

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SIC

DELEGATURA PROPIEDAD INDUSTRIAL

DIVISION DE NUEVAS CREACIONES

SOLICITUD

PATENTE DE INVENCION

PCT

03-104808

21. EXPEDIENTE No

54. TITULO "NUEVOS COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE LAS CATEPSINAS".

51. CLASIFICACION INTERNACIONAL: C07C 317/46

AG 1K31/16

71. SOLICITANTE AXYS PHARMACEUTICALS, INC y

AVENTIS PHARMACEUTICALS INC

DOMICILIO. SOUTH SAN FRANCISCO, ESTADOS UNIDOS y BRIDGEWATER, NEW JERSEY, ESTADOS UNIDOS

74 APODERADO GUSTAVO HOLLMANN RESTREPO

22 SANTAFE DE BOGOTA, D C : 27 DE NOVIEMBRE DE 2003

94

SS

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

03 104808 00

SUPERINTENDENCIA INDUSTRIAL
Radicación: 83144808 00000000 Folios: 363
Fecha (RMI): 2002-11-27 16:44:00
Trámite: 001 PLI-PRIMI 379 FASE NULI 411 PRESEMIAL
Dependencia: 2029 DIVISION DE MARCAS (2029.1002)

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

①

SOLICITUD DE .



Patente de Invención



Patente de Modelo de Utilidad



Capítulo I



Capítulo II

②

SOLICITANTE
(71)

Nombre **AXYS PHARMACEUTICALS, INC.
y AVENTIS PHARMACEUTICALS INC.**

Dirección **180 Kipling Way, South San Francisco, CA 94080 Estados Unidos y
300 Somerset Corporate Blvd., Bridgewater, NJ 08807-2854, USA**

Nacionalidad o Domicilio **1. South San Francisco y
Estados Unidos 2. Bridgewater, New Jersey, Estados Unidos**

Teléfono

E-mail

IDENTIFICACION

CC



NIT



CE



Otro



Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre **GUSTAVO HOLLMANN RESTREPO**

Dirección **Cra. 11A No. 94-76-Of. 308**

Teléfono **6161948**

Fax **6163976**

E-mail

IDENTIFICACIÓN

CC



NIT



CE



Otro



Cual

Numero **2,878,023 TP 5903**

④

INVENTOR (ES)
(72)

Nombre **GRAUPE, Michael**

Dirección **1131 Banyan Way.**

Nacionalidad o Domicilio **Pacifica, CA 94044 Estados Unidos**

⑤ PCT (86)

Solicitud Internacional No **PCT/US02/17411**

Fecha **Junio 3 de 2002**

Publicación Internacional No **NO 02/098850 A2**

Fecha **Junio 12 de 2002**

⑥ Título (54)

**"NUEVOS COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE LAS
CATEPSINAS".**

⑦

Clasificación Internacional (51) **C07C 317/46**

AG 01 E 31/16

⑧

Prioridad

(33) Pais de Origen

(32) Fecha

(31) Numero de Solicitud

SI ☒

NO ☐

Estados Unidos

Junio 1, 2003

60/295,301

⑨

Comprobante de pago No. **86,237**

Fecha **Noviembre 26, 2003**

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

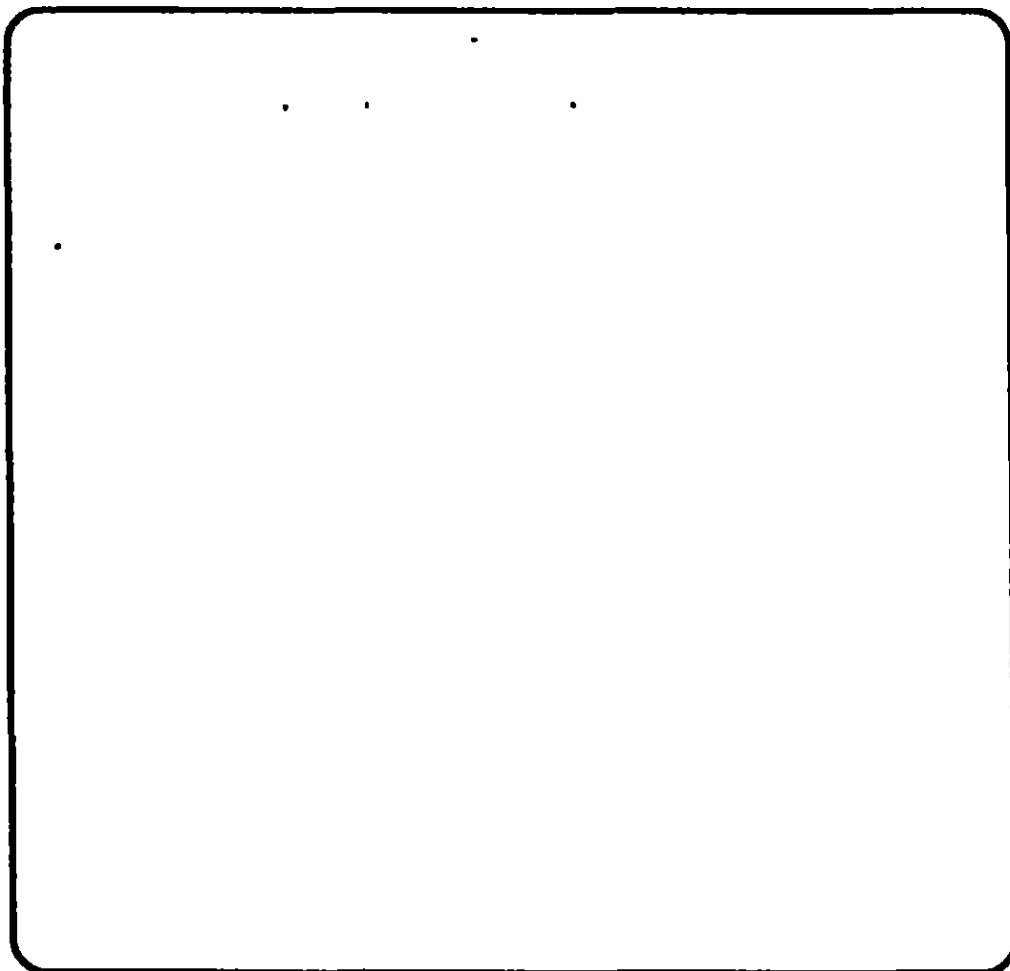
10

ANEXOS

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

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE GUSTAVO HOLLMANN RESTREPO

FIRMA

[Handwritten signature]

CC

TP

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

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

<u>Nombre</u>	<u>Dirección</u>	<u>Domicilio</u>
LI, Jiayao ✓	888 Foster City Blvd ,	Foster City, CA 94404 Estados Unidos
LINK, John, O ✓	12 Prospect Ave ,	San Francisco, CA 94110 Estados Unidos
ZIPFEL, Sheila ✓	Ayys Pharmaceuticals Inc , 180 Kimball Way	South San Francisco, CA 94080 Estados Unidos
TIMM, Andreas, P ✓	97 Bonney Court,	Bridgewater, NJ 08807 Estados Unidos
ALDOUS, David, J ✓	31 Dunbridge Lane,	Gillette, JJ 07933, Estados Unidos
THURAIRATNAM, Sukanthini ✓	6 Smoke Rise Lane,	Bedminster, NJ 07921, Estados Unidos

Otros anexos que se acompañan a la solicitud.

Copia de la solicitud internacional PCT-EASY Versión 2 92

Nota de información al solicitante de la comunicación de la solicitud internacional a las oficinas designadas (Forma PCT/IB/308)

Información respecto a las oficinas elegidas notificadas de su elección (Forma PCT/IB/332)

Notificación relativa a la presentación o transmisión del del documento de prioridad (Forma PCT/IB/304)

Notificación de registro de un cambio (Forma PCT/IB/306)

SUPERINTENDENCIA Y CONTRATO
Radicación : 83104805 00000000 Folios: 364
Fecha (IMP): 2003-11-27 16:44:59
Tramite : 011 PLI-PRIMI 3/3 FASE NO.1 411 PRE-SEÑAL
Dependencia: 2320 DIVISION DE MUESTRAS CENSALES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 86.237
FECHA : NOVIEMBRE 26 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	050-00110-6	8892660	25/11/2003	3.772.000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400.000.00
	TOTAL :	\$ 400.000.00

SON: CUATROCIENTOS MIL PESOS

Solicitud patente PET
Ref : 55253

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

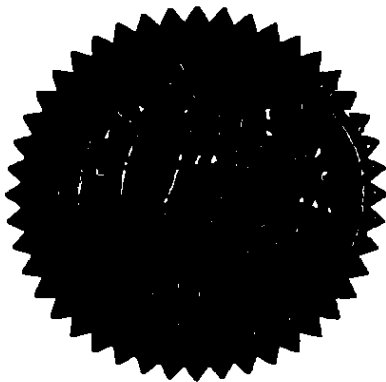
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

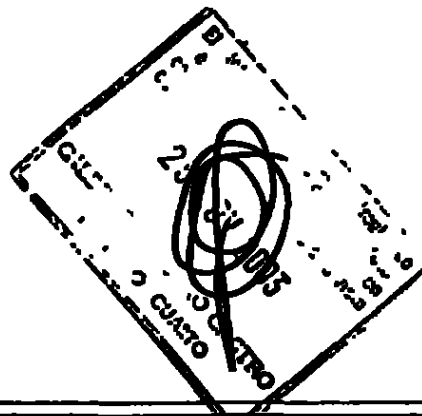
1. COUNTRY. UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
R. PETER WIDIN
3. ACTING IN THE CAPACITY OF:
COUNTY CLERK
4. BEARS THE SEAL/STAMP OF:
COUNTY OF SOMERSET

CERTIFIED

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



John E McCormac



**G. HOLLMANN RESTREPO
ABOGADOS LTDA**

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

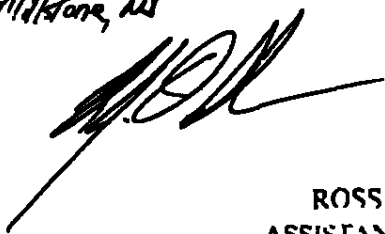
1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, utility models, industrial designs and models, commercial engravings and names, trademarks, slogans, health licenses, copyrights and domain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

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

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

Signed in on this 1st day of March of 2002

East Millstone, NJ



ROSS J. OFILI FR
ASSISTANT SECRETARY

**G. HOLLMANN RESTREPO
ABOGADOS LTDA**

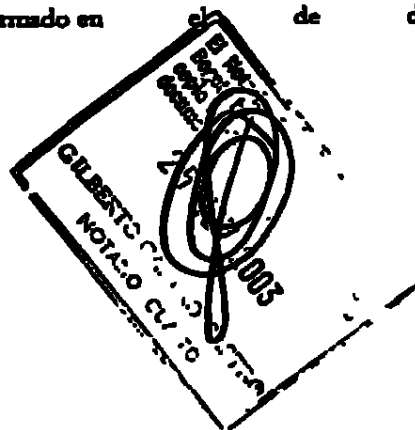
Yo (nosotros), obrando en nombre propio y representación de AVENTIS PHARMACEUTICALS INC., con domicilio en 300 Somerset Corporate Boulevard, Bridgewater, New Jersey, Estados Unidos de América, nombro(amos) a GUSTAVO HOLLMANN RESTREPO y/o LUIS PATIÑO LEYVA, con domicilio en Bogotá D.C., República de Colombia,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

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

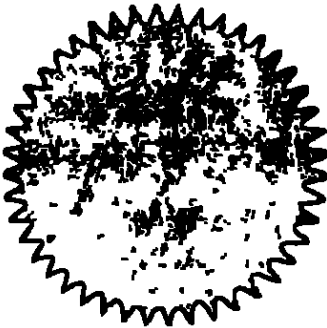
A este efecto, lo facultamos para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la Ley; renunciar o desistir a derechos concedidos o en curso de concesión, recibir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

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

Firmado en el de de



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 Ingerm

whose name is subscribed to the certificate of acknowledgement, proof or affidavit of the annexed instrument, was at the time of taking such acknowledgement, proof or affidavit, a

NOTARY PUBLIC OF NEW JERSEY

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

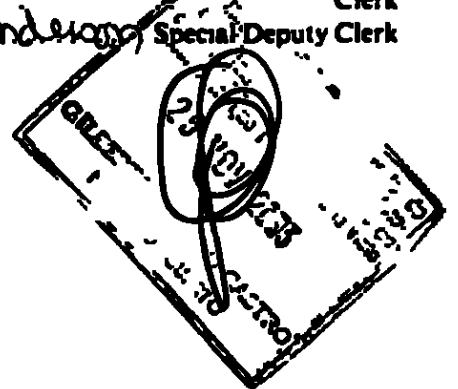
In Testimony Whereof, I have hereunto set my hand and affixed the seal of said County on

APR - 5 2002

R. PETER WIDIN

Clerk

by *Deborah Anderson* Special Deputy Clerk



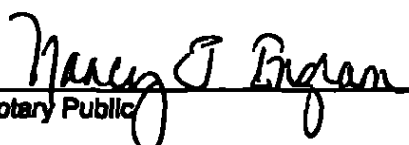
NOTARIAL CERTIFICATE (Corporation)

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

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

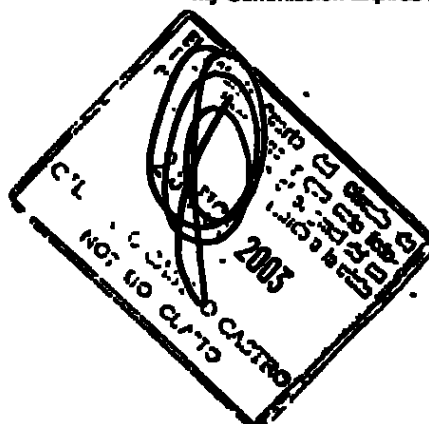
I further certify that said authority, dated November 29, 2000, is based on a Resolution of the Board of Directors of said Corporation, which I have seen, appointing the said individual Attorney-in-fact with full power to sign the foregoing document on behalf of the said Corporation and that the purposes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

SEAL


Notary Public

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

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



ESTADO DE NEW JERSEY, CONDADO DE SOMERSET

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

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

R. Peter Widin, Secretario

Deborah L. Anderson, Secretaria Especial Suplente

(Firma y Sello Oficial)

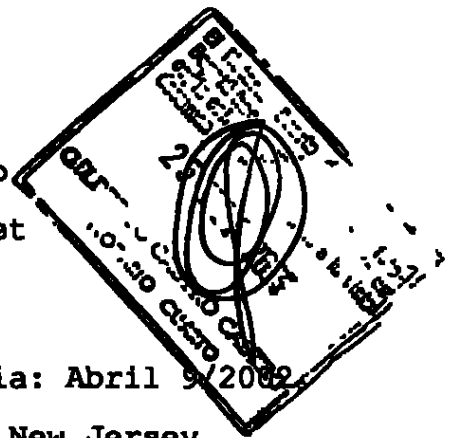
APOSTILLA

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

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

Confirmado

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



M. Méndez S

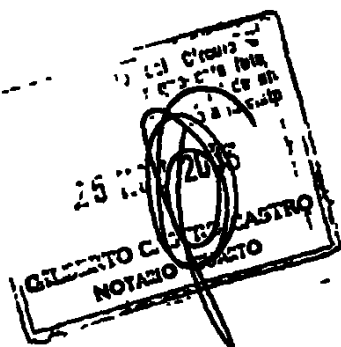
MINISTERIO DE RELACIONES
EXTERIORES

223893
JH Mendez
Cuya firma aparece en el
documento desempeña
las funciones indicadas

BOGOTÁ
RESPONSABLE DEL TEXTO

2002 APR 22 P 12 19

JEFE DE DESALIZACIONES
SANTAFE DE BOGOTÁ D.C.



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

CERTIFICADO NOTARIAL (Sociedad)

ESTADOS UNIDOS DE AMERICA

ESTADO DE NEW JERSEY

CONDADO DE SOMERSET

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

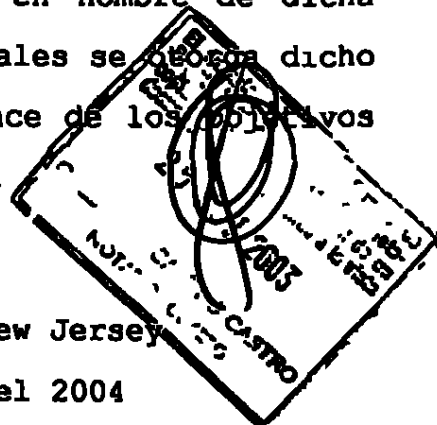
Certifico además que dicha autoridad, fechada el 29 de Noviembre del 2000, se basa en una resolución de la Junta de Directores de la mencionada sociedad, documento que yo he tenido a la vista, nombrando a la mencionada persona apoderado con todo poder para firmar el instrumento adjunto en nombre de dicha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

Nancy J. Ingram

Notaria Pública del Estado de New Jersey

Mi comisión expira Agosto 2 del 2004

(Firma y Sello Oficial)



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 December 2002 (12.12.2002)

PCT

(10) International Publication Number
WO 02/098850 A2

(51) International Patent Classification⁷ C07C 317/46,
A61K 31/16, A61P 19/02, 33/06, C07C 233/31, 255/29,
255/44, 255/46, 271/12, 271/24, 317/44, C07D 205/04,
207/08, 211/66, 239/08, 263/56, 271/10, C07C 271/16,
C07D 223/08, 271/28, 271/64, 271/82, 295/18, 295/20,
333/24, 307/14, 309/14, 413/12, 413/14, 417/12, 498/04,
C07F 7/18

Gillette, NJ 07933 (US) THURAIRATNAM, Sukan-
thini [GB/US], 6 Smoke Rise Lane, Bedminster, NJ 07921
(US)

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

(21) International Application Number PCT/US02/17411

(22) International Filing Date 3 June 2002 (03.06 2002)

(25) Filing Language English

(26) Publication Language English

(30) Priority Data:
60/295,301 1 June 2001 (01.06 2001) US

(71) Applicants (for all designated States except US) AXYS
PHARMACEUTICALS, INC. [US/US], 180 Kimball
Way, South San Francisco, CA 94080 (US). AVENTIS
PHARMACEUTICALS INC [US/US], 300 Somerset
Corporate Blvd, Bridgewater, NJ 08807-2854 (US)

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

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

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

(72) Inventors, and
(75) Inventors/Applicants (for US only) GRAUPE, Michael
[AT/US], 1131 Banyan Way, Pacifica, CA 94044 (US).
LI, Jiyao [CN/US], 888 Foster City Blvd, Foster City,
CA 94404 (US). LINK, John, O [US/US], 12 Prospect
Ave, San Francisco, CA 94110 (US). ZIPFEL, Shella
[US/US], Ayys Pharmaceuticals Inc, 180 Kimball Way,
South San Francisco, CA 94080 (US). TIMM, Andreas,
P [DE/US], 97 Bonney Court, Bridgewater, NJ 08807
(US). ALDOUS, David, J [US/US], 31 Dunbridge Lane,

Published
without international search report and to be republished
upon receipt of that report

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

(54) Title NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

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

WO 02/098850 A2

NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

THE INVENTION

5 This application is based on and claims priority from U S Provisional Application S N 60/295,301
filed on June 1, 2001, incorporated herein by reference

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

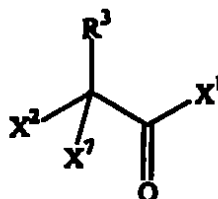
DESCRIPTION OF THE FIELD

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

25

SUMMARY OF THE INVENTION

This Application relates to compounds of Formula I



I

in which

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHX^4$,

X^2 is hydrogen, fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

X^3 is cyano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$, wherein R^5 is hydrogen, (C_{1-4}) alkyl, (C_{3-10}) cycloalkyl, (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl, (C_{0-3}) alkyl, (C_{6-10}) aryl, (C_{0-6}) alkyl, hetero (C_{3-10}) aryl, (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl, (C_{0-6}) alkyl or

hetero (C_{8-10}) bicycloaryl, (C_{0-6}) alkyl, R^6 is hydrogen, hydroxy or (C_{1-6}) alkyl, or where X^3 contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both attached, form hetero (C_{3-10}) cycloalkyl, hetero (C_{3-10}) aryl or hetero (C_{8-10}) bicycloaryl, R^7 is hydrogen or (C_{1-4}) alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo, R^{16} is hydrogen, $-X^4$, $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$, R^9 is hydrogen, halo, (C_{1-4}) alkyl, (C_{3-10}) aryl, (C_{0-6}) alkyl or (C_{5-10}) heteroaryl, (C_{0-6}) alkyl, with the proviso that when X^3 is cyano, then X^2 is hydrogen, fluoro, $-OH$, $-OR^4$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof, with the proviso that when $-X^4$ is other than a heteromonocyclic ring containing 5 ring member atoms, wherein no more than two of the ring member atoms comprising the ring are heteroatoms, then X^2 is fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

wherein within R^5 , X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene,

-3-

cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹²,
 -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹²,
 -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹²,
 -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³
 5 and -X⁵S(O)₂R¹³ and/or 1 radical selected from -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴,
 -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴,
 -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴,
 -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁵ is a bond or (C₁₋₆)alkylene,
 R¹² at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl,
 10 R¹³ is (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl; and R¹⁴ is (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl,
 (C₉₋₁₀)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₀)bicycloaryl(C₀₋₆)alkyl,

R¹ is hydrogen or (C₁₋₆)alkyl and R² is selected from a group consisting of hydrogen,
 cyano, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -R¹², -X⁵NR¹²C(O)NR¹²R¹²,
 15 -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹²,
 -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹²,
 -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴,
 -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹²,
 -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴,
 20 -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁵, R¹², R¹³ and R¹⁴ are as
 defined above, or R¹ and R² taken together with the carbon atom to which both R¹ and R² are
 attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene, wherein within said R² any
 heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is
 unsubstituted or substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl,
 25 (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹²,
 -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹²,
 -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹²,
 -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³,
 -X⁵S(O)₂R¹³ and -X⁵C(O)R¹³, wherein X⁵, R¹² and R¹³ are as defined above,

30 R³ is (C₁₋₆)alkyl or -C(R⁶)(R⁶)X⁶, wherein R⁶ is hydrogen or (C₁₋₆)alkyl and X⁶ is
 selected from -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹²,
 -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹²,
 -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹²,

-X⁵OP(O)(OR¹²)OR¹², -X⁵C(O)R¹³, -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴,
 -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴,
 -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹²,
 -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹² wherein X⁵, R¹², R¹³
 5 and R¹⁴ are as defined above,

R⁴ is selected from -X⁸NR¹²R¹², -X⁸NR¹²C(O)R¹², -X⁸NR¹²C(O)OR¹²,
 -X⁸NR¹²C(O)NR¹²R¹², -X⁸NR¹²C(NR¹²)NR¹²R¹², -X⁸OR¹², -X⁸SR¹², -X⁵C(O)OR¹²,
 -X⁵C(O)R¹², -X⁸OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁸S(O)₂NR¹²R¹², -X⁸NR¹²S(O)₂R¹²,
 -X⁸P(O)(OR¹²)OR¹², -X⁸OP(O)(OR¹²)OR¹², -X⁵C(O)R¹³, -X⁸NR¹²C(O)R¹³, -X⁸S(O)R¹³,
 10 -X⁸S(O)₂R¹³, -R¹⁴, -X⁸OR¹⁴, -X⁸SR¹⁴, -X⁸S(O)R¹⁴, -X⁸S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴,
 -X⁸OC(O)R¹⁴, -X⁸NR¹⁴R¹², -X⁸NR¹²C(O)R¹⁴, -X⁸NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹²,
 -X⁸S(O)₂NR¹⁴R¹², -X⁸NR¹²S(O)₂R¹⁴, -X⁸NR¹²C(O)NR¹⁴R¹² and -X⁸NR¹²C(NR¹²)NR¹⁴R¹²
 wherein X⁸ is (C₁₋₆)alkylene and X⁵, R¹², R¹³ and R¹⁴ are as defined above, with the proviso
 that when X³ is cyano and X² is -OR⁴, where R⁴ is defined as -R¹⁴, then R¹⁴ is

(C₃₋₁₀)cycloalkyl(C₁₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₁₋₃)alkyl, (C₆₋₁₀)aryl(C₁₋₆)alkyl,
 hetero(C₃₋₁₀)aryl(C₁₋₆)alkyl, (C₉₋₁₀)bicycloaryl(C₁₋₆)alkyl or
 hetero(C₈₋₁₀)bicycloaryl(C₁₋₆)alkyl,

R¹⁵ is (C₆₋₁₀)aryl, hetero(C₃₋₁₀)aryl, (C₉₋₁₀)bicycloaryl or hetero(C₈₋₁₀)bicycloaryl,

R¹⁷ is (C₁₋₆)alkyl, (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl,
 20 (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₃₋₁₀)aryl(C₀₋₆)alkyl, (C₉₋₁₀)bicycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₀)bicycloaryl(C₀₋₆)alkyl, with the proviso that when X³ is cyano, then R¹⁷ is
 (C₁₋₆)alkyl, (C₃₋₁₀)cycloalkyl(C₁₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₁₋₆)alkyl,
 (C₆₋₁₀)aryl(C₁₋₆)alkyl, hetero(C₃₋₁₀)aryl(C₁₋₆)alkyl, (C₉₋₁₀)bicycloaryl(C₁₋₆)alkyl or
 hetero(C₈₋₁₀)bicycloaryl(C₁₋₆)alkyl,

R¹⁸ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₃₋₁₀)aryl(C₀₋₆)alkyl,
 (C₉₋₁₀)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₀)bicycloaryl(C₀₋₆)alkyl, with the proviso that when
 X³ is cyano, then R¹⁸ is (C₁₋₆)alkyl, (C₃₋₁₀)cycloalkyl(C₁₋₆)alkyl,
 hetero(C₃₋₁₀)cycloalkyl(C₁₋₆)alkyl, (C₆₋₁₀)aryl(C₁₋₆)alkyl, hetero(C₃₋₁₀)aryl(C₁₋₆)alkyl,
 30 (C₉₋₁₀)bicycloaryl(C₁₋₆)alkyl or hetero(C₈₋₁₀)bicycloaryl(C₁₋₆)alkyl, and

wherein within R³, R⁴, R¹⁵, R¹⁷ and R¹⁸ any alicyclic or aromatic ring system is
 unsubstituted or substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl,
 (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹²,

-5-

$-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$,
 $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$,
 $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$,
 $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$,
5 $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$,
 $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$,
 $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, and within R^3 and R^4 any aliphatic
moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from
cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,
10 $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$,
 $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$,
 $-S(O)R^{13}$ and $-S(O)_2R^{13}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as described above, with the proviso
that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, or $-NHR^{18}$, then any
aromatic ring system present within R^{14} or R^{18} is not substituted further by halo,
15 (C_{3-10}) cycloalkyl, hetero (C_{3-10}) cycloalkyl, (C_{6-10}) aryl, hetero (C_{3-10}) aryl, (C_{9-10}) bicycloaryl or
hetero (C_{8-10}) bicycloaryl, with the proviso that only one bicyclic ring structure is present
within R^3 , R^4 or R^{15} , and the *N*-oxide derivatives, prodrug derivatives, protected derivatives,
individual isomers and mixtures of isomers thereof, and the pharmaceutically acceptable salts
and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected
20 derivatives, individual isomers and mixtures of isomers thereof

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

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

30 A fourth aspect of the invention is the processes for preparing compounds of Formula I and the *N*-oxide
derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof, and
the pharmaceutically acceptable salts thereof

DETAILED DESCRIPTION OF THE INVENTION

35 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.

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

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

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g., (C₁₋₄)alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like) Alkyl represented along with another radical (e.g., as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g., (C₆₋₁₀)aryl(C₁₋₃)alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl 3-phenylpropyl, and the like)

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g., (C₁₋₄)alkylene includes methylene (-CH₂-), ethylene (-CH₂CH₂-), trimethylene (-CH₂CH₂CH₂-), tetramethylene (-CH₂CH₂CH₂CH₂-) 2-butenylene (-CH₂CH=CHCH₂-), 2-methyltetramethylene (-CH₂CH(CH₃)CH₂CH₂-), pentamethylene (-CH₂CH₂CH₂CH₂CH₂-) and the like)

"Alkylidene" means a straight or branched saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g., (C₁₋₄)alkylidene includes methyldene (=CH₂), ethyldene (=CHCH₂), isopropylidene (=C(CH₃)₂), propylidene (=CHCH₂CH₂), allylidene (=CH[•]CH=CH₂), and the like)

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

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

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

"Aryl" means a monocyclic or fused bicyclic ring assembly containing the total number of ring carbon atoms indicated, wherein each ring is comprised of 6 ring carbon atoms and is aromatic or when fused with a second ring forms an aromatic ring assembly. For example, optionally substituted (C₆₋₁₀)aryl as used in this Application includes, but is not limited to, biphenyl-2-yl, 2-bromophenyl, 2-bromocarbonylphenyl, 2-bromo-5-fluorophenyl, 4-*tert*-butylphenyl, 4-carbamoylphenyl, 4-carboxy-2-nitrophenyl, 2-chlorophenyl, 4-chlorophenyl, 3-chlorocarbonylphenyl, 4-chlorocarbonylphenyl, 2-chloro-4-fluorophenyl, 2-chloro-6-fluorophenyl, 4-chloro-2-nitrophenyl, 6-chloro-2-nitrophenyl, 2,6-dibromophenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2-difluoromethoxyphenyl, 3,5-dimethylphenyl, 2-ethoxycarbonylphenyl, 2-fluorophenyl, 2-iodophenyl, 4-isopropylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl,

-7-

3-methylphenyl, 4-methylphenyl, 5-methyl-2-nitrophenyl, 4-methylsulfonylphenyl, naphth-2-yl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2,3,4,5,6-pentafluorophenyl, phenyl, 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-trifluoromethylsulfonylphenyl, 4-trifluoromethylsulfonylphenyl, and the like

5 Optionally substituted (C_{6-10})aryl as used in this Application includes 3-acetylphenyl, 3-*tert*-butoxycarbonylaminoethylphenyl, biphenyl-4-yl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-methoxyphenyl, naphth-2-yl, 3-phenoxyphenyl, phenyl, and the like

"Bicycloaryl" means a bicyclic ring assembly containing the number of ring carbon atoms indicated, wherein the rings are linked by a single bond or fused and at least one of the rings comprising the assembly is aromatic, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{9-10})bicycloaryl includes cyclohexylphenyl, 1,2-dihydronaphthyl, 2,4-dioxo-1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl, and the like)

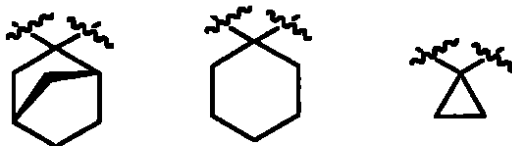
"Carbamoyl" means the radical $-C(O)NH_2$. Unless indicated otherwise, the compounds of the invention containing carbamoyl moieties include protected derivatives thereof. Suitable protecting groups for carbamoyl moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like and both the unprotected and protected derivatives fall within the scope of the invention.

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

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

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

"Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic ring or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, the instance wherein R^1 and R^2 together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-4})cycloalkylene" includes, but is not limited to, the following



"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or

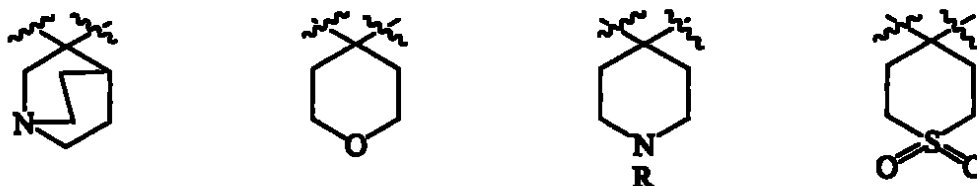
veterinary therapy applied to that animal, i.e., the "side effects" of such therapy

"Halo" means fluoro, chloro, bromo or iodo

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

"Heteroatom moiety" includes -N=, -NR-, -O-, -S- or -S(O)₂-, wherein R is hydrogen, (C₁₋₄)alkyl or a protecting group.

"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 or (C₁₋₄)alkyl. For example, the instance wherein R¹ and R² together with the carbon atom to which both R¹ and R² are attached form hetero(C₃₋₆)cycloalkyl" includes, but is not limited to, the following



in which R is hydrogen, (C₁₋₄)alkyl, or a protecting group

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

Optionally substituted hetero(C₁₋₁₀)aryl as used in this Application to define R⁴ includes benzofur-2-yl, fur-2-yl, fur-3-yl, pyrid-3-yl, pyrid-4-yl, quinol-2-yl, quinol-3-yl, thien-2-yl, thien-3-yl, and the like

"Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₄)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, optionally substituted hetero(C₂₋₁₀)bicycloaryl as used in this Application includes, but is not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, and the like. In general, the term heterobicycloaryl as used in this Application includes, for example, benzo[1,3]dioxol-5-yl, 3,4-dihydro-2H-[1,8]naphthyridinyl, 3,4-dihydro-2H-quinolinyl, 2,4-dioxo-3,4-dihydro-2H-quinazolinyl, 1,2,3,4,5,6-hexahydro[2,2']bipyridinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazmyl, 5,6,7,8-tetrahydroquinolmyl, and the like

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₄)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(C₂₋₁₀)cycloalkyl includes imidazolidinyl, morpholinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinolidinyl, 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.

"Heteromonocyclic ring" means a saturated or partially unsaturated, monocyclic ring assembly containing the number of ring carbon atoms indicated, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by one or more heteroatoms selected from -N=, -NY³-, -O- or -S-, wherein Y³ is hydrogen, alkyl, aryl, arylalkyl, -C(=O)-R¹⁴, -C(=O)-OR¹⁴ or -SO₂R¹⁴

"Heterobicyclic ring" means a saturated or partially unsaturated fused bicyclic or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by one or more heteroatoms selected from -N=, -NY³-, -O- or -S-, wherein Y³ is hydrogen, alkyl, aryl, arylalkyl, -C(=O)-R¹⁴, -C(=O)-OR¹⁴ or -SO₂R¹⁴

"Hydroxy" means the radical -OH. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable protecting groups for hydroxy moieties include benzyl and the like

"Iminoketone derivative" means a derivative containing the moiety -C(NR)-, wherein R is hydrogen or (C₁₋₄)alkyl

"Isomers" mean compounds of Formula I having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2ⁿ⁻¹ enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual

diastereomers or as a mixture of diastereomers, termed a "diastereomeric mixture" When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992) It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers. Thus, for example, the name *N*-[1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide is meant to include (*S*)-*N*-[1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (*R*)-*N*-[1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (*S*)-*N*-[(*R*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (*R*)-*N*-[(*R*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, *N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, *N*-[(*R*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (*S*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide and any mixture, racemic or otherwise, thereof

"Ketone derivative" means a derivative containing the moiety -C(O)- For example, in this Application X^3 can be 2-acetoxy-azetidin-3-yl The "carbocyclic ketone derivative" of this example of X^3 would be 2-acetoxy-4-oxo-azetidin-3-yl (see Table 3, C32)

"Nitro" means the radical -NO₂.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "wherein within R^3 and R^4 any alicyclic or aromatic ring system may be substituted further by 1-5 radicals" means that R^3 and R^4 may or may not be substituted in order to fall within the scope of the invention.

"Oxoalkyl" means alkyl, as defined above, wherein one of the number of carbon atoms indicated is replaced by an oxygen group (-O-), e.g., oxo(C₂₋₄)alkyl includes methoxymethyl, etc

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

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

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

-11-

"Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedithiolic 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 (e.g. by hydrolysis) to a compound of Formula I. For example an ester of a compound of Formula I containing a hydroxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Alternatively an ester of a compound of Formula I containing a carboxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of Formula I containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, malcates, methylenebis-*b*-hydroxynaphthoates, gentisates, methionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinzates. Suitable esters of compounds of Formula I containing a carboxy group, are for example those described by F J Lemmweber, *Drug Metab. Res.*, 1987, 18, page 379. An especially useful class of esters of compounds of Formula I containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et al., *J. Med. Chem.*, 1989, 32, page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T W Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

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

-12-

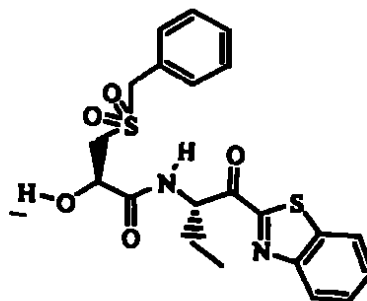
"Thioketone derivative" means a derivative containing the moiety -C(S)-

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

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

Nomenclature

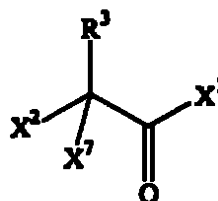
The compounds of Formula I and the intermediates and starting materials used in their preparation are named in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides, etc. Alternatively, the compounds are named by AutoNom 4.0 (Beilstein Information Systems, Inc.). For example, a compound of Formula I wherein X^2 is hydroxy, R^3 is phenylmethanesulfonylmethyl and X^1 is $-NHC(R^1)(R^2)X^3$ (in which R^1 is hydrogen, R^2 is ethyl and X^3 is 1-benzothiazol-2-yl-methanoyl), that is, a compound having the following structure



is named (R)-N-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

Presently Preferred Embodiments.

While the scope of the invention is set forth in the Summary of the Invention, certain aspects of the invention are preferred. For example, preferred is a compound of Formula I



I

in which

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$,

-13-

X^2 is hydrogen, fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

X^3 is cyano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$,
 $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,
 5 $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$, wherein R^5 is hydrogen, (C_{1-4}) alkyl,
 (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl,
 hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{5-10}) bicycloaryl (C_{0-6}) alkyl or
 hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, R^6 is hydrogen, hydroxy or (C_{1-6}) alkyl, or where X^3
 contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both
 10 attached, form hetero (C_{3-10}) cycloalkyl, hetero (C_{5-10}) aryl or hetero (C_{8-10}) bicycloaryl, R^7 is
 hydrogen or (C_{1-4}) alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo, R^{16} is hydrogen, -
 X^4 , $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$, R^9 is hydrogen, halo, (C_{1-4}) alkyl, (C_{5-10}) aryl (C_{0-6}) alkyl or
 (C_{5-10}) heteroaryl (C_{0-6}) alkyl, with the proviso that when X^3 is cyano, then X^2 is hydrogen,
 fluoro, $-OH$, $-OR^4$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

15 X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused
 heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone,
 iminoketone or thioketone derivative thereof, with the proviso that when $-X^4$ is other than a
 heteromonocyclic ring containing 5 ring member atoms, wherein no more than two of the ring
 member atoms comprising the ring are heteroatoms, then X^2 is fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or
 20 $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

wherein within R^5 , X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or
 substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene,
 cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$,
 $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$,
 25 $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$,
 $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$
 and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$,
 $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$,
 $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$,
 30 $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6}) alkylene,
 R^{12} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl,
 R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, and R^{14} is (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,
 hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl,

(C₉₋₁₀)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₀)bicycloaryl(C₀₋₆)alkyl,

R¹ is hydrogen or (C₁₋₆)alkyl and R² is selected from a group consisting of hydrogen, cyano, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -R¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹³)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁵, R¹², R¹³ and R¹⁴ are as defined above, or R¹ and R² taken together with the carbon atom to which both R¹ and R² are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene, wherein within said R² any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³ and -X⁵C(O)R¹³, wherein X⁵, R¹² and R¹³ are as defined above,

R³ is (C₁₋₆)alkyl or -C(R⁶)(R⁶)X⁶, wherein R⁶ is hydrogen or (C₁₋₆)alkyl and X⁶ is selected from -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵C(O)R¹³, -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹² wherein X⁵, R¹², R¹³ and R¹⁴ are as defined above,

R⁴ is selected from -X⁸NR¹²R¹², -X⁸NR¹²C(O)R¹², -X⁸NR¹²C(O)OR¹², -X⁸NR¹²C(O)NR¹²R¹², -X⁸NR¹²C(NR¹²)NR¹²R¹², -X⁸OR¹², -X⁸SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁸OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁸S(O)₂NR¹²R¹², -X⁸NR¹²S(O)₂R¹², -X⁸P(O)(OR¹²)OR¹², -X⁸OP(O)(OR¹²)OR¹², -X⁵C(O)R¹³, -X⁸NR¹²C(O)R¹³, -X⁸S(O)R¹³, -X⁸S(O)₂R¹³, -R¹⁴, -X⁸OR¹⁴, -X⁸SR¹⁴, -X⁸S(O)R¹⁴, -X⁸S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁸OC(O)R¹⁴, -X⁸NR¹⁴R¹², -X⁸NR¹²C(O)R¹⁴, -X⁸NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹²,

-15-

$-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5 is (C_{1-6}) alkylene and X^5 , R^{12} , R^{13} and R^{14} are as defined above, with the proviso that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, then R^{14} is

(C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-3}) alkyl, (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{5-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl,

R^{15} is (C_{6-10}) aryl, hetero (C_{5-10}) aryl, (C_{9-10}) bicycloaryl or hetero (C_{8-10}) bicycloaryl;

R^{17} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, with the proviso that when X^3 is cyano, then R^{17} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{5-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl,

R^{18} is hydrogen, (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,

hetero (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, with the proviso that when X^3 is cyano, then R^{18} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{5-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl, and

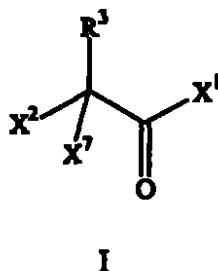
R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C_{4-8}) heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from $-NR^{21}-$ or $-O-$, wherein the ring is unsubstituted or substituted with R^2 , wherein R^2 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12} , R^{13} and R^{14} are as defined above,

wherein within R^3 , R^4 , R^{15} , R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$,

-16-

$-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$,
 $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$,
 $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, and within R^3 and R^4 any aliphatic
 moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from
 cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,
 $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$,
 $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$,
 $-S(O)R^{13}$ and $-S(O)_2R^{13}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as described above, with the proviso
 that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, or $-NHR^{18}$, then any
 aromatic ring system present within R^{14} or R^{18} is not substituted further by halo,
 (C₃₋₁₀)cycloalkyl, hetero(C₃₋₁₀)cycloalkyl, (C₆₋₁₀)aryl, hetero(C₅₋₁₀)aryl, (C₉₋₁₀)bicycloaryl or
 hetero(C₈₋₁₀)bicycloaryl, with the proviso that only one bicyclic ring structure is present
 within R^3 , R^4 or R^{15} ; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives,
 individual isomers and mixtures of isomers thereof, and the pharmaceutically acceptable salts
 and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected
 derivatives, individual isomers and mixtures of isomers thereof

Preferred is a compound of Formula I



in which

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$,

X^2 is hydrogen, fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

X^3 is $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$,
 $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,
 $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$, wherein R^5 is hydrogen, (C₁₋₄)alkyl,
 (C₃₋₁₀)cycloalkyl, (C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl, (C₀₋₃)alkyl, (C₆₋₁₀)aryl, (C₀₋₆)alkyl,
 hetero(C₅₋₁₀)aryl, (C₀₋₆)alkyl, (C₉₋₁₀)bicycloaryl, (C₀₋₆)alkyl or
 hetero(C₈₋₁₀)bicycloaryl, (C₀₋₆)alkyl, R^6 is hydrogen, hydroxy or (C₁₋₆)alkyl, or where X^3

-17-

contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both attached, form hetero(C_{3-10})cycloalkyl, hetero(C_{5-10})aryl or hetero(C_{8-10})bicycloaryl, R^7 is hydrogen or (C_{1-4})alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo, R^{16} is hydrogen, $-X^4$, $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$, R^9 is hydrogen, halo, (C_{1-4})alkyl, (C_{5-10})aryl(C_{0-6})alkyl or (C_{5-10})heteroaryl(C_{0-6})alkyl,

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof, with the proviso that when $-X^4$ is other than a heteromonocyclic ring containing 5 ring member atoms, wherein no more than two of the ring member atoms comprising the ring are heteroatoms, then X^2 is fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

wherein within R^5 , X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6})alkylene, R^{12} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl, R^{13} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl, and R^{14} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl,

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from a group consisting of hydrogen, cyano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as

defined above, or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8}) cycloalkylene or (C_{3-8}) heterocycloalkylene, wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ and $-X^5C(O)R^{13}$, wherein X^5 , R^{12} and R^{13} are as defined above;

R^3 is $-C(R^6)(R^6)X^6$, wherein R^6 is hydrogen or (C_{1-6}) alkyl and X^6 is selected from $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5 , R^{12} , R^{13} and R^{14} are as defined above,

R^4 is selected from $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ and $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^8 is (C_{1-6}) alkylene and X^5 , R^{12} , R^{13} and R^{14} are as defined above;

R^{15} is (C_{6-10}) aryl, hetero (C_{5-10}) aryl, (C_{9-10}) bicycloaryl or hetero (C_{8-10}) bicycloaryl,

R^{17} is hydrogen, (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,

hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{3-10}) aryl (C_{0-6}) alkyl,

(C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl,

R^{18} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{3-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, and

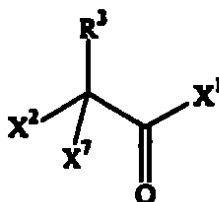
-19-

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C₄₋₈)heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from -NR²¹- or -O-, wherein the ring is unsubstituted or substituted with R¹, wherein R¹ is as defined above, and R²¹ is hydrogen, -C(O)OR¹²,
 5 -C(O)R¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -S(O)R¹³ and -S(O)₂R¹³, -S(O)R¹⁴, -S(O)₂R¹⁴,
 -C(O)R¹⁴, -C(O)OR¹⁴, -C(O)NR¹²R¹² and -S(O)₂NR¹⁴R¹², wherein R¹², R¹³ and R¹⁴ are as defined above;

wherein within R³, R⁴, R¹⁵, R¹⁷ and R¹⁸ any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl,
 10 (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹²,
 -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹²,
 -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹²,
 -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³,
 -X⁵C(O)R¹³ and -X⁵S(O)₂R¹³ and/or 1 radical selected from -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴,
 15 -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹²,
 -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴,
 -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹², and within R³ and R⁴ any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from
 cyano, halo, nitro, -NR¹²R¹², -NR¹²C(O)R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹²,
 20 -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)R¹², -OC(O)R¹², -C(O)NR¹²R¹²,
 -S(O)₂NR¹²R¹², -NR¹²S(O)₂R¹², -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³,
 -S(O)R¹³ and -S(O)₂R¹³, wherein X⁵, R¹², R¹³ and R¹⁴ are as described above, with the proviso that only one bicyclic ring structure is present within R³, R⁴ or R¹⁵, and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of
 25 isomers thereof, and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

Preferred is a compound of Formula I

-20-



I

in which

X^1 is $\text{-NHC(R}^1\text{)(R}^2\text{)X}^3$ or $\text{-NHCH(R}^{19}\text{)C(O)R}^{20}$,

X^2 is hydrogen, fluoro, -OH , -OR^4 or $\text{-NR}^{17}\text{R}^{18}$ and X^7 is hydrogen or X^2 and X^7 both

5 represent fluoro,

X^3 is cyano,

wherein within X^3 any alicyclic or aromatic ring system is unsubstituted or substituted

further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano,

halo, halo-substituted (C_{1-6}) alkyl, nitro, $\text{-X}^5\text{NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{C(O)R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{C(O)OR}^{12}$,

10 $\text{-X}^5\text{NR}^{12}\text{C(O)NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{C(NR}^{12}\text{)NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{OR}^{12}$, $\text{-X}^5\text{SR}^{12}$, $\text{-X}^5\text{C(O)OR}^{12}$,

$\text{-X}^5\text{C(O)R}^{12}$, $\text{-X}^5\text{OC(O)R}^{12}$, $\text{-X}^5\text{C(O)NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{S(O)}_2\text{NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{S(O)}_2\text{R}^{12}$,

$\text{-X}^5\text{P(O)(OR}^{12}\text{)OR}^{12}$, $\text{-X}^5\text{OP(O)(OR}^{12}\text{)OR}^{12}$, $\text{-X}^5\text{NR}^{12}\text{C(O)R}^{13}$, $\text{-X}^5\text{S(O)R}^{13}$ and $\text{-X}^5\text{S(O)}_2\text{R}^{13}$

and/or 1 radical selected from -R^{14} , $\text{-X}^5\text{OR}^{14}$, $\text{-X}^5\text{SR}^{14}$, $\text{-X}^5\text{S(O)R}^{14}$, $\text{-X}^5\text{S(O)}_2\text{R}^{14}$, $\text{-X}^5\text{C(O)R}^{14}$,

$\text{-X}^5\text{C(O)OR}^{14}$, $\text{-X}^5\text{OC(O)R}^{14}$, $\text{-X}^5\text{NR}^{14}\text{R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{C(O)R}^{14}$, $\text{-X}^5\text{NR}^{12}\text{C(O)OR}^{14}$,

15 $\text{-X}^5\text{C(O)NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{S(O)}_2\text{NR}^{14}\text{R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{S(O)}_2\text{R}^{14}$, $\text{-X}^5\text{NR}^{12}\text{C(O)NR}^{14}\text{R}^{12}$ and

$\text{-X}^5\text{NR}^{12}\text{C(NR}^{12}\text{)NR}^{14}\text{R}^{12}$, wherein X^5 is a bond or (C_{1-6}) alkylene, R^{12} at each occurrence

independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, R^{13} is (C_{1-6}) alkyl or

halo-substituted (C_{1-6}) alkyl, and R^{14} is (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,

hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{3-10}) aryl (C_{0-6}) alkyl,

20 (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{3-10}) bicycloaryl (C_{0-6}) alkyl,

R^1 is hydrogen or (C_{1-6}) alkyl and R^2 is selected from a group consisting of hydrogen,

cyano, $\text{-X}^5\text{NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{C(O)R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{C(O)OR}^{12}$, $\text{-X}^5\text{R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{C(O)NR}^{12}\text{R}^{12}$,

$\text{-X}^5\text{NR}^{12}\text{C(NR}^{12}\text{)NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{OR}^{12}$, $\text{-X}^5\text{SR}^{12}$, $\text{-X}^5\text{C(O)OR}^{12}$, $\text{-X}^5\text{C(O)R}^{12}$, $\text{-X}^5\text{OC(O)R}^{12}$,

$\text{-X}^5\text{C(O)NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{S(O)}_2\text{NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{S(O)}_2\text{R}^{12}$, $\text{-X}^5\text{P(O)(OR}^{12}\text{)OR}^{12}$,

25 $\text{-X}^5\text{OP(O)(OR}^{12}\text{)OR}^{12}$, $\text{-X}^5\text{NR}^{12}\text{C(O)R}^{13}$, $\text{-X}^5\text{S(O)R}^{13}$, $\text{-X}^5\text{S(O)}_2\text{R}^{13}$, -R^{14} , $\text{-X}^5\text{OR}^{14}$, $\text{-X}^5\text{SR}^{14}$,

$\text{-X}^5\text{S(O)R}^{14}$, $\text{-X}^5\text{S(O)}_2\text{R}^{14}$, $\text{-X}^5\text{C(O)R}^{14}$, $\text{-X}^5\text{C(O)OR}^{14}$, $\text{-X}^5\text{OC(O)R}^{14}$, $\text{-X}^5\text{NR}^{14}\text{R}^{12}$,

$\text{-X}^5\text{NR}^{12}\text{C(O)R}^{14}$, $\text{-X}^5\text{NR}^{12}\text{C(O)OR}^{14}$, $\text{-X}^5\text{C(O)NR}^{12}\text{R}^{12}$, $\text{-X}^5\text{S(O)}_2\text{NR}^{14}\text{R}^{12}$, $\text{-X}^5\text{NR}^{12}\text{S(O)}_2\text{R}^{14}$,

$\text{-X}^5\text{NR}^{12}\text{C(O)NR}^{14}\text{R}^{12}$ and $\text{-X}^5\text{NR}^{12}\text{C(NR}^{12}\text{)NR}^{14}\text{R}^{12}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as

defined above, or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are

attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene, wherein within said R² any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹²,
 5 -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹²,
 -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹²,
 -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³,
 -X⁵S(O)₂R¹³ and -X⁵C(O)R¹³, wherein X⁵, R¹² and R¹³ are as defined above,

R³ is -C(R⁶)(R⁶)X⁶, wherein R⁶ is hydrogen or (C₁₋₆)alkyl and X⁶ is selected from
 10 -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹²,
 -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹²,
 -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹²,
 -X⁵OP(O)(OR¹²)OR¹², -X⁵C(O)R¹³, -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴,
 -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴,
 15 -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹²,
 -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹² wherein X⁵, R¹², R¹³
 and R¹⁴ are as defined above,

R⁴ is selected from -X⁸NR¹²R¹², -X⁸NR¹²C(O)R¹², -X⁸NR¹²C(O)OR¹²,
 20 -X⁸NR¹²C(O)NR¹²R¹², -X⁸NR¹²C(NR¹²)NR¹²R¹², -X⁸OR¹², -X⁸SR¹², -X⁵C(O)OR¹²,
 -X⁵C(O)R¹², -X⁸OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁸S(O)₂NR¹²R¹², -X⁸NR¹²S(O)₂R¹²,
 -X⁸P(O)(OR¹²)OR¹², -X⁸OP(O)(OR¹²)OR¹², -X⁵C(O)R¹³, -X⁸NR¹²C(O)R¹³, -X⁸S(O)R¹³,
 -X⁸S(O)₂R¹³, -R¹⁴, -X⁸OR¹⁴, -X⁸SR¹⁴, -X⁸S(O)R¹⁴, -X⁸S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴,
 -X⁸OC(O)R¹⁴, -X⁸NR¹⁴R¹², -X⁸NR¹²C(O)R¹⁴, -X⁸NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹²,
 -X⁸S(O)₂NR¹⁴R¹², -X⁸NR¹²S(O)₂R¹⁴, -X⁸NR¹²C(O)NR¹⁴R¹² and -X⁸NR¹²C(NR¹²)NR¹⁴R¹²
 25 wherein X⁸ is (C₁₋₆)alkylene and X⁵, R¹², R¹³ and R¹⁴ are as defined above, with the proviso
 that when X³ is cyano and X² is -OR⁴, where R⁴ is defined as -R¹⁴, then R¹⁴ is

(C₃₋₁₀)cycloalkyl(C₁₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₁₋₃)alkyl, (C₆₋₁₀)aryl(C₁₋₆)alkyl,
 hetero(C₅₋₁₀)aryl(C₁₋₆)alkyl, (C₉₋₁₀)bicycloaryl(C₁₋₆)alkyl or
 hetero(C₈₋₁₀)bicycloaryl(C₁₋₆)alkyl,

30 R¹⁵ is (C₆₋₁₀)aryl, hetero(C₅₋₁₀)aryl, (C₉₋₁₀)bicycloaryl or hetero(C₈₋₁₀)bicycloaryl,

R¹⁷ is (C₁₋₆)alkyl, (C₃₋₁₀)cycloalkyl(C₁₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₁₋₆)alkyl,
 (C₆₋₁₀)aryl(C₁₋₆)alkyl, hetero(C₅₋₁₀)aryl(C₁₋₆)alkyl, (C₉₋₁₀)bicycloaryl(C₁₋₆)alkyl or
 hetero(C₈₋₁₀)bicycloaryl(C₁₋₆)alkyl,

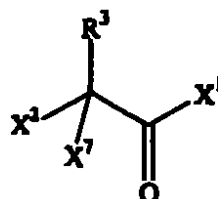
R^{18} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{3-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl, and

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C_{4-8}) heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from $-NR^{21}-$ or $-O-$, wherein the ring is unsubstituted or substituted with R^1 , wherein R^1 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12} , R^{13} and R^{14} are as defined above,

wherein within R^3 , R^4 , R^{15} , R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$; and within R^3 and R^4 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as described above, with the proviso that when X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, or $-NHR^{18}$, then any aromatic ring system present within R^{14} or R^{18} is not substituted further by halo, (C_{3-10}) cycloalkyl, hetero (C_{3-10}) cycloalkyl, (C_{6-10}) aryl, hetero (C_{3-10}) aryl, (C_{9-10}) bicycloaryl or hetero (C_{8-10}) bicycloaryl, with the proviso that only one bicyclic ring structure is present within R^3 , R^4 or R^{15} ; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof, and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

-23-

Preferred is a compound of Formula I



I

in which

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$;

X^2 is $-OH$, $-OC(O)NR^{12}R^{12}$ or $-OC(O)R^{14}$, wherein R^{12} and R^{14} are as defined below,

X^3 is cyano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$,

$-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,

$-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$, wherein R^5 is hydrogen, (C_{1-4}) alkyl,

(C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl,

hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or

hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, R^6 is hydrogen, hydroxy or (C_{1-6}) alkyl, or where X^3

contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both attached, form hetero (C_{3-10}) cycloalkyl, hetero (C_{3-10}) aryl or hetero (C_{8-10}) bicycloaryl, R^7 is

hydrogen or (C_{1-4}) alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo, R^{16} is hydrogen, $-X^4$, $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$, R^9 is hydrogen, halo, (C_{1-4}) alkyl, (C_{3-10}) aryl (C_{0-6}) alkyl or (C_{5-10}) heteroaryl (C_{0-6}) alkyl,

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof,

wherein within R^5 , X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$,

$-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$,

$-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$,

$-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$

and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$,

$-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$,

$-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$,

$-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6}) alkylene, R^{12} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, and R^{14} is (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{3-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl,

R^1 is hydrogen or (C_{1-6}) alkyl and R^2 is selected from a group consisting of hydrogen, cyano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as defined above, or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8}) cycloalkylene or (C_{3-8}) heterocycloalkylene, wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ and $-X^5C(O)R^{13}$, wherein X^5 , R^{12} and R^{13} are as defined above;

R^3 is $-C(R^6)(R^6)X^6$, wherein R^6 is hydrogen or (C_{1-6}) alkyl and X^6 is selected from $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5 , R^{12} , R^{13} and R^{14} are as defined above; and

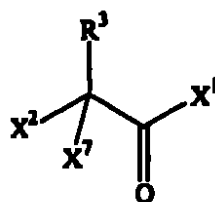
R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C_{4-8}) heterocycloalkylene, wherein no more than one of the ring member atoms comprising

-25-

the ring is a heteroatom selected from $-NR^{21}-$ or $-O-$, wherein and the ring is unsubstituted or substituted with R^1 , wherein R^1 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12} , R^{13} and R^{14} are as defined above,

wherein within R^3 , R^4 , R^{15} , R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, and within R^3 and R^4 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as described above, with the proviso that only one bicyclic ring structure is present within R^3 , R^4 or R^{15} , and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof, and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

Preferred is a compound of Formula I



I

in which.

