, their uses as therapeutic agents and the methods of their making.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/035282 246

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D271/06 A61K31/5377 A61P35/00 C07D271/10 C07D261/08
C07D413/04 C07D263/32 C07D263/56 C07D295/18 A61P29/00
A61P37/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/55144 A (AXYS PHARMACEUTICALS, INC; LINK, JOHN, O; MARTELLI, ARNOLD, J; MARTICH) 21 September 2000 (2000-09-21) Claims 1-53; Formula (I); Table I, Formulae B23-B28; examples 28-31	1-60

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[X] Further documents are listed in the continuation of box C.

[X] 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 2005	31/03/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kirsch, C

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/075836 A (MERCK FROSST CANADA & CO; AXYS PHARMACEUTICALS, INC; BAYLY, CHRISTOPHE) 18 September 2003 (2003-09-18) Claims 1-28; Formula (I); p. 11,. 1. 29-33; Table I: p. 28, 1. 24-25; p. 29, 1. 11-12, 16; Table II: p. 30, 1. 13, p. 32, 1. 8-9, 15; p. 65, 1. 25-26; p. 68, 1. 30-34; p. 69, 1. 7-23, p. 73, 1. 25-32; p. 74, 1. 17-24; p. 75, 1. 16-17, 31-35; p. 77, 1. 29-33; p. 78, 1. 1-2, 27-28; p. 79, 1. 8-12; p. 83, 1. 5-p. 84, 1. 5; examples 16, 18, 38; p. 212, compounds 8-12; p. 213, compounds 1-2; p. 214, compounds 2-3; p. 219, compounds 3-4; p. 221, compound 2; p. 224, compound 9; p. 225, compound 1; p. 225-226	1-60
X	WO 00/55125 A (AXYS PHARMACEUTICALS, INC; BRYANT, CLIFFORD, M; BUNIN, BARRY, A; KRAYN) 21 September 2000 (2000-09-21) Claims 1-35; Formulae (I)	1-60
X	WO 02/069901 A (MERCK FROSST CANADA & CO; PE CORPORATION ; PRASIT, PETPIBOON; BAYLY, C) 12 September 2002 (2002-09-12) Claims 1-29; Formula (I)	1-60
X	WO 02/098850 A (AXYS PHARMACEUTICALS, INC; AVENTIS PHARMACEUTICALS INC; GRAUPE, MICHAE) 12 December 2002 (2002-12-12) Claims 1-20; Formula (I); Table II, Formulae B89 and B92	1-60
X	WO 02/100849 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC) 19 December 2002 (2002-12-19) Claims 1-31; Formula (I); p. 89, compounds 7-8	1-60
P,X	WO 03/097617 A (AXYS PHARMACEUTICALS, INC; GRAUPE, MICHAEL; LAU, AGNES; LINK, JOHN O;) 27 November 2003 (2003-11-27) Claims 1-18; Formula (I)	1-60

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ORVIETO F ET AL: "Novel, potent phenethylamide inhibitors of the hepatitis C virus (HCV) NS3 protease: Probing the role of P2 aryloxyprolines with hybrid structures" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 13, no. 16, 18 August 2003 (2003-08-18), pages 2745-2748, XP002314396 ISSN: 0960-894X Figure 1; compounds 7-11, 15-18	1
X	BENNETT ET AL: "The identification of.alpha.-ketoamides as potent inhibitors of hepatitis c virus NS3-4A proteinase" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 3, 2 February 2001 (2001-02-02), pages 355-357, XP002199467 ISSN: 0960-894X Figure 1; Scheme 1, 2nd compound	1
X	CHEN J ET AL: "alpha-Aminoamides from a carbamoylsilane and aldehyde imines" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 44, no. 43, 20 October 2003 (2003-10-20), pages 8025-8027, XP004458767 ISSN: 0040-4039 Compound (1), entry 4	1
X	DE 28 06 833 A1 (DELALANDE S.A) 24 August 1978 (1978-08-24) Formulae (II), (II'), (XII'); compound 47, 17, 39	1,2
X	FR 2 605 009 A (AYI AYICOUE; PATINO NADIA; MARTOS ALCANIS MARIE LINE; GUEDJ ROGER; CON) 15 April 1988 (1988-04-15) Claim 19	1,2
X	JP 04 049298 A (UNIV NEW YORK STATE; FUJI YAKUHIN KOUGIYOU KK) 18 February 1992 (1992-02-18) Compounds 5-8	1,2