X^1 is $-NHC(R^1)(R^2)C(O)C(O)NR^5R^6$, wherein R^5 is hydrogen, (C_{1-4}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl and R^6 is hydrogen, hydroxy or (C_{1-6}) alkyl or R^5 and R^6 together with the nitrogen atom to which they are both attached form hetero (C_{3-10}) cycloalkyl, hetero (C_{5-10}) aryl or hetero (C_{8-10}) bicycloaryl,

X^2 is hydrogen,

wherein within X^1 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6}) alkylene, R^{12} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, and R^{14} is (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl;

R^1 is hydrogen and R^2 is (C_{1-6}) alkyl, and

R^3 is $-CH_2X^6$, wherein X^6 is $-X^5NR^{12}S(O)_2R^{12}$ or $-X^5S(O)_2R^{14}$ wherein X^5 , R^{12} and R^{14} are as defined above,

wherein within R^3 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and within R^3 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$,

-C(O)R¹², -OC(O)R¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -NR¹²S(O)₂R¹², -P(O)(OR¹²)OR¹²,
 -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³ and -S(O)₂R¹³; wherein X⁵, R¹², R¹³ and R¹⁴ are
 as described above, with the proviso that only one bicyclic ring structure is present within R³,
 and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and
 5 mixtures of isomers thereof, and the pharmaceutically acceptable salts and solvates of such
 compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual
 isomers and mixtures of isomers thereof

Preferred are compounds of the invention in which X¹ is -NHC(R¹)(R²)X³ or
 -NHCH(R¹⁹)C(O)R²⁰, wherein R¹ is hydrogen or (C₁₋₆)alkyl and R² is hydrogen, (C₁₋₆)alkyl,
 10 -X⁵OR¹², -X⁵S(O)R¹³, -X⁵OR¹⁴, (C₆₋₁₀)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl or R¹ and
 R² taken together with the carbon atom to which both R¹ and R² are attached form
 (C₃₋₆)cycloalkylene or (C₃₋₆)heterocycloalkylene, wherein within said R² any heteroaryl, aryl,
 cycloalkylene or heterocycloalkylene is unsubstituted or substituted with (C₁₋₆)alkyl or
 hydroxy, particularly wherein X³ is cyano, -C(O)R¹⁶, -C(R⁶)(OR⁶)₂, -CH=CHS(O)₂R⁵,
 15 -CH₂C(O)R¹⁶, -C(O)CF₂C(O)NR⁵R⁵, -C(O)C(O)NR⁵R⁶, -C(O)C(O)OR⁵, -C(O)CH₂OR⁵,
 -C(O)CH₂N(R⁶)SO₂R⁵ or -C(O)C(O)R⁵, wherein R⁵, R⁶ and R¹⁶ are as described above, and
 R¹⁹ and R²⁰ together with the atoms to which R¹⁹ and R²⁰ are attached form
 (C₄₋₈)heterocycloalkylene, wherein no more than one of the ring member atoms comprising
 the ring is a heteroatom selected from -NR²¹- or -O-, particularly wherein the ring is
 20 unsubstituted or substituted with (C₁₋₆)alkyl or -X⁵C(O)OR¹² and R²¹ is hydrogen, (C₁₋₆)alkyl,
 -X⁵C(O)R¹², -X⁵C(O)OR¹², -R¹⁴, -X⁵C(O)R¹⁴ or -C(O)OR¹⁴

Particularly preferred are compounds of the invention in which X³ is cyano, -C(O)X⁴,
 -C(O)H, -C(O)N(CH₃)OCH₃, -CH(OCH₃)₂, -C(O)CF₃, -C(O)CF₂CF₃, -CH₂C(O)R¹⁶,
 (E)-2-benzenesulfonyl-vinyl, 2-dimethylcarbamoyl-2,2-difluoro-acetyl, 2-oxo-2-pyrrolidin-1-
 25 yl-acetyl, 2-morpholin-4-yl-2-oxo-acetyl, 2-oxo-2-piperazin-1-yl-acetyl, 2-(4-
 methanesulfonyl-piperazin-1-yl)-2-oxo-acetyl, 2-(1,1-dioxo-1λ⁶-thiomorpholin-4-yl)-2-oxo-
 acetyl, dimethylaminooxalyl, tetrahydro-pyran-4-ylaminooxalyl, 2-morpholin-4-yl-
 ethylaminooxalyl, cyclopentyl-ethyl-aminooxalyl, pyridin-3-ylaminooxalyl,
 phenylaminooxalyl, 1-benzoyl-piperidin-4-ylaminooxalyl, 1-benzylcarbamoyl-methanoyl,
 30 1-benzyloxy(oxalyl), 2-benzyloxy-acetyl, 2-benzenesulfonylamino-ethanoyl,
 2-oxo-2-phenyl-ethanoyl, 3*H*-oxazole-2-carbonyl, 5-trifluoromethyl-oxazole-2-carbonyl, 3-
 trifluoromethyl-[1,2,4]oxadiazole-5-carbonyl, 2,2,3,3,3-pentafluoro-propionyl,
 hydroxyaminooxalyl, oxalyl, 2-(1,3-dihydro-isoindol-2-yl)-2-oxo-acetyl, benzothiazol-2-

ylaminooxalyl, 2-oxo-ethyl, 2-oxazol-2-yl-2-oxo-ethyl or 2-benzooxazol-2-yl-2-oxo-ethyl, particularly wherein X^4 is 1*H*-benzimidazol-2-yl, pyrimidin-2-yl, benzooxazol-2-yl, benzothiazol-2-yl, pyridazin-3-yl, 3-phenyl-[1,2,4]oxadiazol-5-yl, 5-ethyl-[1,3,4]-oxadiazol-2-yl, 5-ethyl-[1,2,4]-oxadiazol-3-yl or 3-ethyl-[1,2,4]oxadiazol-5-yl, and R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form 1-benzoyl-3-oxo-piperidin-4-yl, 1-benzoyl-3-oxo-azepan-4-yl, 2-methyl-4-oxo-tetrahydro-furan-3-yl, 2-ethyl-4-oxo-tetrahydro-furan-3-yl, 4-oxo-1-(1-phenyl-methanoyl)-pyrrolidin-3-yl or (S)-2-acetoxy-4-oxo-azetidin-3-yl

Most particularly preferred are compounds of the invention in which X^3 is $-C(O)X^4$, in particular 1*H*-benzimidazol-2-ylcarbonyl, pyrimidin-2-ylcarbonyl, benzooxazol-2-ylcarbonyl, benzothiazol-2-ylcarbonyl, pyridazin-3-ylcarbonyl, 3-phenyl-[1,2,4]oxadiazol-5-ylcarbonyl, 5-ethyl-[1,2,4]-oxadiazol-3-ylcarbonyl, 5-ethyl-[1,3,4]-oxadiazol-2-ylcarbonyl or 3-ethyl-[1,2,4]oxadiazol-5-ylcarbonyl, or $-C(O)C(O)NR^5R^6$, in particular 2-oxo-2-pyrrolidin-1-yl-acetyl, 2-morpholin-4-yl-2-oxo-acetyl, 2-oxo-2-piperazin-1-yl-acetyl, 2-(4-methanesulfonyl-piperazin-1-yl)-2-oxo-acetyl, 2-(1,1-dioxo-1λ⁶-thiomorpholin-4-yl)-2-oxo-acetyl, dimethylaminooxalyl, tetrahydro-pyran-4-ylaminooxalyl, 2-morpholin-4-yl-ethylaminooxalyl, cyclopentyl-ethyl-aminooxalyl, pyridin-3-ylaminooxalyl, phenylaminooxalyl or 1-benzoyl-piperidin-4-ylaminooxalyl. Preferred are compounds of the invention in which X^2 is $-OH$ or $-OC(O)NR^{13}R^{12}$, particularly wherein each R^{12} independently represent hydrogen or (C₁₋₆)alkyl, wherein said alkyl is unsubstituted or substituted with hydroxy or methoxy, or X^2 is $-OC(O)NHR^{14}$, wherein R^{14} is (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl or hetero(C₃₋₁₀)cycloalkyl(C₁₋₃)alkyl, or X^2 is $-OC(O)R^{14}$, wherein R^{14} is $-NR^{22}R^{23}$ and R^{22} and R^{23} together with the nitrogen atom to which both R^{22} and R^{23} attached form a hetero(C₄₋₆)cycloalkyl ring, which ring may be unsubstituted or substituted with hydroxy, particularly in which X^2 is selected from $-OH$, dimethylcarbamoyloxy, morpholin-4-ylcarbonyloxy, piperidin-1-yl-carbonyloxy, pyrrolidin-1-yl-carbonyloxy, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, 1-methyl-piperidin-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, isopropylamino and cyclohexylamino, 4-*tert*-butoxycarbonylpiperazin-1-ylcarbonyloxy, *N*-benzyl-carbamoyloxy, pyrrolidin-1-yl-carbonyloxy, *N,N*-dimethyl-carbamoyloxy, piperidin-1-yl-carbonyloxy, 4-methanesulfonyl-piperazin-1-yl-carbonyloxy, 4-ethoxycarbonylpiperazin-1-ylcarbonyloxy, *N*-cyclohexyl-carbamoyloxy, *N*-phenyl-carbamoyloxy, *N*-(5,6,7,8-tetrahydro-naphthalen-1-yl)-carbamoyloxy, *N*-butyl-*N*-methyl-carbamoyloxy, *N*-pyridin-3-yl-carbamoyloxy, *N*-isopropyl-carbamoyloxy, *N*-pyridin-4-yl-carbamoyloxy, *N*-cyanomethyl-*N*-methyl-carbamoyloxy, *N,N*-bis-(2-methoxy-ethyl)-carbamoyloxy, *N*-phenethyl-carbamoyloxy, piperazine-carbonyloxy,

-29-

N-naphthalen-2-yl-carbamoyloxy, 4-benzyl-piperazine-1-carbamoyloxy, 4-(1-furan-2-yl-carbonyl)-piperazine-1-carbamoyloxy, thiomorpholin-4-yl-carbonyloxy, 1,1-dioxo-1λ⁶-thiomorpholin-4-yl-carbonyloxy, bis-(2-methoxy-ethyl)-carbamoyloxy, morpholin-4-ylcarbonyloxy, 2-methoxyethylcarbamoyloxy, diethylcarbamoyloxy, pyrrolidin-1-ylcarbonyloxy, 2-hydroxyethylcarbamoyloxy, tetrahydro-furan-2-ylmethylcarbamoyloxy, cyclopropylcarbamoyloxy, *tert*-butylcarbamoyloxy, 3-hydroxy-pyrrolidin-1-yl-carbonyloxy and carbamoyloxy, more particularly morpholin-4-ylcarbonyloxy, 2-methoxyethylcarbamoyloxy, diethylcarbamoyloxy, pyrrolidin-1-ylcarbonyloxy, 2-hydroxyethylcarbamoyloxy, tetrahydro-furan-2-ylmethylcarbamoyloxy, cyclopropylcarbamoyloxy, *tert*-butylcarbamoyloxy, 3-hydroxy-pyrrolidin-1-yl-carbonyloxy and carbamoyloxy

Preferred are compounds of the invention in which X² is -NHR¹⁵, wherein R¹⁵ is (C₆₋₁₀)aryl, hetero(C₅₋₁₀)aryl, (C₉₋₁₀)bicycloaryl or hetero(C₈₋₁₀)bicycloaryl, or -NR¹⁷R¹⁸, wherein R¹⁷ is hetero(C₃₋₁₀)cycloalkyl and R¹⁸ is hydrogen or R¹⁷ and R¹⁸ independently are (C₆₋₁₀)aryl(C₁₋₆)alkyl or hetero(C₅₋₁₀)aryl(C₁₋₆)alkyl, wherein within R¹⁵, R¹⁷ and R¹⁸ any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, cyano, halo, nitro, halo-substituted(C₁₋₄)alkyl, -X⁵OR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹³, -X⁵C(O)NR¹²R¹², -X⁵NR¹²S(O)₂R¹² and/or 1 radical selected from -R¹⁴, -X⁵OR¹⁴ and -X⁵C(O)NR¹⁴R¹², in particular in which X² is selected from 5-nitrothiazol-2-ylamino, 2-nitrophenylamino, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, 1-methyl-piperidin-4-ylamino, isopropylamino, di(thien-2-ylmethyl)amino or di(benzyl)amino

Preferred are compounds of the invention in which X² is -OR⁴ wherein R⁴ is 4-methoxy-phenyl, 4'-hydroxymethyl-phenyl, methoxymethyl, phenyl-methanoyl, 1-(4-phenoxy-phenyl)-methanoyl, 3-biphenyl, 4-biphenyl, 1-biphenyl-4-yl-methanoyl, naphthalen-2-yl-methanoyl, benzo[1,3]dioxol-5-yl-methanoyl, (4-methanesulfonylamino-phenyl)-methanoyl, benzo[*b*]thien-2-yl-methanoyl, 4'-chloro-4-biphenyl, 4-hydroxy-phenyl-methanoyl, 3-chloro-benzo[*b*]thien-2-yl-methanoyl, thien-2-yl-methanoyl, thien-3-yl-methanoyl, 3-chloro-thien-2-yl-methanoyl, 5-methyl-thien-2-yl-methanoyl, 4-methoxy-phenyl-methanoyl, 4-trifluoromethoxy-phenyl methanoyl, 4-chloro-phenyl-methanoyl, 3-bromophenyl, cyclohexylmethyl, 3,4-dimethoxy-phenyl-methanoyl, 3,4-difluorophenyl-methanoyl, 3-fluoro, 4-methoxy-phenyl-methanoyl, 4-fluorophenyl-methanoyl, 4-trifluoromethyl-phenyl-methanoyl, 4-formyl-phenyl-formyl, 3-formyl-phenyl-formyl, 4-methyl-pentanoyl, tetrahydro-

pyran-4-ylmethyl 2-morpholin-4-yl-2-oxo-ethyl

Most particularly preferred are compounds of the invention in which X^2 is selected from -OH, dimethylcarbamoyloxy, morpholin-4-ylcarbonyloxy, piperidin-1-yl-carbonyloxy, pyrrolidin-1-yl-carbonyloxy, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, 1-methyl-
 5 piperidin-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, isopropylamino and cyclohexylamino.

Preferred are compounds of the invention in which R^1 is hydrogen or (C_{1-6}) alkyl and R^2 is hydrogen, $-X^5OR^{12}$, $-X^5R^{12}$, (C_{5-10}) heteroaryl (C_{0-6}) alkyl, (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{5-10}) cycloalkyl (C_{0-6}) alkyl, (C_{5-10}) heterocycloalkyl (C_{0-6}) alkyl or (C_{1-6}) alkyl, or R^1 and R^2
 10 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8}) cycloalkylene or (C_{3-8}) heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is optionally substituted
 -- with 1 to 3 radicals independently selected from (C_{1-6}) alkyl and hydroxy; particularly in which R^1 is hydrogen or methyl and R^2 is hydrogen, methoxymethyl, (C_{1-6}) alkyl, phenethyl,
 15 thien-2-yl or 5-methyl-furan-2-yl or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form cyclopropylene, tetrahydro-pyran-4-ylen or methyl-piperidin-4-ylen.

Preferred are compounds of the invention in which R^3 is $-CH_2X^6$, wherein X^6 is selected from $-X^5SR^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2R^{13}$, $-X^5C(O)R^{13}$, $-X^5OR^{12}$, $-X^5SR^{14}$, $-X^5R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$,
 20 $-X^5C(O)NR^{14}R^{12}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as defined above, particularly wherein R^3 is thiophene-2-sulfonyl-methyl, 3-chloro-2-fluoro-phenyl-methane-sulfonyl-methyl, benzene-sulfonyl-methyl, phenyl-methane-sulfonyl-methyl, 2-(1,1-difluoro-methoxy)-phenyl-methane-sulfonyl-methyl, 2-benzene-sulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl, 2-phenyl-methanesulfonyl-ethyl, oxy-pyridin-2-yl-methane-sulfonyl-methyl, prop-2-ene-1-sulfonyl-methyl, 4-methoxy-phenyl-methane-sulfonyl-
 25 methyl, *p*-tolyl-methane-sulfonyl-methyl, 4-chloro-phenyl-methane-sulfonyl-methyl, *o*-tolyl-methane-sulfonyl-methyl, 3,5-dimethyl-phenyl-methane-sulfonyl-methyl, 4-trifluoro-methyl-phenyl-methane-sulfonyl-methyl, 4-trifluoro-methoxy-phenyl-methane-sulfonyl-methyl, 2-bromo-phenyl-methane-sulfonyl-methyl, pyridin-2-yl-methane-sulfonyl-methyl, pyridin-3-yl-methane-sulfonyl-methyl, pyridin-4-yl-methane-sulfonyl-methyl, naphthalen-2-yl-methane-sulfonyl-methyl, 3-methyl-phenyl-methane-sulfonyl-methyl, 3-trifluoro-
 30 methyl-phenyl-methane-sulfonyl-methyl, 3-trifluoro-methoxy-phenyl-methane-sulfonyl-methyl, 4-fluoro-2-trifluoromethoxy-phenyl-methane-sulfonylmethyl, 2-fluoro-6-trifluoromethyl-phenylmethanesulfonylmethyl, 3-chloro-phenylmethanesulfonylmethyl, 2-fluoro-phenylmethanesulfonylmethyl, 2-trifluoro-phenylmethanesulfonylmethyl, 2-cyano-phenylmethanesulfonylmethyl, 4-*tert*-butyl-phenylmethanesulfonylmethyl, 2-fluoro-3-methyl-phenyl-
 35 methane-sulfonyl-methyl, 3-fluoro-phenylmethanesulfonylmethyl, 4-fluoro-phenylmethane-sulfonylmethyl, 2-chloro-phenylmethanesulfonylmethyl, 2,5-difluoro-phenylmethane-sulfonylmethyl,

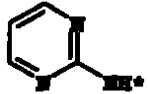
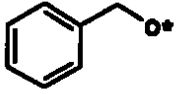
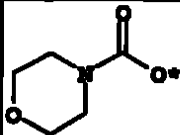
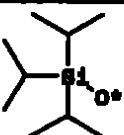
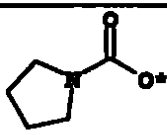
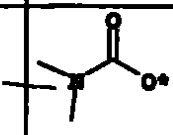
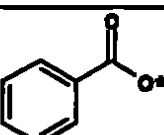
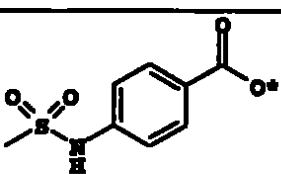
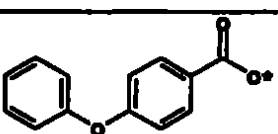
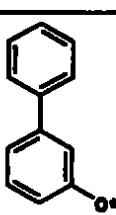
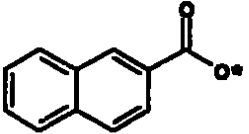
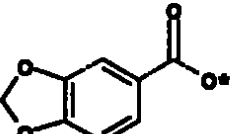
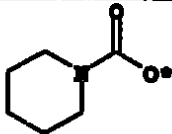
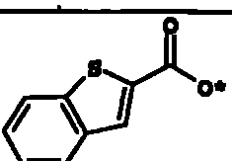
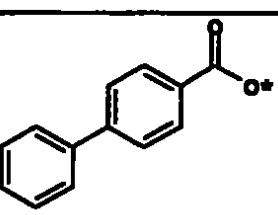
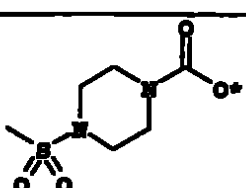
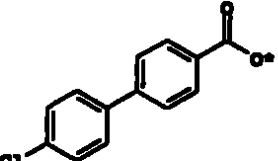
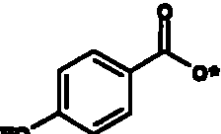
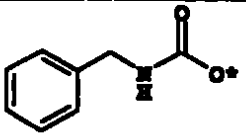
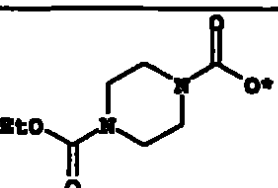
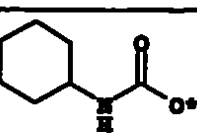
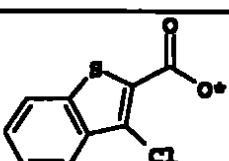
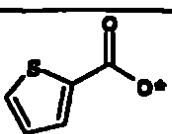
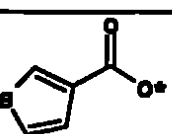
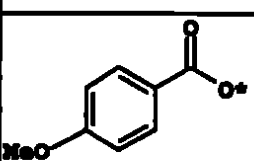
-31-

2,6-difluoro-phenylmethanesulfonylmethyl, 2,5-dichloro-phenyl-methane-sulfonylmethyl,
 3,4-dichloro-phenylmethanesulfonylmethyl, 2-(1,1-difluoro-methoxy)-phenyl-methanesulfonylmethyl,
 2-cyano-phenyl-methane-sulfonyl-methyl, 3-cyano-phenylmethanesulfonylmethyl, 2-trifluoro-methoxy-phenyl-
 methane-sulfonylmethyl, 2,3-difluoro-phenylmethanesulfonylmethyl, 2,5-difluoro-phenyl-
 5 methanesulfonylmethyl, biphenyl-2-ylmethanesulfonylmethyl, cyclohexylmethyl, 3-fluoro-phenyl-
 methanesulfonylmethyl, 3,4-difluoro-phenyl-methanesulfonylmethyl,
 2,4-difluoro-phenylmethanesulfonylmethyl, 2,4,6-trifluoro-phenylmethanesulfonylmethyl,
 2,4,5-trifluoro-phenylmethanesulfonylmethyl, 2,3,4-trifluoro-phenylmethanesulfonylmethyl,
 2,3,5-trifluoro-phenyl-methane-sulfonylmethyl, 2,5,6-trifluoro-phenylmethanesulfonylmethyl,
 10 2-chloro-5-trifluoro-methylphenylmethanesulfonylmethyl, 2-methyl-propane-1-sulfonyl, 2-fluoro-3-trifluoro-
 methylphenylmethanesulfonylmethyl, 2-fluoro-4-trifluoro-methylphenylmethanesulfonylmethyl,
 2-fluoro-5-trifluoro-methyl-phenyl-methane-sulfonyl-methyl, 4-fluoro-3-trifluoro-
 methylphenylmethanesulfonylmethyl, 2-methoxy-phenyl-methanesulfonylmethyl,
 3,5-bis-trifluoromethyl-phenylmethanesulfonylmethyl, 4-difluoromethoxy-phenylmethanesulfonylmethyl,
 15 2-difluoro-methoxy-phenyl-methanesulfonylmethyl, 3-difluoromethoxy-phenylmethanesulfonylmethyl,
 2,6-dichloro-phenylmethanesulfonylmethyl, biphenyl-4-ylmethanesulfonylmethyl,
 3,5-dimethyl-isoxazol-4-ylmethanesulfonylmethyl, 5-chloro-thien-2-yl-methane-sulfonylmethyl,
 2-[4-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-[2-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl,
 2-[3-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl,
 20 2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-(2-trifluoro-methoxy-benzene-sulfonyl)-ethyl,
 (cyanomethyl-methyl-carbamoyl)-methyl, biphenyl-3-ylmethyl, 2-oxo-2-pyrrolidin-1-yl-ethyl,
 2-benzenesulfonyl-ethyl, isobutylsulfanylmethyl, 2-phenylsulfanyl-ethyl, cyclohexylmethanesulfonylmethyl,
 2-cyclohexyl-ethanesulfonyl, benzyl, naphthalen-2-yl, benzylsulfanylmethyl,
 2-trifluoromethyl-benzylsulfanylmethyl, phenylsulfanyl-ethyl, cyclopropyl-methanesulfonylmethyl, 5-bromo-
 25 thien-2-ylmethyl, 3-phenyl-propyl, 2,2-difluoro-3-phenyl-propyl, 3,4,5-trimethoxy-
 phenylmethanesulfonylmethyl, 2,2-difluoro-3-thien-2-yl-propyl, cyclohexylethyl, cyclohexylmethyl, *tert*-
 butylmethyl, 1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-phenylpropyl, 2,2-dimethyl-
 3-phenylpropyl, 1-benzylcyclopropylmethyl, $-X^3S(O)_2R^{13}$ and $-X^3S(O)_2R^{14}$, wherein R^{13} is alkyl and R^{14} is
 phenyl which phenyl is unsubstituted or substituted.

30 Preferred are compounds of the invention in which R^3 is cyclohexylethyl, cyclohexylmethyl, *tert*-
 butylmethyl, 1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-phenylpropyl, 2,2-dimethyl-
 3-phenylpropyl, 1-benzylcyclopropylmethyl, $-X^3S(O)_2R^{13}$ or $-X^3S(O)_2R^{14}$, wherein R^{13} is alkyl and R^{14} is phenyl
 which phenyl is unsubstituted or substituted.

35 The following tables are intended to provide guidance to better carry out the present invention.
 However, they do not limit the scope of the invention. People of ordinary skill may selectively make particular
 compounds by joining O^* , HN^* or H^* of one of the fragments (A1 to A62) shown in Table 1 to the methine
 carbon atom ($*CH^*$) of one of the fragments (B1 to B93) shown in Table 2, and joining the methine carbon atom
 ($*CH^*$ or $*CF^*$) of one of the fragments (B1 to B93) shown in Table 2 to the acyl carbon atom (C^*) of one of the
 40 fragments (C1 to C91) depicted in Table 3

TABLE 1

A1		A2		A3	
A4		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	
A16		A17		A18	
A19		A20		A21	
A22		A23		A24	
A25		A26		A27	

A28		A29		A30	
A31		A32		A33	
A34		A35		A36	
A37		A38		A39	
A40		A41		A42	
A43		A44		A45	
A46		A47		A48	
A49		A50		A51	
A52		A53		A54	
A55		A56		A57	

A58		A59		A60	
A61	H+	A62	F+		

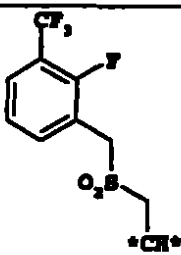
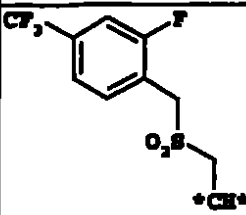
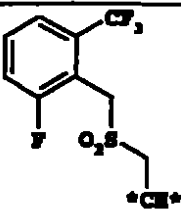
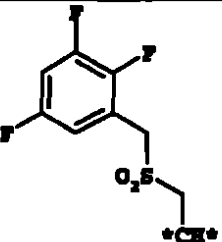
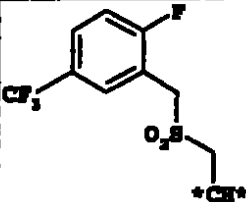
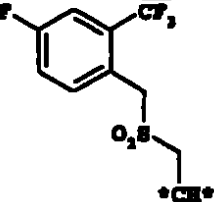
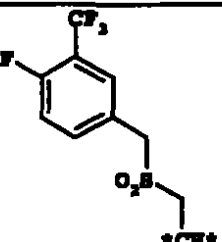
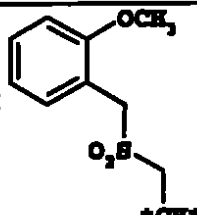
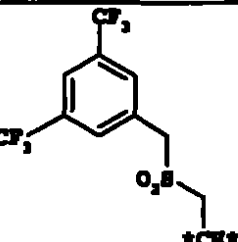
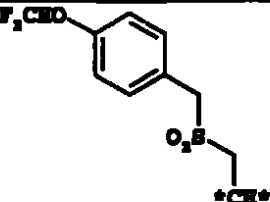
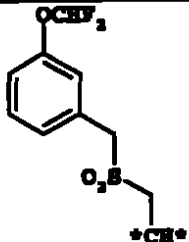
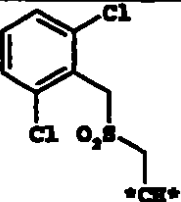
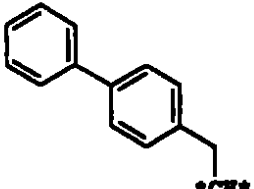
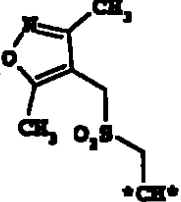
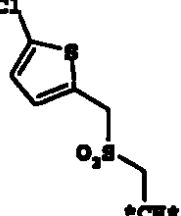
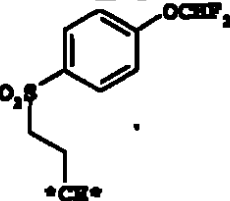
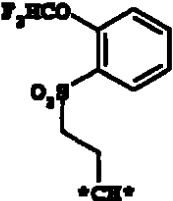
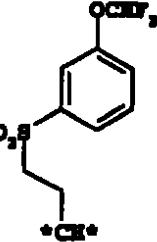
TABLE 2

B1		B2		B3	
B4		B5		B6	
B7		B8		B9	
B10		B11		B12	
B13		B14		B15	

B16		B17		B18	
B19		B20		B21	
B22		B23		B24	
B25		B26		B27	
B28		B29		B30	
B31		B32		B33	

B34		B35		B36	
B37		B38		B39	
B40		B41		B42	
B43		B44		B45	
B46		B47		B48	
B49		B50		B51	
B52		B53		B54	

-37-

B55		B56		B57	
B58		B59		B60	
B61		B62		B63	
B64		B65		B66	
B67		B68		B69	
B70		B71		B72	

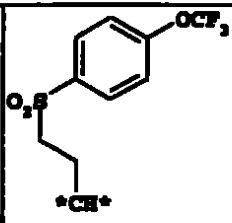
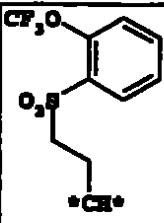
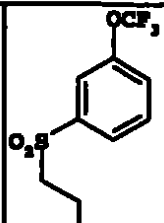
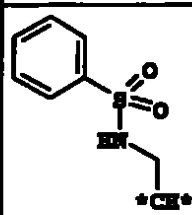
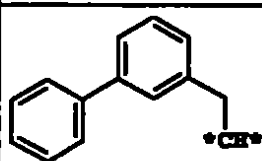
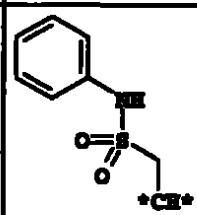
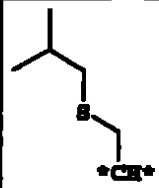
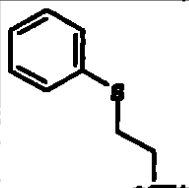
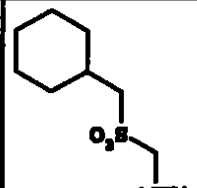
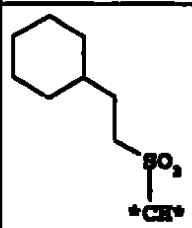
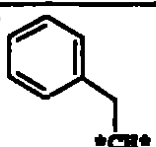
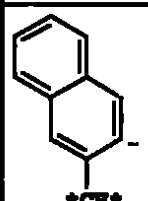
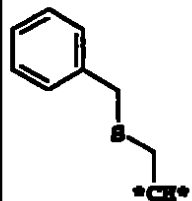
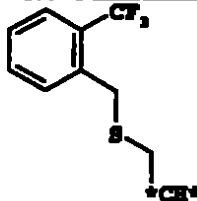
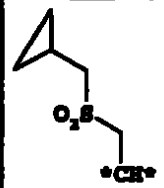
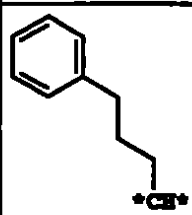
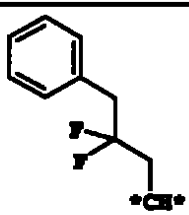
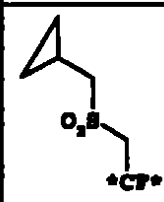
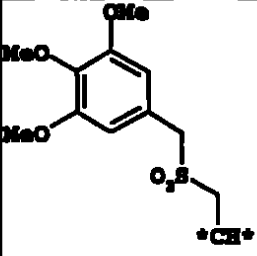
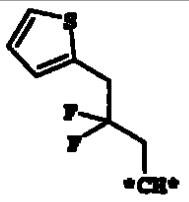
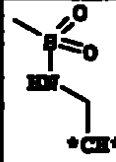
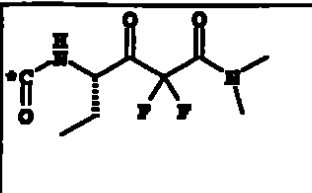
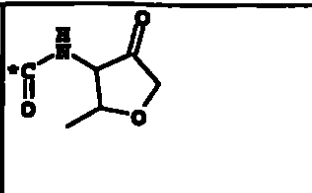
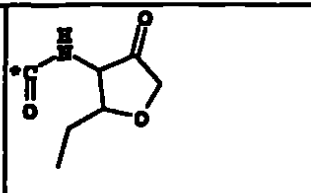
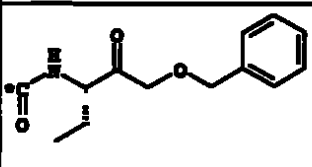
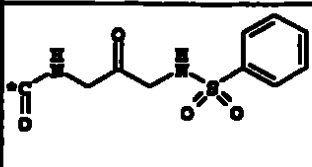
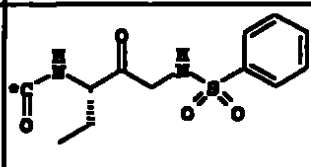
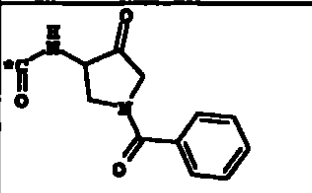
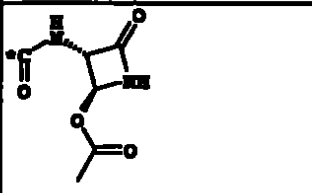
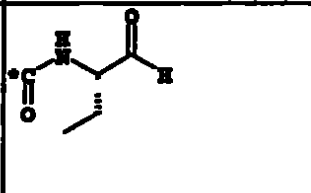
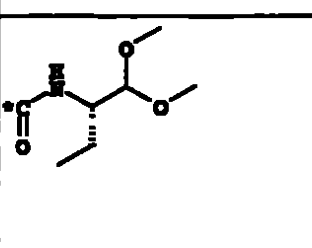
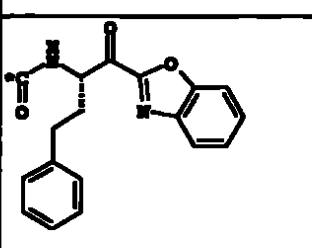
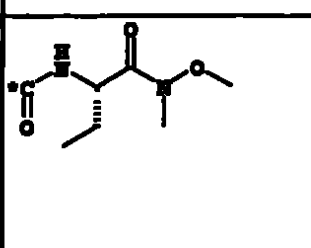
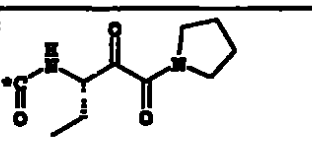
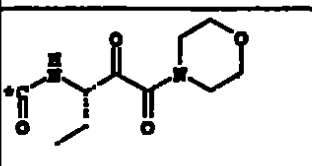
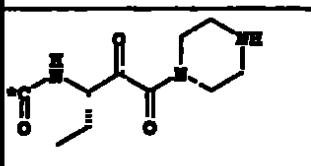
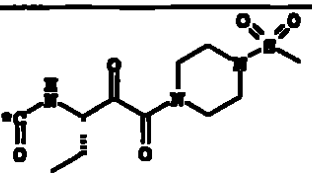
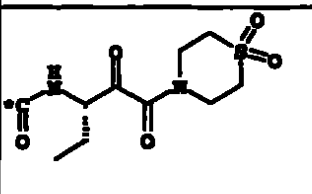
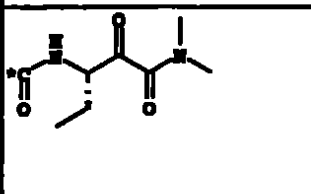
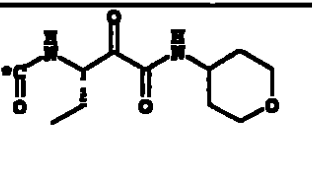
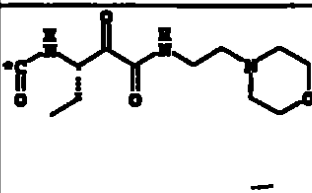
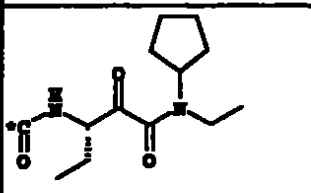
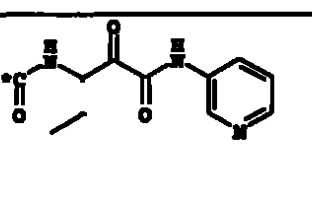
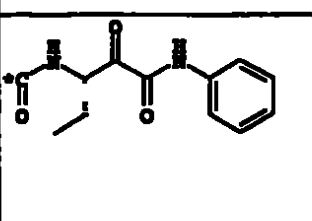
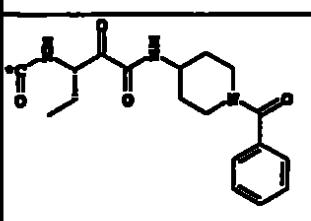
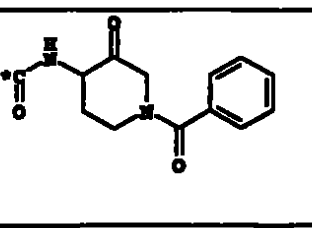
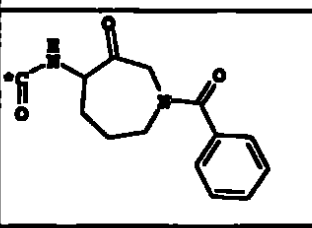
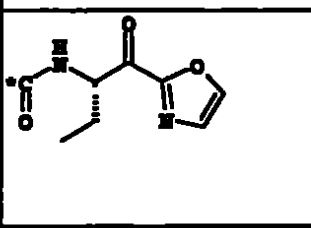
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B76		B77		B78	
B79		B80		B81	
B82		B83		B84	
B85		B86		B87	
B88		B89		B90	
B91		B92		B93	

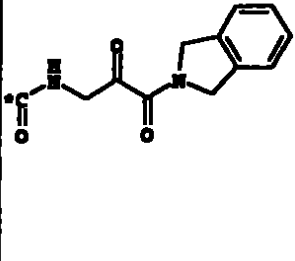
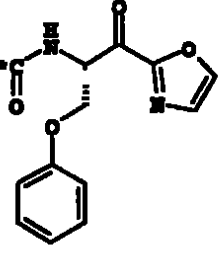
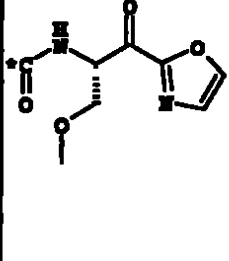
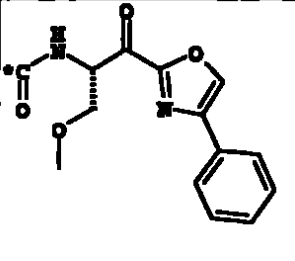
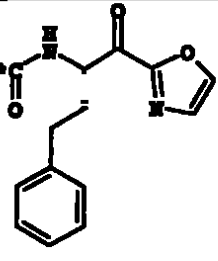
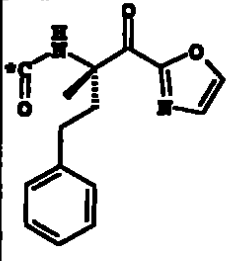
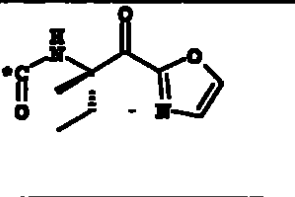
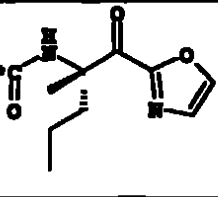
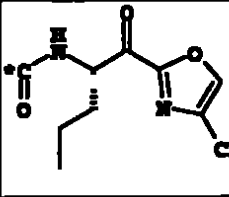
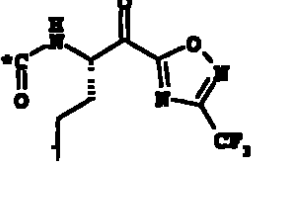
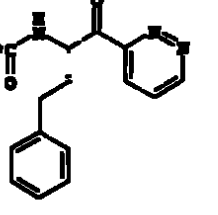
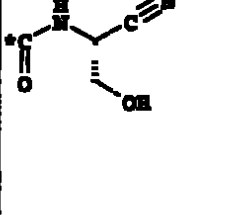
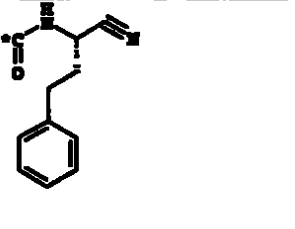
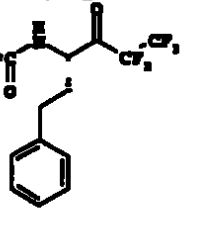
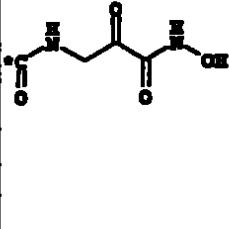
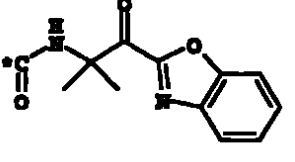
TABLE 3

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

C25		C26		C27	
C28		C29		C30	
C31		C32		C33	
C34		C35		C36	
C37		C38		C39	
C40		C41		C42	
C43		C44		C45	
C46		C47		C48	
C49		C50		C51	

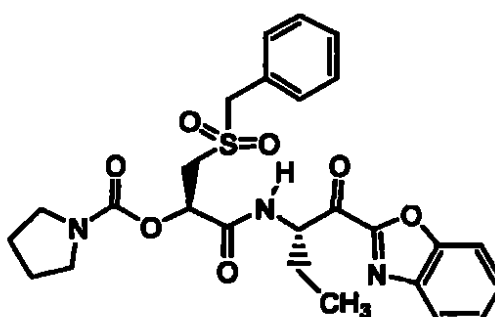
31
32

C52		C53		C54	
C55		C56		C57	
C58		C59		C60	
C61		C62		C63	
C64		C65		C66	
C67		C68		C69	
C70		C71		C72	
C73		C74		C75	

C76		C77		C78	
C79		C80		C81	
C82		C83		C84	
C85		C86		C87	
C88		C89		C90	
C91					

For convenience, compounds of the present invention may be referenced to by their "A", "B", and "C" fragment combinations. Thus, for example, the compound referenced as A7-B4-C13 is the product of the combination of group A7 in Table 1 and B4 in Table 2 and C13 in Table 3, namely pyrrolidine-1-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester

-43-



Further preferred compounds of Formula I are provided in the following

(*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

5 (*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

(*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide,

(*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide,

10 morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester,

morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester,

(*R*)-(2-methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester,

15 (*S*)-diethyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-pyrrolidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-4-Ethyl-piperazine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-2-hydroxymethyl-pyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

20 (*S*)-(2,2,2-Trifluoro-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-(2-hydroxyethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(Tetrahydrofuran-2-ylmethyl)-carbamic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-Azetidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

25 (*S*)-cyclopropyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-piperidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-(2-methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*R*)-3-hydroxy-pyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-3-hydroxy-pyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

30

- (S)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-3-cyclohexyl-propyl ester,
 morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-
 propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester,
 morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-
 5 propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester,
 morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-
 propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester,
 pyrrolidine-1-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-
 propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester,
 10 dimethyl-carbamic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-
 phenylmethanesulfonyl-ethyl ester,
 morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzylcarbamoyl-methanoyl)-
 propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester,
 morpholine-4-carboxylic acid (S)-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-
 15 phenylmethanesulfonyl-ethyl ester,
 morpholine-4-carboxylic acid (S)-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-
 phenylmethanesulfonyl-ethyl ester,
 (S)-2-[(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-
 propanoylamino]-N-methoxy-N-methyl-butylamide,
 20 (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-N-[(S)-1-formyl-propyl]-2-hydroxy-
 propionamide;
 (R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-
 propionamide,
 —
 (S)-3-[3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino]-2-oxo-
 25 pentanoic acid benzylamide,
 N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-
 phenylmethanesulfonyl]-propionamide,
 N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propyl]-3-*p*-tolylmethanesulfonyl-propionamide,
 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-2,3-dioxo-3-pyrrolidin-1-yl-
 30 propyl)-propionamide,
 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-3-morpholin-4-yl-2,3-dioxo-
 propyl)-propionamide,
 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-2,3-dioxo-3-piperazin-1-yl-propyl)-
 propionamide,

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[3-(1,1-dioxo-116-thiomorpholin-4-yl)-1-ethyl-2,3-dioxo-propyl]-propionamide,

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[1-ethyl-3-(4-methyl-sulfonyl-piperazin-1-yl)-2,3-dioxo-propyl]-propionamide,

5 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid dimethylamide,

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid cyclopentyl-ethyl-amide,

10 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid phenylamide,

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid pyridin-3-ylamide,

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (tetrahydro-pyran-4-yl)-amide,

15 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (1-benzoyl-piperidin-4-yl)-amide,

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (2-morpholin-4-yl-ethyl)-amide,

20 (R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide,

N-[1-(benzooxazole-2-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(pyrimidin-2-ylamino)-propionamide.

(R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide,

25 (2S) (4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(S)-cyano-3-phenyl-propyl)-amide,

N-(1(S)-cyano-3-phenyl-propyl)-2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyramide,

N-(1(S)-cyano-3-phenyl-propyl)-2-(S)-fluoro-4-phenyl-butyramide,

N-(1(S)-cyano-3-phenyl-propyl)-2,2-difluoro-4-phenyl-butyramide,

N-(1(S)-cyano-3-phenyl-propyl)-2-(S)-hydroxy-4-phenyl-butyramide,

30 *N*-(1(S)-cyano-3-phenyl-propyl)-2-(R)-hydroxy-4-phenyl-butyramide,

N-(1(S)-cyano-3-phenyl-propyl)-2-(R)-methoxy-4-phenyl-butyramide,

2,2-difluoro-5-phenyl-pentanoic acid (1-cyano-cyclopropyl)-amide,

N-(1(S)-cyano-3-phenyl-propyl)-4-phenyl-butyramide,

- 2,2-difluoro-5-phenyl-pentanoic acid ((S)-1-cyano-3-phenyl-propyl)-amide,
N-(4-cyano-1-ethyl-piperidin-4-yl)-3-cyclohexyl-propionamide,
N-(4-cyano-1-ethyl-piperidin-4-yl)-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide,
 (S)-tert-butyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;
 5 (R)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-(2-difluoromethoxy-phenylmethanesulfonyl)-ethyl ester,
 (S)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;
 (R)-morpholine-4-carboxylic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester;
 (R)-morpholine-4-carboxylic acid 1-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl
 10 ester;
 3-cyclohexyl-2-hydroxy-*N*-[1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propyl]-propionamide,
 (R)-*N*-[1-(benzothiazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide,
 (R)-*N*-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-
 15 ylamino)-propionamide,
 (R)-*N*-[1-(benzothiazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide,
 (R)-*N*-[1-(benzothiazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,
 20 (R)-*N*-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
 (R)-*N*-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide;
 (R)-*N*-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide;
 25 (R)-*N*-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide,
 (S)-*N*-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide;
 30 (S)-*N*-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide,
 (R)-*N*-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
 (R)-*N*-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-
 35 4-ylamino)-propionamide,

- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide,
- 5 (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,
- (1S)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-(S)-fluoro-4-phenyl-butyramide,
- 10 2,2-difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazole-2-carbonyl)-butyl]-amide,
- morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-2-cyclohexyl-ethyl ester,
- morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-ethyl ester,
- 15 morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester,
- morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester,
- morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-3-cyclohexyl-propyl
- 20 ester,
- 4-[4,4-dimethyl-2-(morpholine-4-carbonyloxy)-pentanoylamino]-3-oxo-azepane-1-carboxylic acid benzyl ester,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- 25 (R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethanesulfonyl-propionamide,
- (R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethanesulfonyl-propionamide,
- (R)-3-phenylmethanesulfonyl-N-[(S)-3-phenyl-1-(thiazole-2-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-
- 30 ylamino)-propionamide,
- (R)-3-cyclopropylmethanesulfonyl-N-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- (R)-3-phenylmethanesulfonyl-N-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- 35 (R)-N-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- {(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester,

{{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{{(S)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamic acid tert-butyl ester;

5 {{(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

10 {{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

(R)-1-[1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester;

{{(R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester;

15 {{(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

20 {{(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

(R)-1-[1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester;

25 {{(R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester;

{{(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

30 {{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{{(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

(R)-2-phenylmethanesulfonyl-1-[(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester;

35 (R)-N-[1-(Benzoxazole-2-carbonyl)-butyl]-2-[cyclopropylmethyl-(tetrahydro-pyran-4-ylmethyl)-amino]-3-phenylmethanesulfonyl-propionamide;

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide;

- (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,
- 5 (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-
- 10 phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide,
- (S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide,
- 15 S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide,
- (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- 20 (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-
- 25 phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,
- 30 N-cyanomethyl-3-cyclohexyl-propionamide,
- N-cyanomethyl-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide,
- 3-(3-cyclohexyl-propionylamino)-2-oxo-5-phenyl-pentanoic acid thiazol-2-ylamide;
- 3-cyclohexyl-N-(1-formyl-3-phenyl-propyl)-propionamide,
- 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-
- 35 propionamide,
- N-[(S)-1-(benzoxazole-2-carbonyl)-propyl]-2-(2-cyano-phenylamino)-3-cyclohexyl-propionamide,
- N-Cyanomethyl-3-cyclohexyl-2-(4-methoxy-phenoxy)-propionamide,
- 2-benzyloxy-N-cyanomethyl-3-cyclohexyl-propionamide,

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-benzyloxy-3-phenylmethanesulfonyl-propionamide,

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-methoxymethoxy-3-phenylmethanesulfonyl-propionamide,

5 (*S*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-hydroxy-3-phenyl-propionamide,

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-trisopropylsilyloxy-propionamide,

(*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

10 (*R*)-2-hydroxy-3-phenylmethanesulfonyl-*N*-[(*S*)-1-(1-pyridazin-3-yl-methanoyl)-butyl]-propionamide,

(*S*)-3-((*R*)-2-hydroxy-3-phenylmethanesulfonyl-propanoylamino)-2-oxo-pentanoic acid benzylamide;

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide,

15 (*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide,

(2*R*,5*S*)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl]-6-ethoxy-5-ethyl-

morpholin-3-one; 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 and their N-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof

Pharmacology and Utility

25 The compounds of the invention are selective 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 erythematosus, 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 also is implicated in disorders involving excessive elastolysis, such as

-51-

chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonitis and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibrin formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

5 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 ENZYME ASSAY EXAMPLES, *infra*.

10 Administration and Pharmaceutical Compositions

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I may range from about 1 microgram per kilogram body weight ($\mu\text{g/kg}$) per day to about 60 milligram per kilogram body weight (mg/kg) per day, typically from about 1 $\mu\text{g/kg/day}$ to about 20 mg/kg/day . Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 80 $\mu\text{g/day}$ to about 4.8 g/day, typically from about 80 $\mu\text{g/day}$ to about 1.6 g/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given disease.

15 The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

20 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 Formula I 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 Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I are described in Example 15, *infra*.

Chemistry

Processes for Making Compounds of Formula I

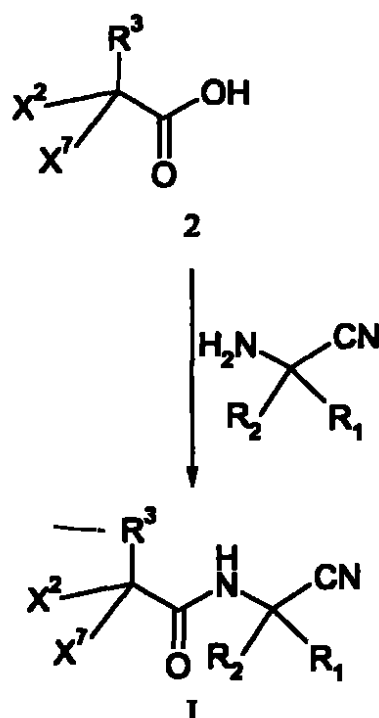
Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R. C. Larock in *Comprehensive Organic Transformations*, VCH publishers, 1989.

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 Formula I, where X^1 is $-NHC(R^1)(R^2)X^3$, can be prepared by proceeding as in the following Reaction Scheme 1.

Reaction Scheme 1

-53-



in which each X², X³, X⁷, R¹, R² and R³ are as defined for Formula I in the Summary of the Invention.

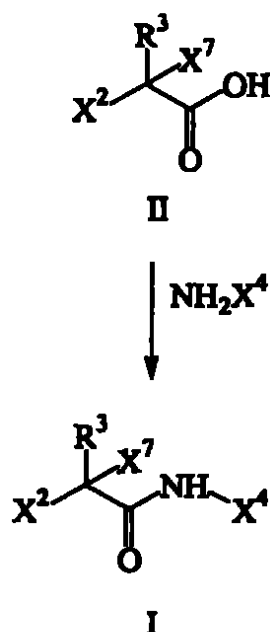
Compounds of Formula I can be prepared by condensing an acid of Formula II with an amino compound of formula NH₂CR¹R²X³. The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP[®]), tetramethyluroniumhexafluorophosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), *N*-cyclohexylcarbodiimide, *N*^ε-methylpolystyrene, or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3, , or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature and requires 5 to 10 hours to complete.

An oxidation step, if required, can be carried out with an oxidizing agent (e.g., Oxone[®], metachloroperbenzoic acid or the like) in a suitable solvent (e.g., methanol, water, or the like, or any suitable combination thereof) at ambient temperature and requires 16 to 24 hours to complete. Detailed descriptions for the synthesis of a compound of Formula I by the processes in Reaction Scheme 1 are set forth in the Examples 1 to 10, *infra*.

Compounds of Formula I, where X¹ is -NHX⁴, can be prepared by proceeding as in the following Reaction Scheme 2

Reaction Scheme 2

-54-



in which each X^2 , X^4 , X^7 and R^3 are as defined for Formula I in the Summary of the Invention.

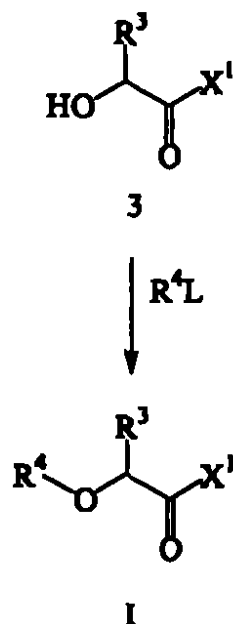
Compounds of Formula I can be prepared by condensing an acid of Formula II with an ammo
 5 compound of formula NH_2X^4 . The condensation reaction can be effected with an appropriate coupling agent
 (e.g., benzotriazol-1-yloxytrispyrrolidmophosphonium hexafluorophosphate (PyBOP[®]), *O*-(7-azabenzotriazol-1-
 yl)-1,1,3,3, tetra-methyluroniumhexafluorophosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
 hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU),
 1,3-dicyclohexylcarbodiimide (DCC), *N*-cyclohexylcarbodiimide, *N'*-methylpolystyrene, or the like) and
 10 optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt),
 or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable
 combination thereof) at ambient temperature and requires 5 to 10 hours to complete.

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

Compounds of Formula I in which X^2 is $-\text{OR}^4$, can be prepared by reacting a
 compound of Formula 3 with a compound of Formula R^4L according to the following reaction
 scheme

Reaction Scheme 3

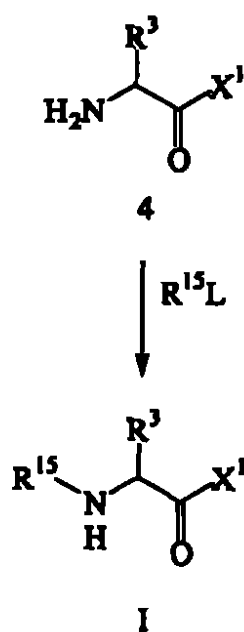
-55-



in which L is a leaving group and X^1 , R^3 and R^4 are as defined in the Summary of the Invention. A detailed description for the synthesis of a compound of Formula I by the process described above is set forth in Example 4, *infra*

5 Compounds of Formula I, in which X^2 is $-\text{NHR}^{15}$, can be prepared by reacting a compound of Formula 4 with a compound of Formula R^{15}L according to the following reaction scheme

Reaction Scheme 4



10

in which L is a leaving group and X^1 , R^3 and R^{15} are as defined in the Summary of the Invention. A detailed description for the synthesis of a compound of Formula I by the process described above is set forth in [update], *infra*

Additional Processes for Preparing Compounds of Formula I

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

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

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

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

Prodrug derivatives of the compounds of Formula I can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al* (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol 4, p 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a

-57-

suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like)

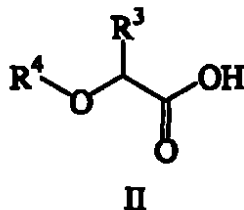
Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T W Greene, *Protecting Groups in Organic Synthesis*, 3rd edition,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

Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol

Compounds of Formula I can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981)

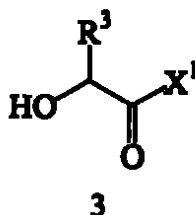
In summary, the compounds of Formula I are made by a process which comprises

(A) reacting a compound of Formula II



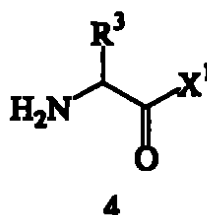
with a compound of the formula $\text{NH}_2\text{CR}^1\text{R}^2\text{X}^3$, in which X^3 , R^1 , R^2 , R^3 and R^4 are as defined in the Summary of the Invention for Formula I, or

- (B) reacting a compound of Formula II with a compound of the formula NH_2X^1 , in which X^1 , R^3 and R^4 are as defined in the Summary of the Invention for Formula I, or
- (C) reacting a compound of Formula 3



with a compound of formula R^4L , in which X^1 , R^3 and R^4 are as defined in the Summary of the Invention and L is a leaving group, or

- (D) reacting a compound of Formula 4



with a compound of formula R^{15}L , in which X^1 , R^3 and R^4 are as defined in the Summary of the Invention and L is a leaving group, and

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

Examples

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

LC/MS-Procedures.

LC/MS (Method A)

Mass Spectrometer (MS) - LCT Time-of-Flight (Micromass UK Ltd) Serial No KA014

-59-

Ionization Mode Electrospray (Positive Ion)

Scan ToF MS (Full Scan m/z 100 - 1200, sum for 0.4 s @ 50us/scan) Centroid Mode

Liquid Chromatograph (LC) Hewlett Packard HP1100 Series Binary Pump (Serial # US80301343)
& Degasser (serial # JP73008973)

5 **Mobile Phase**

A = Water + 0.05% TFA (trifluoroacetic acid) buffer

B = Acetonitrile + 0.05% TFA buffer

Gradient: 5%B to 100%B in 5 minutes

Column: Hypersil BDS C-18, 3u, 4.6mm x 50mm Reverse Phase

10 Injection volume: 5 uL

Flow rate: 1ml/min to column & to UV detector, flow split after UV detector
such that 0.75ml/min to ELS detector and 0.25ml/min to mass spectrometer

Auxiliary Detectors (i) Hewlett Packard Model HP1100 Series UV detector (serial # JP73704703)

15 wavelength = 220nm

(ii) Sedere (France) Model SEDEX 75 Evaporative Light Scattering (ELS) detector
(serial # 9970002A)

temperature = 46 deg C, Nitrogen pressure = 4bar

20 Autosampler / Injector: Gilson Model 215 Liquid Handler with Model 819 injection valve (serial # 259E8280)

LC/MS (Method B)

Same as method A, but with a different gradient: 5%B to 90%B in 3 minutes, 90%B to 100%B in 2
25 min

LC/MS (Method C)

Mass Spectrometer (MS) - LCT Time-of-Flight (Micromass UK Ltd) Serial No KA014

Ionization Mode Electrospray (Positive Ion)

30 Scan ToF MS (Full Scan m/z 100 - 1200, sum for 0.4 s @ 50us/scan) Centroid Mode

Liquid Chromatograph (LC) Hewlett Packard HP1100 Series Binary Pump (Serial # US80301343)
& Degasser (serial # JP73008973)

Mobile Phase

A = Water + 0.1% formic acid buffer

35 B = Acetonitrile + 0.1% formic acid buffer

Gradient: 5%B to 90%B in 3 minutes, 90%B to 100%B in 2 min

-60-

Column Phenomenex Synergi C-18, 2u, 4 mm x 20mm Reverse Phase

Injection volume 5 uL

Flow rate 1ml/min to column & to UV detector, flow split after UV detector
such that 0.75ml/min to ELS detector and 0.25ml/min to mass spectrometer

5

Auxiliary Detectors (i) Hewlett Packard Model HP1100 Series UV detector (serial # JP73704703)
wavelength = 220nm

(ii) Sedere (France) Model SEDEX 75 Evaporative Light Scattering (ELS) detector
(serial # 9970002A)

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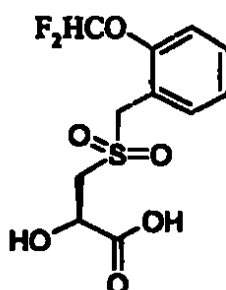
temperature = 46 deg C, Nitrogen pressure = 4bar

Autosampler / Injector Gilson Model 215 Liquid Handler with Model 819 injection valve (serial #
259E8280)

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REFERENCE EXAMPLE 1

(a) (R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid



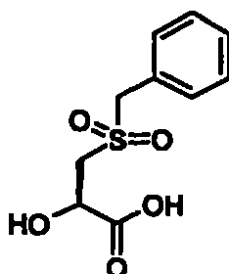
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A solution of (R)-2-*tert*-Butoxycarbonylamino-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-
propionic acid (5.19g) in CH₂Cl₂ (20mL), was treated with trifluoroacetic acid (20mL) at room
temperature. After two hours, the reaction mixture was concentrated under reduced pressure. The
white solid obtained was dissolved in 1M H₂SO₄ (100mL) and dioxane (30mL). The solution was
cooled to 0°C, NaNO₂ (1.95g in 50mL of water) was added with stirring for 1 hour. The reaction
mixture was stirred overnight at ambient temperature. The product was then concentrated and
extracted with ethyl acetate, dried with anhydrous MgSO₄, filtered, concentrated and recrystallized
from ethyl acetate to yield (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-
propionic acid (2.36g)

25

(b) (R)-2-hydroxy-3-phenylmethanesulfonyl-propionic acid

-61-



By proceeding in a manner similar to Reference Example 1(a) above but using (R)-2-*tert*-butoxycarbonylamino-3-[phenylmethanesulfonyl]-propionic acid there was prepared (R)-2-hydroxy-3-phenylmethanesulfonyl-propionic acid

5

REFERENCE EXAMPLE 2

(R)-2-Amino-N-methoxy-N-methyl-butylamide

To a solution of [(R)-1-(methoxy-methyl-carbamoyl)-propyl]-carbamic acid *tert*-butyl ester (4.92g, 20mmol) in CH₂Cl₂ (20ml) was added TFA (10mL) at room temperature. After stirring for 2 hours, the reaction mixture was concentrated to dryness under reduced pressure to produce (R)-2-amino-N-methoxy-N-methyl-butylamide TFA salt (5.4g)

REFERENCE EXAMPLE 3

(R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-2-trisopropylsilyloxy-propionic acid

(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid (7.0g, 22.58mmol), in CH₂Cl₂ (50mL) was reacted with 2, 6-lutidine (12.09g, 112.9mmol) and trisopropylsilyl-trifluoro-methanesulfonate (20.75g, 67.74mmol) at -78°C for one hour. The reaction mixture was allowed to warm to room temperature before being quenched by the addition of saturated ammonium chloride solution. The product was extracted with ethyl acetate, the solvent was removed under reduced pressure and the oil residue was then dissolved in EtOH/THF/H₂O (3:1:1, 60mL). Solid K₂CO₃ (24g) was added at room temperature and the mixture was stirred for one hour, filtered, extracted with ethyl acetate, dried with anhydrous MgSO₄, filtered and concentrated to yield (R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-2-trisopropylsilyloxy-propionic acid (8.58g)

25

Following as in reference 3 provided the following intermediate

(R)-3-Phenylmethanesulfonyl-2-trisopropylsilyloxy-propionic acid

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REFERENCE EXAMPLE 4

3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-propionic acid

A mixture of [2-(1,1-difluoro-methoxy)-phenyl]-methanethiol (190mg, 1.0mmol), acrylic acid (69μL, 1.0mmol), diisopropylethylamine (440 μL, 1.1mmol) and 0.5mL dimethylformamide was stirred at 45°C for 4 hours. Diethyl ether (5mL) and 1N HCl (2mL) was added. The layers were separated and the organic layer was washed with 1N HCl (2mL), dried over MgSO₄ and concentrated. The resulting oil was dissolved in methanol (5mL), treated with an aqueous solution (5mL) of Oxone® (921mg, 1.5mmol), and stirred for 1 hour. Methanol was removed under reduced pressure and 20mL water was added. The mixture was extracted with two 60mL portions of ethyl acetate, dried over MgSO₄ and concentrated to give 3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionic acid (160mg, 0.54mmol, 54% yield).

REFERENCE EXAMPLE 5

3-Benzylsulfanyl-2-(2-nitro-phenylamino)-propionic acid

S-benzylcysteine (1.06g, 5.0mmol), 2-fluoromtrobenzene (1.05mL, 10.0mmol), potassium carbonate (1.38g, 10.0mmol) and dimethylformamide (3mL) were combined and stirred at 100°C for 4 hours. The mixture was diluted with 40mL water and washed with two 15mL portions of diethyl ether. The aqueous layer was acidified to pH 4 with 6N HCl and extracted with two 30mL portions of ethyl acetate. The ethyl acetate layer was dried over MgSO₄ and concentrated. Diethyl ether was added and then decanted to give 3-benzylsulfanyl-2-(2-nitro-phenylamino)-propionic acid (541mg, 1.63mmol, 33%yield).

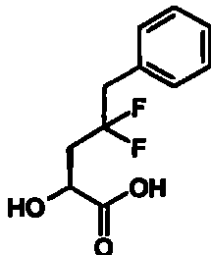
REFERENCE EXAMPLE 6

(R)-3-Benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionic acid

S-benzylcysteine (0.845g, 4mmol) and bis(trimethylsilyl)acetamide (3mL, 16mmol) were stirred at 75°C for 1 hour. 2-Bromo-5-nitrothiazole (837mg, 4mmol) and toluene (8mL) was added and the mixture was stirred at 100°C for 1 day. Toluene was removed under reduced pressure. The residue was stirred in 5mL dioxane and 5mL 1N HCl for 30 minutes. Dioxane was removed under reduced pressure and the mixture was basified with saturated NaHCO₃ and washed with 50mL ethyl acetate. The aqueous layer was acidified with 6N HCl and extracted with two 25mL portions of ethyl acetate, dried over MgSO₄, concentrated and chromatographed using a gradient of 5-10% methanol in methylene chloride to yield (R)-3-benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionic acid (42.7mg, 0.123mmol, 3% yield).

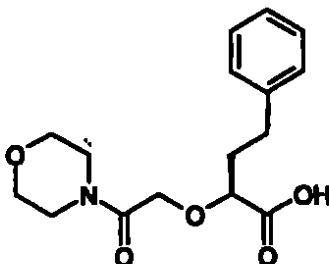
REFERENCE EXAMPLE 7

-63-

(2S)-4,4-Difluoro-2-hydroxy-5-phenyl-pentanoic acid

To a suspension of (S)-2-Amino-4,4-difluoro-5-phenyl-pentanoic acid (1.0 mmol, 230mg) in water (3mL) was added 2M sulfuric acid dropwise until the solid dissolved (ca 3mL). A solution of sodium nitrite (1.5 eq, 1.5 mmol, 104mg) in 1 ml of water was then added dropwise. The mixture was stirred at room temperature for 21 hours then extracted twice with ether (30 ml). The organic layers were dried over MgSO₄ and then concentrated in vacuum to afford **(2S)-4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid** (90 mg, 39%) as a white solid. ¹H NMR (CDCl₃) 7.3 (m, 5H), 5.6 (b, 1H), 4.61 (dd, J=8.5, 2.9 Hz, 1H), 3.3 (t, J=16.8 Hz, 2H), 2.45 (m, 1H), 2.2 (m, 2H).

10

REFERENCE EXAMPLE 8**2-(S)-(2-Morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid**

Step (i) To a cooled (0°C) solution of ethyl (2R)-2-hydroxy-4-phenylbutyrate (1.81g, 8.71 mmol), 4-nitro-benzoic acid (1.1 eq, 9.56 mmol, 1.598g) and triphenyl phosphine (1.1 eq, 9.5 mmol, 2.50g) in dry THF (80mL) under nitrogen was added slowly diethyl azodicarboxylate (1.1 eq, 9.56 mmol, 1.67g). The mixture was stirred at 0°C for 2.5 hours and then concentrated in vacuum. The residue was triturated with a mixture of ethyl acetate and heptane (1:3, 150mL) and the resulting solids were filtered off. The filtrate was concentrated in vacuum and purified over 110g silica gel, eluting with a mixture of ethyl acetate and heptane (1:4, v/v) to afford **4-nitro-benzoic acid (S)-1-ethoxycarbonyl-3-phenyl-propyl ester** (3.4g, 98%).

Step (ii) To a cooled (0°C) solution of 4-nitro-benzoic acid (S)-1-ethoxycarbonyl-3-phenyl-propyl ester (2.04g, 5.83 mmol) in MeOH (30 mL) was added potassium carbonate (1.5 eq, 8.75 mmol, 1.21g). The mixture was stirred at 0°C for 5 minutes then at room temperature for 1.5 hours and concentrated in vacuum. The residue was partitioned between water (40mL) and ethyl acetate (40mL). The organic layer was dried over MgSO₄ and then concentrated in vacuum. The residue was purified

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-64-

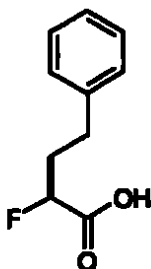
over 35g silica gel, eluted with dichloromethane to afford methyl-(2S)-2-hydroxy-4-phenyl-butyrate as a colorless oil (933mg, 82%)

Step (iii) To a solution of methyl-(2S)-2-hydroxy-4-phenyl-butyrate (300mg, 1.54 mmol) in dry DMF (3mL) under nitrogen was added sodium hydride (60%, 1.5 eq, 2.32 mmol, 92.7mg). After 5 min, 4-(2-chloroacetyl) morpholine (1.1 eq, 1.69 mmol, 277mg) was added and the mixture was stirred at room temperature for 24 hours, then diluted with water (60mL) and then neutralized with 1 N HCl. The aqueous solution was extracted twice with ethyl acetate (40mL). The organic layer was washed with water (50mL), dried over MgSO₄ and then concentrated in vacuum. The residue was purified over 35g silica gel, eluting with ethyl acetate then with 5% MeOH in ethyl acetate to afford (S)-2-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid methyl ester (117mg, 24%)

Step (iv) To a solution of (S)-2-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid methyl ester (117mg, 0.36 mmol) in MeOH:H₂O (2:1 vol, 3mL) was added lithium hydroxide hydrate (2.0 eq, 0.73 mmol, 30.5mg). The mixture was stirred at room temperature for 5 hours, then diluted with water (30mL) and then extracted with ether (30mL). The aqueous layer was acidified with 1N HCl and extracted twice with ether (30mL). The acidic extracts were dried over MgSO₄ and then concentrated in vacuum to afford (S)-2-(2-Morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid (85.5mg, 77%) as a colorless oil. ¹H NMR (CDCl₃) 10.5 (b, 1H), 7.2 (m, 5H), 4.55 (d, J=15.2 Hz, 1H), 4.14 (d, J=15.2 Hz, 1H), 3.9 (dd, J=7.6, 4.2 Hz, 1H), 4.6 (m, 6H), 3.4 (m, 2H), 2.8 (m, 2H), 2.3 (m, 1H), 2.15 (m, 1H). LC/MS 96% (M+1) 308

REFERENCE EXAMPLE 9

(2S)-2-Fluoro-4-phenyl-butyric acid



Step (i) To a cooled (0°C) solution of methyl-(2R)-2-hydroxy-4-phenyl-butyrate (1.00g, 4.80 mmol) in dry dichloromethane (3mL) was added DAST (3.0eq, 14.4 mmol, 2.32g). The mixture was stirred at room temperature for 18 hours then diluted with dichloromethane (20mL) and carefully quenched with saturated sodium bicarbonate (150mL). The aqueous layer was extracted with dichloromethane (30mL) and the organic layers were dried over MgSO₄ and then concentrated in vacuo. The residue

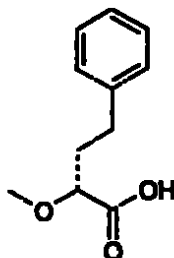
-65-

was purified over 90g silica gel, eluting with a mixture of dichloromethane and heptane (1 2 then 1 1, v/v) to afford methyl-2S-fluoro-4-phenyl-butyrate as a light yellow oil (578 mg, 57%)

5 Step (ii) To a solution of methyl-2S-fluoro-4-phenyl-butyrate (577mg, 2.74 mmol) in a mixture of MeOH H₂O (2.1 vol, 6mL) was added lithium hydroxide monohydrate (1.5 eq, 4.11 mmol, 173mg) The mixture was stirred at room temperature for 5 hours and then concentrated in vacuum The residue was diluted with water (30mL) and extracted with ether (20mL) The aqueous layer was acidified with HCl and extracted with ether (30mL) The acidic extract was dried over MgSO₄ and then concentrated in vacuum to afford 2(S)-fluoro-4-phenyl-butyric acid as a yellow oil (486 mg, 97%) ¹H NMR (CDCl₃) 7.5 (b, 1H), 7.3 (m, 5H), 4.95 (ddd, J=48.9, 6.9, 5.4 Hz, 1H), 2.85 (m, 2H), 2.25 (m, 2H) MS (CI) M+1 183

REFERENCE EXAMPLE 10

2(R)-Methoxy-4-phenyl-butyric acid



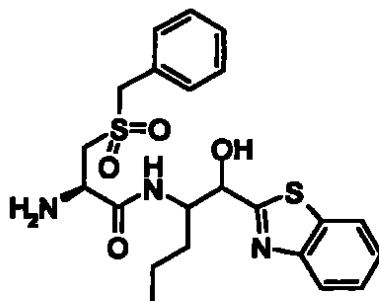
15 Step 1 To a solution of ethyl-(2R)-2-hydroxy-4-phenyl-butyrate (500mg, 2.40 mmol) in dry DMF (4mL) under nitrogen was added sodium hydride (60%, 2.0 eq, 4.80 mmol, 192mg) followed by methyl iodide (3.0 eq, 7.20 mmol, 1.02g) The mixture was stirred at room temperature for 22 hours, then diluted with NH₄Cl (100mL) and extracted with ethyl acetate (50mL) The organic layer was dried over MgSO₄ and then concentrated in vacuum The residue was purified over 35g silica gel, eluting with ethyl acetate and heptane (1 3, v/v) to afford (R)-2-methoxy-4-phenyl-butyric acid ethyl ester (480 mg, 90%)

25 Step 2 To a solution of (R)-2-methoxy-4-phenyl-butyric acid ethyl ester (480mg, 2.8 mmol) in MeOH H₂O (2.1 vol, 9mL) was added lithium hydroxide hydrate (2.0 eq, 4.32 mmol, 181mg) The mixture was stirred at room temperature for 2.5 hours, then diluted with water (20mL) and then extracted with ether (20mL) The aqueous layer was acidified with 1N HCl and then extracted twice with ether (30 mL) The combined extracts were dried over MgSO₄ and then concentrated in vacuum to afford 2(R)-methoxy-4-phenyl-butyric acid (426mg, quant.) as a colorless solid ¹H NMR (CDCl₃) 7.25 (m, 5H), 3.8 (dd, J=6.8, 5.2 Hz, 1H), 3.48 (s, 3H), 2.78 (t, J=7.3 Hz, 2H), 2.1 (m, 2H) MS (CI) M 194

Following as in reference 10 but using benzyl bromide in step 2 provided the following intermediate
2(R)-Benzyloxy-4-phenyl-butyric acid

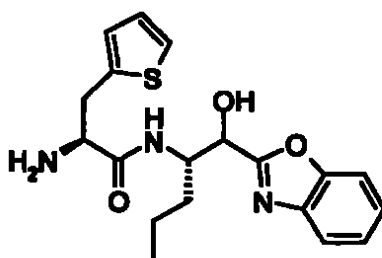
REFERENCE EXAMPLE 11

- 5 (a) (R)-2-Amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide



A solution of {(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamuc acid tert-butyl ester {888mg, 1.58mmol, Example 27(a)} in
 10 dichloromethane (5mL) was treated with trifluoroacetic acid (5mL). The mixture was stirred at room temperature for one hour and then evaporated. The residue was dissolved in dichloromethane (20mL) and this solution was treated with Silicycle Triamine (4.3g, 16mmol). The mixture was stirred at room temperature for two hours and then filtered. The filtrate was evaporated to give the title compound (692mg, 94%). LC/MS $m/z=562$ (M+H)

- 15 (b) (S)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-thiophen-2-yl-propionamide

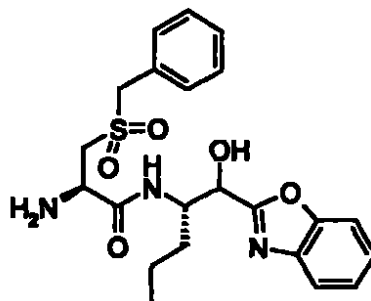


By proceeding in a manner similar to Reference Example 11(a) above but using {(S)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamuc acid tert-butyl
 20 ester {790mg, 1.67mmol, Example 27(c)} and subjecting the reaction product to flash chromatography on silica eluting with a mixture of ethyl acetate and methanol (9:1, v/v) there was prepared (S)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-thiophen-2-yl-propionamide (415mg, 66%). LC/MS $m/z=374$ (M+H)

- 25 (c) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-

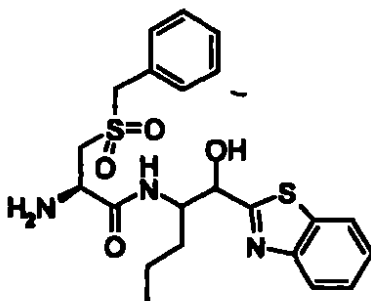
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-67-

propionamide

By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-
 5 (Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid
 tert-butyl ester (908mg, 1.66mmol, Example 27(b)) there was prepared (R)-2-amino-N-[(S)-1-
 (benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (726mg, 98%)
 LC/MS $m/z=446$ (M+H)

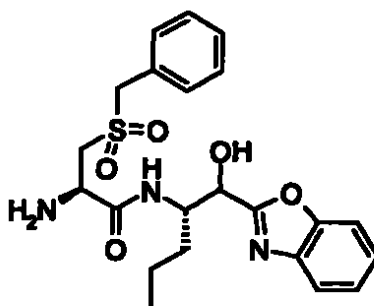
(d) (R)-2-Amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-
 propionamide



By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[1-
 (Benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid
 15 tert-butyl ester (0.63mmol, Example 27(d)) there was prepared (R)-2-Amino-N-[1-(benzothiazol-2-yl-
 hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (212mg, 73%) LC/MS $m/z=462$
 (M+H)

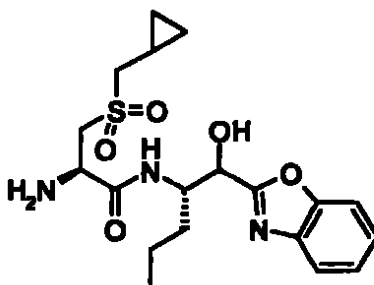
(e) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-
 propionamide

-68-



By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {1.7 mmol, Example 27(c)} there was prepared (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (726mg, 98%) LC/MS $m/z=446$ (M+H)

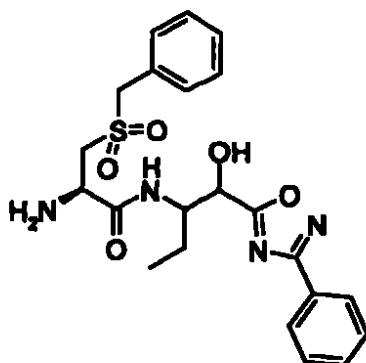
(f) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-propionamide



By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {450mg, 0.88mmol, Example 27(f)} there was prepared (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-propionamide (360mg, 0.879mmol, 100%).
LC/MS $m/z=410$ (M+H)

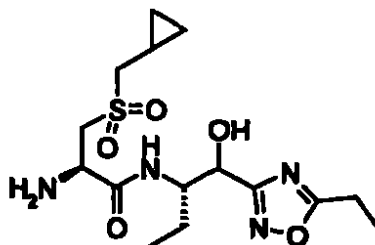
(g) (R)-2-Amino-N-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-3-phenylmethanesulfonyl-propionamide

-69-



By proceeding in a manner similar to Reference Example 11(a) above but using (R)-1-[1-[Hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamate acid tert-butyl ester (Example 27(g)) there was prepared (R)-2-amino-N-[1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl]-3-phenylmethanesulfonyl-propionamide, LC/MS $m/z=481$ (M+Na), 459(M+H)

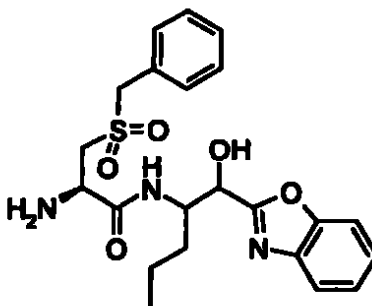
(h) (R)-2-Amino-3-cyclopropylmethanesulfonyl-N-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl]-propionamide



By proceeding in a manner similar to Reference Example 11(a) above but using ((R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl)-carbamate acid tert-butyl ester (Example 27(i)) there was prepared (R)-2-amino-3-cyclopropylmethanesulfonyl-N-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl]-propionamide, LC/MS $m/z=375$ (M+H)

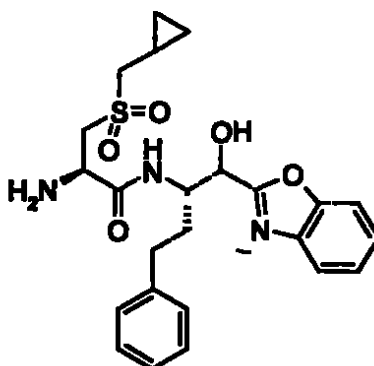
(i) (R)-2-Amino-N-[1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide

-70-



By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {Example 27(j)} there was prepared (R)-2-Amino-N-[1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide LC/MS m/z=446(M+H)

(j) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-propionamide

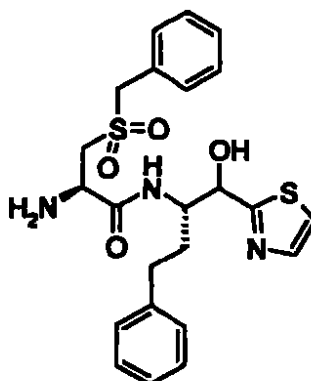


By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {Example 27(k)} there was prepared (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-propionamide, LC/MS m/z=472(M+H)

(k) (R)-2-Amino-N-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-3-phenylmethanesulfonyl-propionamide

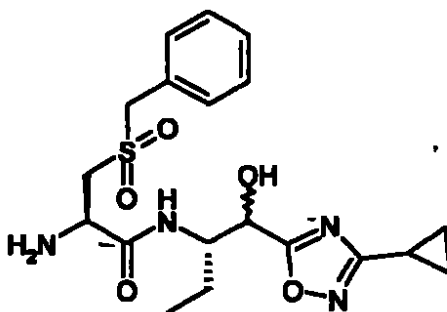
46
47

-71-



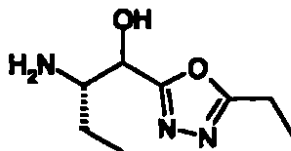
By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamate acid *tert*-butyl ester {Example 27(f)} there was prepared (R)-2-amino-N-[(S)-1-(hydroxy-thiazol-2-yl)-methyl]-3-phenyl-propyl]-3-phenylmethanesulfonyl-propionamide.

(l) (R)-2-Amino-3-phenylmethanesulfonyl-N-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propyl]-propionamide



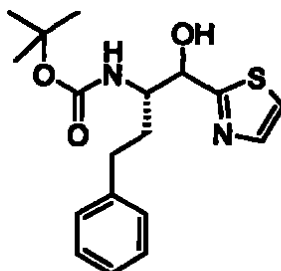
By proceeding in a manner similar to Reference Example 11(a) above but using ((R)-2-phenylmethanesulfonyl-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl)-ethyl)-carbamate acid *tert*-butyl ester {Example 27(g)} there was prepared (R)-2-amino-3-phenylmethanesulfonyl-N-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propyl]-propionamide.

(m) 2-amino-1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-butan-1-ol

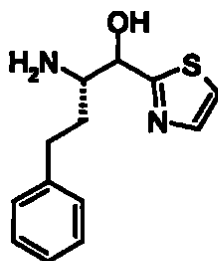


By proceeding in a manner similar to Reference Example 11(a) above but using {1-[(5-ethyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl)-carbamate acid *tert*-butyl ester (Reference Example 16) there was prepared 2-amino-1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-butan-1-ol.

-72-

REFERENCE EXAMPLE 12[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-carbamic acid tert-butyl ester

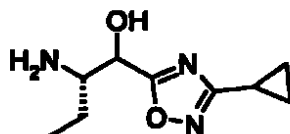
n-Butyllithium (4.2 ml, 10.5 mmol, 2.5 M solution in hexanes) was mixed with 16 ml diethylether and
 5 the resulting solution cooled to -78°C . 2-Bromothiazole (1.64 g, 10 mmol) was dissolved in a mixture
 of 2 ml diethylether and 1 ml THF. This solution was added dropwise to the n-butyllithium solution.
 The resulting reaction mixture was stirred for 15 min. A solution of [(S)-1-(Methoxy-methyl-
 carbamoyl)-3-phenyl-propyl]-carbamic acid tert-butyl ester (1.4 g, 4.3 mmol) in 20 ml THF was added
 dropwise to the reaction mixture. Stirring was continued for one hour and the reaction mixture
 10 quenched by addition of 50 ml water. After warming to room temperature the phases were separated
 and the aqueous phase extracted with ethyl acetate. The combined organic phases were washed with
 brine and dried with magnesium sulfate. The solvents were evaporated under vacuum to give 1.4 g [(S)-
 3-Phenyl-1-(thiazole-2-carbonyl)-propyl]-carbamic acid tert-butyl ester as a brown solid.
 [(S)-3-Phenyl-1-(thiazole-2-carbonyl)-propyl]-carbamic acid tert-butyl ester (1.41 g, 4.1 mmol) was
 15 dissolved in 50 ml ethanol and the solution cooled to 0°C . Sodium borohydride (155 mg, 4.1 mmol) was
 added and the reaction mixture stirred for 90 minutes. Water was added and the aqueous phase
 acidified by addition of 1 M hydrochloric acid. The aqueous phase was extracted with ethyl acetate.
 The combined organic phases were washed with brine and dried with magnesium sulfate. The solvent
 was evaporated under reduced pressure (1.32, 3.8 mmol, 88%). LC/MS $m/z=271$ (M+H-isobutene),
 20 249 (M+H-boc)

REFERENCE EXAMPLE 13(S)-2-Amino-4-phenyl-1-thiazol-2-yl-butan-1-ol

25 [(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-carbamic acid tert-butyl ester (1.32 g,
 3.8 mmol, Reference Example 12) was dissolved in 10 ml dichloromethane. Trifluoroacetic acid was
 added and the resulting reaction mixture stirred for two hours. The solvents were evaporated under

-73-

reduced pressure and saturated sodium bicarbonate solution was added. The solution was extracted with ethyl acetate. The combined organic phases were washed with brine and dried with magnesium sulfate. The solvent was evaporated and the crude product purified via flash chromatography (eluted with ethyl acetate followed by 10% methanol in ethyl acetate) to give (S)-2-amino-4-phenyl-1-thiazol-2-yl-butan-1-ol (466mg, 1.87mmol, 49%) LC/MS $m/z=249(M+H)$

REFERENCE EXAMPLE 14(S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol

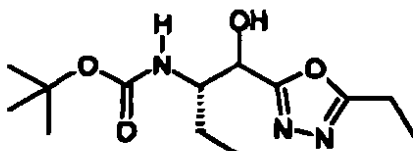
A solution of boc-3S-amino-2-hydroxypentanoic acid (2.00g, 8.57mmol) and 1.20 equivalents of cyclopropanecarboxamidoxime (1.03g, 10.29mmol) in 20 mL of dichloromethane was stirred at 0°C as 1.25 equivalents of N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.70mmol/g, 6.30g, 10.72mmol) was added in portions and the reaction mixture stirred under nitrogen for three hours while warming to 15°C. The reaction mixture was filtered and the resin washed with dichloromethane. Evaporate under vacuum to dryness [LC/MS $m/z=338(M+H+Na)$]. The residue is dissolved in 20 mL of tetrahydrofuran and heated in a microwave reactor at 160°C for three minutes. Evaporate under vacuum to dryness [LC/MS $m/z=320(M+H+Na)$]. The residue is dissolved in 50 mL of dichloromethane and stirred at room temperature as a 50 mL solution of 50% trifluoroacetic acid in dichloromethane was added dropwise. After three hours the reaction was evaporated under vacuum to dryness and dissolved in 50 mL 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 (S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol 1.04g (61% overall) [LC/MS $m/z=198(M+H)$]

REFERENCE EXAMPLE 15Ethyl-1,3,4-oxadiazole.

A mixture of the formic hydrazide (60g, 1mole), triethylorthopropionate (176.26g, 1mole) and p-toluenesulfonic acid (250mg) was heated at 120°C for 12 hours. The ethanol was removed under vacuum and the residue was distilled under vacuum to yield 24g of ethyl-1,3,4-oxadiazole. ^1H NMR (DMSO- d_6) 9.34 (1H, s), 2.86 (2H, q), 1.25 (3H, t)

REFERENCE EXAMPLE 16{1-[(5-Ethyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl}-carbamic acid *tert*-butyl ester

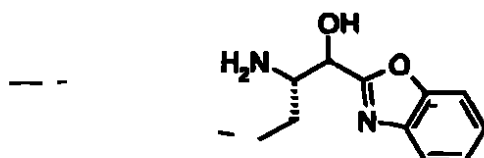
-74-



To a stirred solution of the ethyl-1,3,4-oxadiazole (4.66g, 48mmol, Reference Example 15) in THF (50ml) was added *n*-BuLi (1.6M solution in 30ml of hexane) drop-wise under N₂ at -78°C. After 1 hour, MgBr·Et₂O (12.38g, 48mmol) was added and the reaction mixture was allowed to warm to -45°C for 1 hour before being treated with 2-Boc-Nlu-aldehyde (3.2g, 24mmol) in THF (20ml). The reaction mixture was stirred for 1 hour, quenched with saturated NH₄Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO₄, and concentrated. The residue was purified by silica gel column chromatography to yield 1-((5-ethyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl)-propyl]-carbamate tert-butyl ester (2.13g). ¹H NMR (DMSO-*d*₆) δ 6.65, 6.52 (1H, d, d, J=9.2Hz, J=9.2Hz, NH, diastereomer), 6.14, 5.95 (1H, d, d, J=5.6Hz, J=5.6Hz, OH, diastereomer), 4.758, 4.467 (1H, m, diastereomer), 3.7-3.55 (1H, m), 2.8 (2H, q), 1.33 (12H, t), 1.25-1.21 (2H, m), 0.82 (3H, m). MS 284.1 (M-1), 286 (M+1), 308 (M+Na).

REFERENCE EXAMPLE 17

(a) (S)-2-Amino-1-benzooxazol-2-yl-butan-1-ol

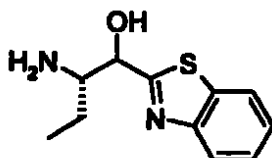


Step 1 Benzooxazole (600 mg, 5 mmol) in 20 ml THF was cooled to -5°C and isopropyl magnesium chloride (2M in THF, 2.5 ml, 5 mmol) was added. After stirring for 1 hour at -5°C, (S)-[1-formyl-propyl]-carbamate tert-butyl ester (561 mg, 3 mmol, Reference Example 18(a)), prepared as in reference 15, in 10 ml THF was added. The reaction was allowed to warm to room temperature with stirring for 2 hours. The reaction was quenched with saturated ammonium chloride solution, excess THF solvent removed. The residue was extracted with EtOAc, washed with brine, dried with anhydrous MgSO₄, filtered and concentrated. The crude residue was purified by chromatograph to yield 688 mg product (75%), LC-MS 305.2 (M-1), 307.0 (M+1).

Step 2 (S)-[1-(Benzooxazol-2-yl)-hydroxy-methyl]-propyl]-carbamate tert-butyl ester (275mg, 0.89mmol) and MeCl₂ (5ml) were mixed and TFA (1ml) was added at room temperature. After stirring for 1 hour, the solvent and excess TFA were removed under vacuum to produce 260mg of (S)-2-amino-1-benzooxazol-2-yl-butan-1-ol TFA salt.

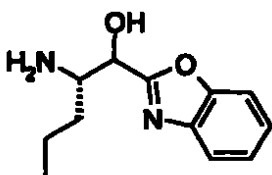
(b) (S)-2-Amino-1-benzothiazol-2-yl-butan-1-ol

-75-



By proceeding in a similar manner to Example 17(a) but using benzothiazole in Step 1 there was prepared (S)-2-amino-1-benzothiazol-2-yl-butanol TFA salt.

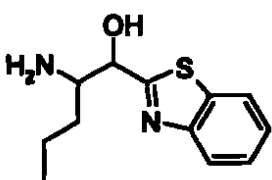
5 (c) (S)-2-amino-1-benzooxazol-2-yl-pentanol



By proceeding in a similar manner to Example 17(a) but using (S)-(1-formyl-butyl)-carbamic acid tert-butyl ester {561 mg, 3 mmol, Reference Example 18(b)} in Step 1 there was prepared (S)-2-amino-1-benzooxazol-2-yl-pentanol

10

(d) 2-amino-1-benzothiazol-2-yl-pentanol



By proceeding in a similar manner to Example 17(a) but using benzothiazole and (S)-(1-formyl-butyl)-carbamic acid tert-butyl ester {561 mg, 3 mmol, Reference Example 18(b)} in Step 1 there was prepared 2-amino-1-benzothiazol-2-yl-pentanol

15

REFERENCE EXAMPLE 18

20 (a) (S)-(1-Formyl-propyl)-carbamic acid tert-butyl ester

(S)-(+)-2-amino-1-butanol (50g, 561mmol) in 200ml of water and 200ml dioxane was cooled to 0°C and mixed with NaOH (26.9g, 673mmol) and di-t-butyl-dicarbonate (146.96g, 673mmol). After the addition, the reaction was allowed to warm to room temperature. The reaction mixture was stirred for 2 hours. After removing the dioxane, the residue was extracted with EtOAc, then washed with brine and dried with anhydrous MgSO₄, filtered and concentrated. Without further purification, the crude product (120g) was used for next step reaction.

25

A solution of oxlyl chloride (40.39g, 265mmol) in 700ml of MeCl₂ was stirred and cooled to -60°C. Dimethylsulfoxide (51.7g, 663mmol) in 100 ml of MeCl₂ was added drop wise. After 10

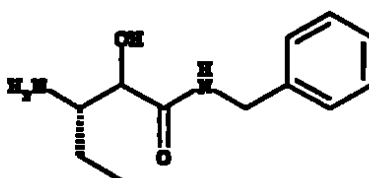
-76-

minutes a solution of (S)-2-boc-amino-1-butanol (50 g, 265 mmol) in 100ml of MeCl₂ was added drop wise at -70°C. The reaction mixture was allowed to warm to -40°C for 10 minutes and then cooled to -70°C again. A solution of triethylamine (74.9 g, 742mmol) in 100 ml of MeCl₂ was added. The reaction mixture was allowed to warm to room temperature over 2 hours. 100mls of saturated sodium dihydrogen phosphate was added, and then the organic layer was washed with brine and dried over MgSO₄. The solvent was removed to yield 45g of (S)-(1-formyl-propyl)-carbamic acid tert-butyl ester; H¹ NMR (DMSO-d₆) 9.4(1H, s), 7.29(1H, br), 3.72(1H, m), 1.69(2H, m), 1.4-1.2(9H, s), 0.86(3H, t).

(b) By proceeding in a similar manner to Reference Example 18(a) but using (S)-(+)-2-amino-1-pentanol there was prepared (S)-(1-formyl-butyl)-carbamic acid tert-butyl ester.

REFERENCE EXAMPLE 19

(S)-3-Amino-2-hydroxy-pentanoic acid benzylamide



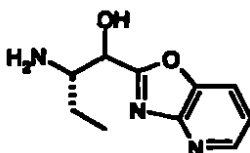
Step 1 (1S)-(2-Cyano-1-ethyl-2-hydroxyethyl)carbamic acid tert-butyl ester (10g, 46.7mmol) was dissolved in 1,4-dioxane (100mL). Anisole (5mL) was added and then concentrated HCl (100mL). The mixture was heated under reflux for 24 hours. The mixture was evaporated to dryness under vacuum and re-dissolved in 100mL water. The solution was washed with ether and then neutralized with saturated aqueous NaHCO₃. Di-tert-butyl dicarbonate (10g, 46mmol) was added with 1,4-dioxane (200mL), and the mixture was stirred at ambient temperature for 24 hours. The dioxane was removed under vacuum and the remaining aqueous solution was washed with ether. The solution was acidified with 1N HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate and evaporated to yield 3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (4.5g) as yellowish oil.

Step 2 3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (300mg, 1.29mmol) was combined with EDC (400mg, 2.1mmol) and HOBt (400mg, 2.6mmol). A solution of benzylamine (0.22mL) and 4-methylmorpholine (0.5mL) in dichloromethyl (4mL) was added in one portion. The mixture was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (150mL), the solution was washed with 1N aqueous HCl, water, saturated aqueous NaHCO₃ solution and brine. The resultant mixture was dried with magnesium sulfate and evaporated under vacuum to yield (S)-3-amino-2-hydroxy-pentanoic acid benzylamide (380mg) as a white solid.

Step 3 (S)-3-Amino-2-hydroxy-pentanoic acid benzylamide was dissolved in a mixture of TFA/dichloromethyl (1 l, 6mL), stirred for 1 hour and evaporated to dryness (3S)-3-Amino-2-hydroxy-pentanoic acid benzylamide was obtained as the TFA salt and used without further purification

REFERENCE EXAMPLE 20

(S)-2-Amino-1-oxazolo[4,5-b]pyridin-2-yl-butan-1-ol



Step 1. A mixture of 2-amino-3-hydroxy pyridine (25g, 227mmol), triethylorthoformate (75ml) and p-toluenesulfonic acid (61mg) was heated at 140°C for 8 hours. Excess triethylorthoformate was removed under vacuum. The product was crystallized from ethyl acetate to yield 22.5g of pyridyloxazole, ¹H NMR (DMSO-d₆) 9.26 (1H, s), 8.78 (1H, d), 8.45 (1H, d), 7.7 (1H, dd), MS 120.8 (M+1)

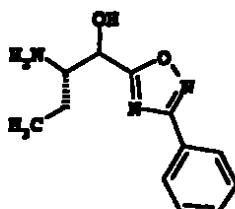
Step 2. Pyridyloxazole (600 mg, 5 mmol) in 30 ml THF was cooled to 0°C before the addition of isopropyl magnesium chloride (2M in THF, 2.5 ml, 5 mmol). After stirring for 1 hour at 0°C, (S)-(1-formyl-propyl)-carbamic acid tert-butyl ester (573 mg, 3 mmol, Reference Example 18) in 20 ml THF was added. The ice bath was removed and the reaction allowed to warm to room temperature. The reaction mixture was stirred for 2 hours and quenched with saturated ammonium chloride solution. Excess THF was removed and the residue was extracted with EtOAc, washed with brine, dried with anhydrous MgSO₄, filtered and concentrated. The crude residue was purified by chromatography to yield [1-(hydroxy-oxazolo[4,5-b]pyridin-2-yl-methyl)-propyl]-carbamic acid tert-butyl ester (383 mg). ¹H NMR (DMSO-d₆) 8.42 (1H, m), 8.18 (1H, m), 7.3 (1H, m), 6.8, 6.6 (1H, dd, d, OH, diastereomeric), 6.3, 6.02 (1H, d, d, NH, diastereomeric), 4.82, 4.5 (1H, m, m, diastereomeric), 1.8-1.3 (2H, m), 1.2, 1.05 (9H, s, s, diastereomeric), 0.89 (3H, m), MS 306.2 (M-1), 308.6 (M+1)

Step 3. To a stirred solution of the [1-(hydroxy-oxazolo[4,5-b]pyridin-2-yl-methyl)-propyl]-carbamic acid tert-butyl ester (12g, 100mmol) in THF (300ml) was added n-BuLi (1.6M solution in 62.5ml of hexane) drop wise under N₂ at -78°C. After 1 hour, MgBr Et₂O (25.8g, 100mmol) was added and the reaction mixture was allowed to warm to -45°C for 1 hour before being treated with 2-boc-amino-butyl-aldehyde (11.46g, 60mmol) in THF (50ml). The reaction mixture was stirred for 1 hour, quenched with saturated NH₄Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with MgSO₄, and concentrated. The residue was purified by silica gel column chromatography to yield 2-boc-amino-1-(5-pyridyloxazole-2-yl)-1-butanol (14.1g)

Step 4 2-Boc-amino-1-(5-pyridyloxazole-2-yl)-1-butanol (311mg, 1mmol) and MeCl_2 (5ml) were mixed and TFA (1ml) was added at room temperature After stirring for 1 hour, the solvent and excess TFA were removed under vacuum to produce 355mg of 2-amino-1-oxazolo[4,5-b]pyridin-2-yl-butan-1-ol TFA salt

REFERENCE EXAMPLE 21

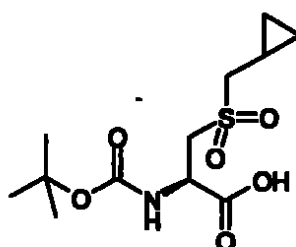
(S)-2-Amino-1-(3-phenyl)-[1,2,4]oxadiazol-5-yl)-butan-1-ol



3-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid (500mg, 2.14mmol) was combined with EDC (600mg, 3.14mmol), HOBt (600mg, 3.92mmol), and N-hydroxy-benzamide (292mg, 2.14mmol) Dichloromethyl (10mL) was added and then 4-methylmorpholine (1mL) The mixture was stirred at ambient temperature for 16 hours After dilution with ethyl acetate (200mL), the solution was washed with water (30mL), saturated aqueous NaHCO_3 solution and brine, dried with MgSO_4 and evaporated under vacuum. The crude product was dissolved in pyridine (10mL) and heated at 80°C for 15 hours The pyridine was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (eluent: ethyl acetate) to yield 290mg (0.83mmol) The oxadiazole (145mg, 0.41mmol) was dissolved in CH_2Cl_2 (4mL) and TFA (4mL) was added After stirring for 1 hour, the mixture was evaporated to dryness to yield (S)-2-Amino-1-(3-phenyl)-[1,2,4]oxadiazol-5-yl)-butan-1-ol

REFERENCE EXAMPLE 22

(R)-2-*tert*-butoxycarbonylamino-3-cyclopropylmethanesulfonyl-propionic acid



Step 1 Sodium hydroxide (2.16g, 54mmol) was dissolved in 27ml water and the solution added to a suspension of (R)-2-*tert*-butoxycarbonylamino-3-mercapto-propionic acid (8.2g, 37mmol) in 54ml methanol After a clear solution had formed bromomethyl-cyclopropane (5g, 37mmol) was added and the resulting reaction mixture stirred for three days Methanol was removed under reduced pressure

40
51

-79-

The residue was treated with 200ml 1M hydrochloric acid and then extracted three times with 200ml of dichloromethane. The combined organic phases were washed with brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give 2-tert-butoxycarbonylamino-3-cyclopropylmethylsulfanyl-propionic acid (7.94g)

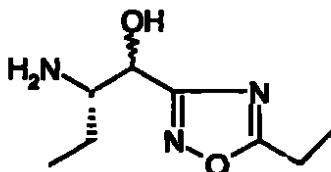
5

Step 2 Sodium hydroxide (2.32g, 58mmol) was dissolved in 75ml water. 2-tert-butoxycarbonylamino-3-cyclopropylmethylsulfanyl-propionic acid (7.94g, 29mmol) was added. A solution of Oxone™ in 100ml water was added slowly. The pH was adjusted to 3 by addition of sodium bicarbonate and the reaction mixture stirred for 30 minutes. It was extracted three times with 200ml ethyl acetate. The combined organic phases were washed with 100ml brine and dried with magnesium sulfate. The solvent was removed to yield (R)-2-tert-butoxycarbonylamino-3-cyclopropylmethanesulfonyl-propionic acid (4.64g, 15mmol, 31%)

10

REFERENCE EXAMPLE 23

15 (S)-2-Amino-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoro-acetic acid salt



Step 1 A solution of (2-Cyano-1-ethyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (1.953g, 44 mmol) in methanol (80 ml) was cooled to 0°C and treated successively with hydroxylamine hydrochloride (3.05, 44 mmol) in methanol (80 ml) and 25% sodium methoxide solution in methanol (10.2 ml). Stirred at 0°C for 5 min, cold bath removed and the reaction mixture stirred at room temperature for 5hr. Methanol evaporated off under reduced pressure, crude partitioned between ethyl acetate and water. Organic layer separated, dried (MgSO₄) and evaporated under reduced pressure to give yellow oil. Purified by mpic eluting with a mixture of ethyl acetate – heptane to give ((S)-1-[Hydroxy-(N¹-hydroxycarbonylmido)-methyl]-propyl)-carbamic acid tert-butyl ester as white solid (3.5 g) MS M(H⁺) 248

25

Step 2 A mixture of ((S)-1-[Hydroxy-(N¹-hydroxycarbonylmido)-methyl]-propyl)-carbamic acid tert-butyl ester (525 mg, 2.16 mmol), propionic anhydride (0.3 ml, 2.37 mmol) in dioxane (5ml) was heated at 150°C in a microwave (Smith Creator, S00219) for 35min. Crude evaporated under reduced pressure and purified by flash column chromatography to give ((S)-1-[(5-Ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl)-carbamic acid tert-butyl ester as yellow solid (0.8g, 67%)

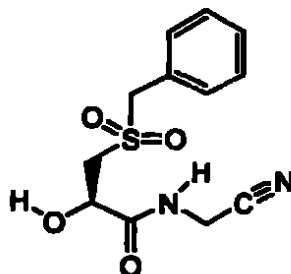
30

¹H NMR (CDCl₃) 4.88-4.80 (2H, m), 4.01-3.84 (1H, 2 broad m), 3.64-3.45 (1H, 2 bs), 2.95-2.86 (2H, dq, J=4.2Hz, 7.6Hz), 1.73-1.62 (1H, m), 1.6-1.32 (13H, m), 1.02-0.94 (3H, q, J=7.5Hz) MS

304(M+1)

Step 3 ((S)-1-[(5-Ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl)-carbamic acid tert-butyl ester (214 mg, 0.75 mmol) in dichloromethane (3 ml)) was treated with trifluoro acetic acid at room temperature for 3h. Solvent evaporated under reduced pressure to give (S)-2-Amino-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoro-acetic acid salt as brown oil (0.3 g). ^1H NMR (CDCl_3) 7.9-7.4 (3H, 2bs), 5.07 & 5.24 (1H, 2 x d, $J=3.5\text{ Hz}$ & 5.5 Hz), 3.8-3.6 (1H, 2bs), 2.96-2.87 (2H, dq, $J=2.4\text{ Hz}$, 7.5 Hz), 1.8-1.4 (2H, m), 1.40-1.34 (3H, dt, $J=1.4\text{ Hz}$, 7.5 Hz), 1.06-0.98 (3H, dt, $J=7.5\text{ Hz}$, 10.5 Hz)

MS 186(M+1)

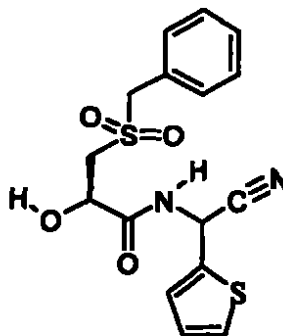
EXAMPLE 1(a) (R)-N-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (Compound 4)

DMF (5mL) was added to a mixture of 2-hydroxy-3-phenylmethanesulfonyl-propionic acid [200mg, 0.82mmol, Reference Example 1(b)], EDC (300mg, 1.57mmol), HOBT (300mg, 1.96mmol) and aminoacetonitrile hydrochloride (200mg, 2.1mmol). 4-Methylmorpholine (0.5mL) was added and the mixture was stirred at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate (200mL), washed with 1N HCl, brine, saturated aqueous NaHCO_3 solution, and brine, dried with MgSO_4 , and evaporated under vacuum. (R)-N-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide was crystallized from ethyl acetate/hexane to yield 154mg (0.55mmol), ^1H NMR (DMSO) 8.89-8.77 (m, 1H), 7.46-7.37 (m, 5H), 6.71-6.62 (m, 1H), 4.60-4.45 (m, 3H), 4.17-4.08 (m, 2H), 3.39-3.28 (m, 2H). MS (M^++1) 283

(b) (R)-N-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (Compound 7),

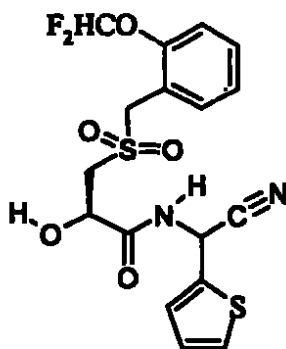
47
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-81-



By proceeding in a manner similar to Example 1(a) above but using (R)-2-hydroxy-3-phenylmethanesulfonyl-propionic acid [Reference Example 1(b)] and DL- α -amino-2-thiopheneacetic acid there was prepared (R)-N-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-propionamide ^1H NMR (DMSO) 9.55(d, J=6.5 Hz, 1H), 7.58(d, J=5.2 Hz, 1H), 7.42-7.39(m, 5H), 7.23(m, 1H), 7.05(dd, J=3.5 Hz, J=5.2 Hz, 1H), 6.58(dd, J=3.4 Hz, J=6.6 Hz, 1H), 6.41(s, 1H), 4.59-4.50(m, 3H), 3.29(s, 2H), MS 362.6(M⁺), 365(M⁺)

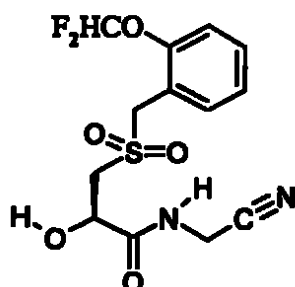
(c) (R)-N-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide, (Compound 8)



By proceeding in a manner similar to Example 1(a) above but using (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid [Reference Example 1(a)] and DL- α -amino-2-thiopheneacetic acid there was prepared (R)-N-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide ^1H NMR (CD₃Cl) δ 7.6-7.2(m, 7H), 7.01(t, J=7.3 Hz, 1H), 6.62(s, 1H), 6.21(d, J=8.1 Hz, 1H), 4.71-4.67(m, 1H), 4.46(s, 2H), 3.68(s, 2H), 3.22-3.18(m, 1H), MS 428.6(M-1), 453(M+23)

(d) (R)-N-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide, (Compound 17)

-82-

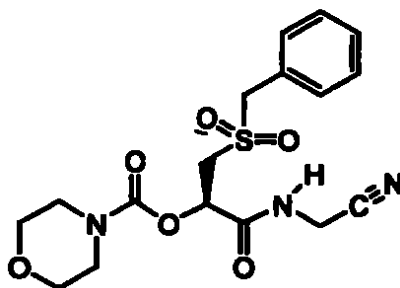


By proceeding in a manner similar to Example 1(a) above but using (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid [Reference Example 1(a)] there was prepared (R)-N-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide

¹H NMR (DMSO) 8.81(t, J=5.67 Hz, 1H), 7.55-7.4(m, 2H), 7.35-7.2(m, 2H), 7.13(t, J=7.36 Hz, 1H), 6.62(d, J=6.67 Hz, 1H), 4.58(s, 2H), 4.52-4.45(m, 1H), 4.12(d, J=5.94 Hz, 2H), 3.45-3.4(m, 2H) MS 347.4(M-1), 371(M+23)

EXAMPLE 2

Morpholine-4-carboxylic acid (R)-1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester, (Compound 6),

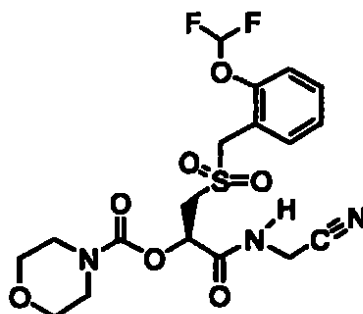


Phosgene solution (0.77 mL, 1.93 M in toluene) was added to CH₂Cl₂ (5 mL) and cooled to 0°C under nitrogen. Quinoline (0.12 mL, 1.0 mmol) was added followed by (R)-N-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide [100 mg, 0.354 mmol, Example 1(a)]. The mixture was stirred at ambient temperature for 3 hours. Morpholine (1 mmol) was added and stirring was continued for 3 hours. The mixture was diluted with ethyl acetate (200 mL) and washed sequentially with 1N HCl, brine, saturated aqueous NaHCO₃ solution and brine. The product was dried with MgSO₄ and evaporated under vacuum and crystallized from an ethyl acetate/hexane solution to yield morpholine-4-carboxylic acid (R)-1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester (85 mg, 0.215 mmol), ¹H NMR (DMSO) 8.99-8.88 (m, 1H), 7.46-7.37 (m, 5H), 5.42-5.32 (m, 1H), 4.60-4.45 (m, 2H), 4.20-4.13 (m, 2H), 3.70-3.28 (m, 10H) MS (M⁺+1) 396

EXAMPLE 3

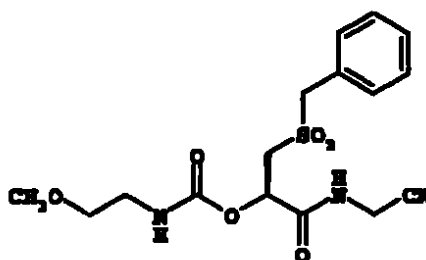
(a) Morpholine-4-carboxylic acid (R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 31)

-83-



(*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide [100mg, 0.287mmol, Example 1(d)], was dissolved in CH₂Cl₂ (2mL). Pyridine (32.4μL, 0.4mmol) and then trichloromethylchloroformate (36.2μL, 0.3mmol) were added. The mixture was stirred at ambient temperature for 3 hours. Morpholine (0.5mL) was added and stirring was continued for 3 hours. The mixture was diluted with ethyl acetate (200mL), washed with 1N HCl, brine, saturated aqueous NaHCO₃ solution and brine. The product was dried with MgSO₄, evaporated under vacuum and crystallized from a solution of ethyl acetate/hexane to yield morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester (60mg, 0.130mmol), ¹H NMR (DMSO) δ 8.95 (t, J=5.2Hz, 1H), 7.51-7.44 (m, 2H), 7.32-7.22 (m, 2H), 7.14 (t, J_{HH}=73Hz, 1H), 5.39-5.35 (m, 1H), 4.67-4.53 (m, 2H), 4.19-4.15 (m, 2H), 3.83-3.28 (m, 10H), MS (M⁺+1) 462.

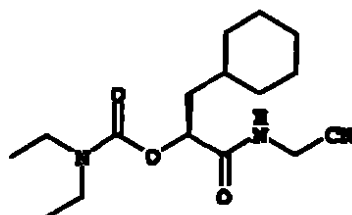
(b) (*R*)-(2-Methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide [Example 1(a)] and 2-methoxyethylamine there was prepared (*R*)-(2-Methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester ¹H NMR. (DMSO) δ 8.91 (t, J=5.6Hz, 1H), 7.64 (t, J=5.6Hz, 1H), 7.40-7.32 (m, 5H), 5.30-5.25 (m, 1H), 4.59-4.50 (m, 2H), 4.17-4.13 (m, 2H), 3.58 (dd, J=9.2Hz, J=14.8Hz, 1H), 3.43 (d, 14.8Hz, 1H), 3.33 (s, 3H), 3.38-3.12 (m, 4H). MS (M+H)⁺ 384.

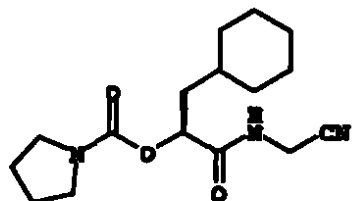
(c) (*S*)-Diethyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester

-84-



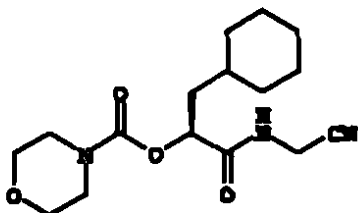
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and diethylamine there was prepared (S)-Diethyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester ¹H NMR (DMSO) 8.62 (t, J=5.6 Hz, 1H), 4.87-4.82 (m, 1H), 4.12 (d, J=5.6, 2H), 3.42-3.10 (m, 4H), 1.72-0.82 (m, 19H) MS (M+H)⁺ 310

(d) (S)-Pyrrolidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



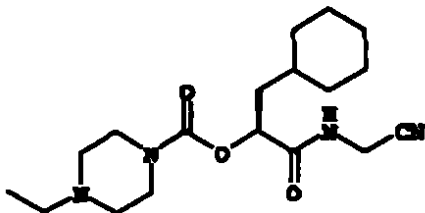
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and pyrrolidine there was prepared (S)-Pyrrolidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester ¹H NMR (DMSO) 8.59 (t, J=4.8 Hz, 1H), 4.86-4.81 (m, 1H), 4.11 (d, J=4.8, 2H), 3.48-3.19 (m, 4H), 1.87-0.82 (m, 17H) MS (M+H)⁺ 308

(e) (S)-Morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and morpholine there was prepared (S)-Morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester ¹H NMR (DMSO) 8.66 (t, J=5.2 Hz, 1H), 4.88-4.83 (m, 1H), 4.13 (d, J=4.8, 2H), 3.60-3.26 (m, 8H), 1.71-0.82 (m, 13H) MS (M+H)⁺ 324

(f) (S)-4-Ethyl-piperazine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



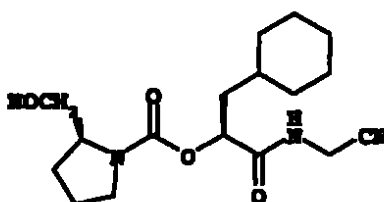
-85-

By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and 4-ethylpiperazine there was prepared (S)-4-Ethyl-piperazine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester LC-MS elution time =

2.08min 349.2(M-1), 351.3(M+1) (MS API 150EX LC HP Agilent 1100 Series Column

- 5 Phenomenex, 5u ODS3 100A 100X3mm, Flow Rate 2ml/min Two solvent gradient Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min Then gradient back to 100% A, 0% B from t = 7 to t = 15 min)

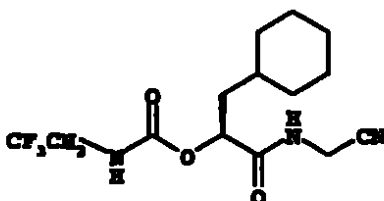
- 10 (g) (S)-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and (*S*)-2-hydroxymethyl-pyrrolidine there was prepared (S)-2-

- 15 Hydroxymethyl-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester LC-MS elution time = 3.73min 336.5(M-1), 338.2(M+1) (MS API 150EX LC HP Agilent 1100 Series Column Phenomenex, 5u ODS3 100A 100X3mm, Flow Rate 2ml/min Two solvent gradient Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min Then gradient back to 100% A, 0% B from t = 7 to t = 15 min)

- (h) (S)-(2,2,2-Trifluoro-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester

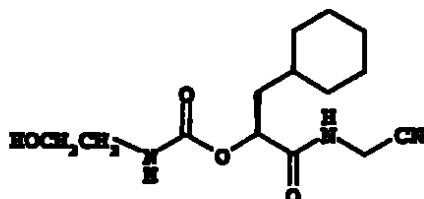


By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and 2,2,2-trifluoroethylamine there was prepared (S)-(2,2,2-Trifluoro-ethyl)-

- 25 carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester LC-MS elution time = 4.07min 334.1(M-1), 336.2(M+1) (MS API 150EX LC HP Agilent 1100 Series Column Phenomenex, 5u ODS3 100A 100X3mm, Flow Rate 2ml/min Two solvent gradient. Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH Gradient from 100% A,

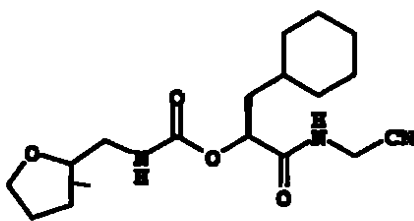
0% B to 0% A, 100% B from t = 0 to t = 6min Then gradient back to 100% A, 0% B from t = 7 to t = 15 min)

(i) (S)-(2-Hydroxyethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



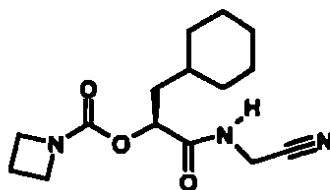
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and 2-hydroxyethylamine there was prepared (S)-(2-Hydroxyethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester ¹H NMR (DMSO) 8.65 (t, J=5.2Hz, 1H), 7.16 (t, J=5.2Hz, 1H), 4.85-4.80 (m, 1H), 4.62 (t, J=5.6Hz, 1H), 4.12 (d, J=5.6Hz, 2H), 3.45-3.33 (m, 2H), 3.12-2.96 (m, 2H), 1.74-0.80 (m, 13H) MS (M+H)⁺ 298

(j) (Tetrahydrofuran-2-ylmethyl)-carbamic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



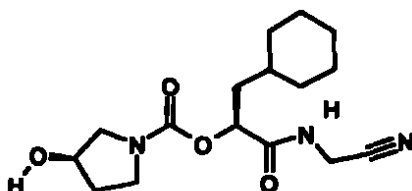
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and tetrahydrofurfurylamine there was prepared (tetrahydrofuran-2-ylmethyl)-carbamic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester as a 1:1 mixture of diastereomers, ¹H NMR (DMSO) 8.66 (t, J=5.2Hz, 1H), 7.28 (t, J=5.2Hz, 1H), 4.86-4.81 (m, 1H), 4.12 (d, J=5.2Hz, 2H), 3.83-3.54 (m, 3H), 3.09-2.92 (m, 2H), 1.89-0.80 (m, 17H) MS (M+H)⁺ 338

(k) (S)-Azetidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



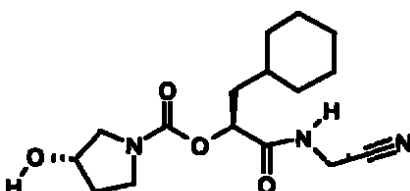
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and azetidine there was prepared (S)-azetidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester ¹H NMR (DMSO) 8.59 (t, J=5.2Hz, 1H), 4.82-

- (o) (R)-3-Hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



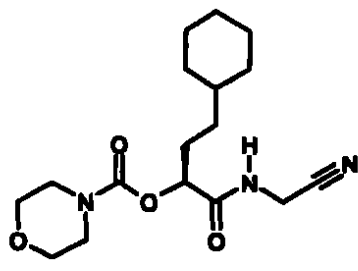
By proceeding in a manner similar to Example 3(a) above but using (R)-N-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and (R)-3-hydroxy-pyrrolidine there was prepared (R)-3-hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ¹H NMR (DMSO) 8.64-8.56 (m, 1H), 4.98-4.80 (m, 2H), 4.29-4.20 (m, 1H), 4.11 (d, J=5.2 Hz, 2H), 3.57-3.12 (m, 4H), 1.91-0.82 (m, 15H) MS (M+H)⁺ 324

- (p) (S)-3-Hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (R)-N-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and (S)-3-hydroxy-pyrrolidine there was prepared (S)-3-hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ¹H NMR (DMSO) 8.63-8.55 (m, 1H), 4.98-4.90 (m, 1H), 4.85-4.80 (m, 1H), 4.28-4.19 (m, 1H), 4.13-4.09 (m, 2H), 3.54-3.09 (m, 4H), 1.93-0.81 (m, 15H) MS. (M+H)⁺ 324

- (q) (S)-Morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-3-cyclohexyl-propyl ester

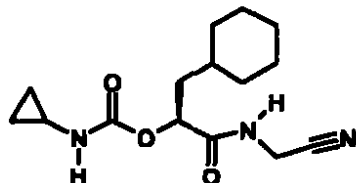


By proceeding in a manner similar to Example 3(a) above but using (R)-N-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and morpholine there was prepared (S)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-3-cyclohexyl-propyl ester. ¹H NMR (DMSO) 8.61 (t, J=5.6 Hz, 1H), 4.79 (t, J=5.6 Hz, 1H), 4.13 (d, J=5.2 Hz, 2H), 3.59-3.26 (m, 8H), 1.73-1.55 (m, 7H), 1.23-1.06 (m, 6H), 0.88-0.76 (m, 2H) MS (M+H)⁺ 338

-87-

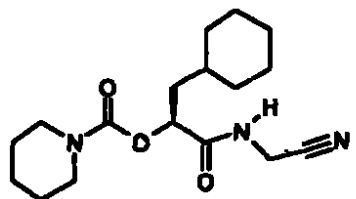
4.77 (m, 1H), 4.11 (d, J=5.2 Hz, 2H), 4.13-3.81 (m, 4H), 2.18 (quint, J=7.6 Hz, 2H), 1.71-0.80 (m, 13H) MS (M+H)⁺ 294

(l) (S)-Cyclopropyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



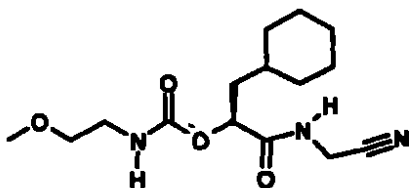
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and cyclopropylamine there was prepared (*S*)-cyclopropyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester ¹H NMR (DMSO) 8.64 (t, J=5.2 Hz, 1H), 7.44 (br, 1H), 4.83-4.78 (m, 1H), 4.11 (d, J=5.2 Hz, 2H), 2.50-2.40 (m, 1H), 1.72-0.78 (m, 13H), 0.58-0.30 (m, 4H) MS (M+H)⁺ 294

(m) (S)-Piperidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and piperidine there was prepared (*S*)-piperidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester ¹H NMR (DMSO) 8.63 (t, J=5.2 Hz, 1H), 4.86-4.81 (m, 1H), 4.11 (d, J=5.6 Hz, 2H), 3.48-3.20 (m, 4H), 1.70-0.82 (m, 19H) MS (M+H)⁺ 322

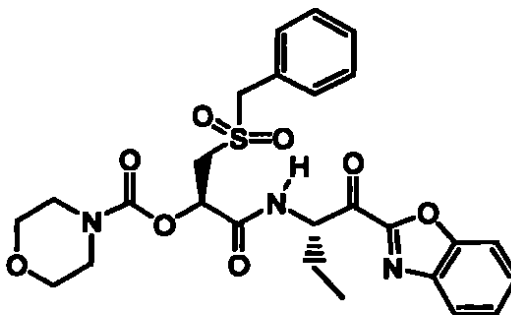
(n) (S)-(2-Methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and 2-methoxyethylamine there was prepared (*S*)-(2-methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester ¹H NMR (DMSO) 8.66 (t, J=5.6 Hz, 1H), 7.27 (t, J=5.6 Hz, 1H), 4.85-4.80 (m, 1H), 4.12 (d, J=5.6 Hz, 2H), 3.40-3.03 (m, 4H), 3.32 (s, 3H), 1.74-0.80 (m, 13H) MS (M+H)⁺ 312

EXAMPLE 4

- (a) Morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 11)



Step 1 (R)-2-Hydroxy-3-phenylmethanesulfonyl-propionic acid {2g, 8.19mmol, Reference Example 1(b)} was dissolved in CH_2Cl_2 (20mL). 4-Methylmorpholine (3.8mL) and then chloromethyl methyl ether (1.52mL, 20mmol) were added. After stirring at ambient temperature for 30 minutes, the reaction was quenched with water (50mL) and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO_3 solution and brine. The product was dried with MgSO_4 , evaporated under vacuum and crystallized from ethyl acetate/hexane to yield 2-hydroxy-3-phenylmethanesulfonyl-propionic acid methoxymethyl ester (1.2g, 4.16mmol).