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1996, no. 10, 31 October 1996 (1996-10-31) -& JP 08 165274 A (SHIONOGI & CO LTD), 25 June 1996 (1996-06-25) Formula (Ia); compounds 25a, 26a; example 1 abstract	1
X	WO 03/087069 A (ELI LILLY AND COMPANY; EVERS, BRITTA; RUEHTER, GERD; TEBBE, MARK, JOSE) 23 October 2003 (2003-10-23) Claims; Formula (I); example 2	1,2
X	WO 99/64442 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P ANGELETTI S.P.A; MATASSA) 16 December 1999 (1999-12-16) Claims; Formula (I); compound 1o	1
X	WO 99/02549 A (TAKEDA CHEMICAL INDUSTRIES, LTD; MIYAGAWA, KEN-ICHIRO; TSUBOTANI, SHIG) 21 January 1999 (1999-01-21) Claims; Formula (I); examples 37-38, 61	1
X	WO 02/079234 A (ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA; COLARUSS) 10 October 2002 (2002-10-10) Claims; Formula (I); example 34, 36-45; compounds 50, 321, 53-56, 58a-58c, 59-63, 523, 526, 539; 551-553, 555, 566, 616, 636, 708a-b, 713, 576; Table 1, compounds 105, 115, 125, 166, 179-180, 187; Table 3, compounds 301, 304-305, 321;Table 4, compound 421;Table 5, compounds 502, 504-505, 509-511, 517-519, 523-524, 526-576; Table 6; Table 7, compounds 705-715, 718-721	1
X	WO 90/09162 A (ABBOTT LABORATORIES) 23 August 1990 (1990-08-23) Example 152	1
X	T. ARAI ET AL.: "The Conformation of de Novo Designed Amphiphilic Peptides with Six or Nine L-2-(2,2,2-Trifluoroethyl)glycines as the Hydrophobic Amino Acid" BULL. CHEM. SOC. JPN, vol. 73, 2000, pages 439-445, XP002320762 Figure 1	1

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International Application No
PCT/US2004/035282

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. BURGER ET AL.: "Synthesis of (2S)-4,4-difluoroproline, (2S,4R)-4-fluoroproline and their derivatives from (S)-aspartic acid" JOURNAL OF FLUORINE CHEMISTRY, vol. 66, 1994, pages 87-90, XP002320763 Compounds 7-8	1,2
X	I. OJIMA ET AL.: "New potent enkephalin analogs containing trifluoromethylamino acid residues" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 2, no. 3, 1992, pages 219-222, XP002320764 Compounds 5-8, 10-11, 13	1,2
X	R.M. BABB ET AL.: "Omega,omega,omega-Trifluoroamino Acids" JOURNAL OF ORGANIC CHEMISTRY, vol. 35, no. 5, 1970, pages 1438-1440, XP002320765 Compound 4	1
X	S. COLARUSSO ET AL.: "Phenethal Amides as Novel Noncovalent Inhibitors of Hepatitis C Virus NS3/4A Protease: Discovery, Initial SAR and Molecular Modeling" JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 3, 2003, pages 345-348, XP002320766 Compounds 1b-1c, 16a-16b, 17-19	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/035282 251

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

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 37, 44-60 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/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 III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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PCT/US04/035282

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DEC 2004 DEPT

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

LIN, JiangD
Aventis Pharmaceuticals Inc.
Route 202-206
Bridgewater, NJ 08807
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 08 December 2004 (08.12.2004)	
Applicant's or agent's file reference US20030086WO	**IMPORTANT NOTIFICATION**
International application No. PCT/US04/035282	International filing date *(day/month/year)* 22 October 2004 (22.10.2004)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 24 October 2003 (24.10.2003)
Applicant AVENTIS PHARMACEUTICALS INC.D et al	

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

2. *(If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(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.