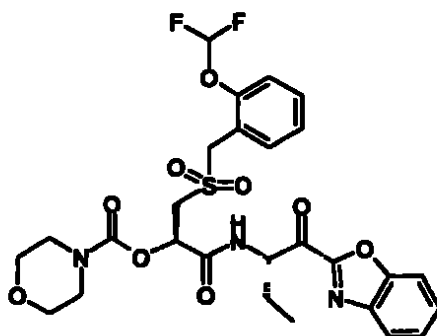
Step 2 Phosgene solution (2.07mL, 1.93M in toluene) was added to CH_2Cl_2 (10mL) and cooled to 0°C under nitrogen. Quinoline (0.95mL) was added followed by 2-hydroxy-3-phenylmethanesulfonyl-propionic acid methoxymethyl ester (250mg, 0.87mmol). The mixture was stirred at ambient temperature for 3 hours. Morpholine (0.35mL, 4mmol) was added and stirring was continued for 3 hours. The mixture was diluted with ethyl acetate (200mL), washed sequentially with 1N HCl, brine, saturated aqueous NaHCO_3 solution and brine. The crude product was dried with MgSO_4 , evaporated under vacuum and dissolved in 1,4-dioxane (20mL). 1N HCl (10mL) was added and the mixture was stirred at ambient temperature for 3 hours. Dioxane was evaporated under vacuum and the product was extracted with ethyl acetate. The combined ethyl acetate layers were washed with saturated aqueous NaHCO_3 solution (3x20mL). The NaHCO_3 solution was acidified with 6N HCl and extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine, dried with MgSO_4 , and evaporated under vacuum to give (R)-morpholine-4-carboxylic acid 1-carboxy-2-phenylmethanesulfonyl-ethyl ester.

Step 3 (R)-Morpholine-4-carboxylic acid 1-carboxy-2-phenylmethanesulfonyl-ethyl ester was combined with EDC (250mg, 1.3mmol), HOBt (250mg, 1.6mmol), and (2S)-2-amino-1-benzooxazol-2-yl-butan-1-ol (250mg, 1.2mmol, Reference Example 17(a)). Dichloromethane (4mL) was added and then 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (150mL), the solution was washed with 1N aqueous HCl, water, saturated aqueous NaHCO_3 solution and brine, dried with MgSO_4 , and evaporated under vacuum. The crude product was dissolved in dry dichloromethane (10mL) and

-90-

Dess Martin Periodinane (500mg, 1.2mmol) was added. After stirring at ambient temperature for 1 hour, the mixture was diluted with ethyl acetate (150mL) and treated with 0.26M Na₂S₂O₃ solution in saturated aqueous NaHCO₃. The organic phase was washed with saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and evaporated. The product was crystallized from ethyl acetate/hexane to yield morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester (190mg, 0.35mmol), ¹H NMR (DMSO) 8.95 (d, J=6.6Hz, 1H), 8.01 (d, J=7.9Hz, 1H), 7.90 (d, J=7.9Hz, 1H), 7.65 (t, J=7.5Hz, 1H), 7.55 (t, J=7.9Hz, 1H), 7.40-7.34 (m, 5H), 5.44-5.35 (m, 1H), 5.26-5.16 (m, 1H), 4.60 (d, J=13.6Hz, 1H), 4.47 (d, J=13.6Hz, 1H), 3.71-3.28 (m, 10H), 2.10-1.94 (m, 1H), 1.81-1.65 (m, 1H), 0.98 (t, J=7.2Hz, 3H), MS (M⁺+1) 544

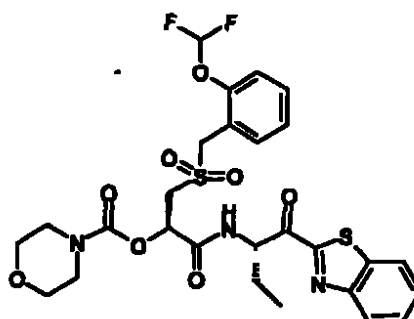
(b) Morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 14)



By proceeding in a manner similar to Example 4(a) above but using (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid {Reference Example 1(a)} in step 1 there was prepared morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester. ¹H NMR (DMSO) 8.95 (d, J=6.4Hz, 1H), 8.01 (d, J=7.9Hz, 1H), 7.90 (d, J=8.4Hz, 1H), 7.65 (t, J=7.4Hz, 1H), 7.54 (t, J=7.5Hz, 1H), 7.52-7.43 (m, 2H), 7.31-7.21 (m, 2H), 7.11 (t, J_{H,F}=73Hz, 1H), 5.43-5.37 (m, 1H), 5.27-5.17 (m, 1H), 4.63 (d, J=13.5Hz, 1H), 4.54 (d, J=13.5Hz, 1H), 3.88-3.28 (m, 10H), 2.10-1.94 (m, 1H), 1.81-1.65 (m, 1H), 0.98 (t, J=7.6Hz, 3H), MS (M⁺+1) 610

(c) morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 15)

-91-

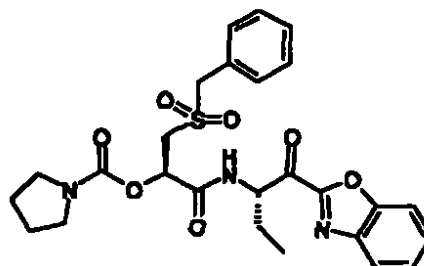


By proceeding in a manner similar to Example 4(a) above but using (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid {Reference Example 1(a)} in step 1 and (2S)-2-amino-1-benzothiazol-2-yl-butan-1-ol {Reference Example 17(b)} in step 3 there was prepared

5 morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester ¹H NMR (DMSO) 8.93 (d, J=6.4 Hz, 1H), 8.30-8.24 (m, 2H), 7.72-7.62 (m, 2H), 7.51-7.44 (m, 2H), 7.32-7.22 (m, 2H), 7.12 (t, J_{HF}=73 Hz, 1H), 5.49-5.35 (m, 2H), 4.64 (d, J=13.5 Hz, 1H), 4.55 (d, J=13.5 Hz, 1H), 3.91-3.28 (m, 10H), 2.08-1.94 (m, 1H), 1.84-1.68 (m, 1H), 0.99 (t, J=7.6 Hz, 3H) MS (M⁺+1) 626.

10

(d) Pyrrolidine-1-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 19)



By proceeding in a manner similar to Example 4(a) above but using pyrrolidine in step 2 there was prepared pyrrolidine-1-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-

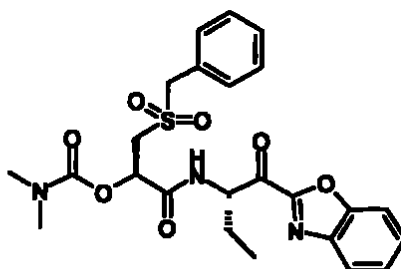
15

propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester ¹H NMR (DMSO) 8.90 (d, J=6.4 Hz, 1H), 7.99 (d, J=7.9 Hz, 1H), 7.89 (d, J=8.4 Hz, 1H), 7.65 (t, J=7.4 Hz, 1H), 7.54 (t, J=7.5 Hz, 1H), 7.40-7.33 (m, 5H), 5.41-5.33 (m, 1H), 5.26-5.15 (m, 1H), 4.59 (d, J=13.5 Hz, 1H), 4.47 (d, J=13.5 Hz, 1H), 3.66-3.17 (m, 6H), 2.10-1.64 (m, 6H), 0.97 (t, J=7.2 Hz, 3H), MS (M⁺+1) 528

20

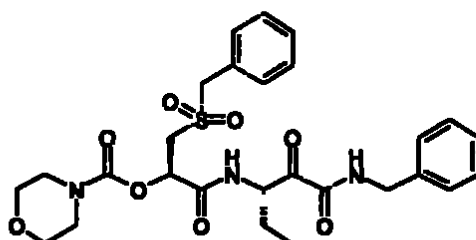
(e) Dimethyl-carbamic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 20)

-92-



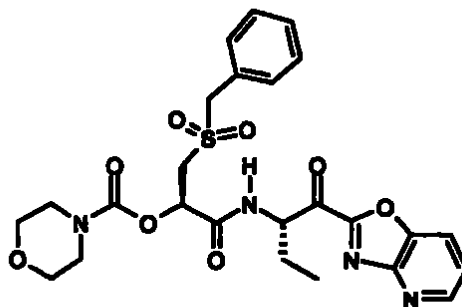
By proceeding in a manner similar to Example 4(a) above but using dimethylamine in step 2 there was prepared dimethyl-carbamic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester ¹H NMR (DMSO) 8.91 (d, J=6.4Hz, 1H), 7.99 (d, J=7.9Hz, 1H), 7.90 (d, J=8.4Hz, 1H), 7.65 (t, J=7.4Hz, 1H), 7.54 (t, J=7.5Hz, 1H), 7.40-7.33 (m, 5H), 5.39-5.33 (m, 1H), 5.26-5.15 (m, 1H), 4.59 (d, J=13.5Hz, 1H), 4.47 (d, J=13.5Hz, 1H), 3.63 (dd, J=14.8Hz, J=10.6Hz, 1H), 3.42 (dd, J=14.8Hz, J=2.5Hz, 1H), 2.89 (s, 3H), 2.79 (s, 3H), 2.10-1.94 (m, 1H), 1.81-1.64 (m, 1H), 0.97 (t, J=7.2Hz, 3H), MS (M⁺+1) 502

(f) Morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 25)



By proceeding in a manner similar to Example 4(a) above but using (R)-3-amino-2-hydroxy-pentanoic acid benzylamide TFA salt (Reference Example 19) in step 3 there was prepared morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester ¹H NMR (DMSO) 9.27 (t, J=5.5Hz, 1H), 8.67 (d, J=8.1Hz, 1H), 7.40-7.20 (m, 10H), 5.42-5.34 (m, 1H), 4.96-4.85 (m, 1H), 4.64-4.24 (m, 4H), 3.66-3.28 (m, 10H), 1.90-1.72 (m, 1H), 1.63-1.46 (m, 1H), 0.89 (t, J=7.2Hz, 3H), MS (M⁺+1) 560

(g) Morpholine-4-carboxylic acid (S)-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester



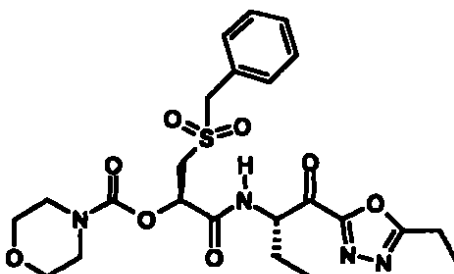
6-2
58

-93-

By proceeding in a manner similar to Example 4(a) above but using (S)-2-amino-1-oxazolo[4,5-b]pyridin-2-yl-butan-1-ol TFA salt (Reference Example 20) there was prepared morpholine-4-carboxylic acid (S)-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-

5 phenylmethanesulfonyl-ethyl ester ¹H NMR (DMSO) 9.00 (d, J=6.4Hz, 1H), 8.73 (m, 1H), 8.39 (d, J=8.4Hz, 1H), 7.69-7.64 (m, 1H), 7.45-7.30 (m, 5H), 5.37 (d, J=10.4Hz, 1H), 5.19-5.13 (m, 1H), 4.57 (d, J=13.6Hz, 1H), 4.46 (d, J=13.6Hz, 1H), 3.67-3.23 (m, 10H), 2.10-1.98 (m, 1H), 1.80-1.69 (m, 1H), 0.99 (t, J=7.0Hz, 3H) MS (M+H)⁺ 545

10 (h) Morpholine-4-carboxylic acid (S)-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester



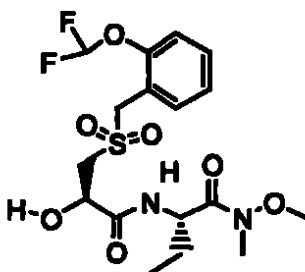
By proceeding in a manner similar to Example 4(a) above but using 2-amino-1-(5-ethyl-[1,3,4]oxadiazol-2-yl)-butan-1-ol (Reference Example 11(m)) there was prepared morpholine-4-carboxylic acid (S)-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-

15 phenylmethanesulfonyl-ethyl ester ¹H NMR (DMSO) 8.95 (d, J=6.0Hz, 1H), 7.41-7.33 (m, 5H), 5.35 (d, J=10.0Hz, 1H), 4.97-4.91 (m, 1H), 4.63-4.45 (m, 2H), 3.64-3.23 (m, 10H), 2.96 (q, J=7.2Hz, 2H), 1.99-1.89 (m, 1H), 1.75-1.64 (m, 1H), 1.30 (t, J=7.6Hz, 3H), 0.94 (t, J=7.2Hz, 3H) MS (M+H)⁺ 523

20

EXAMPLE 5

(S)-2-[(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propanoylamino]-N-methoxy-N-methyl-butylamide, (Compound 32)



25 To a solution of (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propanionic acid {1.24g, 4mmol, Reference Example 1(a)} in CH₂Cl₂ (20ml) was added HOBT (0.74g, 4.8mmol), EDC (1.15g, 6mmol), (R)-2-amino-N-methoxy-N-methyl-butylamide TFA salt (1.04g, 4mmol), prepared as in reference 2, and NMM (1.6g, 16mmol). After stirring for 14 hours at room temperature, the

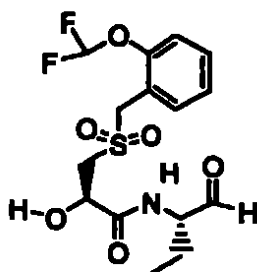
-94-

reaction mixture was diluted with 150ml of ethyl acetate. The mixture was washed with saturated NaHCO₃ and brine before drying with anhydrous MgSO₄. This crude product was then filtered, concentrated and purified by flash column chromatography using silica gel with hexane/ acetate as

eluent to yield (S)-2-((R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propenoylamino)-N-methoxy-N-methyl-butylamide (1.45g), ¹HNMR (CDCl₃) 7.6-7.5(d, J=7.67Hz, 1H), 7.5-7.35(m, 2H), 7.31-7.15(m, 2H), 6.63(t, J=7.34Hz, 1H), 5.0-4.85(br., 1H), 4.7-4.6(m, 1H), 4.55-4.48(m, 2H), 4.45-4.35(m, 1H), 3.80(s, 3H), 3.6-3.8(m, 1H), 3.35-3.2(m, 1H), 1.78(s, 3H), 2.0-1.5(m, 2H), 0.93(t, J=6.9Hz, 3H), MS 437.44(M-1), 439.4(M+1)

EXAMPLE 6

(R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-N-((S)-1-formyl-propyl)-2-hydroxy-propionamide, (Compound 23)

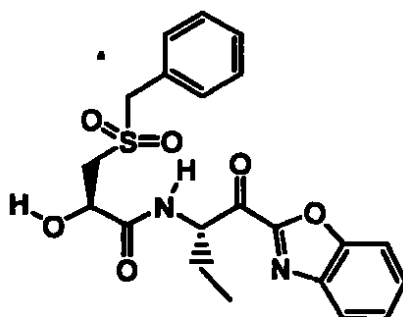


To a solution of (S)-2-((R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propenoylamino)-N-methoxy-N-methyl-butylamide (1.3g, 3mmol, Example 5) in ethyl ether (50mL) at 0°C under N₂, was added 1N LAH solution of ethyl ether (3ml). After stirring for 3 hours at 0°C, 1ml of ethyl acetate and saturated NH₄Cl solution was added. The crude product was then extracted with ether, washed with brine, dried with MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography using silica gel with hexane/ acetate as eluent to yield (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-N-((S)-1-formyl-propyl)-2-hydroxy-propionamide (0.66g), ¹HNMR (DMSO) 9.43(s, 1H), 8.42(d, J=7.45Hz, 1H), 7.6-7.0(m, 4H), 7.12(t, J=7.93Hz, 1H), 6.52(d, J=6.45Hz, 1H), 5.2-5.17(m, 1H), 4.65-4.53(m, 2H), 4.12-4.0(m, 1H), 3.63-3.55(m, 2H), 1.7-1.4(m, 2H), 0.89(t, J=6.8Hz, 3H), MS 378.2(M-1), 380.4(M+1)

EXAMPLE 7

(R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide, (Compound 5)

-95-



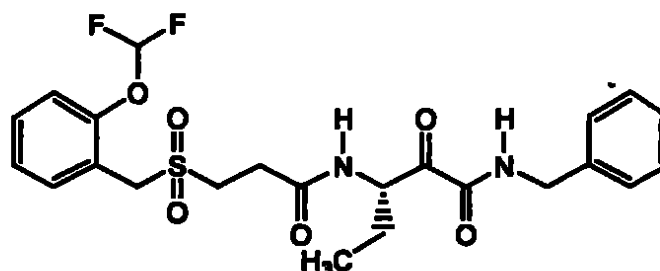
Step 1 To a solution of (R)-3-Phenylmethanesulfonyl-2-trisopropylsilyloxy-propionic acid {556mg, 1mmol, Reference Example 3} in CH_2Cl_2 (10mL) at room temperature was added HOBt (183mg, 1.2mmol), EDC (288mg, 15mmol), (S)-2-Amino-1-benzooxazol-2-yl-butanol (206mg, 1mmol) and NMM (202mg, 2mmol). The mixture was then stirred overnight at room temperature before being diluted with ethyl acetate (100mL), washed with saturated NaHCO_3 , brine, dried with anhydrous MgSO_4 , filtered and concentrated. The crude product was then purified by flash column chromatography using silica gel with hexane/acetate as eluent (to yield 180mgs of product). This compound was dissolved in CH_2Cl_2 , Dess-Martin Periodinane (196mg, 0.46mmol) was added at room temperature and the mixture was stirred for 2 hours. Saturated $\text{Na}_2\text{S}_2\text{O}_3$ - NaHCO_3 solution (5mL) was added and stirred for a further 30 minute before extraction with ethyl acetate and washing sequentially with saturated NaHCO_3 solution and brine. The crude product was then dried with anhydrous MgSO_4 , filtered, concentrated and purified by flash column chromatography using silica gel with hexane/acetate as eluent to yield (R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-trisopropylsilyloxy-propionamide

Step 2 (R)-N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-trisopropylsilyloxy-propionamide (120mg, 0.2mmol), in CH_3CN (10mL), 48% HF/ water solution (1mL) were mixed and stirred at room temperature for 16 hours. Saturated NaHCO_3 solution was added carefully to adjust the pH to between 8 and 9. The product was extracted with ethyl acetate (100mL), washed with brine and dried with magnesium sulfate. The solvent was removed and the product crystallized from acetate and hexane to yield (R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide as a white solid (85% yield), ^1H NMR (DMSO) 8.29 (d, $J=7.9\text{Hz}$, 1H), 7.74 (d, $J=7.9\text{Hz}$, 1H), 7.59 (t, $J=8.1\text{Hz}$, 1H), 7.46-7.35 (m, 7H), 6.52 (d, $J=6.6\text{Hz}$, 1H), 5.08-4.99 (m, 1H), 4.58-4.47 (m, 3H), 3.35-3.28 (m, 2H), 2.05-1.90 (m, 1H), 1.81-1.65 (m, 1H), 0.91 (t, $J=7.2\text{Hz}$, 3H), MS (M^++1) 431

EXAMPLE 8

(a) (S)-3-(3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino)-2-oxo-pentanoic acid benzylamide, (Compound 27)

-96-



Step 1 A mixture of (R)-3-amino-2-hydroxy-pentanoic acid benzylamide TFA salt (70mg, 0.22mmol), 3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionic acid (64mg, 0.22mmol, Reference Example 19) HOBT (33mg, 0.22mmol), EDC (63mg, 0.325mmol), 1mL dichloromethane and N-methyl morpholine (48μL, 0.434mmol) The mixture was allowed to stir 16 hours. The product was extracted into 60mL ethyl acetate and washed with two 10mL portions of 1N HCl, 10mL water, and two 10mL portions of saturated NaHCO₃, dried over MgSO₄ and concentrated to give 105mg of crude (R)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-hydroxy-pentanoic acid benzylamide (0.21mmol, 100% yield)

Step 2 To a 1mL dichloromethane solution of 105 mg of (R)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-hydroxy-pentanoic acid benzylamide (0.21 mmol) was added Dess Martin periodinane (179mg, 0.42 mmol). The mixture was allowed to stir for 16 hours, then 10mL of 0.26M Na₂S₂O₃ in saturated NaHCO₃ was added and the mixture was extracted with two 30mL portions of ethyl acetate and washed with three 15mL portions of saturated NaHCO₃. The organic layer was dried over MgSO₄ and concentrated. The product was purified by silica gel chromatography using 3:1 hexane:ethyl acetate eluent and crystallized from diethyl ether and hexane to give (S)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-oxo-pentanoic acid benzylamide (28mg, 0.054mmol, 26% yield), ¹H NMR. (CDCl₃) 7.0-7.47 (m, 9H), 6.49 (m, 1H), 6.24 (m, 1H), 5.22 (m, 1H), 4.40 (m, 2H), 4.30 (m, 3H), 3.23 (m, 2H), 2.70 (m, 2H), 2.01 (m, 1H), 1.68 (m, 1H), 0.85 (m, 3H), MS (M⁺+1) 499.4, 496.53

The following compounds were prepared by the method of Example 8

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-

phenylmethanesulfonyl]-propionamide (Compound 26), ¹H NMR. (CDCl₃) 7.85 (d, J=7.6Hz, 1H), 7.7-7.0 (m, 7H), 6.51 (m, 2H), 5.60 (m, 1H), 4.34 (m, 3H), 3.29 (m, 2H), 2.80 (m, 2H), 2.13 (m, 1H), 1.87 (m, 1H), 0.96 (m, 3H), MS (M⁺+1) 481, 480.48,

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-3-phenyl-propyl]-3-p-tolylmethanesulfonyl-propionamide

(Compound 30), ¹H NMR. (CDCl₃) 7.9 (m, 1H), 7.62 (m, 1H), 7.56 (td, J=6.9, 1.2Hz, 1H), 7.47 (td, J=7.1, 1.2Hz, 1H), 7.3-7.1 (m, 9H), 6.47 (d, J=7.7Hz, 1H), 5.71 (m, 1H), 4.22 (s, 2H), 3.20 (m, 2H), 2.71 (m, 4H), 2.47 (m, 1H), 2.33 (s, 3H), 2.21 (m, 1H), MS (M⁺+1) 505.2, 504.60

3-[2-Difluoromethoxy-phenylmethanesulfonyl]-N-(1-ethyl-2,3-dioxo-3-pyrrolidin-1-yl-propyl)-

-97-

propionamide,

3-(2-Difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-3-morpholin-4-yl)-2,3-dioxo-propyl)-propionamide,

3-(2-Difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-2,3-dioxo-3-piperazin-1-yl-propyl)-propionamide,

3-(2-Difluoromethoxy-phenylmethanesulfonyl)-N-[3-(1,1-dioxo-1,6-thiomorpholin-4-yl)-1-ethyl-2,3-dioxo-propyl]-propionamide,

3-(2-Difluoromethoxy-phenylmethanesulfonyl)-N-[1-ethyl-3-(4-methyl-sulfonyl-piperazin-1-yl)-2,3-dioxo-propyl]-propionamide;

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid dimethylamide,

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid cyclopentyl-ethyl-amide,

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid phenylamide,

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid pyridin-3-ylamide,

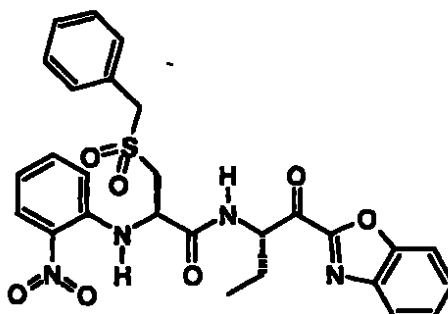
3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (tetrahydro-pyran-4-yl)-amide,

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (1-benzoyl-piperidin-4-yl)-amide, and

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (2-morpholin-4-yl-ethyl)-amide

EXAMPLE 9

(R)-N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide, (Compound 28)



Step 1 3-Benzylsulfonyl-2-(2-nitro-phenylamino)-propionic acid (350mg, 1.05 mmol, Reference Example 5) was dissolved in 20mL methanol, treated with a 20mL aqueous solution of Oxone

-98-

(970mg, 0.12mmol), and stirred for 72 hours. Water (300mL) was added and the precipitate was filtered and dried to give 2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionic acid (215mg, 0.59mmol, 56%yield)

Step 2 A mixture of 2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionic acid (215mg, 0.59mmol), HOBt (136mg, 0.148mmol), EDC (408mg, 2.13mmol), (S)-2-amino-1-benzooxazol-2-yl-butan-1-ol (122mg, 0.59mmol, {Reference Example 17(a)}), 2.4mL dichloromethane and N-methylmorpholine (97μL, 0.89mmol) was allowed to stir 16 hours. The product was extracted into 20mL ethyl acetate and washed with three 5mL portions of 1N HCl, and one 30mL portion of saturated NaHCO₃, dried over MgSO₄ and concentrated to give (R)-N-[(S)-1-(1-benzooxazol-2-yl-1-hydroxy-methyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethane-sulfonyl-propionamide (223mg, 0.40mmol, 45% yield)

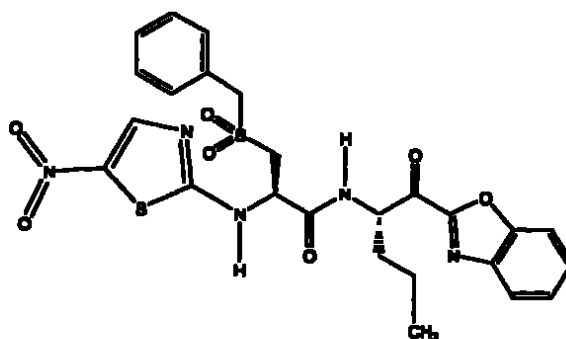
Step 3 (R)-N-[(S)-1-(1-Benzooxazol-2-yl-1-hydroxy-methyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethane-sulfonyl-propionamide (223mg, 0.4mmol) was dissolved in 1.6mL dichloromethane and treated with Dess Martin periodinane (342mg, 0.80mmol). The mixture was allowed to stir for 16 hours, then 20mL of 0.26M Na₂S₂O₃ in saturated NaHCO₃ was added and the mixture was extracted with two 30mL portions of ethyl acetate and washed with three 5mL portions of saturated NaHCO₃. The organic layer was dried over MgSO₄ and concentrated. The crude product was dissolved in a minimum amount of hot ethyl acetate and crystallized by addition of dry diethyl ether. This crystallization was repeated to give clean (R)-N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide (97mg, 0.176mmol, 44% yield), ¹H NMR. (DMSO) 8.67 (m, 1H), 8.12 (m, 1H), 7.81 (m, 1H), 7.65-7.35 (m, 10H), 6.78 (m, 2H), 5.51 (m, 1H), 4.68 (m, 1H), 4.37 (s, 2H), 3.62 (m, 1H), 3.38 (m, 1H), 2.15 (m, 1H), 1.91 (m, 1H), 0.98 (m, 3H), MS (M⁺+1) 551.0, 550.58

The following compound was prepared by the method of Example 9

N-[1-(Benzooxazole-2-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(pyrimidin-2-ylamino)-propionamide

EXAMPLE 10

(R)-N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide, (Compound 29)



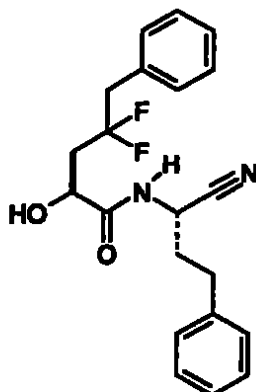
Step 1 A mixture of (R)-3-benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionic acid (42mg, 0.123mmol, Reference Example 6) HOBT (28mg, 0.148mmol), EDC (29mg, 0.148mmol), (S)-2-amino-1-benzooxazol-2-yl-pentan-1-ol (27mg, 0.123mmol, Reference Example 17(c)), 1mL dichloromethane and N-methyl morpholine (14μL, 0.123mmol) was allowed to stir for 16 hours. The product was extracted into 60mL ethyl acetate and washed with one 30mL portion of 1N HCl, and one 30mL portion of saturated NaHCO₃, dried over MgSO₄ and concentrated to give (R)-N-[(S)-1-(1-benzooxazol-2-yl-1-hydroxy-methyl)-butyl]-3-benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionamide (41.8mg, 0.077mmol, 63% yield)

Step 2 (R)-N-[(S)-1-(1-Benzooxazol-2-yl-1-hydroxy-methyl)-butyl]-3-benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionamide (41.8mg, 0.077mmol) was dissolved in 0.5mL methanol, treated with a 0.5mL aqueous solution of Oxone® (43mg, 0.069mmol), and stirred for 1 hour. Methanol was removed under reduced pressure and 2mL water was added. The mixture was extracted with two 10mL portions of ethyl acetate, dried over MgSO₄, and concentrated. It was then dissolved in 0.5mL dichloromethane and treated with Dess Martin periodinane (65mg, 0.154mmol). The mixture was allowed to stir for 16 hours, then 5mL of 0.26M Na₂S₂O₃ in saturated NaHCO₃ was added and the mixture was extracted with two 10mL portions of ethyl acetate and washed with three 5mL portions of saturated NaHCO₃. The organic layer was dried over MgSO₄ and concentrated. The product was purified by triturating with diethyl ether to give (R)-N-[(S)-1-(1-benzooxazol-2-yl)-methanoyl]-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide (28mg, 0.054mmol, 26% yield). ¹H NMR (CDCl₃) 7.96 (s, 1H), 7.87 (m, 1H), 7.7-7.3 (m, 9H), 5.57 (m, 1H), 5.06 (m, 1H), 4.47 (m, 2H), 3.75 (m, 1H), 3.48 (m, 1H), 2.09 (m, 1H), 1.85 (m, 1H), 1.43 (m, 1H), 1.24 (m, 1H), 0.94 (m, 3H), MS (M⁺+1) 572.2, 571.63

EXAMPLE 11

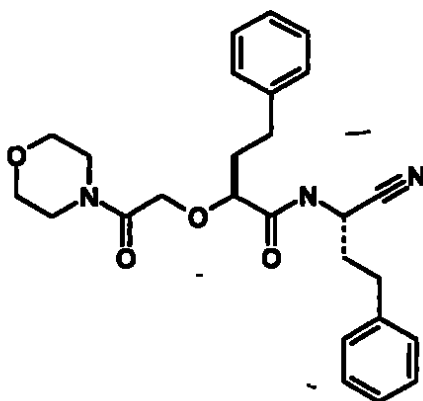
(a) (2S) (4,4-Difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(S)-cyano-3-phenyl-propyl)-amide,
(Compound 33)

-100-



To a mixture of amino-acetonitrile hydrochloride (0.37 mmol, 72.6 mg), (2S)-4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1.0 eq, 0.37 mmol, 85.0 mg, Reference Example 7) and N,N-diisopropylethylamine (2.2 eq, 0.81 mmol, 105.2 mg) in dry dichloromethane (4 mL) under nitrogen was added PyBOP® (1.1 eq, 0.41 mmol, 212 mg). The mixture was stirred at room temperature for 15.5 hours and then concentrated in vacuum. The residue was diluted with ethyl acetate (30 mL) and the mixture was washed with water (30 mL), then with sodium bicarbonate (30 mL) and then with water (30 mL). The organic layer was dried over MgSO₄ and then concentrated in vacuum. The residue was purified over 10 g silica gel, eluting with a mixture of ethyl acetate and heptane (1:2, v/v) to afford (2S)-4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(S)-cyano-3-phenyl-propyl)-amide as a light tan solid (67.4 mg, 48.9%). ¹H NMR (CDCl₃) 7.3 (m, 10H), 7.1 (d, J=7 Hz, 1H), 4.8 (q, J=7.4 Hz, 1H), 4.53 (bd, J=9.5 Hz, 1H), 3.2 (dt, J=16.2, 4.2 Hz, 2H), 2.96 (s, 1H), 2.85 (m, 2H), 2.5 (m, 1H), 2.3-0.9 (m, 3H). LC/MS 89% parent (M+1).

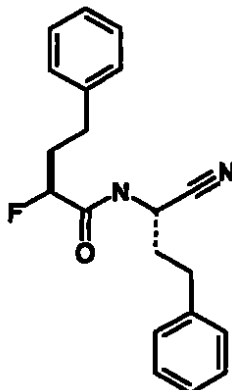
(b) N-(1(S)-cyano-3-phenyl-propyl)-2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyramide (Compound 34)



By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and 2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid [Reference Example 8] there was prepared N-(1(S)-cyano-3-phenyl-propyl)-2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyramide as an oil. ¹H NMR (CDCl₃) 9.4 (d, J=8.2 Hz, 1H), 7.3 (m, 10H),

4.75 (q, J=7.5 Hz, 1H), 4.63 (d, J=15.1 Hz, 1H), 3.95 (d, J=15.3 Hz, 1H), 3.87 (dd, J=8.2, 3.9 Hz, 1H), 3.7 (m, 6H), 3.32 (m, 2H), 2.85 (m, 4H), 2.1 (m, 3H), 2.05 (m, 1H) LC/MS 100% (M+1) 450

(c) N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-fluoro-4-phenyl-butyramide, (Compound 35)

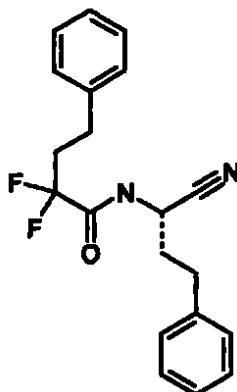


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By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and (2S)-2-fluoro-4-phenyl-butyric acid (Reference Example 9) there was prepared N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-fluoro-4-phenyl-butyramide as a light tan solid ¹H NMR (CDCl₃) 7.3 (m, 10H), 6.6 (bs, 1H), 4.95 (ddd, J=4.9, 2.8, 3.5 Hz, 1H), 4.8 (m, 1H), 3.8 (m, 4H), 2.3 (m, 1H), 2.2 (m, 3H) MS (CI, M+1) 325

10

(d) N-(1-(S)-cyano-3-phenyl-propyl)-2,2-difluoro-4-phenyl-butyramide, (Compound 36)



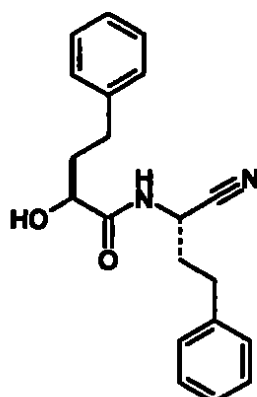
By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and 2,2-difluoro-4-phenyl-butyric acid there was prepared N-(1-(S)-cyano-3-phenyl-propyl)-2,2-difluoro-4-phenyl-butyramide as a white solid ¹H NMR (CDCl₃) 7.3 (m, 10H), 6.6 (d, J=8.1 Hz, 1H), 4.83 (q, J=7.4 Hz, 1H), 2.88 (dt, J=7.5, 2.5 Hz, 2H), 2.79 (t, J=8 Hz, 2H), 2.4 (m, 2H), 2.2 (q, J=7.5 Hz, 2H) LC/MS 50% (M+1) 343

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20

(e) N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-hydroxy-4-phenyl-butyramide, (Compound 37)

-102-

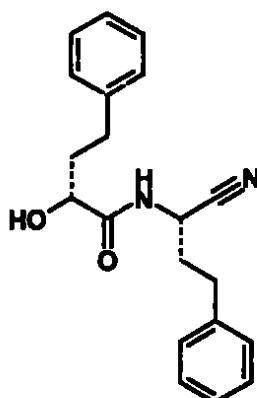


By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and (2S)-2-hydroxy-4-phenyl-butyric acid there was prepared

N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-hydroxy-4-phenyl-butyramide as a white solid ¹H NMR

5 (CDCl₃) 7.3 (m, 10H), 6.9 (d, J=8.4 Hz, 1H), 4.86 (q, J=7.4 Hz, 1H), 4.2 (m, 1H), 2.84 (t, J=7.1 Hz, 2H), 2.77 (t, J=7.8 Hz, 2H), 2.5 (d, J=4.7 Hz, 1H), 2.2 (m, 3H), 1.95 (m, 1H) LC/MS 49% (M+1) 323

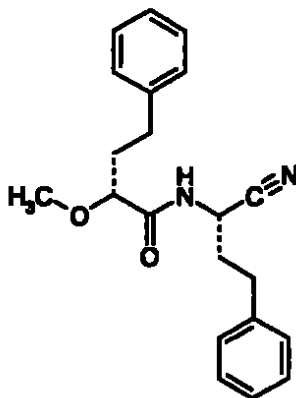
(f) N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-hydroxy-4-phenyl-butyramide, (Compound 38)



By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and (2R)-2-hydroxy-4-phenyl-butyric acid there was prepared N-(1-(S)-

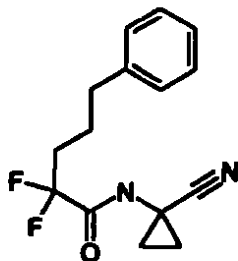
10 cyano-3-phenyl-propyl)-2-(R)-hydroxy-4-phenyl-butyramide as a white solid ¹H NMR (CDCl₃) 7.4-7.1 (m, 10H), 6.9 (d, J=8.7 Hz, 1H), 4.87 (q, J=7.3 Hz, 1H), 4.1 (m, 1H), 2.85 (t, J=7.5 Hz, 2H), 2.77 (t, J=8.4 Hz, 2H), 2.3 (d, J=5.1 Hz, 1H), 2.2 (m, 3H), 2.0 (m, 1H) LC/MS 94% (M+1) 323

-103-

(g) N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-methoxy-4-phenyl-butyramide, (Compound 39)

By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride (0.407 mmol, 80mg) and 2-(R)-methoxy-4-phenyl-butyric acid (Reference Example 10) there was prepared N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-methoxy-4-phenyl-butyramide as a white solid (91.8mg, 67%). ¹H NMR (CDCl₃) 7.2 (m, 10H), 6.8 (d, J=8.5 Hz, 1H), 4.86 (q, J=7.5 Hz, 1H), 3.67 (dd, J=6.5, 4.5 Hz, 1H), 3.35 (s, 3H), 2.85 (m, 2H), 2.68 (t, J=8.0 Hz, 2H), 2.2-2.0 (m, 4H). LC/MS 84% (M⁺1) 337.

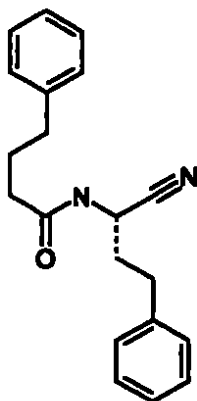
(h) 2,2-Difluoro-5-phenyl-pentanoic acid (1-cyano-cyclopropyl)-amide, (Compound 40)



By proceeding in a manner similar to Example 11(a) above but using 2,2-difluoro-5-phenyl-pentanoic acid and 1-amino-cyclopropanecarbonitrile hydrochloride there was prepared 2,2-difluoro-5-phenyl-pentanoic acid (1-cyano-cyclopropyl)-amide. ¹H NMR (CDCl₃) 8.132 (m, 2H), 1.64 (m, 2H), 1.82 (m, 2H), 2.12 (m, 2H), 2.8-2.56 (m, 2H), 6.82 (m, 1H), 7.36-7.15 (m, 5H). MS (ES-) 277.

(i) N-(1-(S)-Cyano-3-phenyl-propyl)-4-phenyl-butyramide, (Compound 41)

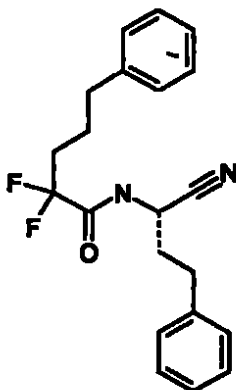
-104-



By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and 4-phenylbutyric acid there was prepared N-(1-(S)-cyano-3-phenyl-propyl)-4-phenyl-butyramide as a colorless oil ¹H NMR (CDCl₃) δ 7.3 (m, 10H), 6.0 (d, J=8.3 Hz, 1H), 4.9 (q, J=7.4 Hz, 1H), 2.8 (m, 2H), 2.65 (t, J=7.4 Hz, 2H), 2.15 (m, 4H), 1.95 (m, 2H) LC/MS 100% (M+1) 307

EXAMPLE 12

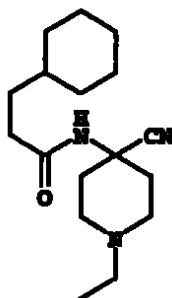
2,2-difluoro-5-phenyl-pentanoic acid ((S)-1-cyano-3-phenyl-propyl)-amide, (Compound 42)



A mixture of 2,2-difluoro-5-phenyl-pentanoic acid (109mg, 0.509 mmol), (S)-2-amino-4-phenyl-butyronitrile hydrochloride (103mg, 0.523 mmol) and HATU (206mg, 0.542 mmol) in DMF (4mL) and stirred at room temperature for 5 hours then evaporated under reduced pressure. The residue was taken in ethyl acetate washed with 1N HCl, sodium bicarbonate and then water. Organic extract was dried over Na₂SO₄ and then evaporated under vacuum to give orange oil. The residue was subjected to mpic, eluting with a mixture of ethyl acetate and heptane (1:9, v/v) to give 2,2-difluoro-5-phenyl-pentanoic acid ((S)-1-cyano-3-phenyl-propyl)-amide as colorless oil (82 mg) ¹H NMR (CDCl₃) 7.3-7.1 (m, 10H), 6.9 (bs, 1H), 4.80 (q, J=7.5 Hz, 1H), 2.80 (dt, J=7.3, 2.7 Hz, 2H), 2.65 (t, J=7.5 Hz, 2H), 2.2-2.0 (m, 4H), 1.8 (m, 2H) MS 357 (MH⁺), 379 (M+Na)

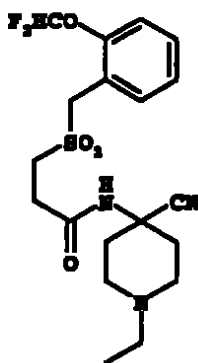
EXAMPLE 13

-105-

(a) N-(4-Cyano-1-ethyl-piperidin-4-yl)-3-cyclohexyl-propionamide

Step 1 To a stirred solution of 1-ethyl-4-piperidone (25g, 0.197mol) in 300ml of diethyl ether, and NH_4Cl (22.3g, 0.41mol), was added NaCN (14.5g, 0.295mol, in 70ml water) drop-wise at room temperature. After stirring for 24h the diethyl ether was separated and the water phase was extracted with n-BuOH, then washed with brine and dried. After removal of most of the n-BuOH under reduced pressure, the residue was diluted with 50ml of diethyl ether and then acidified with 2N HCl in diethyl ether solution at 0°C. The solid was dried under vacuum to yield 45g of 4-amino-1-ethyl-piperidine-4-carbonitrile HCl salt.

Step 2 To a stirred mixture of 3-cyclohexyl-propionic acid (156mg, 1mmol), 4-amino-1-ethyl-piperidine-4-carbonitrile HCl salt (227, 1mmol, prepared as in step 1 above), and HATU (570mg, 1.5mmol) in MeCl_2 (5ml), was added N,N-diisopropylethylamine (516mg, 4mmol) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated NaHCO_3 , brine, dried with MgSO_4 , and concentrated to yield N-(4-Cyano-1-ethyl-piperidin-4-yl)-3-cyclohexyl-propionamide (170mg). LC-MS elution time = 2.25min. 290.2 (M-1), 292.2 (M+1) (MS API 150EX LC HP Agilent 1100 Series Column Phenomenex, 5u ODS3 100A 100X3mm, Flow Rate 2ml/min. Two solvent gradient. Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.)

(b) N-(4-Cyano-1-ethyl-piperidin-4-yl)-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide

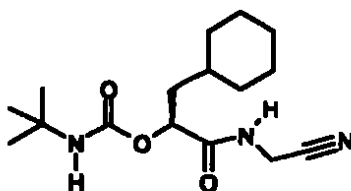
-106-

By proceeding in a similar manner to Example 13(a) but using 3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionic acid (294mg, 1mmol) and 4-amino-1-ethyl-piperidine-4-carbonitrile HCl salt (227, 1mmol) there was N-(4-cyano-1-ethyl-piperidin-4-yl)-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide 260mg) LC-MS $R_T = 1.96$ min, 428.2 (M-1), 430.3 (M+1)

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

EXAMPLE 14

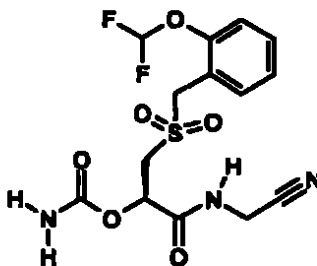
(S)-tert-Butyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



(S)-N-Cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide (53mg, 0.252mmol) was dissolved in dichloromethane (1mL). Triethylamine (0.1mL) was added and then tert-butyl isocyanate (0.034mL, 0.3mmol). The mixture was stirred at room temperature overnight. After dilution with ethyl acetate (100mL), the solution was washed with 1N aqueous HCl, brine, sat. aqueous NaHCO₃, and brine, dried with MgSO₄, and evaporated under vacuum. Flash chromatography on silica gel (hexane/ethyl acetate 1:1) gave (S)-tert-Butyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester (63mg, 0.204mmol) as a white solid.

EXAMPLE 15

(a) (R)-Carbamic acid 1-(cyanomethyl-carbamoyl)-2-(2-difluoromethoxy-phenylmethanesulfonyl)-ethyl ester



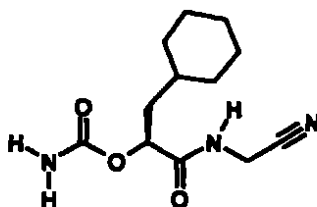
(R)-N-Cyanomethyl-3-(2-(1,1-difluoromethoxy)-phenylmethanesulfonyl)-2-hydroxy-propionamide (100mg, 0.287mmol, Example 1(a)) was dissolved in dichloromethane (2mL) and THF (1mL). Trichloroacetyl isocyanate (0.051mL, 0.43mmol) was added and the mixture was stirred for 1h. The

65

-107-

solvents were removed under vacuum and the residue was dissolved in 1,4-dioxane (10mL). 1N aqueous HCl (5mL) was added and the mixture was heated at 70°C for 4h. After cooling to room temperature, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with MgSO₄, and evaporated under vacuum. Flash chromatography on silica gel (hexane/ethyl acetate 1:3) gave (R)-carbamate acid 1-(cyanomethyl-carbamoyl)-2-(2-difluoromethoxy-phenylmethanesulfonyl)-ethyl ester (35mg, 0.089mmol) as a white solid. ¹H NMR (DMSO) 8.90 (t, J=4.8Hz, 1H), 7.48-7.43 (m, 2H), 7.30-7.21 (m, 2H), 7.11 (t, J_{H-F}=73.6Hz, 1H), 6.98-6.76 (br, 2H), 5.28-5.23 (m, 1H), 4.60 (s, 2H), 4.15 (d, J=4.8Hz, 2H), 3.70 (dd, J=10.0Hz, J=14.8Hz, 1H), 3.54 (d, J=14.4Hz, 1H). MS (M+H)⁺ 392.

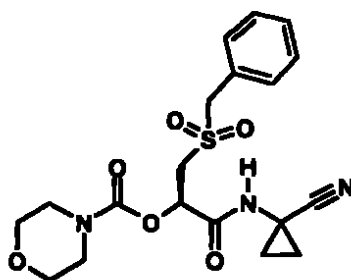
(b) (S)-Carbamate acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 8(a) above but using (R)-N-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide there was prepared (S)-Carbamate acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ¹H NMR (DMSO) 8.63 (t, J=5.6Hz, 1H), 6.63 (br, 2H), 4.81-4.77 (m, 1H), 4.11 (d, J=5.2Hz, 2H), 1.74-0.81 (m, 13H). MS (M+H)⁺ 254.

EXAMPLE 16

(a) (R)-Morpholine-4-carboxylic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester



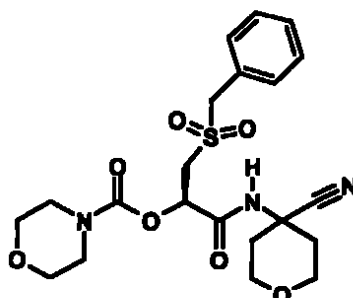
DMF was added to a mixture of (R)-morpholine-4-carboxylic acid 1-carboxy-2-phenylmethanesulfonyl-ethyl ester {from step 2 in Example 4(a)} (60mg, 0.168mmol), HATU (200mg, 0.52mmol), and 1-amino-cyclopropanecarbonitrile hydrochloride (100mg, 0.84mmol). 4-Methylmorpholine (0.5mL) was added and the mixture was stirred overnight. The mixture was diluted with ethyl acetate (100mL), washed with 1N aqueous HCl, brine, sat. aqueous NaHCO₃, brine, dried with MgSO₄, and evaporated under vacuum. Flash chromatography on silica gel (hexane/ethyl acetate

-108-

1 2) gave (R)-morpholine-4-carboxylic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester (7mg, 0.017mmol) ¹H NMR (DMSO) 9.16 (s, 1H), 7.40-7.32 (m, 5H), 5.24-5.19 (m, 1H), 4.55 (d, J=13.2Hz, 1H), 4.48 (d, J=13.2Hz, 1H), 3.63-3.25 (m, 10H), 1.51-1.39 (m, 2H), 1.20-1.07 (m, 2H) MS (M+H)⁺ 422

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(b) (R)-Morpholine-4-carboxylic acid 1-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester

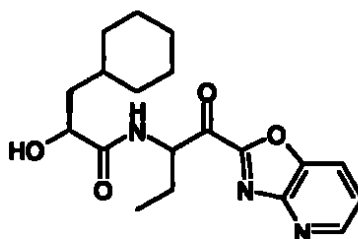


By proceeding in a manner similar to Example 16(a) above but using 4-amino-tetrahydropyran-4-carbonitrile hydrochloride {prepared according to Example 13(a) step1 but using tetrahydropyran-4-one} there was prepared (R)-morpholine-4-carboxylic acid 1-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester LC-MS elution time = 3.20min 464.4(M-1), 466.2(M+1) (MS API 150EX LC HP Agilent 1100 Series Column Phenomenex, 5u ODS3 100A 100X3mm, Flow Rate 2ml/min Two solvent gradient. Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min Then gradient back to 100% A, 0% B from t = 7 to t = 15 min)

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EXAMPLE 17

3-Cyclohexyl-2-hydroxy-N-[1-(oxazolo[4,5-b]pyridin-2-carbonyl)-propyl]-propionamide



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Step 1 To a stirred solution of [1-(hydroxy-oxazolo[4,5-b]pyridin-2-yl-methyl)-propyl]-carbamic acid *tert*-butyl ester (3.11g, 10mmol, prepared as described in Reference Example 20 step2) in dioxane (4ml) was added HCl (4N solution in 5ml of dioxane) at room temperature After 2 hours, ethyl ether(50ml) was added and the reaction mixture was filtered The resultant solid was washed with an additional 20ml of ethyl ether and dried under vacuum to yield 3g of 2-amino-1-oxazolo[4,5-b]pyridin-2-yl-butan-1-ol HCl salt

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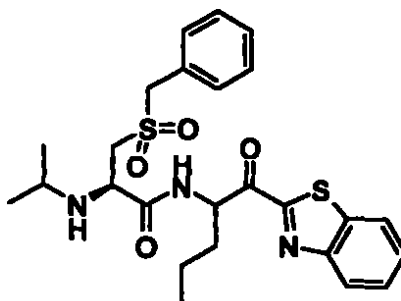
-109-

Step 2 To a stirred mixture of 3-cyclohexyl-2-hydroxy-propionic acid (155mg, 0.9mmol), 2-amino-1-oxazolo[4,5-*b*]pyridin-2-yl-butan-1-ol HCl salt, and HOBt (168mg, 1.1mmol) in MeCN (5ml), was added EDC (270mg, 1.4mmol) and N-methylmorpholine (0.45ml) at 23°C. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated NaHCO₃, brine, dried with MgSO₄, and concentrated to yield 293 mg of 3-cyclohexyl-2-hydroxy-*N*-[1-(hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-propionamide which was used in step 3 following without further purification. MS 360.3 (M-1), 362.3 (M+1), 384.2 (M+Na).

Step 3 To a stirred solution of 3-cyclohexyl-2-hydroxy-*N*-[1-(hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-propionamide (300mg, 0.83mmol) in MeCl₂ (20ml), was added MnO₂ (1.44g, 16.6mmol) at room temperature. After stirring for 30min, the mixture was filtered to remove MnO₂, and washed with 20ml of MeCl₂. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography to yield 3-cyclohexyl-2-hydroxy-*N*-[1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propyl]-propionamide (40mg). ¹H NMR (DMSO-*d*₆) 8.71 (1H, dd, NH, diastereomer), 8.38 (1H, dd,), 8.28 (1H, m), 7.7-7.6 (1H, m), 5.5-5.4 (1H, m), 5.2-5.1 (1H, m), 3.95-3.99 (1H, br, OH), 2.1-1.95 (1H, m), 1.85-1.75 (1, m), 1.7-0.8 (16H, m). MS 358.1 (M-1), 360.1 (M+1), 382 (M+Na).

EXAMPLE 18

(a) (R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide

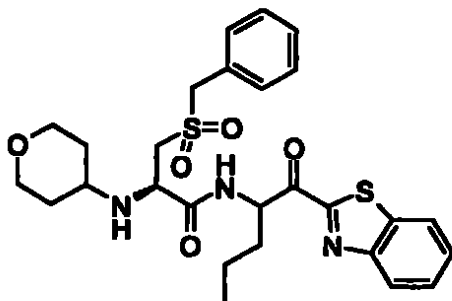


A solution of (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide {30mg, 0.06mmol, Example 30(a)} in dichloromethane (10mL) was treated with Dess-Martin-periodinane (51mg, 0.12mmol). This mixture was stirred at room temperature for 45 minutes then treated with resin-bound thiosulfate (400mg, 0.6mmol) and stirring was continued for a further 24 hours then the mixture was treated with AP-Trisamine (270mg, 0.6mmol). After stirring for a further 24 hours the reaction mixture was filtered and the filtrate was evaporated to give (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide (23mg, 75%) as mixture of diastereomers. ¹H NMR (CDCl₃, 300MHz) 8.29-8.27 (m, 1H), 8.23-8.19 (m, 1H), 8.01-7.98 (m, 1H), 7.63-7.36 (m, 7H), 5.80-5.74 (m,

-110-

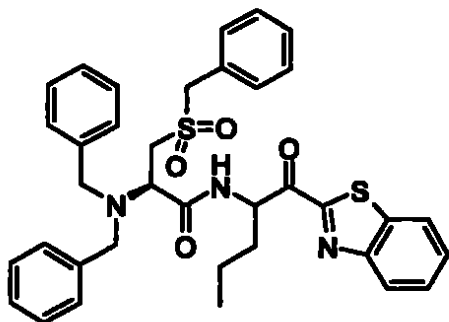
1H), 4.36-4.31 (m, 2H), [3.79 (dd, J=9.5Hz, 3Hz), 3.73 (dd, J=9Hz, 2.5Hz) 1H], 3.41-3.34 (m, 1H), 3.20-3.01 (m, 1H), 2.89-2.85 (m, 1H), 2.17-2.06 (m, 1H), 1.88-1.78 (m, 1H), 1.52-1.25 (m, 3H), 1.12-1.06 (m, 6H), [0.96 (t, J=7.5Hz) 0.95 (t, J=7.5Hz) 1H] LC/MS m/z=502 (M+H)

- 5 (b) (R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



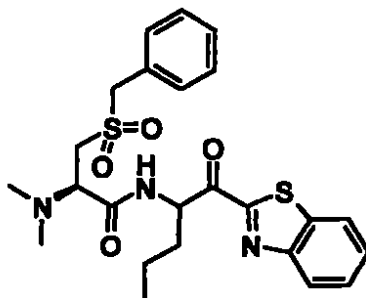
- By proceeding in a similar manner to Example 18(a) but using (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide {0.11 mmol, Example 29(b)} and subjecting the crude product to HPLC there was prepared (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (10mg, 16%) LC/MS retention time 2.92min (TIC), m/z=544 (M+H) (determined with method A)

- 15 (c) (R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide



- By proceeding in a similar manner to Example 18(a) but using (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide {0.11 mmol, Example 29(a)} and subjecting the crude product to HPLC there was prepared (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide (4mg) as mixture of diastereomers ¹H NMR (CDCl₃, 300MHz) 8.33-7.89 (m, 3H), 7.61-7.55 (m, 2H), 7.47-7.29 (m, 15H), 5.75 (m, 1H), [4.54 (d, J=14Hz), 4.51 (d, J=13.5Hz), 1H], [4.27 (d, J=14Hz), 4.25 (d, J=13.5Hz), 1H], 4.11-3.95 (m, 2H), [3.78 (d, J=13Hz), 3.76 (d, J=13Hz), 2H], [3.51 (d, J=13Hz), 3.50 (d, J=13Hz), 2H], 3.19-3.13 (m, 1H), 2.10-1.77 (m, 2H), 1.51-1.37 (m, 2H), 0.91-0.84 (m, 3H) LC/MS m/z=640 (M+H)

- (d) (R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide



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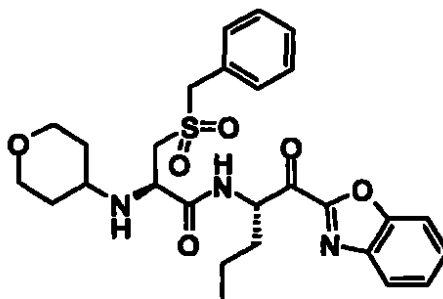
By proceeding in a similar manner to Example 18(a) but using (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (30mg, 0.06mmol, Example 30(b)), and subjecting the crude product to HPLC there was prepared (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (11mg, 38%)

10 LC/MS retention time 2.98min (TIC), $m/z=488$ (M+H) (determined with method A)

EXAMPLE 19

- (a) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide

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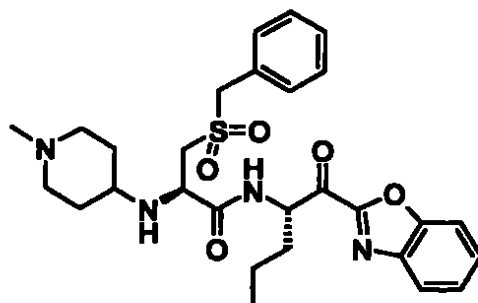


A solution of (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (0.22mmol, Example 31(a)) in dichloromethane (10mL) was treated with Dess-Martin-periodinane (187mg, 0.44mmol). This mixture was agitated at room temperature overnight then treated with resin-bound thiosulfate (1.47g, 2.2mmol) and stirring was continued for a further 24 hours then the mixture was treated with Silicycle Triamine (611mg, 2.2mmol). After agitating for a further 24 hours the reaction mixture was filtered. The filtrate was evaporated and the residue was subjected to HPLC to give (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (9mg, 8%). LC/MS

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25 retention time 3.0min (TIC), $m/z=528$ (M+H) (determined with method B)

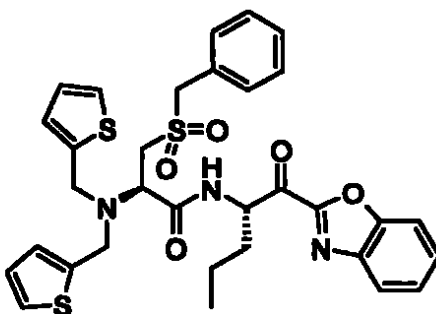
(b) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide



5 By proceeding in a similar manner to Example 19(a) but using (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide {0.22mmol, Example 31(b)} there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide (7mg, 6%)
LC/MS retention time 2.7min (TIC), $m/z=541$ (M+H) (determined with method A)

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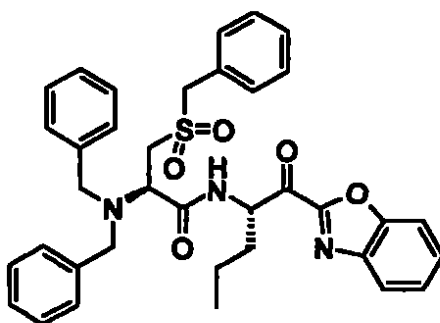
(c) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide



15 By proceeding in a similar manner to Example 19(a) but using (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide {0.22mmol, Example 31(c)} there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide (5.3mg, 4%)
LC/MS retention time 3.7min (TIC), $m/z=636$ (M+H) (determined with method A)

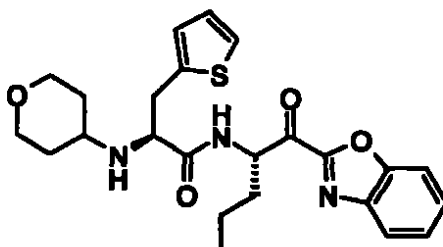
20 (d) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide

-113-



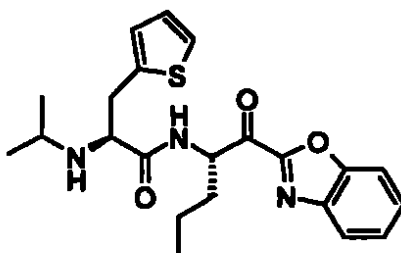
By proceeding in a similar manner to Example 19(a) but using (R)-N-[(S)-1-(benzoxazol-2-yl)-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide (0.22mmol, Example 31(d)) there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide (3.8mg, 3%) LC/MS retention time 4.14min (TIC), $m/z=624$ (M+H) (determined with method B).

(e) (S)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide



By proceeding in a similar manner to Example 19(a) but using (S)-N-[(S)-1-(benzoxazol-2-yl)-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide (0.22mmol, Example 31(e)) there was prepared (S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide (6.5mg, 6%) LC/MS retention time 2.92min (TIC), $m/z=456$ (M+H) (determined with method B)

(f) (S)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide



By proceeding in a similar manner to Example 19(a) but using (S)-N-[(S)-1-(Benzoxazol-2-yl)-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide (0.22mmol, Example 31(f)),

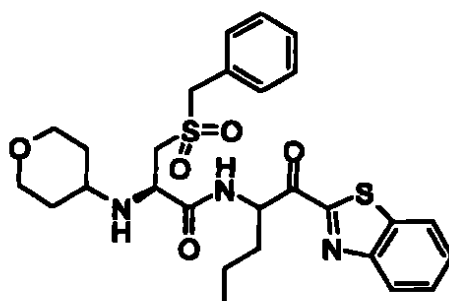
-114-

there was prepared (S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide (10.6 mg, 12%) LC/MS retention time 2.99 min (TIC), $m/z=414$ (M+H) (determined with method B)

5

EXAMPLE 20

(a) (R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



A solution of (R)-N-[1-(benzothiazole-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (0.22 mmol, Example 32(a)) in dichloromethane (10 mL) was treated with Dess-Martin-periodinane (187 mg (0.44 mmol)). After stirring at room temperature for 30 minutes the reaction mixture was treated with saturated sodium thiosulfate solution (50 mL) and saturated sodium bicarbonate solution (50 mL). The phases were separated and the aqueous phase extracted with dichloromethane. The combined organic phases were washed with brine, then dried over magnesium sulfate and then evaporated. The residue was subjected to flash chromatography using a silica gel cartridge to give (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (46 mg, 38%) as mixture of diastereoisomers. The two diastereoisomers were separated by silica gel column chromatography eluting with 1:1 v/v heptane-ethyl acetate mixture.

20 Diastereoisomer A

^1H NMR (CDCl_3 , 300 MHz): 8.23-8.20 (m, 2H), 8.00 (dd, $J=7\text{ Hz}$, 2 Hz, 1H), 7.63-7.53 (m, 2H), 7.48-7.40 (m, 5H), 5.80 (m, 1H), 4.38 (d, $J=14\text{ Hz}$, 1H), 4.32 (d, $J=14\text{ Hz}$, 1H), 3.97-3.90 (m, 2H), 3.80 (dd, $J=9.5\text{ Hz}$, 3 Hz, 1H), 3.43-3.30 (m, 3H), 3.13 (dd, $J=14.5\text{ Hz}$, 9.5 Hz, 1H), 2.70 (m, 1H), 2.27 (m, 1H), 2.09 (m, 1H), 1.91-1.76 (m, 3H), 1.52-1.37 (m, 4H), 0.95 (t, $J=7.5\text{ Hz}$, 3H).

25 LC/MS $m/z=544$ (M+H)

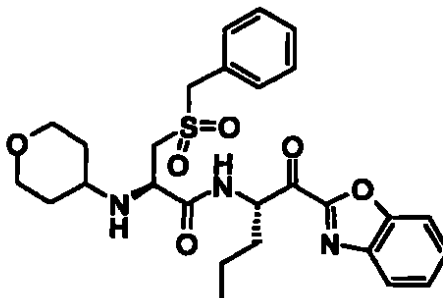
Diastereoisomer B

^1H NMR (CDCl_3 , 300 MHz): 8.22-8.19 (m, 2H), 8.01-7.98 (m, 1H), 7.63-7.53 (m, 2H), 7.44-7.37 (m, 5H), 5.74 (m, 1H), 4.35-4.31 (m, 2H), 3.99-3.94 (m, 2H), 3.86 (dd, $J=9.5\text{ Hz}$, 3 Hz, 1H), 3.49-3.33 (m, 3H), 3.08 (dd, $J=14.5\text{ Hz}$, 9.5 Hz), 2.75-2.70 (m, 1H), 2.22 (m, 1H), 2.15-2.06 (m, 1H), 1.91-1.75 (m, 3H), 1.53-1.37 (m, 4H), 0.96 (t, $J=7.5\text{ Hz}$, 3H).

30

LC/MS $m/z=544$ (M+H)

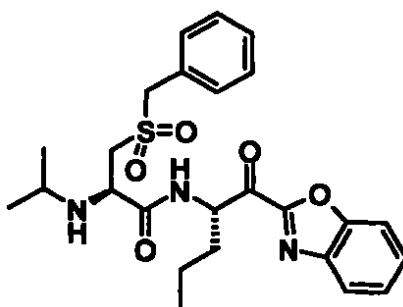
(b) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a similar manner to Example 20(a) but using (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide {0.22mmol, Example 32(b)} there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (48mg, 41%) ^1H NMR (CDCl_3 , 300MHz) 8.22 (d, $J=8.5\text{Hz}$, 1H), 7.92 (d, $J=8\text{Hz}$, 1H), 7.68 (d, $J=8.5\text{Hz}$, 1H), 7.60-7.40 (m, 7H), 5.68-5.61 (m, 1H), 4.37 (d, $J=14\text{Hz}$, 1H), 4.31 (d, $J=14\text{Hz}$, 1H), 3.97-3.91 (m, 2H), 3.80 (dd, $J=9.5\text{Hz}$, 3Hz, 1H), 3.43-3.32 (m, 3H), 3.12 (dd, $J=14.5\text{Hz}$, 9.5Hz, 1H), 2.73-2.66 (m, 1H), 2.26 (m, 1H), 2.13-2.05 (m, 1H), 1.89-1.77 (m, 3H), 1.52-1.39 (m, 4H), 0.97 (t, $J=7.5\text{Hz}$, 3H) LC/MS $m/z=528$ (M+H)

EXAMPLE 21

(a) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide



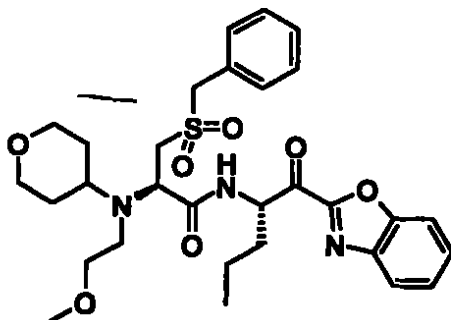
A solution of (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide {30mg, 0.063mmol, Example 31(g)} in dichloromethane (10mL) was treated with Dess-Martin-periodinane (53mg, 0.126mmol) and this mixture was stirred at room temperature for 1 hour then subjected to The Mettler-Toledo AlexTM liquid handler work-up as described below

Dichloromethane (15ml) was added to the reaction mixture, followed by a 1:1 mixture (8ml) of saturated sodium thiosulfate solution and saturated sodium bicarbonate solution. The phases were

-116-

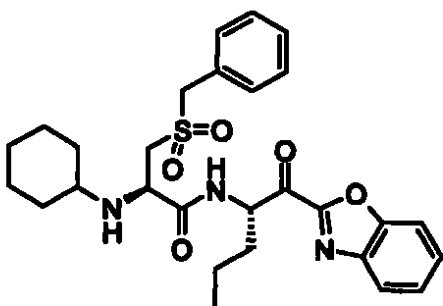
separated and the organic phase washed with another 5ml of the thiosulfate/bicarbonate solution. The organic phase was then washed with brine and then dried over magnesium sulfate. The crude product was subjected to flash chromatography using a silica gel cartridge to give (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide (6.2mg, 20%) LC/MS retention time 2.7min (TIC), $m/z=486$ (M+H) (determined with method C)

(b) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide



By proceeding in a similar manner to Example 21(a) but using (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide (80mg, 0.136 mmol, Example 32(d)) there was prepared (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide (7mg, 9%) LC/MS retention time 3.5min (TIC), $m/z=586$ (M+H) (determined with method C)

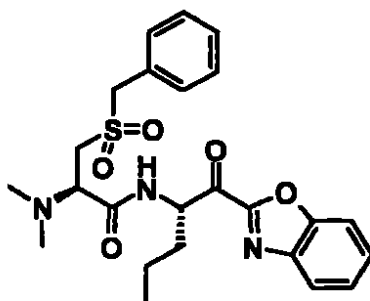
(c) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide



By proceeding in a similar manner to Example 21(a) but using (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide (48mg, 0.091mmol, Example 32(e)) there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide (7.9mg, 16%) LC/MS retention time 2.99-3.02min (TIC), $m/z=526$ (M+H) (determined with method C)

-117-

(d) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide

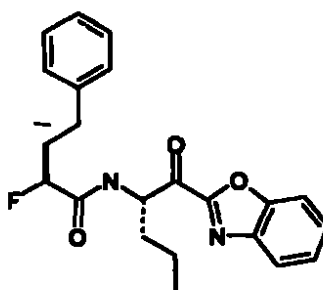


5 By proceeding in a similar manner to Example 21(a) but using (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (10mg, 0.021mmol, Example 32(f)) there was prepared (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (2.5mg, 24%) LC/MS retention time 2.82min (TIC), $m/z=472$ (M+H) (determined with method C)

10

EXAMPLE 22

(1S)-N-[1-(Benzoxazole-2-carbonyl)-butyl]-2-(S)-fluoro-4-phenyl-butyramide



Step 1 To a mixture of (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol (0.549 mmol, 121 mg, Reference Example 17(c)), (S)-2-fluoro-4-phenyl-butyric acid (1.0 eq, 0.549 mmol, 100 mg, Reference Example 9) and N,N-diisopropylethylamine (1.1 eq, 0.604 mmol, 78 mg) in dry dichloromethane (5 mL) under nitrogen was added PyBOP® (1.1 eq, 0.603 mmol, 285 mg). The mixture was stirred at room temperature for 23.5 hr, then concentrated in vacuum. The residue was diluted with ethyl acetate (20 mL) and washed with sodium bicarbonate (30 mL) then water (30 mL). The organic layer was dried (MgSO₄) and concentrated in vacuum. The residue was purified by silica gel column chromatography, eluting with ethyl acetate and heptane (1:2) to afford (S)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-fluoro-4-phenyl-butyramide as mixture of diastereoisomers (167.8 mg, 79.5%)

Step 2 To a solution of (S)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-fluoro-4-phenyl-butyramide in dry dichloromethane (5mL) under nitrogen was added a 15% (wt in dichloromethane,

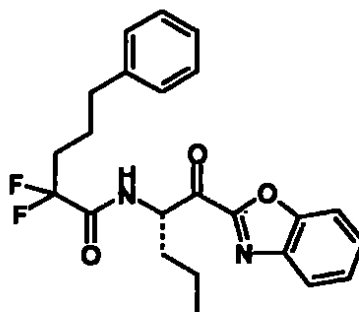
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-118-

2.0 eq, 0.863 mmol, 2.44 g) of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane). The mixture was stirred at room temperature for 2 hr, then quenched by adding a solution of $\text{Na}_2\text{S}_2\text{O}_3$ (4.0 eq, 1.73 mmol, 273 mg) in saturated Sodium bicarbonate solution (30 ml). The organic layer was dried (MgSO_4) and concentrated in vacuum. The residue was purified over 10 g silica gel, eluting with ethyl acetate and heptane (1:3) to afford (1S)-N-[1-(Benzoxazole-2-carbonyl)-butyl]-2-(S)-fluoro-4-phenyl-butylamide as a light yellow solid (156 mg, 94%). ^1H NMR (CDCl_3) 7.95 (d, $J=7.9$ Hz, 1H), 7.7 (d, $J=8.2$ Hz, 1H), 7.6 (t, $J=7.3$ Hz, 1H), 7.51 (t, $J=7.4$ Hz, 1H), 7.2 (m, 6H), 5.8 (m, 1H), 4.95 (ddd, $J=4.9, 8.3, 5.5$ Hz, 1H), 2.8 (m, 2H), 2.4 (m, 1H), 2.2 (m, 2H), 1.85 (m, 1H), 1.5 (m, 2H), 1.0 (t, $J=7.3$ Hz, 3H). LC/MS 86% ($M+1$) 383.

EXAMPLE 23

2,2-Difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazole-2-carbonyl)-butyl]-amide



Step 1 A solution of 2,2-Difluoro-5-phenyl-pentanoic acid (182 mg, 0.85 mmol) in DMF (10 mL) was treated with (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol (187 mg, 0.85 mmol), HATU (323 mg, 0.85 mmol) and N,N -Diisopropylethylamine (0.162 mL) and stirred at room temperature for 5 ½ hrs. DMF evaporate off, crude taken up in ethyl acetate and washed with 1N HCl, saturated NaHCO_3 and brine. Dried over Na_2SO_4 and evaporated under reduced pressure to give an oil. Purification by column chromatography eluting with 1:1 mixture of ethyl acetate and heptane gave 2,2-Difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-amide as orange oil (216 mg). MS 417 (MH^+).

Step 2 A solution of 2,2-Difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-amide (216 mg, 0.52 mmol) in dichloromethane (10 mL) was treated with 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (220 mg, 0.52 mmol) for 1 hr at room temperature. The reaction mixture was washed with 0.5 M $\text{Na}_2\text{S}_2\text{O}_3$, saturated NaHCO_3 , and water and dried over Na_2SO_4 . Solvent evaporated under reduced pressure and crude purified by flash chromatography eluting with mixture of ethyl acetate and heptane to give 2,2-Difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazole-2-carbonyl)-butyl]-amide as off white solid (90 mg).

-119-

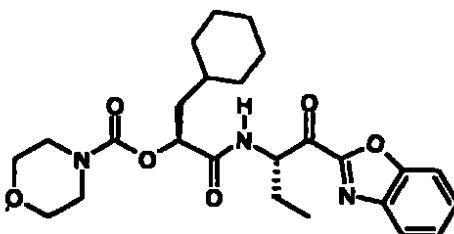
¹H NMR (CDCl₃) 7.93 (d, J=8 Hz, 1H), 7.68 (d, J=8 Hz, 1H), 7.59 (t, J=8 Hz, 1H), 7.49 (t, J=8 Hz, 1H), 7.3-7.11 (m, 5H), 5.72 (m, 1H), 2.67 (t, J=7.5 Hz, 2H), 2.22-2.07 (m, 3H), 1.92-1.77 (m, 3H), 1.55-1.26 (m, 2H), 0.96 (t, J=7.4 Hz, 3H)

LC/MS 415(M+1)

5

EXAMPLE 24

(a) Morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-2-cyclohexyl-ethyl ester



10 Step 1 (S)-3-Cyclohexyl-2-hydroxy-propionic acid (3g, 17.4mmol) was dissolved in methanol (30mL). Trimethylorthoformate (5mL) and p-toluenesulfonic acid monohydrate (100mg) was added. The mixture was stirred at ambient temperature overnight. Water (50mL) was added and stirring was continued for 2h. Methanol was removed under vacuum and the aqueous residue was extracted with ethyl acetate (3x50mL). The combined organic layers were washed with sat. aqueous NaHCO₃ and
15 brine, dried with MgSO₄ and evaporated. (S)-3-Cyclohexyl-2-hydroxy-propionic acid methyl ester was obtained as a colorless liquid (3.1g, 16.7mmol).

Step 2 (S)-3-Cyclohexyl-2-hydroxy-propionic acid methyl ester (1g, 5.37mmol) was dissolved in dichloromethane (20mL). Pyridine (0.57mL, 7mmol) was added and the solution was cooled to 0°C
20 under nitrogen. Trichloromethylchloroformate (0.66mL, 5.5mmol) was added and the mixture was stirred for 30min at room temperature. Morpholine (0.5mL) was added and stirring was continued for 2h. After dilution with ethyl acetate (200mL), the solution was washed with 1N aqueous HCl and brine, dried with MgSO₄ and evaporated under vacuum. The residue was dissolved in methanol (50mL) and 1N aqueous NaOH solution (20mL) was added. The mixture was stirred at room
25 temperature for 4h. Methanol was removed under vacuum and the aqueous residue was washed with diethylether. The aqueous layer was acidified with 1N aqueous HCl and extracted with ethyl acetate (3x100mL). The combined organic layers were washed with brine, dried with MgSO₄ and evaporated under vacuum. The crude (S)-morpholine-4-carboxylic acid 1-carboxy-2-cyclohexyl-ethyl ester was used without further purification.

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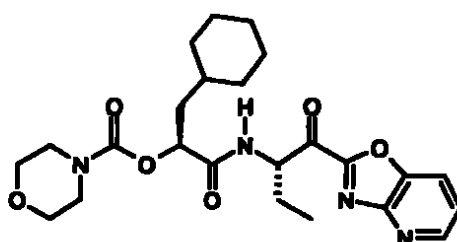
-120-

Step 3 By proceeding in a similar manner to that described in step3 Example 4(a) but using (S)-morpholine-4-carboxylic acid 1-carboxy-2-cyclohexyl-ethyl ester there was prepared morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzooxazole-2-carbonyl)-propylcarbamoyl]-2-cyclohexyl-ethyl ester

¹H NMR (DMSO) 8.61 (d, J=6.4Hz, 1H), 7.97 (d, J=8.0Hz, 1H), 7.87 (d, J=8.0Hz, 1H), 7.61 (t, J=8.0Hz, 1H), 7.52 (t, J=8.0Hz, 1H), 5.15-5.09 (m, 1H), 4.91-4.86 (m, 1H), 3.56-3.20 (m, 8H), 2.05-1.93 (m, 1H), 1.79-0.78 (m, 14H), 0.96 (t, J=7.2Hz, 3H) MS (M+H)⁺ 472 -

By proceeding in a similar manner to Example 24(a) there was prepared

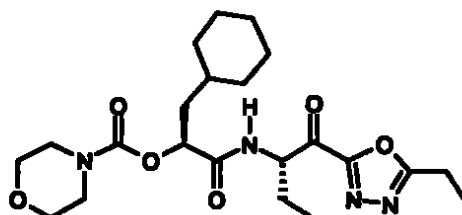
- 10 (b) Morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-ethyl ester



¹H NMR (DMSO) 8.73-8.69 (m, 2H), 8.38 (d, J=8.0Hz, 1H), 7.67-7.62 (m, 1H), 5.08-5.02 (m, 1H), 4.88-4.83 (m, 1H), 3.57-3.20 (m, 8H), 2.07-1.95 (m, 1H), 1.79-0.75 (m, 14H), 0.97 (t, J=7.2Hz, 3H)

15 MS (M+H)⁺ 473, — -

- (c) Morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester

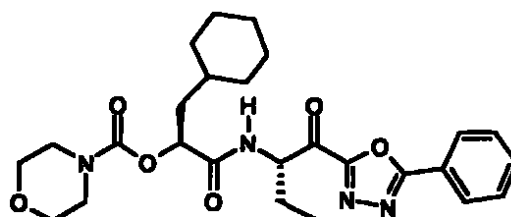


20 ¹H NMR (DMSO) 8.62 (d, J=4.8Hz, 1H), 4.94-4.84 (m, 2H), 3.57-3.20 (m, 8H), 2.95 (q, J=7.2Hz, 2H), 1.98-1.87 (m, 1H), 1.74-0.82 (m, 14H), 1.29 (t, J=7.2Hz, 3H), 0.93 (t, J=7.2Hz, 3H) MS (M+H)⁺ 451,

- 25 (d) Morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester

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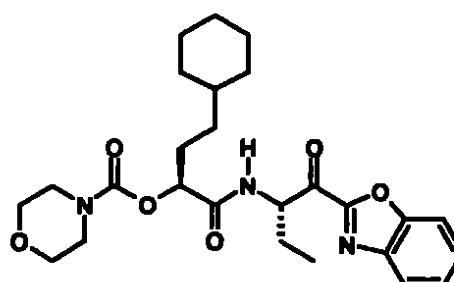
-121-



¹H NMR (DMSO) 8.69 (d, J=6.0Hz, 1H), 8.07 (d, J=8Hz, 2H), 7.70-7.59 (m, 3H), 4.99-4.92 (m, 1H), 4.88-4.83 (m, 1H), 3.57-3.20 (m, 8H), 2.03-1.92 (m, 1H), 1.77-0.77 (m, 14H), 0.96 (t, J=7.2Hz, 3H)
MS (M+H)⁺ 499,

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(c) Morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-3-cyclohexyl-propyl ester

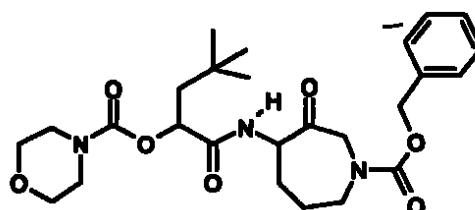


¹H NMR (DMSO) 8.60 (d, J=6.8Hz, 1H), 7.97 (d, J=8.0Hz, 1H), 7.87 (d, J=8.0Hz, 1H), 7.61 (t, J=8.0Hz, 1H), 7.52 (t, J=8.0Hz, 1H), 5.13-5.06 (m, 1H), 4.81-4.76 (m, 1H), 3.56-3.21 (m, 8H), 2.05-1.93 (m, 1H), 1.79-1.46 (m, 8H), 1.19-0.90 (m, 6H), 0.96 (t, J=7.2Hz, 3H), 0.77-0.62 (m, 2H) MS (M+H)⁺ 486,

10

EXAMPLE 25

15 4-[4,4-Dimethyl-2-(morpholine-4-carboxyloxy)-pentanoylamino]-3-oxo-azepane-1-carboxylic acid benzyl ester



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Sodium hydride (60% in mineral oil, 10g, 250mmol) was suspended in dry DMF. Allyl-carbamic acid benzyl ester (19.1g, 100mmol) was added dropwise at ambient temperature. After stirring for 5min, 5-bromo-1-pentene (25g, 168mmol) was added dropwise. Stirring was continued at 50°C for 1h. The reaction was quenched with water and then partitioned between diethylether and water. The ether layer was washed with water and brine, dried with MgSO₄, and evaporated under vacuum. Flash chromatography (ethyl acetate/hexane 1/9) gave 15.5g allyl-pent-4-enyl-carbamic acid benzyl ester.

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

To a solution of 2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (4.5 g, 19.45 mmol) in dichloromethane (50 mL) was added m-chloroperoxybenzoic acid (60 mmol). The mixture was stirred at ambient temperature for 16 h. Saturated aqueous K_2CO_3 solution was added and the mixture was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and evaporated under vacuum. The crude epoxide was dissolved in an 8:1 methanol/water mixture (100 mL). Ammonium chloride (3.2 g, 60 mmol) and sodium azide (3.9 g, 60 mmol) was added and the mixture was heated at 60°C for 48 h. Most of the solvent was removed under vacuum. The residue was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried with $MgSO_4$, and evaporated under vacuum. Flash chromatography of the residue (hexane/ethyl acetate 3:1) gave 3.3 g of 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester.

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

Crude 4-amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester (150 mg, 0.57 mmol), morpholine-4-carboxylic acid 1-carboxy-3,3-dimethyl-butyl ester (120 mg, 0.46 mmol), EDC (400 mg, 2.1 mmol), and HOBt (400 mg, 2.5 mmol) were combined. Dichloromethane (5 mL) was added and then 4-methylmorpholine (0.5 mL). The mixture was stirred at ambient temperature for 2 h. After dilution with ethyl acetate (100 mL) the solution was washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine, dried with $MgSO_4$, and evaporated under vacuum. The residue was dissolved in DMSO (5 mL). Triethylamine (0.3 mL) and then SO_3 pyridine complex (150 mg) were added and the mixture was stirred at ambient temperature for 2 h. After dilution with ethyl acetate (100 mL), the solution was washed with water (50 mL) and brine, dried with $MgSO_4$, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel and gave 4-[4,4-dimethyl-2-(morpholine-4-

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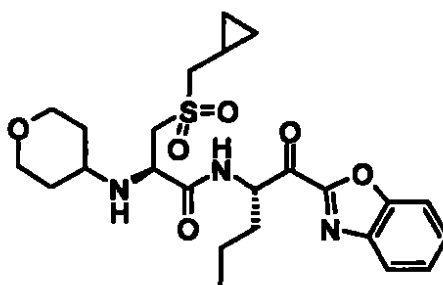
-123-

carbonyloxy)-pentanoylamino]-3-oxo-azepane-1-carboxylic acid benzyl ester (95mg, 0.189mmol) as a white solid

2.1 mixture of diastereomers, ^1H NMR (DMSO) δ 14.808 (m, 1H), 7.40-7.25 (m, 5H), 5.18-4.89 (m, 3H), 4.51-4.33 (m, 2H), 4.01-3.76 (m, 2H), 3.60-3.25 (m, 8H), 2.95-2.79 (m, 1H), 1.84-1.54 (m, 6H), 0.92/0.91 (s, 9H) MS (M+H) $^+$ 504 LC/MS m/z 474(M+H)

EXAMPLE 26

(a) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



Step 1 (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-propionamide {90mg, 0.22mmol, Reference Example 11(f)} was dissolved in 5% acetic acid in acetonitrile (10ml). Tetrahydro-4H-pyran-4-one (110mg, 1.1mmol) was added, followed by (polystyrylmethyl)trimethylammonium cyanoborohydride (107mg, 1.1mmol). The resulting reaction mixture was stirred for four hours and then filtered under suction. The solvents were evaporated under high vacuum. The residue was dissolved in 5ml dichloromethane, Silicycle Triamine (940mg, 2.2mmol) was added and the reaction mixture stirred for four hours. It was filtered under suction and the filtrate concentrated under reduced pressure to give (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (89mg, 0.18mmol, 82%)

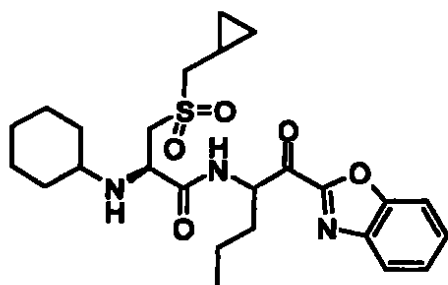
Step 2 (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (89mg, 0.18mmol) was dissolved in 10ml dichloromethane. The Dess-Martin-periodinane (153mg, 0.36mmol) was added and the resulting reaction mixture stirred for two hours. The reaction mixture was poured into a 1/1-mixture of saturated sodium bicarbonate solution and saturated sodium thiosulfate solution. The aqueous phase was extracted with dichloromethane. The combined organic phases were washed with saturated sodium bicarbonate solution and brine. The organic phase was dried with magnesium sulfate and the dichloromethane evaporated under reduced pressure. The crude product was purified via flash chromatography (heptane/ethyl acetate 1/1 to elute) to give (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (24mg,

-124-

0.049mmol, 27%) ¹H NMR (CDCl₃, 300MHz) 8.29 (d, J=8.5Hz, 1H), 7.93 (d, J=8Hz, 1H), 7.68 (d, J=8Hz, 1H), 7.59-7.46 (m, 2H), 5.67 (m, 1H), 3.99-3.93 (m, 2H), 3.84 (dd, J=9.5Hz, 2.5Hz, 1H), 3.56 (dd, J=14.5Hz, 2.5Hz, 1H), 3.42-3.33 (m, 2H), 3.24 (dd, J=14.5Hz, 9.5Hz, 1H), 3.02-2.99 (m, 2H), 2.78-2.71 (m, 1H), 2.13-2.07 (m, 1H), 1.95-1.78 (m, 3H), 1.55-1.41 (m, 5H), 1.23-1.16 (m, 1H), 1.00 (t, J=7.5Hz, 3H), 0.81-0.74 (m, 2H), 0.48-0.43 (m, 2H)

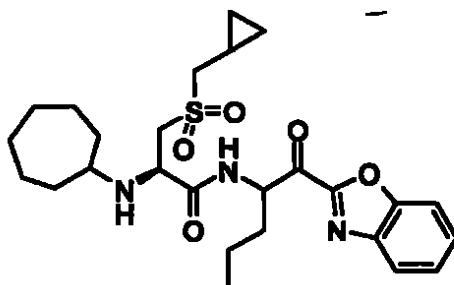
LC/MS m/z=492 (M+H)

(b) (R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethanesulfonyl-propionamide



By proceeding in a similar manner to Example 26(a) but using cyclohexanone there was prepared (R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethanesulfonyl-propionamide (predominantly as one diastereomer) ¹H NMR (CDCl₃, 300MHz) 8.37 (d, J=8.5Hz, 1H), 7.92 (d, J=8Hz, 1H), 7.67 (d, J=8Hz, 1H), 7.59-7.36 (m, 2H), 5.65 (m, 1H), 3.79 (dd, J=9.5Hz, 2.5Hz, 1H), 3.54 (dd, J=14.25Hz, 2.5Hz, 1H), 3.24 (dd, J=14.25Hz, 9.5Hz, 1H), 3.02-2.95 (m, 2H), 2.49 (m, 1H), 2.12-2.07 (m, 1H), 1.96-1.17 (m, 15H), 0.98 (t, J=7Hz, 3H), 0.80-0.72 (m, 2H), 0.48-0.43 (m, 2H) LC/MS m/z=490 (M+H)

(c) (R)-N-[1-(Benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethanesulfonyl-propionamide



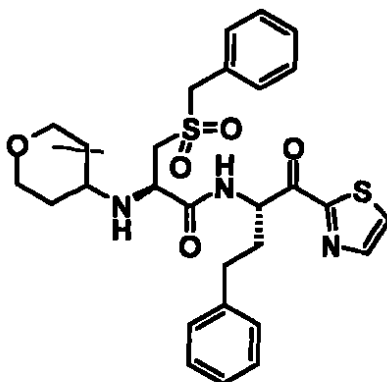
By proceeding in a similar manner to Example 26(a) but using cycloheptanone there was prepared (R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethanesulfonyl-propionamide ¹H NMR (CDCl₃, 300MHz) [8.36 (d, J=8.5Hz), 8.28 (d, J=8.5Hz), 1H], [8.05 (dd, J=8Hz, 1Hz), 7.97 (dd, J=8.5Hz, 1.5Hz), 1H], [7.92 (d, J=8.5Hz), 7.67 (d, J=8Hz), 1H], 7.59-7.48 (m, 1H), [7.44 (ddd, J=8Hz, 7.5Hz, 1Hz), 7.19 (ddd, J=8Hz, 7.5Hz, 1Hz), 1H], [5.65 (m), 5.62 (m), 1H],

-125-

[3.82 (dd, J=10Hz, 3Hz), 3.75 (dd, J=9Hz, 3Hz), 1H], [3.55 (dd, J=14.5Hz, 3Hz), 3.49 (dd, J=14.5Hz, 3Hz), 1H], 3.27 (dd, J=14.5Hz, 9Hz, 1H), 3.03-2.96 (m, 2H), 2.72 (m, 1H), 2.14-2.05 (m, 1H), 1.91-1.39 (m, 16H), 1.23-1.17 (m, 1H), [0.99 (t, J=7.25Hz), 0.98 (t, J=7.25Hz), 1H], 0.79-0.7 (m, 2H), 0.48-0.44 (m, 2H) LC/MS m/z=504 (M+H)

5

(d) (R)-3-Phenylmethanesulfonyl-N-[(S)-3-phenyl-1-(thiazole-2-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide

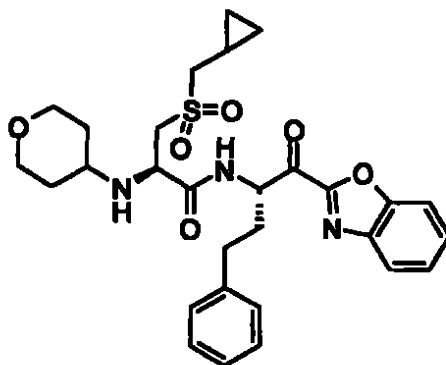


By proceeding in a similar manner to Example 26(a) but using (R)-2-Amino-N-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-3-phenylmethanesulfonyl-propionamide {Reference Example 11(k)} there was prepared (R)-3-phenylmethanesulfonyl-N-[(S)-3-phenyl-1-(thiazole-2-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide ¹H NMR (CDCl₃, 300MHz) δ 2.7 (d, J=9Hz, 1H), 8.06 (d, J=3Hz, 1H), 7.73 (d, J=3Hz, 1H), 7.47-7.39 (m, 5H), 7.25-7.11 (m, 5H), 5.72 (m, 1H), 4.36 (d, J=14Hz, 1H), 4.31 (d, J=14Hz, 1H), 3.97-3.90 (m, 2H), 3.76 (dd, J=9.5Hz, 3Hz, 1H), 3.40-3.31 (m, 3H), 3.01 (dd, J=14.5Hz, 9.5Hz, 1H), 2.76-2.62 (m, 3H), 2.51-2.40 (m, 1H), 2.22-2.09 (m, 1H), 1.87-1.75 (m, 2H), 1.53-1.38 (m, 3H) LC/MS m/z=556 (M+H),

15

(e) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide

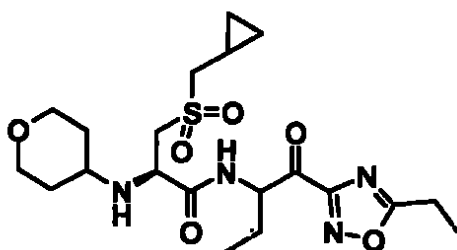
20



By proceeding in a similar manner to Example 26(a) but using (R)-2-amino-N-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-3-phenylmethanesulfonyl-propionamide {Reference Example 11(j)} there was prepared (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-3-phenyl-propyl]-3-

cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide ¹H NMR (CDCl₃, 300MHz) 8.36 (d, J=8.5Hz, 1H), 7.92 (d, J=8Hz, 1H), 7.67 (d, J=8Hz, 1H), 7.60-7.46 (m, 2H), 7.25-7.16 (m, 5H), 5.72 (m, 1H), 3.99-3.93 (m, 2H), 3.81 (dd, J=9.5Hz, 3Hz, 1H), 3.52 (dd, J=14Hz, 3Hz, 1H), 3.41-3.33 (m, 2H), 3.15 (dd, J=14Hz, 9.5Hz, 1H), 3.01-2.70 (m, 2H), 2.81-2.70 (m, 3H), 2.53 (m, 1H), 2.27-2.23 (m, 1H), 1.94-1.44 (m, 5H), 1.22-1.17 (m, 1H), 0.80-0.74 (m, 2H), 0.47-0.42 (m, 2H) LC/MS m/z=554 (M+H),

(f) (R)-3-Cyclopropylmethanesulfonyl-N-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide



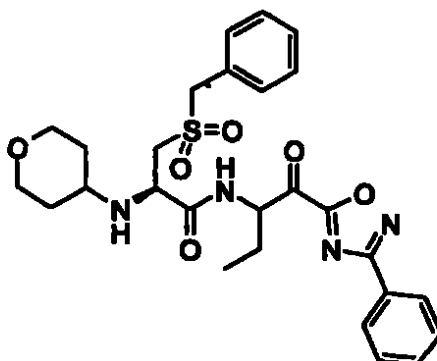
By proceeding in a similar manner to Example 26(a) but using (R)-2-Amino-3-

cyclopropylmethanesulfonyl-N-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl]-propionamide {Reference Example 11(h)} there was prepared (R)-3-cyclopropylmethanesulfonyl-N-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide ¹H NMR (CDCl₃, 300MHz) [8.28 (d, J=8.5Hz), 8.15 (d, J=8Hz), 1H], [5.40 (m), 5.33 (m), 1H], 3.99-3.95 (m, 2H), [3.90 (dd, J=10Hz, 3Hz), 3.84 (dd, J=9.5Hz, 3Hz), 1H], [3.55 (dd, J=14Hz, 3Hz), 3.47 (dd, J=14Hz, 11Hz), 1H], 3.45-3.33 (m, 2H), 3.23 (dd, 14Hz, 10Hz, 1H), 3.07-2.94 (m, 4H), 2.82-2.71 (m, 1H), 2.19-2.08 (m, 1H), 1.95-1.77 (m, 5H), 1.58-1.43 (m, 1H), 1.45 (t, J=7.5Hz, 3H), 1.23-1.14 (m, 1H), [1.00 (t, J=7.5Hz), 0.97 (t, J=7.5Hz), 3H], 0.81-0.73 (m, 2H), 0.48-0.41 (m, 2H) LC/MS m/z=457 (M+H),

(g) (R)-3-Phenylmethanesulfonyl-N-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide

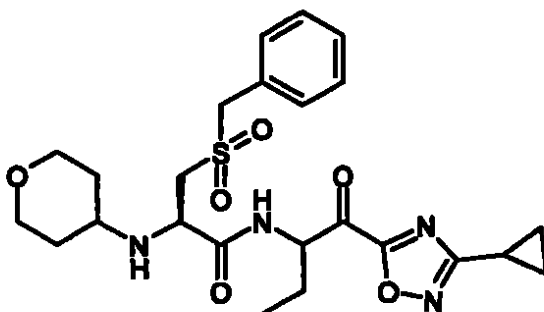
24
75

-127-



By proceeding in a similar manner to Example 26(a) but using (R)-2-Amino-N-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-3-phenylmethanesulfonyl-propionamide {Reference Example 11(g)} there was prepared (R)-3-phenylmethanesulfonyl-N-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide ¹H NMR (CDCl₃, 300MHz) [8.15 (d, J=8Hz), 8.14 (d, J=8Hz), 1H], 7.61-7.39 (m, 10H), [5.46 (m), 5.40 (m), 1H], 4.34-4.28 (m, 2H), 4.09-3.93 (m, 2H), [3.87 (dd, J=9.5Hz, 3Hz), 3.81 (dd, J=9.5Hz, 3Hz), 1H], 3.41-3.32 (m, 3H), [3.16 (dd, J=13.5Hz, 10Hz), 3.11 (dd, J=14Hz, 9.5Hz), 1H], 2.75-2.68 (m, 1H), 2.23-2.13 (m, 1H), 1.96-1.43 (m, 6H), 1.06-0.99 (m, 3H), LC/MS m/z=541 (M+H)

(h) (R)-N-[1-(3-Cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide

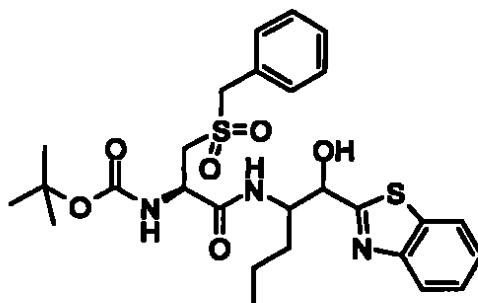


By proceeding in a similar manner to Example 26(a) but using (R)-2-Amino-3-phenylmethanesulfonyl-N-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propyl}-propionamide {Reference Example 11(l)} there was prepared (R)-N-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide ¹H NMR (CDCl₃, 300MHz) [8.19 (d, J=8.5Hz), 8.11 (d, J=7.5Hz), 1H], 7.46-7.40 (m, 5H), [5.33 (m), 5.27 (m), 1H], 4.55-4.35 (m, 2H), 3.99-3.95 (m, 2H), [3.88 (dd, J=10Hz, 3Hz), 3.83 (dd, J=9.5Hz, 3Hz), 1H], 3.44-3.34 (m, 3H), 3.18-3.07 (m, 1H), 2.78-2.67 (m, 1H), 2.24-2.17 (m, 1H), 2.15-2.08 (m, 1H), 1.89-1.72 (m, 3H), 1.55-1.43 (m, 2H), 1.20-1.11 (m, 4H), [0.98 (t, J=7.5Hz), 0.97 (t, J=7.5Hz), 3H] LC/MS m/z=505 (M+H)

-128-

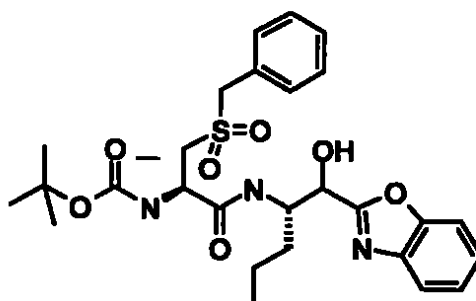
EXAMPLE 27

- (a) {(R)-1-[1-(Benzo[thiazol-2-yl]-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamate acid tert-butyl ester



- 5 N-cyclohexylcarbodiimide, N'-methyl polystyrene (1.74g, 3.4mmol) suspended in a mixture of dichloromethane (10ml) and dimethylformamide (2mL) was treated with hydroxybenzotriazole (391mg, 2.89mmol) and L-N-boc-benzylsulfonylalanine (876mg, 2.55mmol). This mixture was stirred at room temperature for 30 minutes, then treated with 2-amino-1-benzothiazol-2-yl-pentan-1-ol (400mg, 1.7mmol, Reference Example 17(d)) and after stirring for a further 2 hours the mixture was
10 then treated with Silicycle-Triamine (2.36g, 8.5mmol). The reaction mixture was stirred for 2 hours and then filtered. The filtrate was evaporated to give the title compound (888mg, 93%). LC/MS m/z=562

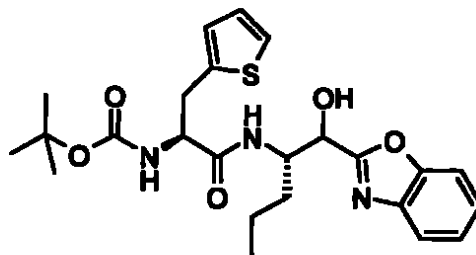
- 15 (b) {(R)-1-[(S)-1-(Benzoxazol-2-yl)-hydroxy-methyl]-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamate acid tert-butyl ester



- By proceeding in a manner similar to Example 27(a) above but using L-N-boc-benzylsulfonylalanine (876mg, 2.55mmol) and (2S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol (374mg, 1.7mmol, Reference Example 17(c)) there was prepared {(R)-1-[(S)-1-(benzoxazol-2-yl)-hydroxy-methyl]-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamate acid tert-butyl ester (908mg, 98%)
20

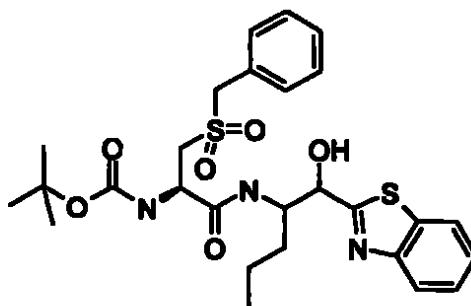
- (c) {(S)-1-[(S)-1-(Benzoxazol-2-yl)-hydroxy-methyl]-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamate acid tert-butyl ester

-129-



By proceeding in a manner similar to Example 27(a) above but using Resin-bound diimide (1.76g, 3.4mmol) suspended in dichloromethane (10mL), hydroxybenzotriazole (391mg, 2.89mmol), (2S)-2-tert-butoxycarbonylamino-3-thiophen-2-yl-propionic acid (692mg, 2.55mmol), (2S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol (374mg, 1.7mmol, Reference Example 17(c)) and Silicycle-Triamine (2.36g, 8.5mmol) there was prepared {{(S)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamate acid tert-butyl ester} (790mg (1.67mmol, 98%) LC/MS $m/z=562$ (M+H)

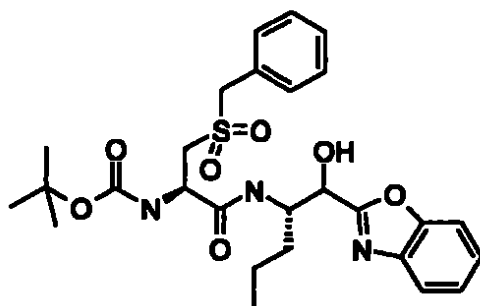
- 10 (d) {{(R)-1-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamate acid tert-butyl ester}



By proceeding in a manner similar to Example 27(a) above but using Resin-bound diimide (741mg, 1.26mmol), hydroxybenzotriazole (144mg, 1.07mmol), L-N-boc-benzylsulfonylalanine (326mg, 0.95mmol), 2-amino-1-benzothiazol-2-yl-pentan-1-ol (150mg, 0.63mmol, Reference Example 17(d)) and Silicycle-Triamine (2.36g, 8.5mmol) there was prepared {{(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamate acid tert-butyl ester}. LC/MS $m/z=562$ (M+H), which was used without further purification

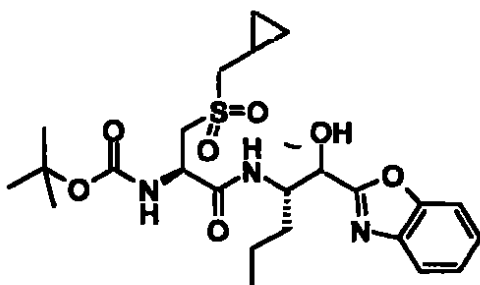
- 20 (e) {{(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamate acid tert-butyl ester}

-130-



By proceeding in a manner similar to Example 27(a) above but using Resin-bound diimide (1.76g, 3.4mmol), hydroxybenzotriazole (391mg, 2.89mmol), L-N-boc-benzylsulfonylalanine (876mg, 2.55mmol), (2S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol (374mg, 1.7mmol, Reference Example 17(c)) and Silicycle-Triamine (2.36g, 8.5mmol) there was prepared {(R)-1-[(S)-1-(benzoxazol-2-yl)-hydroxy-methyl]-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl]-carbamate acid tert-butyl ester, LC/MS $m/z=546$ (M+H), 490 (M-H-butene), which was used directly in the next reaction

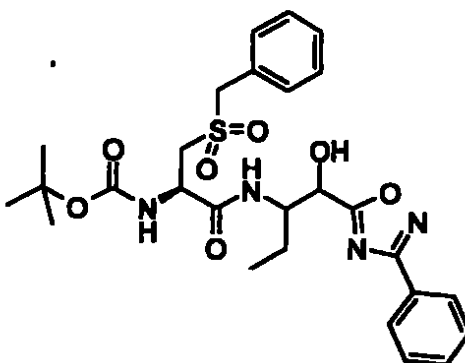
(f) {(R)-1-[(S)-1-(Benzoxazol-2-yl)-hydroxy-methyl]-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl]-carbamate acid tert-butyl ester



By proceeding in a manner similar to Example 27(a) above but using a suspension of Resin-bound diimide (1.07g, 1.82mmol) in dichloromethane (20ml), hydroxybenzotriazole (209mg, 1.55mmol) and (R)-2-tert-butoxycarbonylamino-3-cyclopropylmethanesulfonyl-propionic acid (420mg, 1.365mmol, Reference Example 22), (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol (200mg 0.91mmol, Reference Example 17(c)) and Silicycle-Triamine (2.8g, 9.1mmol) there was prepared {(R)-1-[(S)-1-(benzoxazol-2-yl)-hydroxy-methyl]-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl]-carbamate acid tert-butyl ester (450mg, 97%) LC/MS $m/z=532$ (M+Na), 510 (M+H), 454 (M+H-isobutene)

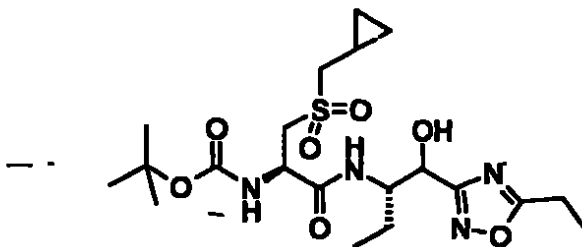
(g) {(R)-1-[(S)-1-[Hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl]-carbamate acid tert-butyl ester

-131-



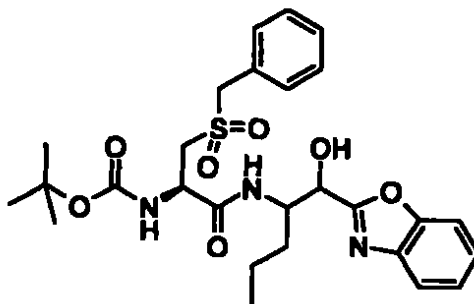
By proceeding in a manner similar to Example 27(f) above but using L-N-boc-benzylsulfonylalanine and (R)-2-tert-butoxycarbonylamino-3-phenylmethanesulfonyl-propionic acid and (S)-2-amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol (Reference Example 21) there was prepared (R)-1-[(1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamamic acid tert-butyl ester. LC/MS m/z =545(M+Na), 467 (M+H-isobutene), 423 (M+H-Boc)

(i) ((R)-2-Cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl)-carbamamic acid tert-butyl ester



By proceeding in a manner similar to Example 27(f) above but using 2-amino-1-(5-ethyl-[1,2,4]-oxadiazol-3-yl)-butan-1-ol (Reference Example 23) there was prepared ((R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl)-carbamamic acid tert-butyl ester. LC/MS m/z =497(M+Na), 419 (M+H-isobutene), 375 (M+H-Boc)

(j) [(R)-1-[(1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamamic acid tert-butyl ester

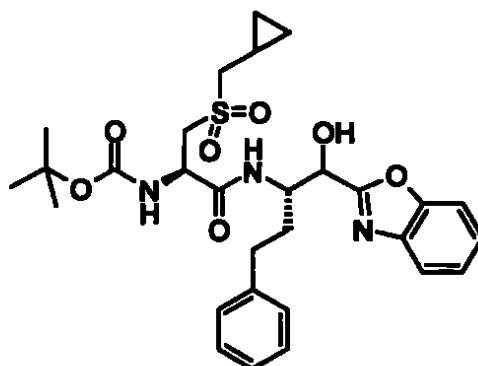


-132-

By proceeding in a manner similar to Example 27(f) above but using L-N-boc-benzylsulfonylalanine and (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol {Reference Example 17(c)} there was prepared [(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl]-carbamic acid tert-butyl ester LC/MS m/z=546(M+H), 490 (M+H-isobutene)

5

(k) [(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl]-carbamic acid tert-butyl ester

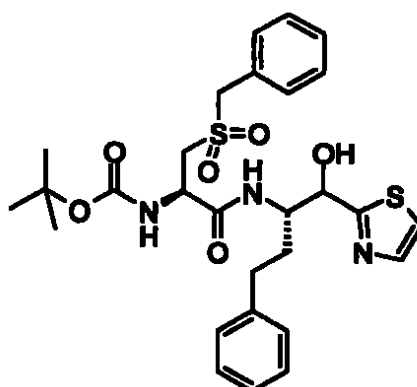


10

By proceeding in a manner similar to Example 27(f) above but using (2S)-2-amino-4-phenyl-1-benzoxazol-2-yl-butan-1-ol there was prepared [(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl]-carbamic acid tert-butyl ester LC/MS m/z=572(M+H), 516 (M+H-isobutene)

15

(l) [(R)-1-[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl]-carbamic acid tert-butyl ester



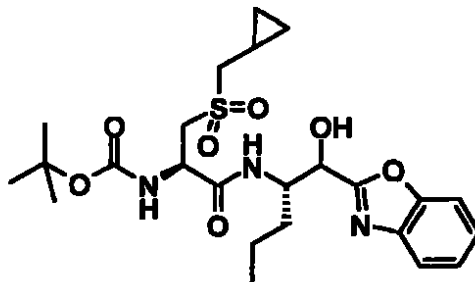
20

By proceeding in a manner similar to Example 27(f) above but using L-N-boc-benzylsulfonylalanine and (2S)-2-amino-4-phenyl-1-thiazol-2-yl-butan-1-ol (Reference Example 13) there was prepared [(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl]-carbamic acid tert-butyl ester, LC/MS m/z=574(M+H)

27
78

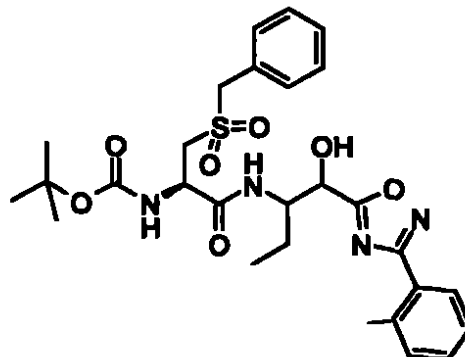
-133-

- (m) {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



- 5 By proceeding in a manner similar to Example 27(f) above but using *N*-Cyclohexylcarbodiimide, *N*-methyl polystyrene (1.07g, 1.82mmol) suspended in dichloromethane (20mL), hydroxybenzotriazole (209mg, 1.55mmol), (R)-2-tert-butoxycarbonylamino-3-cyclopropylmethanesulfonyl-propionic acid (420mg, 1.365mmol, Reference Example 22), (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol (200mg, 0.91mmol, Reference Example 17(c)) and Silicycle-Triamine (2.8g, 9.1mmol) there was prepared {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester (450mg, 0.88mmol, 97%) LC/MS $m/z=532(M+Na)$, 510 (M+H), 454 (M+H-isobutene)
- 10

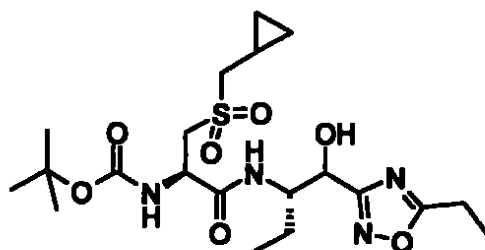
- (n) (R)-1-[1-[Hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



- 15 By proceeding in a manner similar to Example 27(m) above but using L-N-boc-benzylsulfonylalanine and (S)-2-amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol (Reference Example 21) there was prepared (R)-1-[1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester LC/MS $m/z=545(M+Na)$, 467 (M+H-isobutene), 423 (M+H-Boc)
- 20

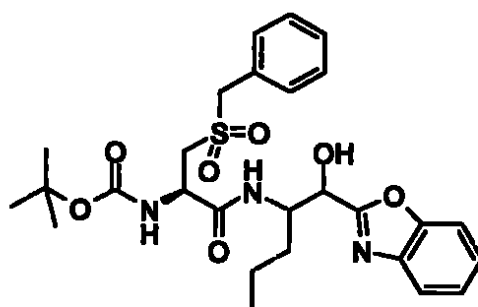
- (o) ((R)-2-Cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester

-134-



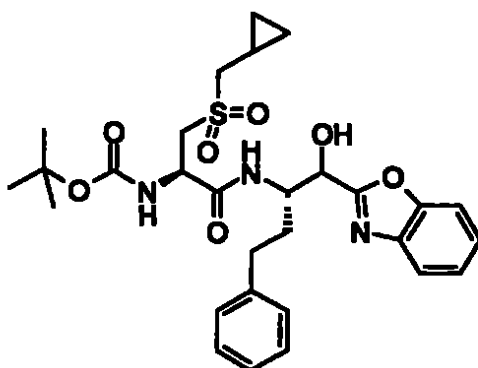
By proceeding in a manner similar to Example 27(m) above but using (S)-2-amino-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol there was prepared ((R)-2-Cyclopropylmethanesulfonyl-1-((S)-1-((5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl)-propylcarbamoyl)-ethyl)-carbamic acid tert-butyl ester LC/MS $m/z=497(M+Na)$, 419 (M+H-isobutene), 375 (M+H-Boc)

(p) ((R)-1-[1-(Benzoxazol-2-yl)-hydroxy-methyl]-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester



By proceeding in a manner similar to Example 27(m) above but using L-N-boc-benzylsulfonylalanine and (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol (200mg 0.91mmol, Reference Example 17(c)) there was prepared ((R)-1-[1-(Benzoxazol-2-yl)-hydroxy-methyl]-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester, LC/MS $m/z=546(M+H)$, 490 (M+H-isobutene)

(q) ((R)-1-((S)-1-(Benzoxazol-2-yl)-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester

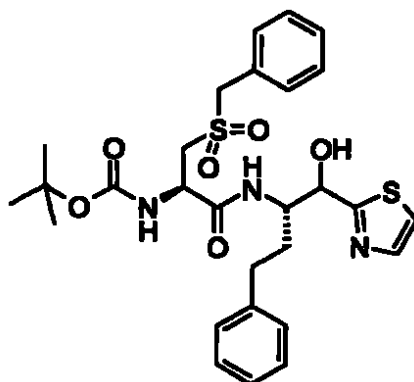


By proceeding in a manner similar to Example 27(m) above but using (2S)-2-amino-4-phenyl-1-benzoxazol-2-yl-butan-1-ol there was prepared ((R)-1-((S)-1-(Benzoxazol-2-yl)-hydroxy-methyl)-3-

-135-

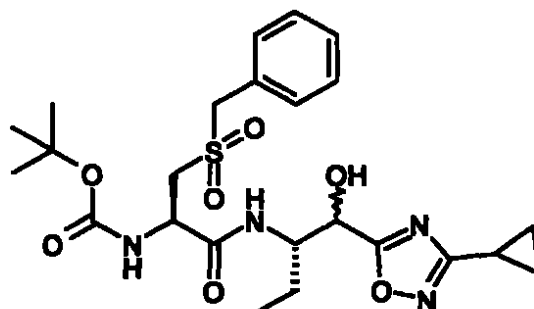
phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester
 LC/MS m/z =572(M+H), 516 (M+H-isobutene)

(r) {(R)-1-[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester



By proceeding in a manner similar to Example 27(m) above but using L-N-boc-benzylsulfonylalanine and (2S)-2-amino-4-phenyl-1-thiazol-2-yl-butan-1-ol (Reference Example 13) there was prepared {(R)-1-[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester LC/MS m/z =574(M+H)

(s) {(R)-2-phenylmethanesulfonyl-1-[(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester

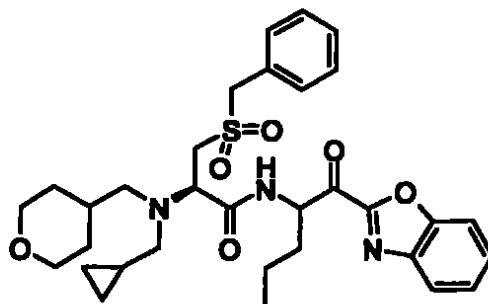


By proceeding in a manner similar to Example 27(m) above but using L-N-boc-benzylsulfonylalanine and (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol (Reference Example 14) there was prepared {(R)-2-phenylmethanesulfonyl-1-[(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester

EXAMPLE 28

(R)-N-[1-(Benzoxazole-2-carbonyl)-butyl]-2-[cyclopropylmethyl-(tetrahydro-pyran-4-ylmethyl)-amino]-3-phenylmethanesulfonyl-propionamide

-136-

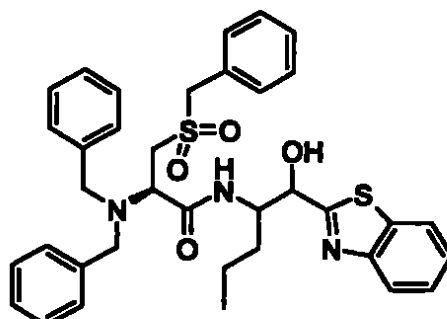


Step 1 (R)-2-Amino-N-[1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (200mg, 0.448mmol, Reference Example 11(i)) was dissolved in 5% acetic acid in acetonitrile (10ml). Tetrahydro-pyran-4-carbaldehyde (51mg, 0.448mmol) was added and the reaction mixture stirred for 16 hours. (Polystyrylmethyl)trimethylammonium cyanoborohydride (218mg, 0.896mmol) was added and the reaction mixture stirred for 3 hours. Cyclopropanecarbaldehyde (157mg, 2.24mmol) was added and stirring continued for 3 hours. The mixture was filtered under suction and the filtrate concentrated under high vacuum.