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

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
24 October 2003 (24.10.2003)	60/514,373	US	22 November 2004 (22.11.2004)

NO ACTION DUE file

DUE DATE 12/30/04

DICTD BY

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

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Authorized officer

Olaiz Alicia

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Telephone No. +41 22 338 9288

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256

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-038081- -00000-0000 Fec: 2006-04-21 17:01:21
Dep: 2020 NUECREACIONES
Tra: 11 PATENTEYM Eva 379 FASENACIONALII
Act 411 PRESENTACION Folios: 253

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 30,673
FECHA : ABRIL 21 DE 2006

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	050-00110-6	31163593	19/04/2006	2,838,000.00

C O N C E P T O

CANT.	REMISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

257

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radi: 05-[illegible] - -00000-0000 Fecr: 2005-04-01 17:01:21
Dep: 2020 RADICACIONES
Tac: 11 PATENTEYI Eve 379 PASINACIONALII
Act 411 PRESENTACION Folios: 263

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

(2) SOLICITANTE (71)	Nombre: AVENTIS PHARMACEUTICALS INC. Dirección: 300 Somerset Corporate Boulevard, Bridgewater, NJ 08807 Estados Unidos Nacionalidad o Domicilio: Bridgewater, New Jersey, Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail:	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
(3) REPRESENTANTE O APODERADO	Nombre: LUIS PATIÑO LEYVA Dirección Cra. 11ª No. 94-76 – Of. 308 Teléfono: 6161948 Fax: 6163976 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☒ Cual _____ Número 2.930.616 TP 2998
(4) INVENTOR (ES) (72)	Nombre: THURAIRATNAM Sukathiri Dirección: 6 Smoke Rise Lane, Nacionalidad o Domicilio: Bedminister, NJ 07921, Estados Unidos	

(5) PCT (86)

Solicitud Internacional No. PCT/US2004/035282 Fecha Octubre 22 de 2004

Publicación Internacional No. WO 2005/040142 A1 Fecha Mayo 6 de 2005

(6) Título (54) NUEVOS DERIVADOS DE CETO-OXADIAZOL COMO INHIBIDORES DE LAS CATEPSINAS.

(7) Clasificación Internacional (51) C07D 271/06

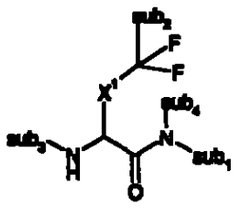
(8) PRIORIDAD:	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	Estados Unidos	Octubre 24 de 2003	60/514,373

Continuación nombre, dirección y domicilio de inventores:

Nombre	Dirección	Domicilio
ALDOUS David John	268 Gates Avenue,	Gillette, NJ 07933, Estados Unidos
LEROY Vincent	1 JFK Boulevard, Franklin Green Apt. #36K,	Somerset, NJ08873, Estados Unidos
TIMM Andreas Paul	97 Bonney Court, Bridgewater	New Jersey 08807, Estados Unidos

REIVINDICACIONES:

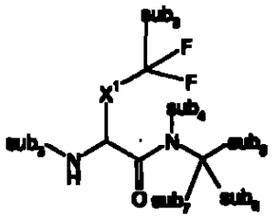
1. Un compuesto que tiene una estructura de cadena principal de la fórmula II:



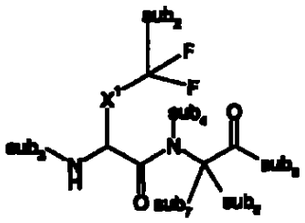
II

en la que X^1 es metileno, etileno o un enlace y sub_1-sub_4 son sustituyentes generales.

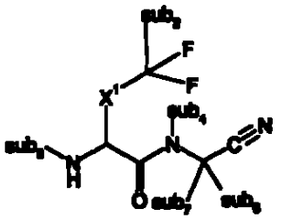
2. Un compuesto de la reivindicación 1, que tiene una estructura de cadena principal seleccionada del grupo que consiste en las fórmulas III, IV y V:



III



IV



V

en las que X^1 es metileno, etileno o un enlace y sub_1-sub_8 son sustituyentes generales.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-038081- -00000-0000 Fec: 2006-04-21 17:01:21
Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII Eva 379 FASENACIONALII
Act 411 PRESENTACION Folios: 253

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (✓) 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, X	( )	( )
-Comprobante de Pago de las tasas establecidas. ✓	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
ESQUEMA DE TRAZADO ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: Abril 21 de 2006

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
PATIÑO LEYVA LUIS
Apoderado(a) y/o Representante de
AVENTIS PHARMACEUTICALS INC.

REFERENCIA	Radicación No.	6 38081
	Solicitud internacional	US2004/035282
	Fecha inicio fase nacional	24/05/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	6327

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. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

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 CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 JUN. 2006
adpa11