Step 2 The residue was dissolved in 10ml dichloromethane. The Dess-Martin-periodinane (380mg, 0.896mmol) was added and the resulting reaction mixture stirred for two hours. The reaction mixture was poured into a 1/1-mixture of saturated sodium bicarbonate solution and saturated sodium thiosulfate solution. The aqueous phase was extracted with dichloromethane. The combined organic phases were washed with saturated sodium bicarbonate solution and brine. The organic phase was dried with magnesium sulfate and the dichloromethane evaporated under reduced pressure. The crude product was purified via flash chromatography (heptane/ethyl acetate 2/1 followed by heptane/ethyl acetate 1/1 to elute) to give (R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-[cyclopropylmethyl-(tetrahydro-pyran-4-ylmethyl)-amino]-3-phenylmethanesulfonyl-propionamide as mixture of diastereomers (83mg, 0.139mmol, 31%). LC/MS m/z =596 (M+H) retention time 3.84 (method C).

EXAMPLE 29

(a) (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide

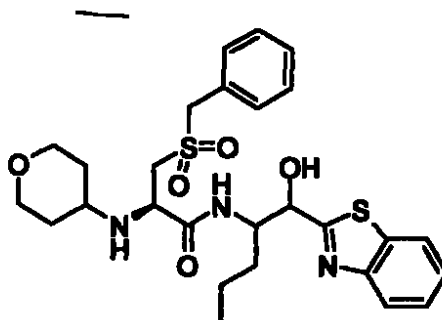


(R)-2-Amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-

-137-

propionamide (50mg, 0.11mmol, Reference Example 11(a)) was dissolved in a mixture of acetonitrile (5ml) and acetic acid (1ml). Benzaldehyde (56 μ l, 0.55mmol, 5 equivalents) and resin bound cyanoborohydride (54mg, 0.22mmol, 2 equivalents) were added. The reaction mixture was stirred overnight, filtered under suction and the filtrate evaporated to give the (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide which was used without further purification in the preparation of Example 18(c).

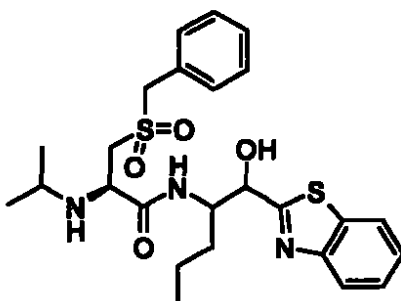
(b) (R)-N-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a manner similar to Example 29(a) above but using tetrahydro-4H-pyran-4-one (51 μ l, 0.55mmol, 5 equivalents) there was prepared (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide LC/MS m/z =546 (M+H).

EXAMPLE 30

(a) (R)-N-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide



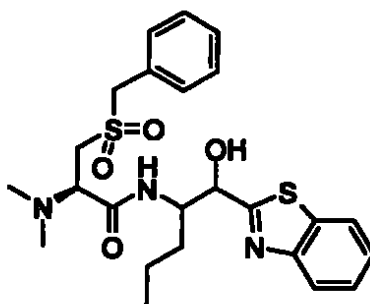
(R)-2-Amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (50mg, 0.11mmol, Reference Example 11(a)) was dissolved in a mixture of acetonitrile (5ml) and acetic acid (1ml). Acetone (500 μ l) and resin bound cyanoborohydride (54mg, 0.22mmol, 2 equivalents) were added. The reaction mixture was stirred overnight, filtered under suction and

-138-

concentrated under vacuum. The residue was dissolved in dichloromethane and AP Trisamine (Argonaut Technology) (550mg, 1.2mmol) was added. The mixture was stirred for two hours, filtered under suction and the filtrate concentrated under vacuum to give (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide (30mg, 0.06mmol, 54%)

5 LC/MS $m/z=504$ (M+H)

(b) (R)-N-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide

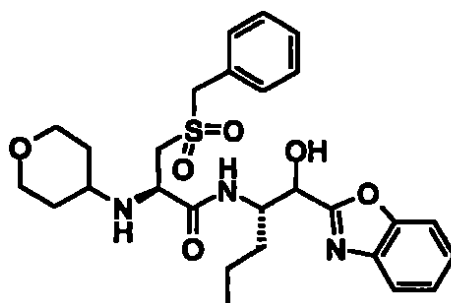


10 By proceeding in a manner similar to Example 30(a) above but using formaldehyde solution (75 μ l, 1mmol, 37w-% aqueous solution) there was prepared (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (30mg, 54%) LC/MS $m/z=490$ (M+H)

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EXAMPLE 31

(a) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



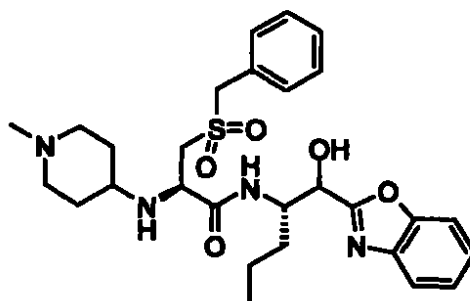
20 A solution of (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (100mg, 0.22mmol, Reference Example 11(c)) in a mixture of acetonitrile (5mL) and acetic acid (1mL) was treated with tetrahydro-4H-pyran-4-one (101 μ l, 1.1mmol). After agitating at room temperature for 3 hours the mixture was then treated with resin-bound cyanoborohydride (108mg, 0.44mmol) and agitation was continued overnight. The reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved in dichloromethane (10mL) and the solution was treated with Silicycle Triamine (611mg, 2.2mmol), then agitated for 2

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-139-

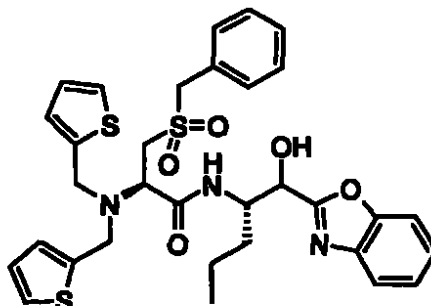
hours and then filtered. The solution of (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide was used directly in the preparation of Example 20(b)

- 5 (b) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide



- 10 By proceeding in a manner similar to Example 31(a) above but using 1-methyl-4-piperidone (136μl, 1.1mmol) there was prepared (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide was used directly in the preparation of Example 19(b)

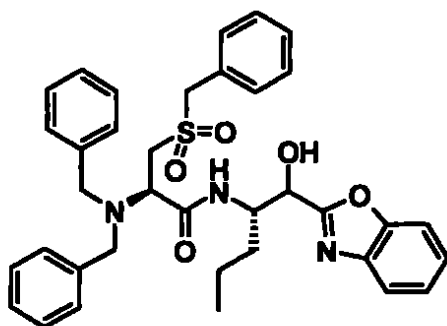
- 15 (c) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide



- 20 By proceeding in a manner similar to Example 31(a) above but using 2-thiophenecarboxaldehyde (20μl, 0.22mmol) there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide was used directly in the preparation of Example 19(c)

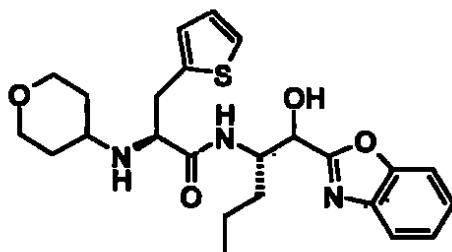
- (d) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-di-benzylamino-3-phenylmethanesulfonyl-propionamide

-140-



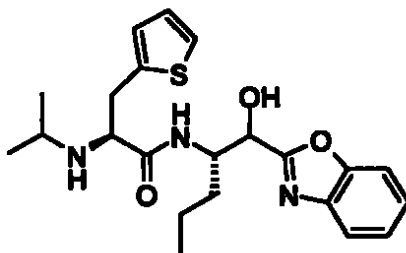
By proceeding in a manner similar to Example 31(a) above but using benzaldehyde (22 μ l, 0.22mmol) there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide which was used directly in the preparation of Example 19(d)

(e) (S)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide



By proceeding in a manner similar to Example 317(a) above but using (S)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-thiophen-2-yl-propionamide {82mg, 0.22mmol, Reference Example 11(b)} and tetrahydro-4H-pyran-4-one (101 μ l, 1.1mmol) there was prepared (S)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide which was used directly in the preparation of Example 19(e)

(f) (S)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide

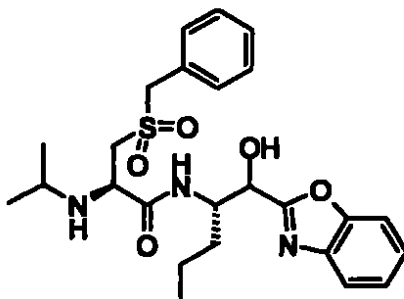


By proceeding in a manner similar to Example 31(a) above but using (S)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-thiophen-2-yl-propionamide {82mg, 0.22mmol, Reference

-141-

Example 11(b)) and acetone (100 μ l) there was prepared (S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide which was used directly in the preparation of Example 19(f)

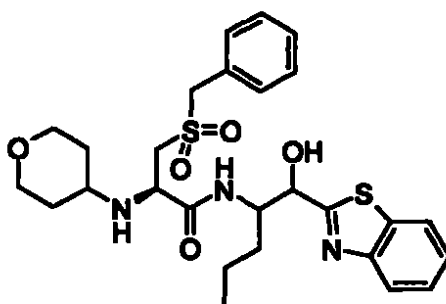
- 5 (g) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide



- 10 By proceeding in a manner similar to Example 31(a) above but using acetone (500 μ l) there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide (30.5 mg, 29%) LC/MS m/z 488 (M+H)

EXAMPLE 32

- (a) (R)-N-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide

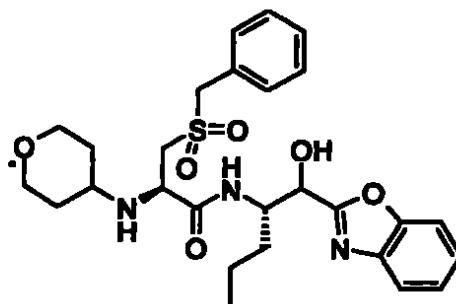


- 15 A solution of (R)-2-amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (100 mg, 0.22 mmol, Reference Example 11(a)) in a mixture of acetonitrile and acetic acid (10 mL, 95:5, v/v) was treated with tetrahydro-4H-pyran-4-one (101 μ l, 1.1 mmol) and resin-bound cyanoborohydride (108 mg, 0.44 mmol). This mixture was stirred at room temperature overnight then
20 evaporated. The residue was dissolved in dichloromethane and the solution was treated with Silicycle Triamine (611 mg, 2.2 mmol) then stirred at room temperature for 2 hours then filtered. The filtrate was evaporated to give (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide, LC/MS m/z 546 (M+H), which was used directly in the preparation of Example 18(b)

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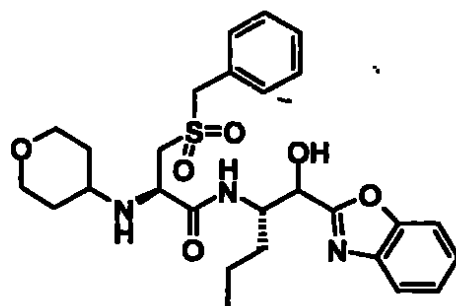
-142-

- (b) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a manner similar to Example 32(a) above but using (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {98mg, 0.22mmol, Reference Example 11(c)} there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide, LC/MS $m/z=530$ (M+H), which was used directly in the preparation of Example 19(a)

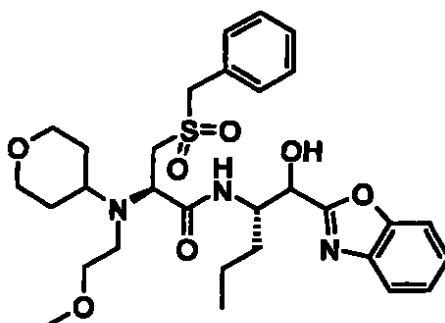
- (c) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a manner similar to Example 32(a) above but using (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {Reference Example 11(c)} there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (106mg, 91%) LC/MS $m/z=530$ (M+H)

- (d) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide

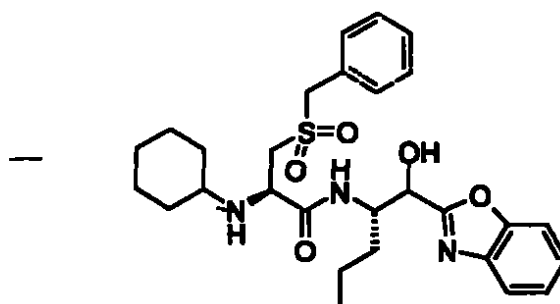
-143-



By proceeding in a manner similar to Example 32(a) above but using (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (53mg, 0.1mmol, Reference Example 32(c)) and 2-methoxyethanal (53mg, 0.55mmol) there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide (56mg, 95%)

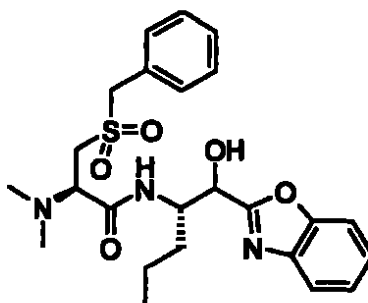
LC/MS m/z =588 (M+H)

(e) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide



By proceeding in a manner similar to Example 32(a) above but using (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (49mg, 0.11mmol, Reference 11(c)) and cyclohexanone (52μl, 0.5mmol) there was prepared (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide (48mg, 83%)

(f) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide

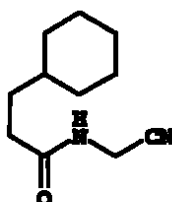


-144-

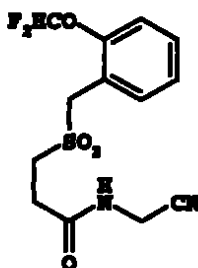
By proceeding in a manner similar to Example 32(a) above but using (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {49mg, 0.11mmol, Reference Example 11(c)} and formaldehyde (75 μ l, 1mmol, 37 w-% in water), there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (10mg, 19%) LC/MS m/z =474 (M+H)

EXAMPLE 33

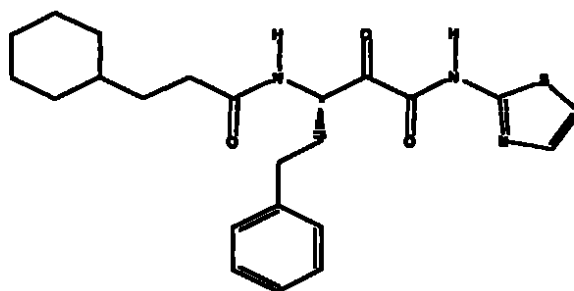
The following compounds of Formula 1 are provided by methods described in the application

(a) N-Cyanomethyl-3-cyclohexyl-propionamide

¹H NMR (CDCl₃) 6.22 (br s, 1H), 4.20 (s, 2H), 2.23 (m, 2H), 1.65 (m, 5H), 1.50 (m, 2H), 1.10-1.30 (m, 4H), 0.90 (m, 2H), LC-MS t_r 3.67min, 193.0 (M-1), 195.1 (M+1) MS API 150EX. (LC Agilent 1100Series, Column Phenomenex, 5 μ ODS3 100A 100X3mm. Flow Rate 2ml/min Two solvent gradient Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH Gradient from 100% A, 0% B to 0% A, 100% B from $t = 0$ to $t = 6$ min Then gradient back to 100% A, 0% B from $t = 7$ to $t = 15$ min),

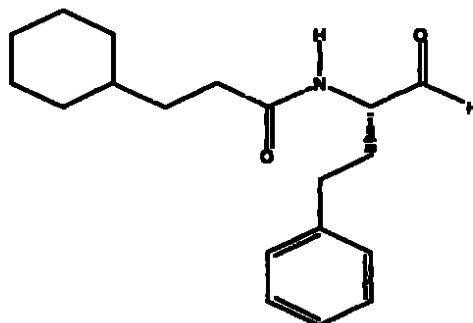
(b) N-Cyanomethyl-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide

¹H NMR (CDCl₃) 7.52 (d, 1H, J=8Hz), 7.43 (t, 1H, J=8Hz), 7.29 (d, 1H, J=8Hz), 7.20 (d, 1H, J=8Hz), 6.40 (m, 1H), 4.41 (s, 2H), 4.16 (d, 2H, J=6Hz), 3.72 (s, 1H), 3.34 (t, 2H, J=8Hz), 2.77 (t, 2H, J=8Hz), LC-MS t_r 3.02min, 331.1 (M-1), 333.1 (M+1) MS API 150EX. (LC Agilent 1100Series, Column Phenomenex, 5 μ ODS3 100A 100X3mm. Flow Rate 2ml/min Two solvent gradient Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH Gradient from 100% A, 0% B to 0% A, 100% B from $t = 0$ to $t = 6$ min Then gradient back to 100% A, 0% B from $t = 7$ to $t = 15$ min)

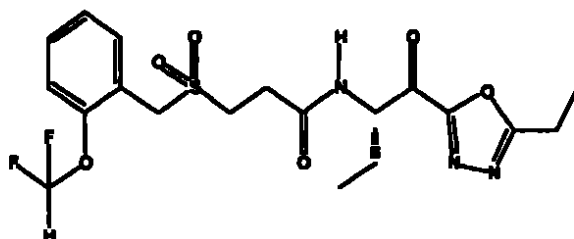
(c) 3-(3-Cyclohexyl-propionylamino)-2-oxo-5-phenyl-pentanoic acid thiazol-2-ylamide

data for the compound as drawn and for it's enol and hydrate forms LC-MS t_r 4.74min 426.4(M-1), 428.2(M+1), 4.97min, 426.2(M-1), 428.2(M+1), 5.57min, 426.3(M-1), 427.9(M+1) MS API

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

(d) 3-Cyclohexyl-N-(1-formyl-3-phenyl-propyl)-propionamide

LC-MS t_r 4.57min., 300.4(M-1), 302.3(M+1) MS API 150EX (LC Agilent 1100Series, Column Phenomenex, 5u ODS3 100A 100X3mm. Flow Rate 2ml/min Two solvent gradient. Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH Gradient from 100% A, 0% B to 0% A, 100% B from $t = 0$ to $t = 6$ min Then gradient back to 100% A, 0% B from $t = 7$ to $t = 15$ min)

(f) 3-(2-Difluoromethoxy-phenylmethanesulfonyl)-N-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-propionamide

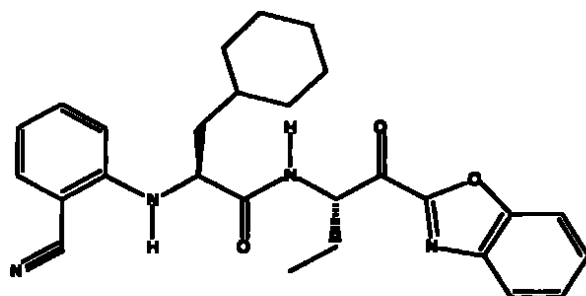
LC-MS R_T 2.32min , 460.3(M+1) 482.2(M+23) MS API 150EX (LC Agilent 1100Series, Column Phenomenex, 5u ODS3 100A 100X3mm. Flow Rate 2ml/min Two solvent gradient

-146-

Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH Gradient from 100% A, 0% B to 0% A, 100% B from $t = 0$ to $t = 2.5$ min Then gradient back to 100% A, 0% B from $t = 3.0$ to $t = 3.5$ min Then gradient held at 100% A, 0% B from $t = 3.5$ to 5 min)

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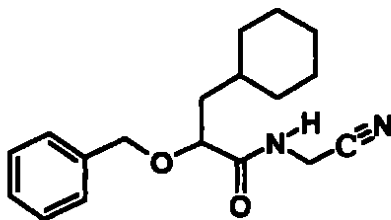
(g) N-[(S)-1-(Benzooxazole-2-carbonyl)-propyl]-2-(2-cyano-phenylamino)-3-cyclohexyl-propionamide



^1H NMR (CDCl_3) 7.83 (d, 1H, $J=8\text{Hz}$), 7.59 (d, 1H, $J=8\text{Hz}$), 7.43-7.58 (m, 2H), 7.02-7.25 (m, 4H), 6.59 (t, 1H, $J=8\text{Hz}$), 6.49 (d, 1H, $J=8\text{Hz}$), 5.40-5.47 (m, 1H), 4.77 (m, 1H), 3.83-3.88 (m, 1H), 2.12-2.22 (m, 1H), 1.85-2.00 (m, 2H), 1.55-1.83 (m, 8H), 1.12-1.35 (m, 4H), 0.95-1.10 (m, 3H), LC-MS $t_r = 2.97$ min, 457.5 ($M-1$), 459.3 ($M+1$), 481.4 ($M+23$) MS API 150EX (LC Agilent 1100 Series, Column. Phenomenex, 5u ODS3 100A 100X3mm Flow Rate 2ml/min Two solvent gradient Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH Gradient from 100% A, 0% B to 0% A, 100% B from $t = 0$ to $t = 2.5$ min Then gradient back to 100% A, 0% B from $t = 3.0$ to $t = 3.5$ min Then gradient held at 100% A, 0% B from $t = 3.5$ to 5 min)

(h) N-Cyanomethyl-3-cyclohexyl-2-(4-methoxy-phenoxy)-propionamide (Compound 1), ^1H NMR (CDCl_3) 7.42-7.36 (m, 5H), 6.90 (t, 1H), 4.55 (d, 1H), 4.51 (d, 1H), 4.22 (dd, 1H), 4.16 (dd, 1H), 4.00 (t, 1H), 1.70-0.80 (m, 13H), MS (M^++1) 301,

(i) 2-Benzoyloxy-N-cyanomethyl-3-cyclohexyl-propionamide (Compound 2)



using 2(R)-benzyloxy-4-phenyl-butyric acid as starting material ^1H NMR (CDCl_3) δ 6.84-6.80 (m, 4H), 6.75 (t, 1H), 4.55 (dd, 1H), 4.24 (dd, 1H), 4.12 (dd, 1H), 3.78 (s, 3H), 1.80-0.85 (m, 13H), MS ($M-1$) 315

25

(j) (R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-benzyloxy-3-phenylmethanesulfonyl-propionamide (Compound 3), ¹H NMR (CDCl₃) 7.89 (d, 1H), 7.68 (d, 1H), 7.60-7.32 (m, 13H), 5.70 (m, 1H), 4.79 (d, 1H), 4.77 (d, 1H), 4.53 (dd, 1H), 4.33 (d, 1H), 4.30 (d, 1H), 3.38 (dd, 1H), 3.25 (dd, 1H), 2.15-2.05 (m, 1H), 1.84-1.75 (m, 1H), 1.45-1.30 (m, 2H), 0.93 (t, 3H), MS (M⁺+1) 535, (M-1) 533,

(k) (R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-methoxymethoxy-3-phenylmethanesulfonyl-propionamide (Compound 9), ¹H NMR (DMSO) 8.87 (d, J=6.91 Hz, 1H), 7.99 (d, J=7.91 Hz, 1H), 7.89 (d, J=8.15 Hz, 1H), 7.64 (t, J=8.1 Hz, 1H), 7.54 (t, J=8.1 Hz, 1H), 7.4-7.3 (m, 5H), 5.3-5.2 (m, 1H), 4.7-4.65 (m, 1H), 4.65-4.63 (m, 2H), 4.55-4.50 (m, 2H), 3.53-3.26 (m, 2H), 3.34 (s, 3H), 2.11-1.98 (m, 1H), 1.81-1.69 (m, 1H), 0.97 (t, J=7.15 Hz, 3H), MS 473 (M-1), 497 (M+23),

(l) (S)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-hydroxy-3-phenyl-propionamide (Compound 10),

(m) (R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-trisopropylsilyloxy-propionamide (Compound 12), ¹H NMR (CD₃Cl) 7.93 (d, J=8.15 Hz, 1H), 7.6 (d, J=8.1 Hz, 1H), 7.6-7.4 (m, 3H), 7.4-7.3 (m, 5H), 5.85-5.73 (m, 1H), 4.85-4.74 (m, 1H), 4.5-4.3 (m, 2H), 3.47-3.35 (m, 2H), 2.35-2.15 (m, 1H), 2.15-1.95 (m, 1H), 1.3-0.8 (m, 24H), MS 609.4 (M+23),

(n) (R)-N-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide (Compound 13), ¹H NMR (CD₃Cl) 8.21 (d, J=8.67 Hz, 1H), 7.98 (d, J=8.6 Hz, 1H), 7.7-7.55 (m, 3H), 7.45-7.3 (m, 5H), 5.8-5.7 (m, 1H), 4.75-4.6 (m, 1H), 4.4-4.3 (m, 2H), 4.08 (br, 1H), 3.62-3.5 (m, 1H), 3.3-3.1 (m, 1H), 2.3-2.15 (m, 1H), 2.05-1.9 (m, 1H), 0.997 (t, J=7.4 Hz, 3H), MS 469.2 (M+23),

(o) (R)-2-hydroxy-3-phenylmethanesulfonyl-N-[(S)-1-(1-pyridazin-3-yl-methanoyl)-butyl]-propionamide (Compound 16), ¹H NMR (CD₃Cl) 9.35 (dd, J=4.93 Hz, J=1.72 Hz, 1H), 8.14 (dd, J=1.72 Hz, J=8.39 Hz, 1H), 7.69 (dd, J=4.93 Hz, J=8.39 Hz, 1H), 7.65 (d, J=7.6 Hz, 1H), 7.5-7.36 (m, 5H), 6.04-5.96 (m, 1H), 4.75-4.63 (m, 1H), 4.45-4.3 (m, 3H), 3.53 (dd, J=2.48 Hz, J=14.85 Hz, 1H), 3.22 (dd, J=14.82 Hz, J=2.48 Hz, 1H), 2.2-2.07 (m, 1H), 1.81-1.65 (m, 1H), 1.6-1.2 (m, 2H), 0.93 (t, J=7.18 Hz, 3H), MS 403.6 (M-1), 428 (M+23),

(p) (S)-3-[(R)-2-hydroxy-3-phenylmethanesulfonyl-propanoylamino]-2-oxo-pentanoic acid benzylamide (Compound 18), ¹H NMR (CD₃Cl) 7.45-7.25 (m, 10H), 5.34-5.26 (m, 1H), 4.7-4.6 (m,

-148-

1H), 4.47(d, J=6.18Hz, 2H), 4.4-4.3(m, 2H), 4.15-4.05(m, 1H), 3.55-3.45(m, 1H), 3.25-3.13(m, 1H), 2.2-2.0(m, 1H), 1.8-1.6(m, 1H), 1.61(s, 2H), 0.95(t, J=6.91Hz, 3H), MS 469.2(M+23),

(q) (R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-

5 phenylmethanesulfonyl]-2-hydroxy-propionamide (Compound 21), ¹HNMR (CD₃Cl) 7.91(d, J=7.91Hz, 1H), 7.75(d, J=7.9Hz, 1H), 7.7-7.2(m, 6H), 6.63(t, J=73.41Hz, 1H), 5.7-5.58(m, 1H), 5.4-5.29(m, 1H), 4.7-4.6(m, 1H), 4.51(s, 2H), 4.19(br, 1H), 3.72-3.63(m, 1H), 3.35-3.2(m, 1H), 2.3-2.0(m, 1H), 2.0-1.7(m, 1H), 0.99(t, J=6.9Hz, 3H), MS 495.5(M-1), 497.2(M+1),

(r) (R)-N-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-

10 phenylmethanesulfonyl]-2-hydroxy-propionamide (Compound 22), ¹HNMR (CD₃Cl) 8.21(d, J=8.15Hz, 1H), 7.99(d, J=8.1Hz, 1H), 7.73-7.2(m, 6H), 6.63(t, J=73.4Hz, 1H), 5.85-5.75(m, 1H), 5.3(s, 1H), 4.78-4.7(m, 1H), 4.56-4.4(m, 2H), 4.19-4.09(m, 1H), 3.7-3.6(m, 1H), 3.35-3.2(m, 1H), 2.28(s, 2H), 1.27(t, J=6.9Hz, 3H), MS 511.4(M-1), 513.6(M+1), and

(s) (2R,5S)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl]-6-ethoxy-5-

15 ethyl-morpholin-3-one (Compound 24)

ENZYME ASSAY EXAMPLE

Cathepsin S Assay

20 Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising MES, 50 mM (pH 6.5), EDTA, 2.5 mM, and NaCl, 100 mM). Human cathepsin S (0.158 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Val-Val-Arg-AMC (9 nMoles in 25 μ L of assay buffer) was added to the assay solutions and

25 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.

ENZYME ASSAY EXAMPLE

Cathepsin B Assay

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

-149-

spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models

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ENZYME ASSAY EXAMPLE

Cathepsin K Assay

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

15

ENZYME ASSAY EXAMPLE

Cathepsin L Assay

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

25

According to applicants' assays conducted as described above, the apparent inhibition constants (K_i) for the following listed compounds of the invention, against Cathepsin S, were about or below 0.01 μ M:

30

morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 31), Example 3(a),

35

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 11), Example 4(a),

40

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 14), Example 4(b),

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 15), Example 4(c),

pyrrolidine-1-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 19) Example 4(d),

dimethyl-carbamic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 20), Example 4(e),

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 25) Example 4(f),

morpholine-4-carboxylic acid (*S*)-1-[(*S*)-1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, Example 4(g),

morpholine-4-carboxylic acid (*S*)-1-[(*S*)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, Example 4(h),

(*R*)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-*N*-[(*S*)-1-formyl-propyl]-2-hydroxy-propionamide (Compound 23), Example 6,

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide, (Compound 5), Example 7,

(*S*)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-oxo-pentanoic acid benzylamide, (Compound 27), Example 8(a),

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide, (Compound 28), Example 9,

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide, (Compound 29), Example 10,

(*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide, Example 19(a),

(*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl propionamide, Example 21(a),

(*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide, Example 21(b),

(*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide, Example 21(c),

morpholine-4-carboxylic acid (*S*)-2-cyclohexyl-1-[(*S*)-1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propylcarbamoyl]-ethyl ester, Example 24(b),

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[(*S*)-1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propyl]-propionamide, Example 33(e),

(*S*)-3-[(*R*)-2-hydroxy-3-phenylmethanesulfonyl-propanoylamino]-2-oxo-pentanoic acid benzylamide (Compound 18), Example 33(p),

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide (Compound 21), Example 33(q),

Moreover, the compounds of the present invention were observed to have varying degrees of selective inhibitory action on cathepsin S protease. For example, the above listed 22 compounds were found to inhibit

-151-

cathepsin S protease activity at concentrations that are more than 75 fold less than those concentrations required to produce an equactive inhibition on cathepsin K protease

-152-

EXAMPLE

Representative Pharmaceutical Formulations Containing a Compound of Formula I

ORAL FORMULATION

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

10

INTRAVENOUS FORMULATION

	Compound of Formula I	0.1-10 mg
	Dextrose Monohydrate	q s. to make isotonic
	Citric Acid Monohydrate	105 mg
15	Sodium Hydroxide	0.18 mg
	Water for Injection	q s. to 10 mL

15

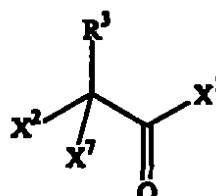
TABLET FORMULATION

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

20

WE CLAIM

1 A compound of Formula I



I

in which

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHX^4$,

X^2 is hydrogen, fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and

10 X^7 both represent fluoro;

X^3 is cyano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$,

$-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,

$-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$, wherein R^5 is hydrogen, (C_{1-4}) alkyl,

(C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl,

15 hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or

hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, R^6 is hydrogen, hydroxy or (C_{1-6}) alkyl, or where X^3

contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both

attached, form hetero (C_{3-10}) cycloalkyl, hetero (C_{5-10}) aryl or hetero (C_{8-10}) bicycloaryl, R^7 is

hydrogen or (C_{1-4}) alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo, R^{16} is hydrogen, -

20 X^4 , $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$, R^9 is hydrogen, halo, (C_{1-4}) alkyl, (C_{5-10}) aryl (C_{0-6}) alkyl or

(C_{5-10}) heteroaryl (C_{0-6}) alkyl, with the proviso that when X^3 is cyano, then X^2 is hydrogen,

fluoro, $-OH$, $-OR^4$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused

heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone,

25 iminoketone or thioketone derivative thereof, with the proviso that when $-X^4$ is other than a

heteromonocyclic ring containing 5 ring member atoms, wherein no more than two of the ring

member atoms comprising the ring are heteroatoms, then X^2 is fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or

$-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

wherein within R^5 , X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or

substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³ and -X⁵S(O)₂R¹³ and/or 1 radical selected from -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁵ is a bond or (C₁₋₆)alkylene, R¹² at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl, R¹³ is (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl, and R¹⁴ is (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₃₋₁₀)aryl(C₀₋₆)alkyl, (C₉₋₁₀)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₀)bicycloaryl(C₀₋₆)alkyl,

R¹ is hydrogen or (C₁₋₆)alkyl and R² is selected from a group consisting of hydrogen, cyano, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -R¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁵, R¹², R¹³ and R¹⁴ are as defined above, or R¹ and R² taken together with the carbon atom to which both R¹ and R² are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene, wherein within said R² any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³ and -X⁵C(O)R¹³, wherein X⁵, R¹² and R¹³ are as defined above,

R³ is (C₁₋₆)alkyl or -C(R⁶)(R⁶)X⁶, wherein R⁶ is hydrogen or (C₁₋₆)alkyl and X⁶ is selected from -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹²,

$-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$,
 $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$,
 $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$,
 $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$,
5 $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5 , R^{12} , R^{13}
and R^{14} are as defined above,

R^4 is selected from $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$,
 $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$,
 $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$,
10 $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$,
 $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$,
 $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$,
 $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ and $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$
wherein X^8 is (C_{1-6}) alkylene and X^5 , R^{12} , R^{13} and R^{14} are as defined above, with the proviso
15 that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, then R^{14} is
 (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-3}) alkyl, (C_{6-10}) aryl (C_{1-6}) alkyl,
hetero (C_{5-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or
hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl;

R^{15} is (C_{6-10}) aryl, hetero (C_{5-10}) aryl, (C_{9-10}) bicycloaryl or hetero (C_{8-10}) bicycloaryl,
20 R^{17} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl,
 (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{3-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or
hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, with the proviso that when X^3 is cyano, then R^{17} is
 (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-6}) alkyl,
 (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{5-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or
25 hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl,

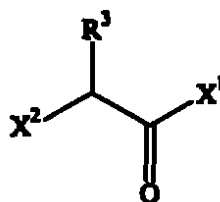
R^{18} is hydrogen, (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,
hetero (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl,
 (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, with the proviso that when
 X^3 is cyano, then R^{18} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{1-6}) alkyl,
30 hetero (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{5-10}) aryl (C_{1-6}) alkyl,
 (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl, and

wherein within R^3 , R^4 , R^{15} , R^{17} and R^{18} any alicyclic or aromatic ring system is
unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl,

-156-

(C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹²,
 -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹²,
 -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹²,
 -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³,
 5 -X⁵C(O)R¹³ and -X⁵S(O)₂R¹³ and/or 1 radical selected from -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴,
 -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹²,
 -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴,
 -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹², and within R³ and R⁴ any aliphatic
 moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from
 10 cyano, halo, nitro, -NR¹²R¹², -NR¹²C(O)R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹²,
 -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)R¹², -OC(O)R¹², -C(O)NR¹²R¹²,
 -S(O)₂NR¹²R¹², -NR¹²S(O)₂R¹², -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³,
 -S(O)R¹³ and -S(O)₂R¹³, wherein X⁵, R¹², R¹³ and R¹⁴ are as described above, with the proviso
 that when X³ is cyano and X² is -OR⁴, where R⁴ is defined as -R¹⁴, or -NHR¹⁸, then any
 15 aromatic ring system present within R¹⁴ or R¹⁸ is not substituted further by halo,
 (C₃₋₁₀)cycloalkyl, hetero(C₃₋₁₀)cycloalkyl, (C₆₋₁₀)aryl, hetero(C₃₋₁₀)aryl, (C₉₋₁₀)bicycloaryl or
 hetero(C₃₋₁₀)bicycloaryl, with the proviso that only one bicyclic ring structure is present
 within R³, R⁴ or R¹⁵, and the *N*-oxide derivatives, prodrug derivatives, protected derivatives,
 individual isomers and mixtures of isomers thereof, and the pharmaceutically acceptable salts
 20 and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected
 derivatives, individual isomers and mixtures of isomers thereof

2 A compound of Claim 1, which is of the following formula



in which X² is hydrogen, fluoro, -OH, -OR⁴, -NHR¹⁵,
 R³, R⁴, R¹⁵ and X¹ are the same as defined in claim 1

3 A compound of Claim 1 or Claim 2 in which.

-157-

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{15})C(O)R^{20}$,

X^2 is hydrogen, fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

X^3 is cyano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$,

$-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,

$-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$, wherein R^5 is hydrogen, (C_{1-4}) alkyl,

(C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl,

hetero (C_{3-10}) aryl (C_{0-6}) alkyl, (C_{3-10}) bicycloaryl (C_{0-6}) alkyl or

hetero (C_{6-10}) bicycloaryl (C_{0-6}) alkyl, R^6 is hydrogen, hydroxy or (C_{1-6}) alkyl, or where X^3

contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both attached, form hetero (C_{3-10}) cycloalkyl, hetero (C_{3-10}) aryl or hetero (C_{6-10}) bicycloaryl, R^7 is

hydrogen or (C_{1-4}) alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo, R^{16} is hydrogen, -

X^4 , $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$, R^9 is hydrogen, halo, (C_{1-4}) alkyl, (C_{3-10}) aryl (C_{0-6}) alkyl or

(C_{3-10}) heteroaryl (C_{0-6}) alkyl, with the proviso that when X^3 is cyano, then X^2 is hydrogen,

fluoro, $-OH$, $-OR^4$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof, with the proviso that when $-X^4$ is other than a

heteromonocyclic ring containing 5 ring member atoms, wherein no more than two of the ring member atoms comprising the ring are heteroatoms, then X^2 is fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

wherein within R^5 , X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$,

$-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$,

$-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$,

$-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$

and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$,

$-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$,

$-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$,

$-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6}) alkylene;

R^{12} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl,

R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl; and R^{14} is (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,

hetero(C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₃₋₁₀)aryl(C₀₋₆)alkyl, (C₉₋₁₀)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₀)bicycloaryl(C₀₋₆)alkyl,

R¹ is hydrogen or (C₁₋₆)alkyl and R² is selected from a group consisting of hydrogen, cyano, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -R¹², -X⁵NR¹²C(O)NR¹²R¹²,
 5 -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹²,
 -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹²,
 -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴,
 -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹²,
 -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴,
 10 -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁵, R¹², R¹³ and R¹⁴ are as
 defined above, or R¹ and R² taken together with the carbon atom to which both R¹ and R² are
 attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene, wherein within said R² any
 heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is
 unsubstituted or substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl,
 15 (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹²,
 -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹²,
 -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹²,
 -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³,
 -X⁵S(O)₂R¹³ and -X⁵C(O)R¹³, wherein X⁵, R¹² and R¹³ are as defined above;

R³ is (C₁₋₆)alkyl or -C(R⁶)(R⁶)X⁶, wherein R⁶ is hydrogen or (C₁₋₆)alkyl and X⁶ is
 selected from -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹²,
 -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹²,
 -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹²,
 -X⁵OP(O)(OR¹²)OR¹², -X⁵C(O)R¹³, -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴,
 25 -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴,
 -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹²,
 -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹² wherein X⁵, R¹², R¹³
 and R¹⁴ are as defined above,

R⁴ is selected from -X⁸NR¹²R¹², -X⁸NR¹²C(O)R¹², -X⁸NR¹²C(O)OR¹²,
 30 -X⁸NR¹²C(O)NR¹²R¹², -X⁸NR¹²C(NR¹²)NR¹²R¹², -X⁸OR¹², -X⁸SR¹², -X⁵C(O)OR¹²,
 -X⁵C(O)R¹², -X⁸OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁸S(O)₂NR¹²R¹², -X⁸NR¹²S(O)₂R¹²,
 -X⁸P(O)(OR¹²)OR¹², -X⁸OP(O)(OR¹²)OR¹², -X⁵C(O)R¹³, -X⁸NR¹²C(O)R¹³, -X⁸S(O)R¹³,
 -X⁸S(O)₂R¹³, -R¹⁴, -X⁸OR¹⁴, -X⁸SR¹⁴, -X⁸S(O)R¹⁴, -X⁸S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴,

-159-

$-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$,
 $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ and $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$
 wherein X^8 is (C_{1-6}) alkylene and X^5 , R^{12} , R^{13} and R^{14} are as defined above, with the proviso
 that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, then R^{14} is

5 (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-3}) alkyl, (C_{6-10}) aryl (C_{1-6}) alkyl,
 hetero (C_{5-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or
 hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl,

R^{15} is (C_{6-10}) aryl, hetero (C_{5-10}) aryl, (C_{9-10}) bicycloaryl or hetero (C_{8-10}) bicycloaryl,

R^{17} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl,
 10 (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or
 hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, with the proviso that when X^3 is cyano, then R^{17} is
 (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-6}) alkyl,
 (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{5-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or
 hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl,

15- R^{18} is hydrogen, (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,
 hetero (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl,
 (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, with the proviso that when
 X^3 is cyano, then R^{18} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{1-6}) alkyl,
 hetero (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{5-10}) aryl (C_{1-6}) alkyl,
 20 (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl, and

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form
 (C_{4-8}) heterocycloalkylene, wherein no more than one of the ring member atoms comprising
 the ring is a heteroatom selected from $-NR^{21}-$ or $-O-$, wherein the ring is unsubstituted or
 substituted with R^2 , wherein R^2 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$,
 25 $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$,
 $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12} , R^{13} and R^{14} are as
 defined above,

wherein within R^3 , R^4 , R^{15} , R^{17} and R^{18} any alicyclic or aromatic ring system is
 unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl,
 30 (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$,
 $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$,
 $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$,
 $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$,

$-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$,
 $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$,
 $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$,
 $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, and within R^3 and R^4 any aliphatic
 5 moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from
 cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,
 $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$,
 $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$,
 $-S(O)R^{13}$ and $-S(O)_2R^{13}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as described above, with the proviso
 10 that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, or $-NHR^{18}$, then any
 aromatic ring system present within R^{14} or R^{18} is not substituted further by halo,
 (C_{3-10}) cycloalkyl, hetero (C_{3-10}) cycloalkyl, (C_{6-10}) aryl, hetero (C_{5-10}) aryl, (C_{9-10}) bicycloaryl or
 hetero (C_{8-10}) bicycloaryl; with the proviso that only one bicyclic ring structure is present
 within R^3 , R^4 or R^{15} , and the *N*-oxide derivatives, prodrug derivatives, protected derivatives,
 15 individual isomers and mixtures of isomers thereof, and the pharmaceutically acceptable salts
 and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected
 derivatives, individual isomers and mixtures of isomers thereof

4 The compound of Claim 1 or Claim 2 in which

20 X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$;

X^2 is hydrogen, fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and
 X^7 both represent fluoro,

X^3 is $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$,

$-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,

25 $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$, wherein R^5 is hydrogen, (C_{1-4}) alkyl,

(C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl,

hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or

hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, R^6 is hydrogen, hydroxy or (C_{1-6}) alkyl, or where X^3

contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both

30 attached, form hetero (C_{3-10}) cycloalkyl, hetero (C_{5-10}) aryl or hetero (C_{8-10}) bicycloaryl, R^7 is

hydrogen or (C_{1-4}) alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo, R^{16} is hydrogen, -

X^4 , $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$; R^9 is hydrogen, halo, (C_{1-4}) alkyl, (C_{3-10}) aryl (C_{0-6}) alkyl or

(C_{5-10}) heteroaryl (C_{0-6}) alkyl,

91
92

-161-

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof, with the proviso that when $-X^4$ is other than a heteromonocyclic ring containing 5 ring member atoms, wherein no more than two of the ring member atoms comprising the ring are heteroatoms, then X^2 is fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

wherein within R^5 , X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6}) alkylene, R^{12} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, and R^{14} is (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl,

R^1 is hydrogen or (C_{1-6}) alkyl and R^2 is selected from a group consisting of hydrogen, cyano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as defined above, or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8}) cycloalkylene or (C_{3-8}) heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$,

$-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$,
 $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$,
 $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$,
 $-X^5S(O)_2R^{13}$ and $-X^5C(O)R^{13}$, wherein X^5 , R^{12} and R^{13} are as defined above;

5 R^3 is (C_{1-6}) alkyl or $-C(R^6)(R^6)X^6$, wherein R^6 is hydrogen or (C_{1-6}) alkyl and X^6 is
 selected from $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$,
 $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$,
 $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$,
 $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$,
 10 $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$,
 $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$,
 $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5 , R^{12} , R^{13}
 and R^{14} are as defined above,

R^4 is selected from $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$,
 15 $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$,
 $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$,
 $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$,
 $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$,
 $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$,
 20 $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ and $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$
 wherein X^8 is (C_{1-6}) alkylene and X^5 , R^{12} , R^{13} and R^{14} are as defined above,

R^{15} is (C_{6-10}) aryl, hetero (C_{5-10}) aryl, (C_{9-10}) bicycloaryl or hetero (C_{8-10}) bicycloaryl,

R^{17} is hydrogen, (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,
 hetero (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl,
 25 (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl,

R^{18} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,
 (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or
 hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, and

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form
 30 (C_{4-8}) heterocycloalkylene, wherein no more than one of the ring member atoms comprising
 the ring is a heteroatom selected from $-NR^{21}-$ or $-O-$, wherein the ring is unsubstituted or
 substituted with R^2 , wherein R^2 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$,
 $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$,

-163-

$-\text{C}(\text{O})\text{R}^{14}$, $-\text{C}(\text{O})\text{OR}^{14}$, $-\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$ and $-\text{S}(\text{O})_2\text{NR}^{14}\text{R}^{12}$, wherein R^{12} , R^{13} and R^{14} are as defined above,

wherein within R^3 , R^4 , R^{15} , R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-\text{X}^5\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{OR}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{OR}^{12}$, $-\text{X}^5\text{SR}^{12}$, $-\text{X}^5\text{C}(\text{O})\text{OR}^{12}$, $-\text{X}^5\text{C}(\text{O})\text{R}^{12}$, $-\text{X}^5\text{OC}(\text{O})\text{R}^{12}$, $-\text{X}^5\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{S}(\text{O})_2\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$, $-\text{X}^5\text{P}(\text{O})(\text{OR}^{12})\text{OR}^{12}$, $-\text{X}^5\text{OP}(\text{O})(\text{OR}^{12})\text{OR}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{R}^{13}$, $-\text{X}^5\text{S}(\text{O})\text{R}^{13}$, $-\text{X}^5\text{C}(\text{O})\text{R}^{13}$ and $-\text{X}^5\text{S}(\text{O})_2\text{R}^{13}$ and/or 1 radical selected from $-\text{R}^{14}$, $-\text{X}^5\text{OR}^{14}$, $-\text{X}^5\text{SR}^{14}$, $-\text{X}^5\text{S}(\text{O})\text{R}^{14}$, $-\text{X}^5\text{S}(\text{O})_2\text{R}^{14}$, $-\text{X}^5\text{C}(\text{O})\text{R}^{14}$, $-\text{X}^5\text{C}(\text{O})\text{OR}^{14}$, $-\text{X}^5\text{OC}(\text{O})\text{R}^{14}$, $-\text{X}^5\text{NR}^{14}\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{R}^{14}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{OR}^{14}$, $-\text{X}^5\text{C}(\text{O})\text{NR}^{14}\text{R}^{12}$, $-\text{X}^5\text{S}(\text{O})_2\text{NR}^{14}\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{14}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{NR}^{14}\text{R}^{12}$ and $-\text{X}^5\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{14}\text{R}^{12}$, and within R^3 and R^4 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-\text{NR}^{12}\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{OR}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{12}\text{R}^{12}$, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{C}(\text{O})\text{R}^{12}$, $-\text{OC}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{S}(\text{O})_2\text{NR}^{12}\text{R}^{12}$, $-\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$, $-\text{P}(\text{O})(\text{OR}^{12})\text{OR}^{12}$, $-\text{OP}(\text{O})(\text{OR}^{12})\text{OR}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$ and $-\text{S}(\text{O})_2\text{R}^{13}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as described above, with the proviso that only one bicyclic ring structure is present within R^3 , R^4 or R^{15} , and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof, and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

5 A compound of Claim 1 or Claim 2 in which:

25 X^1 is $-\text{NHC}(\text{R}^1)(\text{R}^2)\text{X}^3$ or $-\text{NHCH}(\text{R}^{19})\text{C}(\text{O})\text{R}^{20}$,

X^2 is hydrogen, fluoro, $-\text{OH}$, $-\text{OR}^4$ or $-\text{NR}^{17}\text{R}^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro,

X^3 is cyano,

30 wherein within X^3 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-\text{X}^5\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{OR}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{OR}^{12}$, $-\text{X}^5\text{SR}^{12}$, $-\text{X}^5\text{C}(\text{O})\text{OR}^{12}$, $-\text{X}^5\text{C}(\text{O})\text{R}^{12}$, $-\text{X}^5\text{OC}(\text{O})\text{R}^{12}$, $-\text{X}^5\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{S}(\text{O})_2\text{NR}^{12}\text{R}^{12}$, $-\text{X}^5\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$,

-X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³ and -X⁵S(O)₂R¹³ and/or 1 radical selected from -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² and

5 -X⁵NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁵ is a bond or (C₁₋₆)alkylene, R¹² at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl, R¹³ is (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl, and R¹⁴ is (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₃₋₁₀)aryl(C₀₋₆)alkyl, (C₉₋₁₀)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₀)bicycloaryl(C₀₋₆)alkyl,

10 R¹ is hydrogen or (C₁₋₆)alkyl and R² is selected from a group consisting of hydrogen, cyano, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -R¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² and -X⁵NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁵, R¹², R¹³ and R¹⁴ are as defined above, or R¹ and R² taken together with the carbon atom to which both R¹ and R² are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene, wherein within said R² any

15 heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³ and -X⁵C(O)R¹³, wherein X⁵, R¹² and R¹³ are as defined above,

20

R³ is (C₁₋₆)alkyl or -C(R⁶)(R⁶)X⁶, wherein R⁶ is hydrogen or (C₁₋₆)alkyl and X⁶ is selected from -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵C(O)R¹³, -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵S(O)₂R¹³, -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹²,

30

$-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5 , R^{12} , R^{13} and R^{14} are as defined above,

R^4 is selected from $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$,
 $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$,
 5 $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$,
 $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$,
 $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$,
 $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$,
 $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ and $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$

10 wherein X^8 is (C_{1-6}) alkylene and X^5 , R^{12} , R^{13} and R^{14} are as defined above, with the proviso that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, then R^{14} is

(C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-3}) alkyl, (C_{6-10}) aryl (C_{1-6}) alkyl,
 hetero (C_{5-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or
 hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl,

15 R^{15} is (C_{6-10}) aryl, hetero (C_{3-10}) aryl, (C_{9-10}) bicycloaryl or hetero (C_{8-10}) bicycloaryl,
 R^{17} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-6}) alkyl,
 (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{5-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or
 hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl,

20 R^{18} is (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{1-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{1-6}) alkyl,
 (C_{6-10}) aryl (C_{1-6}) alkyl, hetero (C_{3-10}) aryl (C_{1-6}) alkyl, (C_{9-10}) bicycloaryl (C_{1-6}) alkyl or
 hetero (C_{8-10}) bicycloaryl (C_{1-6}) alkyl, and

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form
 (C_{4-8}) heterocycloalkylene, wherein no more than one of the ring member atoms comprising
 the ring is a heteroatom selected from $-NR^{21}-$ or $-O-$, wherein the ring is unsubstituted or
 25 substituted with R^2 , wherein R^2 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$,
 $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$,
 $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12} , R^{13} and R^{14} are as
 defined above,

wherein within R^3 , R^4 , R^{15} , R^{17} and R^{18} any alicyclic or aromatic ring system is
 30 unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl,
 (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$,
 $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$,
 $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$,

$-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$,
 $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$,
 $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$,
 $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$,
5 $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, and within R^3 and R^4 any aliphatic
moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from
cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,
 $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$,
 $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$,
10 $-S(O)R^{13}$ and $-S(O)_2R^{13}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as described above, with the proviso
that when X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, or $-NHR^{18}$, then any aromatic ring system
present within R^{14} or R^{18} is not substituted further by halo, (C_{3-10}) cycloalkyl,
hetero (C_{3-10}) cycloalkyl, (C_{6-10}) aryl, hetero (C_{5-10}) aryl, (C_{9-10}) bicycloaryl or
hetero (C_{8-10}) bicycloaryl, with the proviso that only one bicyclic ring structure is present
15 within R^3 , R^4 or R^{15} , and the *N*-oxide derivatives, prodrug derivatives, protected derivatives,
individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts
and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected
derivatives, individual isomers and mixtures of isomers thereof

6. A compound of Claim 1 or 2 in which
 X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$,
 X^2 is $-OH$, $-OC(O)NR^{12}R^{12}$ or $-OC(O)R^{14}$, wherein R^{12} and R^{14} are as defined below,
 X^3 is cyano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$,
 $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,
25 $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$, wherein R^5 is hydrogen, (C_{1-4}) alkyl,
 (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl,
hetero (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or
hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl, R^6 is hydrogen, hydroxy or (C_{1-6}) alkyl, or where X^3
contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both
30 attached, form hetero (C_{3-10}) cycloalkyl, hetero (C_{5-10}) aryl or hetero (C_{8-10}) bicycloaryl, R^7 is
hydrogen or (C_{1-4}) alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo, R^{16} is hydrogen, -
 X^4 , $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$, R^9 is hydrogen, halo, (C_{1-4}) alkyl, (C_{5-10}) aryl (C_{0-6}) alkyl or
 (C_{5-10}) heteroaryl (C_{0-6}) alkyl,

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof,

wherein within R^5 , X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}\bar{C}(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C₁₋₆)alkylene, R^{12} at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl, R^{13} is (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl, and R^{14} is (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl, (C₄₋₁₀)bicycloaryl(C₀₋₆)alkyl or hetero(C₄₋₁₀)bicycloaryl(C₀₋₆)alkyl,

R^1 is hydrogen-or (C₁₋₆)alkyl and R^2 is selected from a group consisting of hydrogen, cyano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as defined above, or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene, wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$,

$-X^5S(O)_2R^{13}$ and $-X^5C(O)R^{13}$, wherein X^5 , R^{12} and R^{13} are as defined above,

R^3 is (C_{1-6}) alkyl or $-C(R^6)(R^6)X^6$, wherein R^6 is hydrogen or (C_{1-6}) alkyl and X^6 is selected from $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5 , R^{12} , R^{13} and R^{14} are as defined above, and

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C_{4-8}) heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from $-NR^{21}-$ or $-O-$, wherein and the ring is unsubstituted or substituted with R^2 , wherein R^2 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12} , R^{13} and R^{14} are as defined above;

wherein within R^3 , R^4 , R^{15} , R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, and within R^3 and R^4 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, wherein X^5 , R^{12} , R^{13} and R^{14} are as described above, with the proviso that only one bicyclic ring structure is present within R^3 , R^4 or R^{15} , and the *N*-oxide

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

5

7 The compound of Claim 1 or Claim 2 in which

— X^1 is $-NHC(R^1)(R^2)C(O)C(O)NR^5R^6$, wherein R^5 is hydrogen, (C_{1-6}) alkyl, (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{3-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or
10 hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl and R^6 is hydrogen, hydroxy or (C_{1-6}) alkyl or R^5 and R^6 together with the nitrogen atom to which they are both attached form hetero (C_{3-10}) cycloalkyl, hetero (C_{3-10}) aryl or hetero (C_{8-10}) bicycloaryl,

X^2 is hydrogen,

wherein within X^1 any alicyclic or aromatic ring system is unsubstituted or substituted

15 further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-6}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$
20 and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6}) alkylene, R^{12} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, R^{13} is (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl, and R^{14} is (C_{3-10}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{3-10}) cycloalkyl (C_{0-3}) alkyl, (C_{6-10}) aryl (C_{0-6}) alkyl, hetero (C_{3-10}) aryl (C_{0-6}) alkyl, (C_{9-10}) bicycloaryl (C_{0-6}) alkyl or hetero (C_{8-10}) bicycloaryl (C_{0-6}) alkyl,

R^1 is hydrogen and R^2 is (C_{1-6}) alkyl, and

R^3 is $-CH_2X^6$, wherein X^6 is $-X^5NR^{12}S(O)_2R^{12}$ or $-X^5S(O)_2R^{14}$ wherein X^5 , R^{12} and R^{14}

30 are as defined above,

wherein within R^3 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-6}) alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$,

$-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$,
 $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$,
 $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and
 $-X^5S(O)_2R^{13}$ and within R^3 any aliphatic moiety is unsubstituted or substituted further by 1 to
5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$,
 $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$,
 $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$,
 $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$; wherein X^5 , R^{12} , R^{13} and R^{14} are
as described above, with the proviso that only one bicyclic ring structure is present within R^3 ,
10 and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and
mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such
compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual
isomers and mixtures of isomers thereof.

8 The compound of Claim 3 in which.

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$, wherein R^1 is hydrogen or
 (C_{1-6}) alkyl and R^2 is hydrogen, (C_{1-6}) alkyl, $-X^5OR^{12}$, $-X^5S(O)R^{13}$, $-X^5OR^{14}$,
 (C_{6-10}) aryl (C_{0-6}) alkyl or hetero (C_{3-10}) aryl (C_{0-6}) alkyl or R^1 and R^2 taken together with
the carbon atom to which both R^1 and R^2 are attached form (C_{3-6}) cycloalkylene or
20 (C_{3-6}) heterocycloalkylene, wherein within said R^2 any heteroaryl, aryl, cycloalkylene
or heterocycloalkylene is unsubstituted or substituted with (C_{1-6}) alkyl or hydroxy,
wherein X^3 is cyano, $-C(O)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH=CHS(O)_2R^5$, $-CH_2C(O)R^{16}$,
 $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,
 $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$ and R^{19} and R^{20} together with the atoms to
25 which R^{19} and R^{20} are attached form (C_{4-8}) heterocycloalkylene, wherein no more than
one of the ring member atoms comprising the ring is a heteroatom selected from
 $-NR^{21}$ or $-O-$, wherein the ring is unsubstituted or substituted with (C_{1-6}) alkyl or
 $-X^5C(O)OR^{12}$ and R^{21} is hydrogen, (C_{1-6}) alkyl, $-X^5C(O)R^{12}$, $-X^5C(O)OR^{12}$, $-R^{14}$,
 $-X^5C(O)R^{14}$ or $-C(O)OR^{14}$,

X^2 is $-OH$ or $-OC(O)NR^{12}R^{12}$, wherein each R^{12} independently represent
hydrogen or (C_{1-6}) alkyl, wherein said alkyl is unsubstituted or substituted with
hydroxy or methoxy, or X^2 is $-OC(O)NHR^{14}$, wherein R^{14} is
30 (C_{3-10}) cycloalkyl (C_{0-6}) alkyl or hetero (C_{3-10}) cycloalkyl (C_{1-3}) alkyl, or X^2 is $-OC(O)R^{14}$,

-171-

wherein R^{14} is $-NR^{22}R^{23}$ and R^{22} and R^{23} together with the nitrogen atom to which both R^{22} and R^{23} attached form a hetero(C_{4-6})cycloalkyl ring, which ring may be unsubstituted or substituted with hydroxy; and

R^3 is $-CH_2X^6$, wherein X^6 is selected from $-X^5SR^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2R^{13}$, $-X^5C(O)R^{13}$, $-X^5OR^{12}$, $-X^5SR^{14}$, $-X^5R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)NR^{14}R^{12}$, and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof, and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

9 The compound of Claim 8 in which

X^3 is cyano, $-C(O)X^4$, $-C(O)H$, $-C(O)N(CH_3)OCH_3$, $-CH(OCH_3)_2$, $-C(O)CF_3$, $-C(O)CF_2CF_3$, $-CH_2C(O)R^{16}$, (E)-2-benzenesulfonyl-vinyl, 2-dimethylcarbamoyl-2,2-difluoro-acetyl, 2-oxo-2-pyrrolidin-1-yl-acetyl, 2-morpholin-4-yl-2-oxo-acetyl, 2-oxo-2-piperazin-1-yl-acetyl, 2-(4-methanesulfonyl-piperazin-1-yl)-2-oxo-acetyl, 2-(1,1-dioxo-1 λ^6 -thiomorpholin-4-yl)-2-oxo-acetyl, dimethylaminooxalyl, tetrahydro-pyran-4-ylaminooxalyl, 2-morpholin-4-yl-ethylaminooxalyl, cyclopentyl-ethyl-aminooxalyl, pyridin-3-ylaminooxalyl, phenylaminooxalyl, 1-benzoyl-piperidin-4-ylaminooxalyl, 1-benzylcarbamoyl-methanoyl, 1-benzyloxy(oxalyl), 2-benzyloxy-acetyl, 2-benzenesulfonylamino-ethanoyl, 2-oxo-2-phenyl-ethanoyl, 3*H*-oxazole-2-carbonyl, 5-trifluoromethyl-oxazole-2-carbonyl, 3-trifluoromethyl-[1,2,4]oxadiazole-5-carbonyl, 2,2,3,3,3-pentafluoro-propionyl, hydroxyaminooxalyl, oxalyl, 2-(1,3-dihydro-isoindol-2-yl)-2-oxo-acetyl, benzothiazol-2-ylaminooxalyl, 2-oxo-ethyl, 2-oxazol-2-yl-2-oxo-ethyl or 2-benzooxazol-2-yl-2-oxo-ethyl,

X^2 is selected from $-OH$, dimethylcarbamoyloxy, morpholin-4-ylcarbonyloxy, piperidin-1-yl-carbonyloxy, pyrrolidin-1-yl-carbonyloxy, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, 1-methyl-piperidin-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, isopropylamino and cyclohexylamino, 4-*tert*-butoxycarbonylpiperazin-1-ylcarbonyloxy, *N*-benzyl-carbamoyloxy, pyrrolidin-1-yl-carbonyloxy, *N,N*-dimethyl-carbamoyloxy, piperidin-1-yl-carbonyloxy, 4-methanesulfonyl-piperazin-1-yl-carbonyloxy, 4-ethoxycarbonylpiperazin-1-

ylcarbonyloxy, *N*-cyclohexyl-carbamoyloxy, *N*-phenyl-carbamoyloxy, *N*-(5,6,7,8-tetrahydro-naphthalen-1-yl)-carbamoyloxy, *N*-butyl-*N*-methyl-carbamoyloxy, *N*-pyridin-3-yl-carbamoyloxy, *N*-isopropyl-carbamoyloxy, *N*-pyridin-4-yl-carbamoyloxy, *N*-cyanomethyl-*N*-methyl-carbamoyloxy, *N,N*-bis-(2-methoxy-ethyl)-carbamoyloxy, *N*-phenethyl-carbamoyloxy, piperazine-carbonyloxy, *N*-naphthalen-2-yl-carbamoyloxy, 4-benzyl-piperazine-1-carbamoyloxy, 4-(1-furan-2-yl-carbonyl)-piperazine-1-carbamoyloxy, thiomorpholin-4-yl-carbonyloxy, 1,1-dioxo-1λ⁶-thiomorpholin-4-yl-carbonyloxy, bis-(2-methoxy-ethyl)-carbamoyloxy, morpholin-4-ylcarbonyloxy, 2-methoxyethylcarbamoyloxy, diethylcarbamoyloxy, pyrrolidin-1-ylcarbonyloxy, 2-hydroxyethylcarbamoyloxy, tetrahydro-furan-2-ylmethylcarbamoyloxy, cyclopropylcarbamoyloxy, *tert*-butylcarbamoyloxy, 3-hydroxy-pyrrolidin-1-yl-carbonyloxy and carbamoyloxy; and

R^3 is thiophene-2-sulfonyl-methyl, 3-chloro-2-fluoro-phenyl-methane-sulfonyl-methyl, benzene-sulfonyl-methyl, phenyl-methane-sulfonyl-methyl, 2-(1,1-difluoro-methoxy)-phenyl-methane-sulfonyl-methyl, 2-benzene-sulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl, 2-phenyl-methanesulfonyl-ethyl, oxy-pyridin-2-yl-methane-sulfonyl-methyl, prop-2-ene-1-sulfonyl-methyl, 4-methoxy-phenyl-methane-sulfonyl-methyl, *p*-tolyl-methane-sulfonyl-methyl, 4-chloro-phenyl-methane-sulfonyl-methyl, *o*-tolyl-methane-sulfonyl-methyl, 3,5-dimethyl-phenyl-methane-sulfonyl-methyl, 4-trifluoro-methyl-phenyl-methane-sulfonyl-methyl, 4-trifluoro-methoxy-phenyl-methane-sulfonyl-methyl, 2-bromo-phenyl-methane-sulfonyl-methyl, pyridin-2-yl-methane-sulfonyl-methyl, pyridin-3-yl-methane-sulfonyl-methyl, pyridin-4-yl-methane-sulfonyl-methyl, naphthalen-2-yl-methane-sulfonyl-methyl, 3-methyl-phenyl-methane-sulfonyl-methyl, 3-trifluoro-methyl-phenyl-methane-sulfonyl-methyl, 3-trifluoro-methoxy-phenyl-methane-sulfonyl-methyl, 4-fluoro-2-trifluoromethoxy-phenyl-methane-sulfonylmethyl, 2-fluoro-6-trifluoromethyl-phenylmethanesulfonylmethyl, 3-chloro-phenylmethanesulfonylmethyl, 2-fluoro-phenylmethanesulfonylmethyl, 2-trifluoro-phenylmethanesulfonylmethyl, 2-cyano-phenylmethanesulfonylmethyl, 4-*tert*-butyl-phenylmethanesulfonylmethyl, 2-fluoro-3-methyl-phenyl-methane-sulfonyl-methyl, 3-fluoro-phenylmethanesulfonylmethyl, 4-fluoro-phenylmethane-sulfonylmethyl, 2-chloro-phenylmethanesulfonylmethyl, 2,5-difluoro-phenylmethane-sulfonylmethyl, 2,6-difluoro-phenylmethanesulfonylmethyl, 2,5-dichloro-phenyl-

methane-sulfonylmethyl, 3,4-dichloro-phenylmethanesulfonylmethyl,
2-(1,1-difluoro-methoxy)-phenyl-methanesulfonylmethyl, 2-cyano-phenyl-methane-
sulfonyl-methyl, 3-cyano-phenylmethanesulfonylmethyl, 2-trifluoro-methoxy-phenyl-
methane-sulfonylmethyl, 2,3-difluoro-phenylmethanesulfonylmethyl,
5 2,5-difluoro-phenyl-methanesulfonylmethyl, biphenyl-2-ylmethanesulfonylmethyl,
cyclohexylmethyl, 3-fluoro-phenyl-methanesulfonylmethyl, 3,4-difluoro-phenyl-
methanesulfonylmethyl, 2,4-difluoro-phenylmethanesulfonylmethyl, 2,4,6-trifluoro-
phenylmethanesulfonylmethyl, 2,4,5-trifluoro-phenylmethanesulfonylmethyl,
2,3,4-trifluoro-phenylmethanesulfonylmethyl, 2,3,5-trifluoro-phenyl-methane-
10 sulfonylmethyl, 2,5,6-trifluoro-phenylmethanesulfonylmethyl, 2-chloro-5-trifluoro-
methylphenylmethanesulfonylmethyl, 2-methyl-propane-1-sulfonyl,
2-fluoro-3-trifluoro-methylphenylmethanesulfonylmethyl, 2-fluoro-4-trifluoro-
methylphenylmethanesulfonylmethyl, 2-fluoro-5-trifluoro-methyl-phenyl-methane-
sulfonyl-methyl, 4-fluoro-3-trifluoro-methylphenylmethanesulfonylmethyl,
15 2-methoxy-phenyl-methanesulfonylmethyl,
3,5-bis-trifluoromethyl-phenylmethanesulfonylmethyl,
4-difluoromethoxy-phenylmethanesulfonylmethyl, 2-difluoro-methoxy-phenyl-
methanesulfonylmethyl, 3-difluoromethoxy-phenylmethanesulfonylmethyl,
2,6-dichloro-phenylmethanesulfonylmethyl, biphenyl-4-ylmethanesulfonylmethyl,
20 3,5-dimethyl-isoxazol-4-ylmethanesulfonylmethyl, 5-chloro-thien-2-yl-methane-
sulfonylmethyl, 2-[4-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl,
2-[2-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-[3-(1,1-difluoro-
methoxy)-benzenesulfonyl]-ethyl, 2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl,
2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-(2-trifluoro-methoxy-benzene-
25 sulfonyl)-ethyl, (cyanomethyl-methyl-carbamoyl)-methyl, biphenyl-3-ylmethyl,
2-oxo-2-pyrrolidin-1-yl-ethyl, 2-benzenesulfonyl-ethyl, isobutylsulfanylmethyl,
2-phenylsulfanyl-ethyl, cyclohexylmethanesulfonylmethyl, 2-cyclohexyl-
ethanesulfonyl, benzyl, naphthalen-2-yl, benzylsulfanylmethyl,
2-trifluoromethyl-benzylsulfanylmethyl, phenylsulfanyl-ethyl, cyclopropyl-
30 methanesulfonylmethyl, 5-bromo-thien-2-ylmethyl, 3-phenyl-propyl, 2,2-difluoro-
3-phenyl-propyl, 3,4,5-trimethoxy-phenylmethanesulfonylmethyl, 2,2-difluoro-
3-thien-2-yl-propyl, cyclohexylethyl, cyclohexylmethyl, *tert*-butylmethyl,
1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-phenylpropyl,

-174-

2,2-dimethyl-3-phenylpropyl, 1-benzylcyclopropylmethyl, $-X^5S(O)_2R^{13}$ and $-X^5S(O)_2R^{14}$, wherein R^{13} is alkyl and R^{14} is phenyl which phenyl is unsubstituted or substituted, and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof, and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

10 A compound of Claim 9 in which

X^3 is 1*H*-benzimidazol-2-ylcarbonyl, pyrimidin-2-ylcarbonyl, benzooxazol-2-ylcarbonyl, benzothiazol-2-ylcarbonyl, pyridazin-3-ylcarbonyl, 3-phenyl-[1,2,4]oxadiazol-5-ylcarbonyl or 3-ethyl-[1,2,4]oxadiazol-5-ylcarbonyl, 2-oxo-2-pyrrolidin-1-yl-acetyl, 2-morpholin-4-yl-2-oxo-acetyl, 2-oxo-2-piperazin-1-yl-acetyl, 2-(4-methanesulfonyl-piperazin-1-yl)-2-oxo-acetyl, 2-(1,1-dioxo-1 λ^6 -thiomorpholin-4-yl)-2-oxo-acetyl, dimethylaminooxalyl, tetrahydropyran-4-ylaminooxalyl, 2-morpholin-4-yl-ethylaminooxalyl, cyclopentyl-ethylaminooxalyl, pyridin-3-ylaminooxalyl, phenylaminooxalyl or 1-benzoyl-piperidin-4-ylaminooxalyl,

X^2 is selected from -OH, dimethylcarbamoyloxy, morpholin-4-ylcarbonyloxy, piperidin-1-yl-carbonyloxy, pyrrolidin-1-yl-carbonyloxy, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, 1-methyl-piperidin-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, isopropylamino and cyclohexylamino,

R^3 is cyclohexylethyl, cyclohexylmethyl, *tert*-butylmethyl, 1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-phenylpropyl, 2,2-dimethyl-3-phenylpropyl, 1-benzylcyclopropylmethyl, $-X^5S(O)_2R^{13}$ or $-X^5S(O)_2R^{14}$, wherein R^{13} is alkyl and R^{14} is phenyl which phenyl is unsubstituted or substituted, and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

11 The compound of Claim 3 in which

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$, wherein R^1 is hydrogen or (C_{1-6}) alkyl and R^2 is hydrogen, (C_{1-6}) alkyl, $-X^5OR^{12}$, $-X^5S(O)R^{13}$, $-X^5OR^{14}$, (C_{6-10}) aryl (C_{0-6}) alkyl or hetero (C_{3-10}) aryl (C_{0-6}) alkyl or R^1 and R^2 taken together with

-175-

the carbon atom to which both R^1 and R^2 are attached form (C_{3-6}) cycloalkylene or (C_{3-6}) heterocycloalkylene, wherein within said R^2 any heteroaryl, aryl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with (C_{1-6}) alkyl or hydroxy, wherein X^3 is cyano, $-C(O)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH=CHS(O)_2R^5$, $-CH_2C(O)R^{16}$,
 5 $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,
 $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$ and R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C_{4-6}) heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from $-NR^{21}$ - or $-O-$, wherein the ring is unsubstituted or substituted with (C_{1-6}) alkyl or
 10 $-X^5C(O)OR^{12}$ and R^{21} is hydrogen, (C_{1-6}) alkyl, $-X^5C(O)R^{12}$, $-X^5C(O)OR^{12}$, $-R^{14}$,
 $-X^5C(O)R^{14}$ or $-C(O)OR^{14}$;

X^2 is $-NHR^{15}$, wherein R^{15} is (C_{6-10}) aryl, hetero (C_{5-10}) aryl, (C_{9-10}) bicycloaryl or hetero (C_{8-10}) bicycloaryl, or $-NR^{17}R^{18}$, wherein R^{17} is hetero (C_{3-10}) cycloalkyl and R^{18} is hydrogen or R^{17} and R^{18} independently are (C_{6-10}) aryl (C_{1-6}) alkyl or
 15 hetero (C_{5-10}) aryl (C_{1-6}) alkyl, wherein within R^{15} , R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, cyano, halo, nitro, halo-substituted (C_{1-4}) alkyl, $-X^5OR^{12}$,
 $-X^5C(O)OR^{12}$, $-X^5C(O)R^{13}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$ and $-X^5C(O)NR^{14}R^{12}$, and

20 R^3 is $-CH_2X^6$, wherein X^6 is selected from $-X^5SR^{12}$, $-X^5C(O)NR^{12}R^{12}$,
 $-X^5S(O)_2R^{13}$, $-X^5C(O)R^{13}$, $-X^5OR^{12}$, $-X^5SR^{14}$, $-X^5R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$,
 $-X^5C(O)NR^{14}R^{12}$, and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof, and the
 25 pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

12 The compound of Claim 11 in which

30 X^3 is cyano, $-C(O)X^4$, $-C(O)H$, $-C(O)N(CH_3)OCH_3$, $-CH(OCH_3)_2$, $-C(O)CF_3$,
 $-C(O)CF_2CF_3$, $-CH_2C(O)R^{16}$, (E)-2-benzenesulfonyl-vinyl,
 2-dimethylcarbamoyl-2,2-difluoro-acetyl, 2-oxo-2-pyrrolidin-1-yl-acetyl, 2-morpholin-4-yl-2-oxo-acetyl, 2-oxo-2-piperazin-1-yl-acetyl, 2-(4-methanesulfonyl-piperazin-1-yl)-2-oxo-acetyl, 2-(1,1-dioxo-1 λ^6 -thiomorpholin-4-yl)-2-oxo-acetyl,

dimethylaminooxalyl, tetrahydro-pyran-4-ylaminooxalyl, 2-morpholin-4-yl-ethylaminooxalyl, cyclopentyl-ethyl-aminooxalyl, pyridin-3-ylaminooxalyl, phenylaminooxalyl, 1-benzoyl-piperidin-4-ylaminooxalyl, 1-benzylcarbamoyl-methanoyl, 1-benzyloxy(oxalyl), 2-benzyloxy-acetyl, 2-benzenesulfonylamino-ethanoyl, 2-oxo-2-phenyl-ethanoyl, 3*H*-oxazole-2-carbonyl, 5-trifluoromethyl-oxazole-2-carbonyl, 3-trifluoromethyl-[1,2,4]oxadiazole-5-carbonyl, 2,2,3,3,3-pentafluoro-propionyl, hydroxyaminooxalyl, oxalyl, 2-(1,3-dihydro-isoindol-2-yl)-2-oxo-acetyl, benzothiazol-2-ylaminooxalyl, 2-oxo-ethyl, 2-oxazol-2-yl-2-oxo-ethyl or 2-benzooxazol-2-yl-2-oxo-ethyl,

X^2 is selected from 5-nitrothiazol-2-ylamino, 2-nitrophenylamino, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, 1-methyl-piperidin-4-ylamino, isopropylamino, di(thien-2-ylmethyl)amino or di(benzyl)amino, and

R^3 is thiophene-2-sulfonyl-methyl, 3-chloro-2-fluoro-phenyl-methane-sulfonyl-methyl, benzene-sulfonyl-methyl, phenyl-methane-sulfonyl-methyl, 2-(1,1-difluoro-methoxy)-phenyl-methane-sulfonyl-methyl, 2-benzene-sulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl, 2-phenyl-methanesulfonyl-ethyl, oxy-pyridin-2-yl-methane-sulfonyl-methyl, prop-2-ene-1-sulfonyl-methyl, 4-methoxy-phenyl-methane-sulfonyl-methyl, *p*-tolyl-methane-sulfonyl-methyl, 4-chloro-phenyl-methane-sulfonyl-methyl, *o*-tolyl-methane-sulfonyl-methyl, 3,5-dimethyl-phenyl-methane-sulfonyl-methyl, 4-trifluoromethyl-phenyl-methane-sulfonyl-methyl, 4-trifluoro-methoxy-phenyl-methane-sulfonyl-methyl, 2-bromo-phenyl-methane-sulfonyl-methyl, pyridin-2-yl-methane-sulfonyl-methyl, pyridin-3-yl-methane-sulfonyl-methyl, pyridin-4-yl-methane-sulfonyl-methyl, naphthalen-2-yl-methane-sulfonyl-methyl, 3-methyl-phenyl-methane-sulfonyl-methyl, 3-trifluoro-methyl-phenyl-methane-sulfonyl-methyl, 3-trifluoromethoxy-phenyl-methane-sulfonyl-methyl, 4-fluoro-2-trifluoromethoxy-phenyl-methane-sulfonylmethyl, 2-fluoro-6-trifluoromethyl-phenylmethanesulfonylmethyl, 3-chloro-phenylmethanesulfonylmethyl, 2-fluoro-phenylmethanesulfonylmethyl, 2-trifluoro-phenylmethanesulfonylmethyl, 2-cyano-phenylmethanesulfonylmethyl, 4-*tert*-butyl-phenylmethanesulfonylmethyl, 2-fluoro-3-methyl-phenyl-methane-sulfonyl-methyl, 3-fluoro-phenylmethanesulfonylmethyl, 4-fluoro-phenylmethane-sulfonylmethyl, 2-chloro-phenylmethanesulfonylmethyl, 2,5-difluoro-phenylmethane-

-177-

sulfonylmethyl, 2,6-difluoro-phenylmethanesulfonylmethyl, 2,5-dichloro-phenyl-methane-sulfonylmethyl, 3,4-dichloro-phenylmethanesulfonylmethyl,
2-(1,1-difluoro-methoxy)-phenyl-methanesulfonylmethyl, 2-cyano-phenyl-methane-sulfonyl-methyl, 3-cyano-phenylmethanesulfonylmethyl, 2-trifluoro-methoxy-phenyl-
5 methane-sulfonylmethyl, 2,3-difluoro-phenylmethanesulfonylmethyl,
2,5-difluoro-phenyl-methanesulfonylmethyl, biphenyl-2-ylmethanesulfonylmethyl, cyclohexylmethyl, 3-fluoro-phenyl-methanesulfonylmethyl, 3,4-difluoro-phenyl-methanesulfonylmethyl, 2,4-difluoro-phenylmethanesulfonylmethyl, 2,4,6-trifluoro-phenylmethanesulfonylmethyl, 2,4,5-trifluoro-phenylmethanesulfonylmethyl,
10 2,3,4-trifluoro-phenylmethanesulfonylmethyl, 2,3,5-trifluoro-phenyl-methane-sulfonylmethyl, 2,5,6-trifluoro-phenylmethanesulfonylmethyl, 2-chloro-5-trifluoro-methylphenylmethanesulfonylmethyl, 2-methyl-propane-1-sulfonyl,
2-fluoro-3-trifluoro-methylphenylmethanesulfonylmethyl, 2-fluoro-4-trifluoro-methylphenylmethanesulfonylmethyl, 2-fluoro-5-trifluoro-methyl-phenyl-methane-sulfonyl-methyl, 4-fluoro-3-trifluoro-methylphenylmethanesulfonylmethyl,
15 2-methoxy-phenyl-methanesulfonylmethyl,
3,5-bis-trifluoromethyl-phenylmethanesulfonylmethyl,
4-difluoromethoxy-phenylmethanesulfonylmethyl, 2-difluoro-methoxy-phenyl-methanesulfonylmethyl, 3-difluoromethoxy-phenylmethanesulfonylmethyl,
20 2,6-dichloro-phenylmethanesulfonylmethyl, biphenyl-4-ylmethanesulfonylmethyl, 3,5-dimethyl-isoxazol-4-ylmethanesulfonylmethyl, 5-chloro-thien-2-yl-methane-sulfonylmethyl, 2-[4-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl,
2-[2-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-[3-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl,
25 2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-(2-trifluoro-methoxy-benzene-sulfonyl)-ethyl, (cyanomethyl-methyl-carbamoyl)-methyl, biphenyl-3-ylmethyl, 2-oxo-2-pyrrolidin-1-yl-ethyl, 2-benzenesulfonyl-ethyl, isobutylsulfanylmethyl, 2-phenylsulfanyl-ethyl, cyclohexylmethanesulfonylmethyl, 2-cyclohexyl-ethanesulfonyl, benzyl, naphthalen-2-yl, benzylsulfanylmethyl,
30 2-trifluoromethyl-benzylsulfanylmethyl, phenylsulfanyl-ethyl, cyclopropyl-methanesulfonylmethyl, 5-bromo-thien-2-ylmethyl, 3-phenyl-propyl, 2,2-difluoro-3-phenyl-propyl, 3,4,5-trimethoxy-phenylmethanesulfonylmethyl, 2,2-difluoro-3-thien-2-yl-propyl, cyclohexylethyl, cyclohexylmethyl, *tert*-butylmethyl,

-178-

1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-phenylpropyl, 2,2-dimethyl-3-phenylpropyl, 1-benzylcyclopropylmethyl, $-X^3S(O)_2R^{13}$ and $-X^3S(O)_2R^{14}$, wherein R^{13} is alkyl and R^{14} is phenyl which phenyl is unsubstituted or substituted, and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

13 A compound of Claim 12 in which

X^3 is 1*H*-benzimidazol-2-ylcarbonyl, pyrimidin-2-ylcarbonyl, benzooxazol-2-ylcarbonyl, benzothiazol-2-ylcarbonyl, pyridazin-3-ylcarbonyl, 3-phenyl-[1,2,4]oxadiazol-5-ylcarbonyl or 3-ethyl-[1,2,4]oxadiazol-5-ylcarbonyl, 2-oxo-2-pyrrolidin-1-yl-acetyl, 2-morpholin-4-yl-2-oxo-acetyl, 2-oxo-2-piperazin-1-yl-acetyl, 2-(4-methanesulfonyl-piperazin-1-yl)-2-oxo-acetyl, 2-(1,1-dioxo-1λ⁶-thiomorpholin-4-yl)-2-oxo-acetyl, dimethylaminooxalyl, tetrahydropyran-4-ylaminooxalyl, 2-morpholin-4-yl-ethylaminooxalyl, cyclopentyl-ethylaminooxalyl, pyridin-3-ylaminooxalyl, phenylaminooxalyl or 1-benzoyl-piperidin-4-ylaminooxalyl;

X^2 is selected from -OH, dimethylcarbamoyloxy, morpholin-4-ylcarbonyloxy, piperidin-1-yl-carbonyloxy, pyrrolidin-1-yl-carbonyloxy, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, 1-methyl-piperidin-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, isopropylamino and cyclohexylamino,

R^3 is cyclohexylethyl, cyclohexylmethyl, *tert*-butylmethyl, 1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-phenylpropyl, 2,2-dimethyl-3-phenylpropyl, 1-benzylcyclopropylmethyl, $-X^3S(O)_2R^{13}$ or $-X^3S(O)_2R^{14}$, wherein R^{13} is alkyl and R^{14} is phenyl which phenyl is unsubstituted or substituted; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof

14 A compound of Claim 1 selected from the group consisting of

(*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

(*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

(*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide,

(*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide, morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester;

5 morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester;

(*R*)-(2-methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester;

(*S*)-diethyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

10 (*S*)-pyrrolidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-4-Ethyl-piperazine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-2-hydroxymethyl-pyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

15 (*S*)-(2,2,2-Trifluoro-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-(2-hydroxyethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(Tetrahydrofuran-2-ylmethyl)-carbamic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-Azetidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-cyclopropyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

20 (*S*)-piperidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-(2-methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*R*)-3-hydroxy-pyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-3-hydroxy-pyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-3-cyclohexyl-propyl ester;

25 morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester;

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester;

30 pyrrolidine-1-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

dimethyl-carbamic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

35 morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

morpholine-4-carboxylic acid (S)-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

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

5 (S)-2-[(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propanoylamino]-N-methoxy-N-methyl-butamide,

(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-N-[(S)-1-formyl-propyl]-2-hydroxy-propionamide,

10 (R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide,

(S)-3-[3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino]-2-oxo-pentanoic acid benzylamide,

N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionamide,

15 N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propyl]-3-*p*-tolylmethanesulfonyl-propionamide, 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-2,3-dioxo-3-pyrrolidin-1-yl-propyl)-propionamide,

3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-3-morpholin-4-yl-2,3-dioxo-propyl)-propionamide,

20 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-2,3-dioxo-3-piperazin-1-yl-propyl)-propionamide,

3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-[3-(1,1-dioxo-1,6-thiomorpholin-4-yl)-1-ethyl-2,3-dioxo-propyl]-propionamide,

25 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-[1-ethyl-3-(4-methyl-sulfonyl-piperazin-1-yl)-2,3-dioxo-propyl]-propionamide,

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid dimethylamide;

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid cyclopentyl-ethyl-amide,

30 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid phenylamide,

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid pyridin-3-ylamide,

35 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (tetrahydro-pyran-4-yl)-amide,

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (1-benzoyl-

- piperidin-4-yl)-amide,
3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (2-morpholin-4-yl-ethyl)-amide,
(R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide,
5 N-[1-(benzooxazole-2-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(pyrimidin-2-ylamino)-propionamide
(R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide,
10 (2S) (4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(S)-cyano-3-phenyl-propyl)-amide,
N-(1(S)-cyano-3-phenyl-propyl)-2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyramide,
N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-fluoro-4-phenyl-butyramide,
N-(1-(S)-cyano-3-phenyl-propyl)-2,2-difluoro-4-phenyl-butyramide,
N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-hydroxy-4-phenyl-butyramide,
15 N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-hydroxy-4-phenyl-butyramide,
N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-methoxy-4-phenyl-butyramide,
2,2-difluoro-5-phenyl-pentanoic acid (1-cyano-cyclopropyl)-amide,
N-(1-(S)-cyano-3-phenyl-propyl)-4-phenyl-butyramide,
2,2-difluoro-5-phenyl-pentanoic acid ((S)-1-cyano-3-phenyl-propyl)-amide,
20 N-(4-cyano-1-ethyl-piperidin-4-yl)-3-cyclohexyl-propionamide,
N-(4-cyano-1-ethyl-piperidin-4-yl)-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide,
(S)-tert-butyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,
(R)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-(2-difluoromethoxy-phenylmethanesulfonyl)-ethyl ester,
25 (S)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,
(R)-morpholine-4-carboxylic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester,
(R)-morpholine-4-carboxylic acid 1-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester,
30 3-cyclohexyl-2-hydroxy-N-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-propionamide,
(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide,
(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
35 (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide,

- (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- 5 (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide,
- 10 (S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide,
- (S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide,
- (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- 15 (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide,
- 20 (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide,
- (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,
- 25 (1S)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-(S)-fluoro-4-phenyl-butyramide,
- 2,2-difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazole-2-carbonyl)-butyl]-amide,
- morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-2-cyclohexyl-ethyl ester,
- 30 morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-ethyl ester,
- morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester,
- morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester,
- 35

morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-3-cyclohexyl-propyl ester;

4-[4,4-dimethyl-2-(morpholine-4-carbonyloxy)-pentanoylamino]-3-oxo-azepane-1-carboxylic acid benzyl ester;

5 (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

(R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethanesulfonyl-propionamide,

10 (R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethanesulfonyl-propionamide,

(R)-3-phenylmethanesulfonyl-N-[(S)-3-phenyl-1-(thiazole-2-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide,

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

15 (R)-3-cyclopropylmethanesulfonyl-N-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide,

(R)-3-phenylmethanesulfonyl-N-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide,

20 (R)-N-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

{(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

25 {(S)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

30 {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

(R)-1-[1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

35 ((R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester;

{(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-
cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

5 {(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-
ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-
ethyl}-carbamic acid tert-butyl ester;

10 (R)-1-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl}-2-
phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

((R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-
propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester;

{(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
carbamic acid tert-butyl ester;

15 {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-
cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-
ethyl}-carbamic acid tert-butyl ester;

20 (R)-2-phenylmethanesulfonyl-1-[(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-
propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester;

(R)-N-[1-(Benzoxazole-2-carbonyl)-butyl]-2-[cyclopropylmethyl-(tetrahydro-pyran-4-ylmethyl)-
amino]-3-phenylmethanesulfonyl-propionamide;

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-
propionamide;

25 (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-
ylamino)-propionamide;

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-
propionamide;

30 (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-
propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-
4-ylamino)-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-
phenylmethanesulfonyl-propionamide;

35 (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-
phenylmethanesulfonyl-propionamide;

- (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide,
(S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide,
5 S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide,
(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide,
(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
10 R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,
15 (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide,
(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide,
(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,
20 N-cyanomethyl-3-cyclohexyl-propionamide,
N-cyanomethyl-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide,
3-(3-cyclohexyl-propionylamino)-2-oxo-5-phenyl-pentanoic acid thiazol-2-ylamide,
3-cyclohexyl-N-(1-formyl-3-phenyl-propyl)-propionamide;
25 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-propionamide,
N-[(S)-1-(benzoxazole-2-carbonyl)-propyl]-2-(2-cyano-phenylamino)-3-cyclohexyl-propionamide,
N-Cyanomethyl-3-cyclohexyl-2-(4-methoxy-phenoxy)-propionamide,
2-benzyloxy-N-cyanomethyl-3-cyclohexyl-propionamide,
30 (R)-N-[(S)-1-(1-benzoxazol-2-yl-methanoyl)-butyl]-2-benzyloxy-3-phenylmethanesulfonyl-propionamide,
(R)-N-[(S)-1-(1-benzoxazol-2-yl-methanoyl)-propyl]-2-methoxymethoxy-3-phenylmethanesulfonyl-propionamide,
(S)-N-[(S)-1-(1-benzoxazol-2-yl-methanoyl)-butyl]-2-hydroxy-3-phenyl-propionamide,
35 (R)-N-[(S)-1-(1-benzoxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-trisopropylsilyloxy-propionamide,

(*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

(*R*)-2-hydroxy-3-phenylmethanesulfonyl-*N*-[(*S*)-1-(1-pyridazin-3-yl-methanoyl)-butyl]-propionamide,

(*S*)-3-[(*R*)-2-hydroxy-3-phenylmethanesulfonyl-propanoylamino]-2-oxo-pentanoic acid benzylamide,

5 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide,

(*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide,

10 (2*R*,5*S*)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl]-6-ethoxy-5-ethyl-morpholin-3-one; 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 and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof

15 15 A compound of claim 14 selected from the group consisting of

(*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

(*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

(*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide,

20 (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide, morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester, morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester,

25 (*R*)-(2-methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester;

(*S*)-diethyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,

(*S*)-pyrrolidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-4-Ethyl-piperazine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

30 (*S*)-2-hydroxymethyl-pyrrolidine-1-carboxylic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-(2,2,2-Trifluoro-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-(2-hydroxyethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(Tetrahydrofuran-2-ylmethyl)-carbamic acid (*S*)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

35 (*S*)-Azetidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(*S*)-cyclopropyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

- (S)-piperidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;
 (S)-(2-methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;
 (R)-3-hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;
 (S)-3-hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;
 5 (S)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-3-cyclohexyl-propyl ester;
 morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
 morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester;
 10 morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester;
 pyrrolidine-1-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
 dimethyl-carbamic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
 15 morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
 morpholine-4-carboxylic acid (S)-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
 20 morpholine-4-carboxylic acid (S)-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;
 (S)-2-[(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propanoylamino]-N-methoxy-N-methyl-butamide;
 (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-N-[(S)-1-formyl-propyl]-2-hydroxy-propionamide;
 25 (R)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide;
 (S)-3-[3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino]-2-oxo-pentanoic acid benzylamide;
 30 N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionamide;
 N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propyl]-3-p-tolylmethanesulfonyl-propionamide;
 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-2,3-dioxo-3-pyrrolidin-1-yl-propyl)-propionamide;
 35 3-(2-difluoromethoxy-phenylmethanesulfonyl)-N-(1-ethyl-3-morpholin-4-yl-2,3-dioxo-propyl)-propionamide;

- 3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-(1-ethyl-2,3-dioxo-3-piperazin-1-yl-propyl)-propionamide,
- 3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[3-(1,1-dioxo-1,6-thiomorpholin-4-yl)-1-ethyl-2,3-dioxo-propyl]-propionamide;
- 5 3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[1-ethyl-3-(4-methyl-sulfonyl-piperazin-1-yl)-2,3-dioxo-propyl]-propionamide,
- 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid dimethylamide,
- 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid cyclopentyl-ethyl-amide,
- 10 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid phenylamide,
- 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid pyridin-3-ylamide,
- 15 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (tetrahydropyran-4-yl)-amide,
- 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (1-benzoyl-piperidin-4-yl)-amide,
- 3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (2-morpholin-4-yl-ethyl)-amide;
- 20 (R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide,
- N*-[1-(benzooxazole-2-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(pyrimidin-2-ylamino)-propionamide
- 25 (R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide,
- (2S) (4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(S)-cyano-3-phenyl-propyl)-amide,
- N*-(1(S)-cyano-3-phenyl-propyl)-2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyramide;
- N*-(1(S)-cyano-3-phenyl-propyl)-2-(S)-fluoro-4-phenyl-butyramide,
- 30 *N*-(1(S)-cyano-3-phenyl-propyl)-2,2-difluoro-4-phenyl-butyramide,
- N*-(1(S)-cyano-3-phenyl-propyl)-2-(S)-hydroxy-4-phenyl-butyramide,
- N*-(1(S)-cyano-3-phenyl-propyl)-2-(R)-hydroxy-4-phenyl-butyramide,
- N*-(1(S)-cyano-3-phenyl-propyl)-2-(R)-methoxy-4-phenyl-butyramide,
- 2,2-difluoro-5-phenyl-pentanoic acid (1-cyano-cyclopropyl)-amide,
- 35 *N*-(1(S)-cyano-3-phenyl-propyl)-4-phenyl-butyramide,

-189-

- 2,2-difluoro-5-phenyl-pentanoic acid ((S)-1-cyano-3-phenyl-propyl)-amide,
N-(4-cyano-1-ethyl-piperidin-4-yl)-3-cyclohexyl-propionamide,
N-(4-cyano-1-ethyl-piperidin-4-yl)-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide,
(S)-tert-butyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,
5 (R)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-(2-difluoromethoxy-phenylmethanesulfonyl)-ethyl
ester,
(S)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester,
(R)-morpholine-4-carboxylic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-phenylmethanesulfonyl-ethyl
ester,
10 (R)-morpholine-4-carboxylic acid 1-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-2-
phenylmethanesulfonyl-ethyl ester,
3-cyclohexyl-2-hydroxy-N-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-propionamide,
(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-
propionamide,
15 (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-
ylamino)-propionamide,
(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide,
(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-
propionamide,
20 (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-
ylamino)-propionamide,
(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-
phenylmethanesulfonyl-propionamide,
(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-
25 phenylmethanesulfonyl-propionamide,
(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-
propionamide,
(S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-
propionamide,
30 (S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide,
(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-
ylamino)-propionamide,
(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-
ylamino)-propionamide,
35 (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-
propionamide,

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide,

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide,

5 (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,

(1S)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-(S)-fluoro-4-phenyl-butyramide,

2,2-difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazole-2-carbonyl)-butyl]-amide,

10 morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-2-cyclohexyl-ethyl ester,

morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-ethyl ester,

morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester,

15 morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester,

morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-3-cyclohexyl-propyl ester,

20 4-[4,4-dimethyl-2-(morpholine-4-carbonyloxy)-pentanoylamino]-3-oxo-azepane-1-carboxylic acid benzyl ester,

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

(R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethanesulfonyl-propionamide;

25 (R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethanesulfonyl-propionamide,

(R)-3-phenylmethanesulfonyl-N-[(S)-3-phenyl-1-(thiazole-2-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide,

30 (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

(R)-3-cyclopropylmethanesulfonyl-N-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide,

(R)-3-phenylmethanesulfonyl-N-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide,

35 (R)-N-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

-191-

- {{(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
carbamic acid tert-butyl ester;
- {{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
carbamic acid tert-butyl ester;
- 5 {{(S)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamic
acid tert-butyl ester;
- {{(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
carbamic acid tert-butyl ester;
- {{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
10 carbamic acid tert-butyl ester;
- {{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-
ethyl}-carbamic acid tert-butyl ester;
- (R)-1-[1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-
phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester;
- 15 ((R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-
propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester;
- {{(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
carbamic acid tert-butyl ester;
- {{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-
20 cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;
- {{(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-
ethyl}-carbamic acid tert-butyl ester;
- {{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-
ethyl}-carbamic acid tert-butyl ester;
- 25 (R)-1-[1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl]-2-
phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester;
- ((R)-2-cyclopropylmethanesulfonyl-1-[(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-
propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester;
- {{(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-
30 carbamic acid tert-butyl ester;
- {{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-
cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;
- {{(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-
ethyl}-carbamic acid tert-butyl ester;
- 35 (R)-2-phenylmethanesulfonyl-1-[(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-
propylcarbamoyl]-ethyl)-carbamic acid tert-butyl ester;

(R)-N-[1-(Benzoxazol-2-carbonyl)-butyl]-2-[cyclopropylmethyl-(tetrahydro-pyran-4-ylmethyl)-amino]-3-phenylmethanesulfonyl-propionamide,

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide,

5 (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide,

10 (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide,

15 (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide,

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide,

20 (S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide;

S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide,

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide,

25 (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

30 (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide,

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide,

35 (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide,

- N*-cyanomethyl-3-cyclohexyl-propionamide,
N-cyanomethyl-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide,
 3-(3-cyclohexyl-propionylamino)-2-oxo-5-phenyl-pentanoic acid thiazol-2-ylamide,
 3-cyclohexyl-*N*-(1-formyl-3-phenyl-propyl)-propionamide,
 5 3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[(*S*)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-propionamide,
N-[(*S*)-1-(benzooxazole-2-carbonyl)-propyl]-2-(2-cyano-phenylamino)-3-cyclohexyl-propionamide,
N-Cyanomethyl-3-cyclohexyl-2-(4-methoxy-phenoxy)-propionamide,
 2-benzyloxy-*N*-cyanomethyl-3-cyclohexyl-propionamide,
 10 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-benzyloxy-3-phenylmethanesulfonyl-propionamide,
 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-methoxymethoxy-3-phenylmethanesulfonyl-propionamide,
 (*S*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-hydroxy-3-phenyl-propionamide,
 15 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-trisopropylsilyloxy-propionamide,
 (*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide,
 (*R*)-2-hydroxy-3-phenylmethanesulfonyl-*N*-[(*S*)-1-(1-pyridazin-3-yl-methanoyl)-butyl]-propionamide,
 20 (*S*)-3-[(*R*)-2-hydroxy-3-phenylmethanesulfonyl-propanoylamino]-2-oxo-pentanoic acid benzylamide,
 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide,
 (*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide, and
 25 (2*R*,5*S*)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl]-6-ethoxy-5-ethyl-morpholin-3-one

- 16 A compound of claim 15 selected from the group consisting of
 morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 31),
 30 morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 11),
 35 morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 14),
 morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 15),
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-194-

pyrrolidine-1-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 19),

5 dimethyl-carbamic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 20),

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 25),

10 morpholine-4-carboxylic acid (*S*)-1-[(*S*)-1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester,

morpholine-4-carboxylic acid (*S*)-1-[(*S*)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

15 (*R*)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-*N*-[(*S*)-1-formyl-propyl]-2-hydroxy-propionamide,

20 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide,

(*S*)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-oxo-pentanoic acid benzylamide,

25 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide,

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide,

30 (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide,

35 (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl propionamide,

(*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide,

40 (*R*)-*N*-[(*S*)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide,

morpholine-4-carboxylic acid (*S*)-2-cyclohexyl-1-[(*S*)-1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propylcarbamoyl]-ethyl ester,

45 (*S*)-3-[(*R*)-2-hydroxy-3-phenylmethanesulfonyl-propanoylamino]-2-oxo-pentanoic acid benzylamide,

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide

17 A pharmaceutical composition comprising a therapeutically effective amount

-195-

of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient

18 A pharmaceutical composition comprising a therapeutically effective amount
5 of a compound of Claim 2 in combination with a pharmaceutically acceptable excipient

19 A method for treating a disease in an animal in which inhibition of Cathepsin S
can prevent, inhibit or ameliorate the pathology and/or symptomology of the
10 disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or Claim 2

20 The use of a compound of Claim 1 or 2 in the manufacture of a medicament for
treating a disease in an animal in which Cathepsin S activity contributes to the
15 pathology and/or symptomology of the disease

109
110

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 December 2002 (12.12.2002)

PCT

(10) International Publication Number
WO 02/098850 A3

(51) International Patent Classification⁷: C07C 317/46, A61K 31/16, A61P 19/02, 33/06, C07C 233/31, 255/29, 255/44, 255/46, 271/12, 271/24, 317/44, C07D 205/04, 207/08, 211/66, 239/08, 263/56, 271/10, C07C 271/16, C07D 223/08, 277/28, 277/64, 277/82, 295/18, 295/20, 333/24, 307/14, 309/14, 413/12, 413/14, 417/12, C07C 317/46, 255/29, 317/44, A61K 31/16, C07C 255/44, C07D 205/04, A61P 19/02, C07C 255/44, C07D 207/08, A61P 33/06, C07C 271/12, C07D 211/66, C07C 233/31, 271/24, C07D 239/08

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(21) International Application Number: PCT/US02/17411

(22) International Filing Date: 3 June 2002 (03.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/295,301 1 June 2001 (01.06.2001) US

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

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

Declaration under Rule 4.17:

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

Published

— with international search report

(88) Date of publication of the international search report:
24 April 2003

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

(54) Title: CHEMICAL COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS AS CATHEPSIN S INHIBITORS

(57) Abstract: The present invention relates to compounds of formula (I) (in which X¹ is -NHC(R¹)(R²)X³ or -NHX⁴ and the other variables are as defined in the claims) and the pharmaceutically acceptable salts and N-oxides thereof, useful as selective cathepsin S inhibitors, their uses as therapeutic agents and the methods for their making. Formula (I)

INTERNATI NAL SEARCH REP RT

Int. Application No
PCT/US 02/17411

111

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C317/46 A61K31/16 A61P19/02 A61P33/06 C07C233/31.
C07C255/29 C07C255/44 C07C255/46 C07C271/12 C07C271/24
C07C317/44 C07D205/04 C07D207/08 C07D211/66 C07D239/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D C07F 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, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 55144 A (AXYS PHARMACEUTICALS) 21 September 2000 (2000-09-21) page 2 -page 7	1-20
A	WO 01 19796 A (AXYS PHARMACEUTICALS) 22 March 2001 (2001-03-22) page 2 -page 4	1-20
A	WO 01 19808 A (AXYS PHARMACEUTICALS) 22 March 2001 (2001-03-22) page 2 -page 4	1-20

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Date of the actual completion of the international search

14 January 2003

Date of mailing of the international search report

30/01/2003

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/56 C07D271/10 C07C271/16 C07D223/08 C07D277/28
C07D277/64 C07D277/82 C07D295/18 C07D295/20 C07D333/24
C07D307/14 C07D309/14 C07D413/12 C07D413/14 C07D417/12

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

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Minimum documentation searched (classification system followed by classification symbols)

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

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"&" document member of the same patent family

Date of the actual completion of the international search

14 January 2003

Date of mailing of the international search report

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/04 C07F7/18

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)

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

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search

14 January 2003

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P. B. 6818 Patentkan 2
NL - 2280 LV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

English, R

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos · 1-15,17,18 (in part)

Present claims 1-13, 17 and 18 relate to an extremely large number of possible compounds or pharmaceutical compositions. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds or pharmaceutical compositions claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples.

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

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

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☒ Claims Nos. because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos. 1-15, 17, 18 (in part) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 02/17411

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0055144	A	21-09-2000	AU 3750700 A	04-10-2000
			BG 105969 A	31-05-2002
			BR 0009044 A	15-01-2002
			CN 1345314 T	17-04-2002
			CZ 20013247 A3	15-05-2002
			EP 1161422 A1	12-12-2001
			HU 0200572 A2	29-06-2002
			NO 20014483 A	01-11-2001
			SK 12872001 A3	09-05-2002
			TR 200103335 T2	22-04-2002
			WO 0055144 A1	21-09-2000
WO 0119796	A	22-03-2001	AU 7490900 A	17-04-2001
			AU 7703300 A	17-04-2001
			EP 1212302 A1	12-06-2002
			WO 0119808 A1	22-03-2001
			WO 0119796 A1	22-03-2001
			US 6492362 B1	10-12-2002
WO 0119808	A	22-03-2001	AU 7490900 A	17-04-2001
			AU 7703300 A	17-04-2001
			EP 1212302 A1	12-06-2002
			WO 0119808 A1	22-03-2001
			WO 0119796 A1	22-03-2001
			US 6492362 B1	10-12-2002

43
114

PCT



To.

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

No ACTION DUE file USA2001/0082-W2

DUE DATE —

DKTD BY JP 5/12/03

ATTY G. WANG

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference US2001/0082	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below	
International application No. PCT/US 02/17411	International filing date (day/month/year) 03/06/2002	(Earliest) Priority Date (day/month/year) 01/06/2001
Applicant AXYS 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 9 sheets.

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

1 Basis of the report

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

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

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

☐ contained in the international application in written form

☐ filed together with the international application in computer readable form

☐ furnished subsequently to this Authority in written form

☐ furnished subsequently to this Authority in computer readable form

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

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

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

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

4 With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows.

CHEMICAL COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS AS CATHEPSIN S INHIBITORS

5 With regard to the abstract,

☐ the text is approved as submitted by the applicant.

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

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

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention

☒ None of the figures



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116

Please forward to

PHOENIX SCANNING

CENTRAL UNIT RECEIVING SECTION

The attached document should be indexed and scanned for PHOENIX
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DocCode ABSTMOD

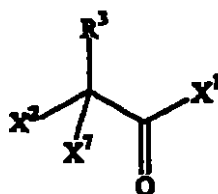
Group PCTISA

Sent by : Eva Bleijs

Date request 22/01/2003

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

The present invention relates to compounds of formula I (in which X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHX^4$ and the other variables are as defined in the claims) and the pharmaceutically acceptable salts and N-oxides thereof, useful as selective cathepsin S inhibitors, their uses as therapeutic agents and the methods for their making



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/17411

118

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C317/46 A61K31/16 A61P19/02 A61P33/06 C07C233/31
C07C255/29 C07C255/44 C07C255/46 C07C271/12 C07C271/24
C07C317/44 C07D205/04 C07D207/08 C07D211/66 C07D239/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D C07F 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, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 55144 A (AXYS PHARMACEUTICALS) 21 September 2000 (2000-09-21) page 2 -page 7	1-20
A	WO 01 19796 A (AXYS PHARMACEUTICALS) 22 March 2001 (2001-03-22) page 2 -page 4	1-20
A	WO 01 19808 A (AXYS PHARMACEUTICALS) 22 March 2001 (2001-03-22) page 2 -page 4	1-20

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

☒ Patent family members are listed in annex.

* Special categories of cited documents

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

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

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

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

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

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

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

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

"Z" document member of the same patent family

Date of the actual completion of the international search

14 January 2003

Date of mailing of the international search report

30/01/2003

Name and mailing address of the ISA

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

Authorized officer

English, R

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/17411

119

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D263/56 C07D271/10 C07C271/16 C07D223/08 C07D277/28
C07D277/64 C07D277/82 C07D295/18 C07D295/20 C07D333/24
C07D307/14 C07D309/14 C07D413/12 C07D413/14 C07D417/12

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

☒ Patent family members are listed in annex.

* Special categories of cited documents

- 'A' document defining the general state of the art which is not considered to be of particular relevance
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- '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.
- 'A' document member of the same patent family

Date of the actual completion of the international search

14 January 2003

Date of mailing of the international search report

Name and mailing address of the ISA

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

Authorized officer

English, R

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/17411

120

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/04 C07F7/18

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

☒ Patent family members are listed in annex.

* Special categories of cited documents

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- "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

14 January 2003

Date of mailing of the International search report

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

Authorized officer

English, R

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I 2

Claims Nos.: 1-15,17,18 (in part)

Present claims 1-13, 17 and 18 relate to an extremely large number of possible compounds or pharmaceutical compositions. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds or pharmaceutical compositions claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples.

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

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

INTERNATI NAL SEARCH REPORT

International application No
PCT/US 02/17411

123

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

- 1 ☒ Claims Nos.
because they relate to subject matter not required to be searched by this Authority, namely
Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition
- 2 ☒ Claims Nos 1-15,17,18 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically
see FURTHER INFORMATION sheet PCT/ISA/210
- 3 ☐ Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/17411

123

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0055144	A	21-09-2000	AU 3750700 A	04-10-2000
			BG 105969 A	31-05-2002
			BR 0009044 A	15-01-2002
			CN 1345314 T	17-04-2002
			CZ 20013247 A3	15-05-2002
			EP 1161422 A1	12-12-2001
			HU 0200572 A2	29-06-2002
			NO 20014483 A	01-11-2001
			SK 12872001 A3	09-05-2002
			TR 200103335 T2	22-04-2002
			WO 0055144 A1	21-09-2000
WO 0119796	A	22-03-2001	AU 7490900 A	17-04-2001
			AU 7703300 A	17-04-2001
			EP 1212302 A1	12-06-2002
			WO 0119808 A1	22-03-2001
			WO 0119796 A1	22-03-2001
			US 6492362 B1	10-12-2002
WO 0119808	A	22-03-2001	AU 7490900 A	17-04-2001
			AU 7703300 A	17-04-2001
			EP 1212302 A1	12-06-2002
			WO 0119808 A1	22-03-2001
			WO 0119796 A1	22-03-2001
			US 6492362 B1	10-12-2002

TRATADO DE COOPERACION EN PATENTES

PCT

REPORTE DE BUSQUEDA INTERNACIONAL

(Artículo 18 y Normas 43 y 44 PCT)

Referencia del solicitante o abogado: US2001/0082

PROCEDIMIENTO ADICIONAL: ver Notificación sobre el envío del Informe de Búsqueda Internacional (Formulario PCT/ISA/220) y, si es relevante, el Punto 5 más abajo

Número de referencia internacional: PCT/US02/17411

Fecha de solicitud internacional: 03/06/2002

Fecha (más antigua) de prioridad: 01/06/2001

Solicitante: AXYS PHARMACEUTICALS, INC.

Este Reporte de Búsqueda Internacional fue elaborado por la Autoridad de Búsqueda y se le envía al solicitante conforme al Artículo 18. Una copia se envía a la Oficina Internacional.

Este Reporte de Búsqueda Internacional contiene 9 hojas.

X Se adjunta además una copia de los documentos respecto al estado de la técnica mencionados en este reporte.

1. Base del Reporte

a. Respecto al idioma, la búsqueda internacional se hizo sobre la base de la solicitud internacional en el idioma en el que ésta fue presentada, en tanto bajo este Punto no se indique otra cosa distinta.

 La Búsqueda Internacional se hizo sobre la base de una traducción de la solicitud internacional presentada ante la Autoridad (Norma 23.1 b).

b. Respecto a la secuencia nucleótida y/o de aminoácidos revelada en la solicitud internacional, la Búsqueda Internacional se hizo sobre la base del protocolo de secuencia que:

- ☐ está contenido en la solicitud internacional en forma escrita.
 - ☐ fue entregado junto con la solicitud internacional en forma legible por computadora.
 - ☐ fue entregado posteriormente a la Autoridad en forma escrita.
 - ☐ fue entregado posteriormente a la Autoridad en forma legible por computadora.
 - ☐ Se presentó la explicación de que el protocolo de secuencia escrito entregado posteriormente no va más allá del contenido revelado de la solicitud internacional en el momento de la solicitud.
 - ☐ Se presentó la explicación de que la informaciones contenidas en la forma legible por computadora corresponden al protocolo de secuencia escrito.
2. ☒ Determinadas reivindicaciones no pudieron ser sometidas a búsqueda (**ver Casilla I**).
3. ☐ Defectuosa unidad de la invención (**ver Casilla II**)
4. Respecto al título de la invención
- ☐ Se acepta el texto presentado por el solicitante.
 - ☒ Esta Autoridad estableció el texto como sigue:
COMPUESTOS QUIMICOS Y COMPOSICIONES FARMACEUTICAS COMO INHIBIDORES DE CATHEPSIN S
5. Respecto al resumen
- ☐ Se acepta el texto presentado por el solicitante.
 - ☒ El solicitante puede presentar su punto de vista a la Autoridad dentro del plazo de un mes luego de la fecha del envío de este reporte de búsqueda internacional.
6. El siguiente dibujo se ha de publicar junto con el resumen: Figura No. ---
- ☐ como lo sugiere el solicitante.
 - ☐ porque el solicitante no sugirió ninguna Figura.
 - ☐ porque esta Figura identifica mejor la invención.
 - ☒ ninguna de las figuras.

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No. PCT/US 02/17411

A. CLASIFICACION DEL ASUNTO

IPC 7 C07317/46 A61K31/16 A61P19/02 A61P33/06 C07C233/31
 C07C255/29 C07C255/44 C07C255/46 C07C271/12 C07C271/24
 C07C317/44 C07D205/04 C07D207/08 C07D211/66 C07D239/08
 C07D263/56 C07D271/10 C07D271/16 C07D223/08 C07D277/28
 C07D277/64 C07D277/82 C07D295/18 C07D295/20 C07D333/24
 C07D307/14 C07D309/14 C07D413/12 C07D413/14 C07D317/12
 C07D498/04 C07F7/18

De acuerdo con la Clasificación Internacional de Patentes (IPC) o
 tanto con la clasificación nacional como con la IPC.

B. AREAS BUSCADAS

Material mínimo de examen sometido a búsqueda (sistema de clasifica-
 ción seguido por símbolos de clasificación):

IPC 7 C07C C07D C07F A61K A61P

Documentación buscada que no hace parte del material mínimo de exa-
 men, si ella pertenece a las áreas buscadas: -

Base de datos electrónica consultada durante la búsqueda internacio-
 nal (nombre de la base de datos, términos de búsqueda usados)

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

C DOCUMENTOS CONSIDERADOS RELEVANTES

<u>Categoría*</u>	<u>Documento</u>	<u>No. de reivindicación relevante</u>
A	WO 00 55144 A (AXYS PHARMACEUTICALS) 21 Septiembre 2000 página 2 - página 7	1-20
A	WO 01 19796 A (AXYS PHARMACEUTICALS) 22 Marzo 2001 página 2 - página 4	1-20
A	WO 01 19808 A (AXYS PHARMACEUTICALS) 22 Marzo 2001 página 2 - página 4	1-20

 En la continuación del Campo C se citan otros documentos

X Ver en Anexo miembros de la familia de patentes

*** Categorías especiales de los documentos citados:**

- "A" Documento que define el estado general de la técnica y que no es considerado como particularmente relevante.
- "E" Documento anterior pero publicado en la fecha de presentación internacional o posteriormente.
- "L" documento que puede hacer aparecer dudosa la reivindicación de prioridad o que se cita para establecerla fecha de publicación de otro documento o por otra razón especial (especificada)
- "O" Documento referente a una revelación oral, un uso, una exhibición u otros medios.
- "P" Documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.
- "T" Documento posterior publicado después de la fecha de presentación internacional o de la fecha de prioridad y que no está en conflicto con la solicitud pero que se cita para comprender el principio o la teoría subyacente a la invención.
- "X" Documento de particular relevancia; la invención reivindicada no puede ser considerada novedosa o no puede ser considerada basada en una actividad inventiva cuando el documento se toma individualmente
- "Y" Documento de particular relevancia; no se puede considerar que la invención reivindicada involucre un paso inventivo cuando el documento se combina con uno o con varios de dichos documentos, siendo tal combinación obvia para las personas que tienen experiencia en este campo de la técnica.
- "Z" Documento miembro de la misma familia de patentes

Fecha de la conclusión de la búsqueda internacional:

14 de Enero del 2003

Fecha de envío del reporte de búsqueda internacional:

30/01/2003

Nombre y dirección postal de la autoridad internacional de búsqueda:

Oficina Europea de Patentes

P.B. 5818 Patentlaan 2

NL - 2280 HV Rijswijk

Funcionario autorizado:

English, R

Solicitud de escaneo	NO usar grapas!
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Por favor enviar a

PHOENIX SCANNING

SECCION DE RECEPCION DE LA UNIDAD CENTRAL

El documento adjunto debe ser incluido en el índice y
escaneado para PHOENIX con el número **XS SA410838 16 MA**

CódigoDoc ABSTMOD

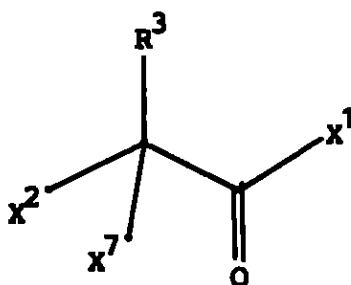
Grupo PCTISA

Enviado por: Eva Bleijs

Fecha solicitud: 22/01/2003

Casilla III**TEXTO DEL RESUMEN** (continuación del punto 5 de la 1ª página)

La presente invención se refiere a compuestos de la fórmula I (en la cual X^1 es $\text{NHC}(\text{R}^1)(\text{R}^2)\text{X}^3$ o $-\text{NHX}^4$ y las otras variables son como se definen en las reivindicaciones) y sus sales farmacéuticamente aceptables y sus N-óxidos, útiles como inhibidores selectivos de cathepsin S, a sus usos como agentes terapéuticos y a los métodos para su preparación.



INFORMACION ADICIONAL

Continuación del Punto I.2

Reivindicaciones No.: 1-15, 17, 18 (en parte)

Las presentes reivindicaciones 1-13, 17 y 18 se refieren a un número sumamente grande de posibles compuestos o composiciones farmacéuticas. Sin embargo, sustento en el sentido del Artículo 6 PCT y/o revelación en el sentido del Artículo 5 PCT se puede encontrar únicamente para una muy pequeña proporción de los compuestos o composiciones farmacéuticas reivindicadas. En el presente caso las reivindicaciones carecen de sustento en forma tal y la solicitud carece de revelación en forma tal que es imposible una búsqueda coherente respecto a la totalidad del campo o alcance reivindicado. Por tanto se ha efectuado la búsqueda para aquellas partes de las reivindicaciones que parecen estar sustentadas y reveladas, a saber aquellas partes referentes a los compuestos preparados en los ejemplos.

El campo o alcance de las reivindicaciones 1-14, en lo que se refiere a las expresiones "prodroga" y "derivados protegidos", es tan poco claro (Artículo 6 PCT) que es imposible una búsqueda internacional coherente respecto a dichas expresiones.

Se llama la atención del solicitante sobre el hecho de que las reivindicaciones o las partes de las reivindicaciones referentes a invenciones respecto a las cuales no se ha establecido una búsqueda internacional no necesitan ser sometidas a un examen preliminar internacional (Norma 66.1(e) PCT). Se le comunica al solicitante que normalmente la política de la Oficina Europea de Patentes al actuar como Autoridad Examinadora Preliminar Internacional es no efectuar un examen preliminar de asuntos que no han sido sometidos a búsqueda. Este es el caso independientemente de si las reivindicaciones son enmendadas o no después del recibo del reporte de búsqueda o durante cualquier procedimiento del Capítulo II.

(Continuación de la 1ª página del Formulario PCT/ISA/210)

Casilla 1

Observaciones cuando ciertas reivindicaciones no pudieron ser sometidas a búsqueda (continuación del Punto 1 de la primera página)

Este Reporte de Búsqueda Internacional no ha sido establecido respecto a ciertas reivindicaciones conforme al Artículo 17(2)(a) por las siguientes razones:

1. X Reivindicaciones No..

porque se refieren a un tema que no es necesario que esta Autoridad someta a búsqueda, a saber:

Aunque la reivindicación 19 se dirige a un método de tratamiento del cuerpo humano/animal, la búsqueda se efectuó y se fundamentó en los pretendidos efectos del compuesto/composición.

2. X Reivindicaciones No.: 1-15, 17, 18 (en parte)

porque se refieren a partes de la Solicitud Internacional que no cumplen con los requisitos establecidos en tal grado que no se efectuó una Búsqueda Internacional coherente, específicamente:

ver INFORMACION ADICIONAL formulario PCT/ISA/210

3. Reivindicaciones No.:

porque son reivindicaciones dependientes y no están redactadas conforme a la segunda y tercera frases de la Norma 6.4(a)

Casilla II

Observaciones cuando falta unidad de la invención (continuación del Punto 3 de la primera página)

Esta Autoridad Internacional encontró múltiples invenciones en esta solicitud internacional, a saber:

1. Todos los honorarios adicionales de búsqueda exigidos fueron pagados oportunamente por el solicitante, este Reporte de Búsqueda Internacional cubre todas las reivindicaciones sometibles a búsqueda

2. Todas las reivindicaciones sometibles a búsqueda fueron sometidas a búsqueda sin un esfuerzo que justifique honorarios adicionales, esta Autoridad no solicitó pago de honorarios adicionales.

3. _ Como el solicitante solamente pagó algunos de los honorarios adicionales de búsqueda exigidos, entonces este Reporte de Búsqueda Internacional cubre únicamente aquellas reivindicaciones para las cuales se pagaron los honorarios, específicamente las reivindicaciones No.: -
4. _ El solicitante no pagó los honorarios adicionales de búsqueda exigidos. Por tanto este Reporte de Búsqueda Internacional se limita a la invención primeramente mencionada en las reivindicaciones; dicha invención es cubierta por las reivindicaciones No.: -

Observaciones sobre la protesta

- _ A la protesta del solicitante se adjuntaron los honorarios de búsqueda adicionales
- _ Al pago de los honorarios de búsqueda adicionales no se le adjuntó protesta alguna

REPORTE DE BUSQUEDA INTERNACIONAL

Información sobre miembros de la familia de patentes

Solicitud internacional No. PCT/US 02/17411

Documento Patente citado en el reporte de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
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(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL
TRATADO DE COOPERACIÓN DE PATENTES (PCT)

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

(43) Fecha de Publicación Internacional
12 Diciembre 2002 (12 12 2002)

PCT

(10) Número de Publicación Internacional
WO 02/098850 A3

-
- (51) Clasificación Internacional de Patentes C07C 317/46, A61K 31/16, A61P 19/02, A61P 19/02, 33/06, C07C 233/31, 255/29, 255/44, 255/46, 271/12, 271/24, 317/44, C07D 205/04, 207/08, 211/66, 239/08, 263/56, 271/10, C07C 271/16, C07D 223/08, 277/28, 277/64, 277/82, 295/18, 295/20, 333/24, 307/14, 309/14, 413/12, 413/14, 417/12, C07C 317/46, 255/29, 317/44, A61K 31/16, C07C 255/44, C07D 207/08, A61P 33/05, C07C 271/12, C07D 211/66, C07C 233/31, 271/24, C07D 239/08
- (21) Número de Solicitud Internacional PCT/EP02/17411
- (22) Fecha de Presentación Internacional 3 Junio 2002 (03 06 2002)
- (25) Idioma de Presentación Inglés
- (26) Idioma de Publicación Inglés
- (30) Datos de Prioridad
60/295, 301 1 Junio 2001 (01 06 2001) US
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- (81) Estados Designados (nacional) AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW
- (84) Estados Designados (regional) ARIPO patente (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Declaración bajo la Regla 4 17

de relación de inventores (Regla 4 17(iv)) solo para US

Publicada

- con reporte de búsqueda internacional

- (88) Fecha de publicación del reporte de búsqueda internacional
24 Abril 2003

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

(54) Título COMPUESTOS QUÍMICOS Y COMPOSICIONES FARMACÉUTICAS COMO INHIBIDORES DE CATEPSINA S

(57) Extracto La presente invención se relaciona con compuestos de fórmula (I) (donde X^1 es $-NHC(R^1)(R^2)X^3$ o $-NHX^4$ y las otras variables son como se definieron en las reivindicaciones) y sus sales y N-óxidos farmacéuticamente aceptables, útiles como inhibidores selectivos de catepsina S, sus usos como agentes terapéuticos y los métodos para su elaboración Fórmula (I)

NUEVOS COMPUESTOS Y COMPOSICIONES COMO INHIBIDORES DE LAS CATEPSINAS

LA INVENCION

Esta Solicitud está basada en, y reivindica prioridad con respecto a la Solicitud de Patente Provisional S N US 60/295 301, presentada el 1 de junio de 2001, que se incorpora en la presente por referencia

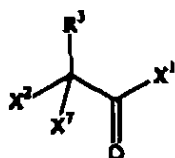
Esta Solicitud se refiere a compuestos y composiciones para el tratamiento de enfermedades asociadas con actividad de cisteína-proteasas, en particular enfermedades asociadas con actividad de catepsina S

DESCRIPCION DEL CAMPO

Las cisteína-proteasas representan una clase de peptidasas caracterizadas por la presencia de un residuo cisteína en el sitio catalítico de la enzima. Las cisteína-proteasas están asociadas con la degradación y el procesamiento normales de las proteínas. Sin embargo, la actividad aberrante de las cisteína-proteasas, v g, como resultado del incremento de la expresión o la activación aumentada, puede tener consecuencias patológicas. En este sentido, ciertas cisteína-proteasas están asociadas con cierto número de estados de enfermedad, que incluyen artritis, distrofia muscular, inflamación, invasión de tumores, glomerulonefritis, malaria, enfermedad periodontal, leucodistrofia metacromática y otras. Un aumento en la actividad de catepsina S contribuye a la patología y/o sintomatología de cierto número de enfermedades. De acuerdo con ello, las moléculas que inhiben la actividad de la proteasa catepsina S son útiles como agentes terapéuticos en el tratamiento de tales enfermedades.

SUMARIO DE LA INVENCION

Esta Solicitud se refiere a compuestos de Fórmula I



I

en la cual

X¹ es -NHC(R¹)(R²)X³ o -NHX⁴,

X² es hidrógeno, fluoro, -OH, -OR⁴, -NHR¹⁵ o -NR¹⁷R¹⁸ y X⁷ es hidrógeno o X² y X⁷ representan ambos fluoro,

X³ es ciano, -C(R⁷)(R⁸)R¹⁶, -C(R⁶)(OR⁶)₂, -CH₂C(O)R¹⁶, -CH=CHS(O)₂R⁵, -C(O)CF₂C(O)NR⁵R⁵, -C(O)C(O)NR⁵R⁶, -C(O)C(O)OR⁵, -C(O)CH₂OR⁵, -C(O)CH₂N(R⁶)SO₂R⁵ o -C(O)C(O)R⁵, en cuyas fórmulas R⁵ es hidrógeno, (C₁-₄)alquilo,

(C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₀₋₃)alquilo, (C₆₋₁₀)aril(C₀₋₆)alquilo, hetero(C₅₋₁₀)aril(C₀₋₆)alquilo, (C₉₋₁₀)bicicloaril(C₀₋₆)alquilo o hetero(C₈₋₁₀)bicicloaril(C₀₋₆)alquilo, R⁶ es hidrógeno, hidroxilo o (C₁₋₆)alquilo, o donde X³ contiene un grupo -NR⁵R⁶, R⁵ y R⁶ junto con el átomo de nitrógeno al cual están unidos ambos, forman hetero(C₃₋₁₀)cicloalquilo, hetero(C₅₋₁₀)arilo o hetero(C₈₋₁₀)bicicloarilo, R⁷ es hidrógeno o (C₁₋₄)alquilo y R⁸ es hidroxilo o R⁷ y R⁸ forman juntos oxo, R¹⁶ es hidrógeno, -X⁴, -CF₃, -CF₂CF₂R⁹ o -N(R⁶)OR⁶, R⁹ es hidrógeno, halo, (C₁₋₄)alquilo, (C₅₋₁₀)aril(C₀₋₆)alquilo o (C₅₋₁₀)heteroaril(C₀₋₆)alquilo, con la salvedad de que cuando X³ es ciano, entonces X² es hidrógeno, fluoro, -OH, -OR⁴ o -NR¹⁷R¹⁸ y X⁷ es hidrógeno o X² y X⁷ representan ambos fluoro,

X⁴ comprende un anillo heteromonocíclico que contiene 4 a 7 átomos miembros de anillo o un sistema de anillos heterobicíclico condensado que contiene 8 a 14 átomos miembros de anillo y cualquier derivado carbocíclico cetona, iminocetona o tiocetona de los mismos, con la salvedad de que cuando -X⁴ es distinto de un anillo heteromonocíclico que contiene 5 átomos miembros de anillo, en el cual no más de dos de los átomos miembros de anillo que comprende el anillo son heteroátomos, entonces X² es fluoro, -OH, -OR⁴, -NHR¹⁵ o -NR¹⁷R¹⁸ y X⁷ es hidrógeno o X² y X⁷ representan ambos fluoro,

en la cual dentro de R⁵, X³ o X⁴ cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C₁₋₆)alquilo, (C₁₋₆)alquilideno, ciano, halo, (C₁₋₄)alquilo sustituido con halo, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S-(O)₂N-R¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)-(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³ y -X⁵S(O)₂R¹³ y/o 1 radical seleccionado de -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S-(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹²R¹², -X⁵S(O)₂N-R¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² y -X⁵NR¹²C(NR¹²)N-R¹⁴R¹², en cuyas fórmulas X⁵ es un enlace o (C₁₋₆)alquileno, R¹² es en cada aparición independientemente hidrógeno, (C₁₋₆)alquilo o (C₁₋₆)alquilo sustituido con halo, R¹³ es (C₁₋₆)alquilo o (C₁₋₆)alquilo sustituido con halo, y R¹⁴ es (C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, hetero- (C₃₋₁₀)cicloalquil(C₀₋₃)alquilo, (C₆₋₁₀)aril(C₀₋₆)alquilo, hetero(C₅₋₁₀)aril(C₀₋₆)alquilo, (C₉₋₁₀)bicicloaril(C₀₋₆)alquilo o hetero(C₈₋₁₀)bicicloaril(C₀₋₆)alquilo,

R¹ es hidrógeno o (C₁₋₆)alquilo y R² se selecciona de un grupo constituido por hidrógeno, ciano, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -R¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵N-R¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹²,

$-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$,
 $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$,
 $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$,
 $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$,
 $-X^5S(O)_2N-R^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})N-R^{14}R^{12}$, en
cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto
con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-8}) cicloalquileno o
 (C_{3-8}) heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroarilo, arilo,
cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituido o
sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo,
 (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$,
 $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$,
 $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$,
 $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$,
 $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13}
son como se define arriba,

R^3 es (C_{1-6}) alquilo o $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y
 X^6 se selecciona de $-X^5N-R^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$,
 $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$,
 $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2N-R^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$,
 $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$,
 $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$,
 $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$,
 $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en
cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^4 se selecciona de $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8N-R^{12}C(O)OR^{12}$,
 $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8O-R^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$,
 $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$,
 $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$,
 $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$,
 $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$,
 $-X^8S(O)_2NR^{14}R^{12}$, $-X^8N-R^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ y $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$, en
cuyas fórmulas X^8 es (C_{1-6}) alquileno y X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, con la
salvedad de que cuando X^3 es ciano y X^2 es $-OR^4$, donde R^4 se define como $-R^{14}$, entonces R^{14}
es (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero- (C_{3-10}) cicloalquil (C_{1-3}) alquilo,
 (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{3-10}) aril (C_{1-6}) alquilo, (C_{9-10}) bicicloaril (C_{1-6}) alquilo o

hetero(C₈₋₁₀)bícicloaril(C₁₋₆)alquilo,

R¹⁵ es (C₆₋₁₀)arilo, hetero(C₅₋₁₀)arilo, (C₉₋₁₀)bíciclo-arilo o hetero(C₈₋₁₀)bícicloarilo,

R¹⁷ es (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₀₋₃)alquilo, (C₆₋₁₀)aril(C₀₋₆)alquilo, hetero(C₅₋₁₀)aril(C₀₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₀₋₆)alquilo o hetero(C₈₋₁₀)bícicloaril(C₀₋₆)alquilo, con la salvedad de que cuando X³ es ciano, entonces R¹⁷ es (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, (C₆₋₁₀)aril(C₁₋₆)alquilo, hetero(C₅₋₁₀)aril(C₁₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₁₋₆)alquilo o hetero(C₈₋₁₀)bícicloaril(C₁₋₆)alquilo,

R¹⁸ es hidrógeno, (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, (C₆₋₁₀)aril(C₀₋₆)alquilo, hetero(C₅₋₁₀)aril(C₀₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₀₋₆)alquilo o hetero(C₈₋₁₀)bícicloaril(C₀₋₆)alquilo, con la salvedad de que cuando X³ es ciano, entonces R¹⁸ es (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, (C₆₋₁₀)aril(C₁₋₆)alquilo, hetero(C₅₋₁₀)aril(C₁₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₁₋₆)alquilo o hetero(C₈₋₁₀)bícicloaril(C₁₋₆)alquilo, y

en la cual dentro de R³, R⁴, R¹⁵, R¹⁷ y R¹⁸ cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C₁₋₆)alquilo, (C₁₋₆)alquilideno, ciano, halo, (C₁₋₄)alquilo sustituido con halo, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵C(O)R¹³ y -X⁵S(O)₂R¹³ y/o 1 radical seleccionado de -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂N-R¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² y -X⁵NR¹²C(NR¹²)N-R¹⁴R¹², y dentro de R³ y R⁴ cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, -NR¹²R¹², -NR¹²C(O)R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹², -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)R¹², -OC(O)R¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -NR¹²S(O)₂R¹², -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³ y -S(O)₂R¹³, en cuyas fórmulas X⁵, R¹², R¹³ y R¹⁴ son como se describe arriba, con la salvedad de que cuando X³ es ciano y X² es -OR⁴, donde R⁴ se define como -R¹⁴, o -NHR¹⁸, entonces cualquier sistema aromático de anillos presente dentro de R¹⁴ o R¹⁸ no está sustituido adicionalmente con halo, (C₃₋₁₀)cicloalquilo, hetero(C₃₋₁₀)cicloalquilo, (C₆₋₁₀)arilo, hetero(C₅₋₁₀)arilo, (C₉₋₁₀)bícicloarilo o hetero(C₈₋₁₀)bícicloarilo, con la salvedad de que solamente está presente una estructura bicíclica de anillos dentro de R³, R⁴ o R¹⁵, y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y

mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y sus derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

Un segundo aspecto de la invención es una composición farmacéutica que contiene un compuesto de Fórmula I o sus derivados N-óxido, isómeros individuales o mezclas de isómeros del mismo, o sus sales farmacéuticamente aceptables, en mezcla con uno o más excipientes adecuados

Un tercer aspecto de la invención es un método para tratar una enfermedad en un animal en el cual la inhibición de la catepsina S puede prevenir, inhibir o mejorar la patología y/o la sintomatología de la enfermedad, método que comprende administrar al animal una cantidad terapéuticamente eficaz de un compuesto de Fórmula I o un derivado N-óxido, isómero individual o mezclas de isómeros del mismo, o una sal farmacéuticamente aceptable del mismo

Un cuarto aspecto de la invención es el proceso para preparar compuestos de Fórmula I y sus derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales farmacéuticamente aceptables de los mismos

DESCRIPCIÓN DETALLADA DE LA INVENCION

Definiciones

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

"Alicíclico" significa un resto caracterizado por la disposición de los átomos de carbono en estructuras cerradas de anillos no aromáticos que tienen propiedades que se asemejan a las de los alifáticos y pueden ser saturados o parcialmente insaturados con dos o más enlaces dobles o triples

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

"Alquilo", representado por sí mismo, significa un radical alifático lineal o ramificado, saturado o insaturado, que tiene el número de átomos de carbono indicado (v g , (C₁₋₆)alquilo 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 análogos) Alquilo representado junto con otro radical (v g como en arilalquilo) significa un radical alifático bivalente lineal o ramificado, saturado o insaturado, que tiene el número de átomos indicado o, cuando no se indica átomo alguno, significa un

140
141

enlace (v g., (C₆₋₁₀)aril(C₀₋₃)alquilo incluye fenilo, bencilo, fenetilo, 1-feniletilo, 3-fenilpropilo, y análogos)

"Alquileno", a no ser que se indique otra cosa, significa un radical alifático bivalente lineal o ramificado, saturado o insaturado, que tiene el número de átomos de carbono indicado (v g., (C₁₋₆)alquileno incluye metileno (-CH₂-), etileno (-CH₂CH₂-), trimetileno (-CH₂-CH₂CH₂-), tetrametileno (-CH₂CH₂CH₂CH₂-), 2-butenileno (-CH₂CH=CHCH₂-), 2-metiltetrametileno (-CH₂CH(CH₃)CH₂CH₂-), pentametileno (-CH₂CH₂CH₂CH₂CH₂-) y análogos)

"Alquilideno" significa un radical alifático bivalente lineal o ramificado, saturado o insaturado, que tiene el número de átomos de carbono indicado (v g. (C₁₋₆)alquilideno incluye metilideno (=CH₂), etilideno (=CHCH₃), isopropilideno (=C(CH₃)₂), propilideno (=CHCH₂CH₃), alilideno (=CHCH=CH₂), y análogos)

"Amino" significa el radical -NH₂. A no ser que se indique otra cosa, los compuestos de la invención que contienen restos amino incluyen derivados protegidos de los mismos. Grupos protectores adecuados para restos amino incluyen acetilo, *tert*-butoxicarbonilo, benciloxicarbonilo, y análogos

"Animal" incluye humanos, mamíferos no humanos (v g., perros, gatos, conejos, bovinos, caballos, ovejas, cabras, cerdos, ciervos, y análogos) y no mamíferos (v g., aves, y análogos)

"Aromático" significa un resto en el cual los átomos constituyentes forman un sistema de anillo insaturado, en el cual todos los átomos del sistema de anillos presentan hibridación sp^2 y el número total de electrones π es igual a $4n+2$

"Arilo" significa un ensamblaje de anillos monocíclico o bicíclico condensado que contiene el número total de átomos de carbono del anillo indicados, en el cual cada anillo está constituido por 6 átomos de carbono del anillo y es aromático o, cuando está condensado con un segundo anillo, forma un ensamblaje aromático de anillos. Por ejemplo, (C₆₋₁₀)arilo opcionalmente sustituido tal como se utiliza en esta Solicitud incluye, pero sin carácter limitante, bifenil-2-ilo, 2-bromofenilo, 2-bromocarbonilfenilo, 2-bromo-5-fluorofenilo, 4-*tert*-butilfenilo, 4-carbamoylfenilo, 4-carboxi-2-nitrofenilo, 2-clorofenilo, 4-clorofenilo, 3-clorocarbonilfenilo, 4-clorocarbonilfenilo, 2-cloro-4-fluorofenilo, 2-cloro-6-fluorofenilo, 4-cloro-2-nitrofenilo, 6-cloro-2-nitrofenilo, 2,6-dibromofenilo, 2,3-diclorofenilo, 2,5-diclorofenilo, 3,4-diclorofenilo, 2-difluorometoxifenilo, 3,5-dimetilfenilo, 2-etoxycarbonilfenilo, 2-fluorofenilo, 2-yodofenilo, 4-isopropilfenilo, 2-metoxifenilo, 4-metoxifenilo, 2-metilfenilo, 3-metilfenilo, 4-metilfenilo, 5-metil-2-nitrofenilo, 4-metilsulfonilfenilo, naft-2-ilo, 2-nitrofenilo, 3-nitrofenilo, 4-nitrofenilo, 2,3,4,5,6-pentafluorofenilo, fenilo, 2-trifluorometoxifenilo, 3-trifluorometoxifenilo,

4-trifluorometoxifenilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-trifluorometilsulfanilfenilo, 4-trifluorometilsulfanilfenilo, y análogos (C₆₋₁₀)anilo opcionalmente sustituido, tal como se utiliza en esta Solicitud, incluye 3-acetilfenilo, 3-*tert*-butoxicarbonilaminometilfenilo, bifenil-4-ilo, 3-hidroxifenilo, 4-hidroxifenilo, 3-metoxifenilo, naft-2-ilo, 3-fenoxifenilo, fenilo, y análogos

"Bicicloarilo" significa un ensamblaje bicíclico de anillos que contiene el número de átomos de carbono del anillo indicados, en el cual los anillos están enlazados por un enlace simple o condensados y al menos uno de los anillos que comprende el ensamblaje es aromático, y cualquier derivado carbocíclico cetona, tiocetona o iminocetona del mismo (v g , (C₉₋₁₀)bicicloarilo incluye ciclohexilfenilo, 1,2-dihidronaftilo, 2,4-dioxo-1,2,3,4-tetrahidronaftilo, indanilo, indenilo, 1,2,3,4-tetrahidronaftilo, y análogos)

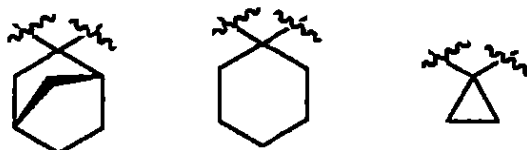
"Carbamofilo" significa el radical -C(O)NH₂ A no ser que se indique otra cosa, los compuestos de la invención que contienen restos carbamofilo incluyen derivados protegidos de los mismos Grupos protectores adecuados para restos carbamofilo incluyen acetilo, *tert*-butoxicarbonilo, benciloxicarbonilo, y análogos, y tanto los derivados no protegidos como los derivados protegidos están comprendidos dentro del alcance de la invención

"Derivado carbocíclico cetona" significa un derivado que contiene el resto -C(O)-

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

"Cicloalquilo" significa un ensamblaje de anillos monocíclico, bicíclico condensado o policíclico puenteado saturado o parcialmente insaturado, que contiene el número de átomos de carbono indicado, y cualquier derivado carbocíclico cetona, tiocetona o iminocetona del mismo (v g , (C₃₋₁₀)cicloalquilo 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 análogos

"Cicloalquileno" significa un anillo monocíclico o un ensamblaje policíclico de anillos puenteado bivalente, saturado o parcialmente insaturado, que contiene el número de átomos de carbono del anillo indicados, y cualquier derivado carbocíclico cetona, tiocetona o iminocetona del mismo Por ejemplo, el caso en que "R¹ y R² junto con el átomo de carbono al cual están unidos a la vez R¹ y R² forman (C₃₋₈)cicloalquileno" incluye, pero sin carácter limitante, lo siguiente



"Enfermedad" incluye específicamente cualquier condición malsana de un animal o parte del mismo e incluye una condición morbosa que puede estar causada por, o que puede ser incidencia de, una terapia médica o veterinaria aplicada a dicho animal, es decir, los "efectos secundarios" de dicha terapia.

"Halo" significa fluoro, cloro, bromo o yodo

"Alquilo sustituido con halo", como un grupo aislado o parte de un grupo mayor, significa "alquilo" sustituido con uno o más átomos "halo", como se definen dichos términos en esta Solicitud. Alquilo sustituido con halo incluye haloalquilo, dihaloalquilo, trihaloalquilo, perhaloalquilo y análogos (v.g. (C₁₋₃)alquilo sustituido con halo incluye clorometilo, diclorometilo, difluorometilo, trifluorometilo, 2,2,2-trifluoroetilo, perfluoroetilo, 2,2,2-trifluoro-1,1-dicloroetilo, y análogos)

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

"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 heteroatómico seleccionado de -N=, -NR-, -O-, -S- o -S(O)₂-, donde R es hidrógeno o (C₁₋₆)alquilo. Por ejemplo, el caso en que "R¹ y R² junto con el átomo de carbono al cual están unidos a la vez R¹ y R² forman hetero(C₃₋₈)cicloalquilo" incluye, pero sin carácter limitante, lo siguiente



donde R es hidrógeno, (C₁₋₆)alquilo, o un grupo protector

"Heteroarilo" significa arilo, 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 heteroatómico seleccionado de -N=, -NR-, -O- o -S-, donde R es hidrógeno, (C₁₋₆)alquilo, un grupo protector o representa la valencia libre que sirve como punto de unión a un nitrógeno del anillo, y cada anillo está constituido por 5 ó 6 átomos de anillo. Por ejemplo,

hetero(C₃₋₁₀)arilo opcionalmente sustituido tal como se utiliza en esta Solicitud incluye, pero sin carácter limitante, 4-amino-2-hidroxipirimidin-5-ilo, benzotiazol-2-ilo, 1*H*-benzimidazol-2-ilo, 2-bromopirid-5-ilo, 5-bromopirid-2-ilo, 4-carbamoyltiazol-2-ilo, 3-carboxipirid-4-ilo, 5-carboxi-2,6-dimetilpirid-3-ilo, 3,5-dimetilisoxazol-4-ilo, 5-etoxi-2,6-dimetilpirid-3-ilo, 5-fluoro-6-hidroxipirimidin-4-ilo, fur-2-ilo, fur-3-ilo, 5-hidroxi-4,6-dimetilpirid-3-ilo, 8-hidroxi-5,7-dimetilquinolin-2-ilo, 5-hidroximetilisoxazol-3-ilo, 3-hidroxi-6-metilpirid-2-ilo, 3-hidroxipirid-2-ilo, 1*H*-imidazol-2-ilo, 1*H*-imidazol-4-ilo, 1*H*-indol-3-ilo, isotiazol-4-ilo, isoxazol-4-ilo, 2-metilfur-3-ilo, 5-metilfur-2-ilo, 1-metil-1*H*-imidazol-2-ilo, 5-metil-3-*H*-imidazol-4-ilo, 5-metilisoxazol-3-ilo, 5-metil-2*H*-pirazol-3-ilo, 3-metilpirid-2-ilo, 4-metilpirid-2-ilo, 5-metilpirid-2-ilo, 6-metilpirid-2-ilo, 2-metilpirid-3-ilo, 2-metiltiazol-4-ilo, 5-nitropirid-2-ilo, 2*H*-pirazol-3-ilo, 3*H*-pirazol-4-ilo, piridazin-3-ilo, pirid-2-ilo, pirid-3-ilo, pirid-4-ilo, 5-pirid-3-il-2*H*-[1,2,4]tiazol-3-ilo, pirimidin-4-ilo, pirimidin-5-ilo, 1*H*-pirrol-3-ilo, quinolin-2-ilo, 1*H*-tetrazol-5-ilo, tiazol-2-ilo, tiazol-5-ilo, tien-2-ilo, tien-3-ilo, 2*H*-[1,2,4]triazol-3-ilo, 3*H*-[1,2,3]triazol-4-ilo, 5-trifluorometilpirid-2-ilo, y análogos Grupos protectores adecuados incluyen *tert*-butoxicarbonilo, benciloxycarbonilo, bencilo, 4-metoxibencilo, 2-nitrobencilo, y análogos Hetero(C₃₋₁₀)arilo opcionalmente sustituido tal como se utiliza en esta Solicitud para definir R⁴ incluye benzofur-2-ilo, fur-2-ilo, fur-3-ilo, pirid-3-ilo, pirid-4-ilo, quinol-2-ilo, quinol-3-ilo, tien-2-ilo, tien-3-ilo, y análogos

"Heterobicicloarilo" significa bicicloarilo, 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 heteroatómico seleccionado de -N=, -NR-, -O- o -S-, donde R es hidrógeno, (C₁₋₆)alquilo, un grupo protector o representa la valencia libre que sirve como el punto de unión a un nitrógeno del anillo, y cualquier derivado carbocíclico cetona, tiocetona o iminocetona del mismo Por ejemplo, hetero(C₃₋₁₀)bicicloarilo opcionalmente sustituido tal como se utiliza en esta Solicitud incluye, pero sin carácter limitante, 2-amino-4-oxo-3,4-dihidropteridinil-6-ilo, y análogos En general, el término heterobicicloarilo tal como se utiliza en esta Solicitud incluye, por ejemplo, benzo[1,3]dioxol-5-ilo, 3,4-dihidro-2*H*-[1,8]naftiridin-ilo, 3,4-dihidro-2*H*-quinolinilo, 2,4-dioxo-3,4-dihidro-2*H*-quinazolinilo, 1,2,3,4,5,6-exahidro[2,2']-bipiridin-ilo, 3-oxo-2,3-dihidrobenczo[1,4]oxazinilo, 5,6,7,8-tetrahydroquinolinilo, y análogos

"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 heteroatómico seleccionado de -N=, -NR-, -O- o -S-, donde R es hidrógeno, (C₁₋₆)alquilo, un grupo protector o representa la valencia libre que sirve como el punto de unión a un nitrógeno de anillo, y cualquier derivado carbocíclico cetona, tiocetona o

144
145

iminocetona del mismo (v g , el término hetero(C₃₋₁₀)cicloalquilo incluye imidazolidinilo, morfolinilo, piperazinilo, piperidilo, pirrolidinilo, pirrolinilo, quinucidinilo, y análogos) Grupos protectores adecuados incluyen *tert*-butoxicarbonilo, benciloxicarbonilo, bencilo, 4-metoxibencilo, 2-nitrobencilo, y análogos Tanto los derivados no protegidos como los derivados protegidos están comprendidos dentro del alcance de la invención

"Anillo heteromonocíclico" significa un ensamblaje de anillos monocíclico saturado o parcialmente insaturado que tiene el número de átomos de carbono del anillo indicados, 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 uno o más heteroátomos seleccionados de -N=, -NY³-, -O- o -S-, donde Y³ es hidrógeno, alquilo, arilo, arilalquilo, -C(=O)-R¹⁴, -C(=O)OR¹⁴ o -SO₂R¹⁴

"Anillo heterobicíclico" significa un anillo bicíclico condensado o policíclico puenteado, saturado o parcialmente insaturado, que tiene el número de átomos de carbono del anillo indicados, 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 uno o más heteroátomos seleccionados de -N=, -NY³-, -O- o -S-, donde Y³ es hidrógeno, alquilo, arilo, arilalquilo, -C(=O)-R¹⁴, -C(=O)-OR¹⁴ o -SO₂R¹⁴

"Hidroxil" significa el radical -OH A no ser que se indique otra cosa, los compuestos de la invención que contienen radicales hidroxil incluyen derivados protegidos de los mismos Grupos protectores adecuados para restos hidroxil incluyen bencilo y análogos

"Derivado iminocetona" significa un derivado que contiene el resto -C(NR)-, donde R es hidrógeno o (C₁₋₆)alquilo

"Isómeros" significan compuestos de Fórmula I que tienen fórmulas moleculares idénticas pero difieren en la naturaleza o secuencia de enlace de sus átomos o en la disposición de sus átomos en el espacio Los isómeros que difieren en la disposición de sus átomos en el espacio se denominan "estereoisómeros" Los estereoisómeros que no son imágenes especulares uno de otro se denominan "diastereoisómeros" y los estereoisómeros que son imágenes especulares no superponibles se denominan "enantiómeros" o a veces "isómeros ópticos" Un átomo de carbono enlazado a cuatro sustituyentes no idénticos se denomina un "centro quiral" Un compuesto con un centro quiral tiene dos formas enantiómeras de quiralidad opuesta y se denomina una "mezcla racémica" Un compuesto que tiene más de un centro quiral tiene 2ⁿ⁻¹ pares enantioméricos, donde n es el número de centros quirales Los compuestos con más de un centro quiral pueden existir como un diastereoisómero individual o como una mezcla de diastereoisómeros, denominada una "mezcla diastereoisómera" Cuando está presente un solo centro quiral, un estereoisómero puede caracterizarse por la configuración absoluta de dicho centro quiral La configuración

absoluta hace referencia a la disposición en el espacio de los sustituyentes unidos al centro quiral. Los enantiómeros se caracterizan por la configuración absoluta de sus centros quirales y se describen por las reglas de secuenciación *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 (v.g. véase "Advanced Organic Chemistry", 4ª edición, March, Jerry, John Wiley & Sons, Nueva York, 1992). Debe entenderse que los nombres y las ilustraciones utilizados en esta Solicitud para describir los compuestos de Fórmula I tienen por objeto abarcar todos los estereoisómeros posibles. Así, por ejemplo, debe entenderse que el nombre *N*-[1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida incluye (*S*)-*N*-[1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida, (*R*)-*N*-[1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida, (*R*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida, (*S*)-*N*-[(*R*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida, (*R*)-*N*-[(*R*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida, *N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida, *N*-[(*R*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida, (*S*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida, y cualquier mezcla, racémica o de otro tipo, de los mismos.

"Derivado cetona" significa un derivado que contiene el resto -C(O)-. Por ejemplo, en esta Solicitud X^3 puede ser 2-acetoxiazetidín-3-ilo. El "derivado cetona carbo-cíclico" de este ejemplo de X^3 sería 2-acetoxi-4-oxoazetidín-3-ilo (véase Tabla 3, C32).

"Nitro" significa el radical -NO₂.

"Opcional" u "opcionalmente" significa que el suceso o circunstancia descrito a continuación puede ocurrir o no, y que la descripción incluye casos en los cuales el suceso o circunstancia ocurre y casos en los que no lo hace. Por ejemplo, la frase "en la cual dentro de R³ y R⁴ cualquier sistema de anillos alicíclico o aromático puede estar sustituido adicionalmente con 1-5 radicales" significa que R³ y R⁴ pueden estar sustituidos o no para caer dentro del alcance de la invención.

"Oxoalquilo" significa alquilo, como se define arriba, en el cual uno del número de átomos de carbono indicado está reemplazado por un grupo oxígeno (-O-), v.g., oxo(C₂₋₆)alquilo incluye metoximetilo, etc.

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

farmacológica deseada

La "patología" de una enfermedad significa la naturaleza esencial, las causas y el desarrollo de la enfermedad, así como los cambios estructurales y funcionales que son resultado de los procesos de la enfermedad

"Farmacéuticamente aceptable" significa aquello que es útil en la preparación de una composición farmacéutica que es generalmente segura, no tóxica y que no es indeseable biológicamente ni desde ningún otro punto de vista, e incluye aquello que es aceptable para uso veterinario así como para uso farmacéutico humano

"Sales farmacéuticamente aceptables" significa sales de los compuestos de Fórmula I que son aceptables desde el punto de vista farmacéutico, como se define arriba, y que poseen la actividad farmacológica deseada. Dichas sales incluyen sales de adición de ácido formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y análogos, o con ácidos orgánicos tales como ácido acético, ácido propiónico, ácido hexanoico, ácido heptanoico, ácido ciclopentanopropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido malónico, ácido succínico, ácido málico, ácido maleico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido *o*-(4-hidroxibenzoil)benzoico, ácido cinámico, ácido mandélico, ácido metanosulfónico, ácido etanosulfónico, ácido 1,2-etanodisulfónico, ácido 2-hidroxietanosulfónico, ácido bencenosulfónico, ácido *p*-clorobencenosulfónico, ácido 2-naftalenosulfónico, ácido *p*-toluenosulfónico, ácido canfosulfónico, ácido 4-metilbicyclo[2.2.2]oct-2-eno-1-carboxílico, ácido glucoheptónico, ácido 4,4'-metilenobis(3-hidroxi-2-eno-1-carboxílico), ácido 3-fenilpropiónico, ácido tri-metilacético, ácido *tert*-butilacético, ácido lauril-sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico y análogos

Las sales farmacéuticamente aceptables incluyen también sales de adición de base que pueden formarse cuando los protones ácidos presentes son capaces de reaccionar con bases inorgánicas u orgánicas. Bases inorgánicas aceptables incluyen hidróxido de sodio, carbonato de sodio, hidróxido de potasio, hidróxido de aluminio e hidróxido de calcio. Bases orgánicas aceptables incluyen etanolamina, dietanolamina, trietanolamina, trometamina, *N*-metilglucamina y análogas

"Profármaco" significa un compuesto que puede convertirse in vivo por medios metabólicos (v.g. por hidrólisis) en un compuesto de Fórmula I. Por ejemplo, un éster de un compuesto de Fórmula I que contiene un grupo hidroxilo puede ser convertible por hidrólisis in vivo en la molécula originaria. Alternativamente, un éster de un compuesto de Fórmula I que contiene un grupo carboxilo puede ser convertible por hidrólisis in vivo en la molécula originaria. Ésteres adecuados de compuestos de Fórmula I que contienen un grupo hidroxilo,

son por ejemplo acetatos, citratos, lactatos, tartratos, malonatos, oxalatos, salicilatos, propionatos, succinatos, fumaratos, maleatos, metileno-bis-b-hidroxinaftoatos, gentisatos, isetionatos, di-*p*-toluilitartratos, metanosulfonatos, etanosulfonatos, bencenosulfonatos, *p*-toluenosulfonatos, ciclohexilsulfamatos y quinatos. Ésteres adecuados de compuestos de Fórmula I que contienen un grupo carboxi son, por ejemplo, los descritos por F J Leinweber, *Drug Metab Res*, 1987, 18, página 379. Una clase especialmente útil de ésteres de compuestos de Fórmula I que contienen un grupo hidroxilo, pueden formarse a partir de restos ácidos seleccionados de los descritos por Bundgaard et al, *J Med Chem*, 1989, 32, página 2503-2507, e incluyen (aminometil)-benzoatos sustituidos, por ejemplo, dialquilamino-metilbenzoatos en los cuales los dos grupos alquilo pueden estar unidos uno a otro y/o interrumpidos por un átomo de oxígeno o por un átomo de nitrógeno opcionalmente sustituido, v g un átomo de nitrógeno alquilado, más especialmente (morfolino-metil)benzoatos, v g 3- o 4-(morfolinometil)benzoatos, y (4-alkilpiperazin-1-il)-benzoatos, v g 3- o 4-(4-alkilpiperazin-1-il)benzoatos.

"Derivados protegidos" significa derivados de compuestos de Fórmula I en los cuales uno o más sitios reactivos están bloqueados con grupos protectores. Los derivados protegidos de compuestos de Fórmula I son útiles en la preparación de compuestos de Fórmula I o pueden ser en sí mismos individuales activos de la catepsina S. Una lista exhaustiva de grupos protectores adecuados puede encontrarse en T W Greene, *Protecting Groups in Organic Synthesis*, 3ª edición, John Wiley & Sons, Inc 1999.

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

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

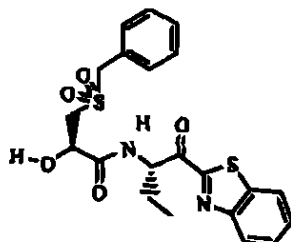
"Tratamiento" o "terapia" significa cualquier administración de un compuesto de la presente invención e incluye

- (1) prevención de la aparición de la enfermedad en un animal que puede estar predispuesto para la enfermedad pero no experimenta o exhibe todavía la patología o sintomatología de la enfermedad,
- (2) inhibición de la enfermedad en un animal que está experimentando o exhibiendo la patología o sintomatología de la enfermedad (es decir, detención del desarrollo ulterior de la patología y/o sintomatología), o
- (3) mejora de la enfermedad en un animal que está experimentando o exhibiendo la patología o sintomatología de la enfermedad (es decir, reversión de la patología y/o sintomatología)

148
149

Nomenclatura

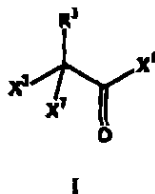
Los compuestos de Fórmula I y los compuestos intermedios y materiales de partida utilizados en su preparación se nombran de acuerdo con las reglas de nomenclatura de la IUPAC en las cuales los grupos característicos tienen prioridad decreciente para su citación como el grupo principal como sigue ácidos, ésteres, amidas, y análogos Alternativamente, los compuestos se nombran conforme a AutoNom 4.0 (Beilstein Information Systems, Inc.) Por ejemplo, un compuesto de Fórmula I en la cual X^2 es hidroxilo, R^3 es fenilmetanosulfonilmetilo y X^1 es $-NHC(R^1)(R^2)X^3$ (en cuya fórmula R^1 es hidrógeno, R^2 es etilo y X^3 es 1-benzotiazol-2-il-metanilo), es decir, un compuesto que tiene la estructura siguiente



se nombra (R)-N-[(S)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxil-3-fenilmetano-sulfonilpropionamida

Realizaciones Actualmente Preferidas

Si bien el alcance de la invención se expone en el Sumario de la Invención, se prefieren ciertos aspectos de la invención. Por ejemplo, se prefiere un compuesto de Fórmula I



en la cual

X^1 es $-NHC(R^1)(R^2)X^3$ o $-NHCH(R^{19})C(O)R^{20}$,

X^2 es hidrógeno, fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ o $-NR^{17}R^{18}$ y X^7 es hidrógeno o X^2 y X^7

representan ambos fluoro,

X^3 es ciano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ o $-C(O)C(O)R^5$, en cuyas fórmulas R^5 es hidrógeno, (C_{1-4}) alquilo, (C_{3-10}) cicloalquil, (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil, (C_{0-3}) alquilo, (C_{6-10}) aril, (C_{0-6}) alquilo, hetero (C_{5-10}) aril, (C_{0-6}) alquilo, (C_{9-10}) bicicloaril, (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril, (C_{0-6}) -

148
150

alquilo, R^6 es hidrógeno, hidroxilo o (C_{1-6}) alquilo, o donde X^3 contiene un grupo $-NR^5R^6$, R^5 y R^6 junto con el átomo de nitrógeno al cual están unidos ambos, forman hetero (C_{3-10}) cicloalquilo, hetero (C_{5-10}) arilo o hetero (C_{8-10}) bicicloarilo, R^7 es hidrógeno o (C_{1-4}) alquilo y R^8 es hidroxilo o R^7 y R^8 forman juntos oxo, R^{16} es hidrógeno, $-X^4$, $-CF_3$, $-CF_2CF_2R^9$ o $-N(R^6)OR^6$, R^9 es hidrógeno, halo, (C_{1-4}) alquilo, (C_{5-10}) aril (C_{0-6}) alquilo o (C_{5-10}) heteroaril (C_{0-6}) alquilo, con la salvedad de que cuando X^3 es ciano, entonces X^2 es hidrógeno, fluoro, $-OH$, $-OR^4$ o $-NR^{17}R^{18}$ y X^7 es hidrógeno o X^2 y X^7 representan ambos fluoro,

X^4 comprende un anillo heteromonocíclico que contiene 4 a 7 átomos miembros de anillo o un sistema de anillos heterobicíclico condensado que contiene 8 a 14 átomos miembros de anillo y cualquier derivado carbocíclico cetona, iminocetona o tiocetona de los mismos, con la salvedad de que cuando $-X^4$ es distinto de un anillo heteromonocíclico que contiene 5 átomos miembros de anillo, en el cual no más de dos de los átomos miembros de anillo que comprende el anillo son heteroátomos, entonces X^2 es fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ o $-NR^{17}R^{18}$ y X^7 es hidrógeno o X^2 y X^7 representan ambos fluoro,

en la cual dentro de R^5 , X^3 o X^4 cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13} es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo,

R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 se selecciona de un grupo constituido por hidrógeno, ciano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$,

$-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-9}) cicloalquileno o (C_{3-9}) heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroanillo, anillo, cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitró, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13} son como se define arriba,

R^3 es (C_{1-6}) alquilo o $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y X^6 se selecciona de $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^4 se selecciona de $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ y $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^8 es (C_{1-6}) alquileno y X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, con la salvedad de que cuando X^3 es ciano y X^2 es $-OR^4$, donde R^4 se define como $-R^{14}$, entonces R^{14} es (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-3}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{5-10}) aril (C_{1-6}) alquilo, (C_{9-10}) bicicloaril (C_{1-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo,

R^{15} es (C_{6-10}) arilo, hetero (C_{5-10}) arilo, (C_{9-10}) bicicloarilo o hetero (C_{8-10}) bicicloarilo,

R^{17} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo,

(C₆₋₁₀)aril(C₀₋₆)alquilo, hetero(C₅₋₁₀)aril(C₀₋₆)alquilo, (C₉₋₁₀)bicicloaril(C₀₋₆)alquilo o hetero(C₈₋₁₀)bicicloaril(C₀₋₆)alquilo, con la salvedad de que cuando X³ es ciano, entonces R¹⁷ es (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, (C₆₋₁₀)aril(C₁₋₆)alquilo, hetero(C₅₋₁₀)aril(C₁₋₆)alquilo, (C₉₋₁₀)bicicloaril(C₁₋₆)alquilo o hetero(C₈₋₁₀)bicicloaril(C₁₋₆)alquilo,

R¹⁸ es hidrógeno, (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, (C₆₋₁₀)aril(C₀₋₆)alquilo, hetero(C₅₋₁₀)aril(C₀₋₆)alquilo, (C₉₋₁₀)bicicloaril(C₀₋₆)alquilo o hetero(C₈₋₁₀)bicicloaril(C₀₋₆)alquilo, con la salvedad de que cuando X³ es ciano, entonces R¹⁸ es (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, (C₆₋₁₀)aril(C₁₋₆)alquilo, hetero(C₅₋₁₀)aril(C₁₋₆)alquilo, (C₉₋₁₀)bicicloaril(C₁₋₆)alquilo o hetero(C₈₋₁₀)bicicloaril(C₁₋₆)alquilo, y

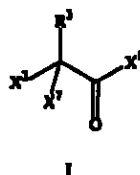
R¹⁹ y R²⁰, junto con los átomos a los cuales están unidos R¹⁹ y R²⁰, forman (C₄₋₈)heterocicloalquileno, en el cual no más de uno de los átomos miembros de anillo que comprende el anillo es un heteroátomo seleccionado de -NR²¹- o -O-, donde el anillo está insustituido o sustituido con R², donde R² es como se define arriba, y R²¹ es hidrógeno, -C(O)OR¹², -C(O)R¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -S(O)R¹³ y -S(O)₂R¹³, -S(O)R¹⁴, -S(O)₂R¹⁴, -C(O)R¹⁴, -C(O)OR¹⁴, -C(O)NR¹²R¹² y -S(O)₂NR¹⁴R¹², en cuyas fórmulas R¹², R¹³ y R¹⁴ son como se define arriba,

en la cual dentro de R³, R⁴, R¹⁵, R¹⁷ y R¹⁸ cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C₁₋₆)alquilo, (C₁₋₆)alquilideno, ciano, halo, (C₁₋₄)alquilo sustituido con halo, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵C(O)R¹³ y -X⁵S(O)₂R¹³ y/o 1 radical seleccionado de -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² y -X⁵NR¹²C(NR¹²)NR¹⁴R¹², y dentro de R³ y R⁴ cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, -NR¹²R¹², -NR¹²C(O)R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹², -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)R¹², -OC(O)R¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -NR¹²S(O)₂R¹², -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³ y -S(O)₂R¹³, en cuyas fórmulas X⁵, R¹², R¹³ y R¹⁴ son como se describe arriba, con la salvedad de que cuando X³ es ciano y X² es -OR⁴, donde R⁴ se define como -R¹⁴, o -NHR¹⁸, entonces cualquier sistema aromático de anillos presente dentro de R¹⁴ o R¹⁸ no está sustituido

152
153

adicionalmente con halo, (C₃₋₁₀)cicloalquilo, hetero(C₃₋₁₀)cicloalquilo, (C₆₋₁₀)arilo, hetero(C₅₋₁₀)arilo, (C₉₋₁₀)bícicloarilo o hetero(C₈₋₁₀)bícicloarilo, con la salvedad de que solamente está presente una estructura bicíclica de anillos dentro de R³, R⁴ o R¹⁵, y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y sus derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

Se prefiere un compuesto de Fórmula I



en la cual

X¹ es -NHC(R¹)(R²)X³ o -NHCH(R¹⁵)C(O)R²⁰,

X² es hidrógeno, fluoro, -OH, -OR⁴, -NHR¹⁵ o -NR¹⁷R¹⁸ y X⁷ es hidrógeno o X² y X⁷ representan ambos fluoro,

X³ es -C(R⁷)(R⁸)R¹⁶, -C(R⁶)(OR⁶)₂, -CH₂C(O)R¹⁶, -CH=CH-S(O)₂R⁵, -C(O)CF₂C(O)NR⁵R⁵, -C(O)C(O)NR⁵R⁶, -C(O)C(O)O-R⁵, -C(O)CH₂OR⁵, -C(O)CH₂N(R⁶)SO₂R⁵ o -C(O)C(O)R⁵, en cuyas fórmulas R⁵ es hidrógeno, (C₁₋₄)alquilo, (C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₀₋₃)alquilo, (C₆₋₁₀)aril(C₀₋₆)alquilo, hetero(C₅₋₁₀)aril(C₀₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₀₋₆)alquilo o hetero(C₈₋₁₀)bícicloaril(C₀₋₆)alquilo, R⁶ es hidrógeno, hidroxilo o (C₁₋₄)alquilo, o donde X³ contiene un grupo -NR⁵R⁶, R⁵ y R⁶ junto con el átomo de nitrógeno al cual están unidos ambos, forman hetero(C₃₋₁₀)cicloalquilo, hetero(C₅₋₁₀)arilo o hetero(C₈₋₁₀)bícicloarilo, R⁷ es hidrógeno o (C₁₋₄)alquilo y R⁸ es hidroxilo o R⁷ y R⁸ forman juntos oxo, R¹⁶ es hidrógeno, -X⁴, -CF₃, -CF₂CF₂R⁹ o -N(R⁶)OR⁶, R⁹ es hidrógeno, halo, (C₁₋₄)alquilo, (C₅₋₁₀)aril(C₀₋₆)alquilo o (C₅₋₁₀)heteroaril(C₀₋₆)alquilo,

X⁴ comprende un anillo heteromonocíclico que contiene 4 a 7 átomos miembros de anillo o un sistema de anillos heterobícíclico condensado que contiene 8 a 14 átomos miembros de anillo y cualquier derivado carbocíclico cetona, iminocetona o tiocetona de los mismos, con la salvedad de que cuando -X⁴ es distinto de un anillo heteromonocíclico que contiene 5 átomos miembros de anillo, en el cual no más de dos de los átomos miembros de anillo que comprende el anillo son heteroátomos, entonces X² es fluoro, -OH, -OR⁴, -NHR¹⁵ o -NR¹⁷R¹⁸, y X⁷ es hidrógeno o X² y X⁷ representan ambos fluoro,

153
154

en la cual dentro de R^5 , X^3 o X^4 cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13} es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{3-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{3-10}) bicicloaril (C_{0-6}) alquilo,

R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 se selecciona de un grupo constituido por hidrógeno, ciano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-9}) cicloalquileno o (C_{3-9}) heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13} son como se define arriba,

R^3 es $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y X^6 se selecciona de $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$,

104
155

$-X^5NR^{12}C(NR^{12})-NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)-R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^4 se selecciona de $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8O-R^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ y $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^8 es (C_{1-6}) alquileo y X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^{15} es (C_{6-10}) arilo, hetero (C_{5-10}) arilo, (C_{9-10}) bicicloarilo o hetero (C_{8-10}) bicicloarilo,

R^{17} es hidrógeno, (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo,

R^{18} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-6}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo, y

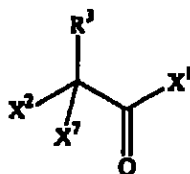
R^{19} y R^{20} , junto con los átomos a los cuales están unidos R^{19} y R^{20} , forman (C_{4-8}) heterocicloalquileno, en el cual no más de uno de los átomos miembros de anillo que comprende el anillo es un heteroátomo seleccionado de $-NR^{21}-$ o $-O-$, donde el anillo está insustituido o sustituido con R^1 , donde R^1 es como se define arriba, y R^{21} es hidrógeno, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ y $-S(O)_2NR^{14}R^{12}$, en cuyas fórmulas R^{12} , R^{13} y R^{14} son como se define arriba,

en la cual dentro de R^3 , R^4 , R^{15} , R^{17} y R^{18} cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1

155
156

radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, y dentro de R^3 y R^4 cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, $-NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se describe arriba, con la salvedad de que sólo está presente una estructura de anillo bicíclica en R^3 , R^4 o R^{15} , y sus derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos y sus derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

Se prefiere un compuesto de Fórmula I



I

en la cual

X^1 es $-NHC(R^1)(R^2)X^3$ o $-NHCH(R^{19})C(O)R^{20}$,

X^2 es hidrógeno, fluoro, $-OH$, $-OR^4$, o $-NR^{17}R^{18}$ y X^7 es hidrógeno o X^2 y X^7

representan ambos fluoro,

X^3 es ciano,

en la cual dentro de X^3 [sic] cualquier sistema de anillo alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$,

156
157

$-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13} es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil($C_{0-6})$ alquilo, hetero($C_{3-10})$ cicloalquil($C_{0-3})$ alquilo, (C_{6-10}) aril($C_{0-6})$ alquilo, hetero($C_{5-10})$ aril($C_{0-6})$ alquilo, (C_{9-10}) bicicloaril($C_{0-6})$ alquilo o hetero($C_{8-10})$ bicicloaril($C_{0-6})$ alquilo,

R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 se selecciona de un grupo constituido por hidrógeno, ciano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-8}) cicloalquileno o (C_{3-8}) heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitró, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13} son como se define arriba,

R^3 es $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y X^6 se selecciona de $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^4 se selecciona de $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$,

107
158

$-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$,
 $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$,
 $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$,
 $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$,
 $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en
cuyas fórmulas X^5 es (C_{1-6}) alquileo y X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, con la
salvedad de que cuando X^3 es ciano y X^2 es $-OR^4$, donde R^4 se define como $-R^{14}$, entonces R^{14}
es (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-3}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo,
hetero (C_{5-10}) aril (C_{1-6}) alquilo, (C_{9-10}) bicicloaril (C_{1-6}) alquilo o
hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo,

R^{15} es (C_{6-10}) arilo, hetero (C_{5-10}) arilo, (C_{9-10}) bicicloarilo o hetero (C_{8-10}) bicicloarilo,

R^{17} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-6}) alquilo,
 (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{5-10}) aril (C_{1-6}) alquilo, (C_{9-10}) bicicloaril (C_{1-6}) alquilo o
hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo, R^{18} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{1-6}) alquilo,
hetero (C_{3-10}) cicloalquil (C_{1-6}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{5-10}) aril (C_{1-6}) alquilo,
 (C_{9-10}) bicicloaril (C_{1-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo, y

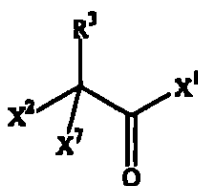
R^{19} y R^{20} , junto con los átomos a los cuales están unidos R^{19} y R^{20} , forman
 (C_{4-8}) heterocicloalquileo, en el cual no más de uno de los átomos miembros de anillo que
comprende el anillo es un heteroátomo seleccionado de $-NR^{21}-$ o $-O-$, donde el anillo está
insustituido o sustituido con R^1 , donde R^1 es como se define arriba, y R^{21} es hidrógeno,
 $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, $-S(O)R^{14}$,
 $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ y $-S(O)_2NR^{14}R^{12}$, en cuyas fórmulas R^{12} , R^{13}
y R^{14} son como se define arriba,

en la cual dentro de R^3 , R^4 , R^{15} , R^{17} y R^{18} cualquier sistema de anillos alicíclico o
aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados
independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido
con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$,
 $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$,
 $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$,
 $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1
radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$,
 $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$,
 $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y
 $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, y dentro de R^3 y R^4 cualquier resto alifático está insustituido o
sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano,
halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,

159

$-\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{12}\text{R}^{12}$, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{C}(\text{O})\text{OR}^{12}$, $-\text{C}(\text{O})\text{R}^{12}$, $-\text{OC}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{S}(\text{O})_2\text{NR}^{12}\text{R}^{12}$, $-\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$, $-\text{P}(\text{O})(\text{OR}^{12})\text{OR}^{12}$, $-\text{OP}(\text{O})(\text{OR}^{12})\text{OR}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$ y $-\text{S}(\text{O})_2\text{R}^{13}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se describe arriba, con la salvedad de que cuando X^2 es $-\text{OR}^4$, donde R^4 se define como $-\text{R}^{14}$, o $-\text{NHR}^{18}$, entonces cualquier sistema de anillos aromático presente dentro de R^{14} o R^{18} no está sustituido adicionalmente con halo, (C_{3-10}) cicloalquilo, hetero (C_{3-10}) cicloalquilo, (C_{6-10}) arilo, hetero (C_{5-10}) arilo, (C_{9-10}) bicicloarilo o hetero (C_{8-10}) bicicloarilo, con la salvedad de que sólo está presente una estructura bicíclica de anillos en R^3 , R^4 o R^{15} , y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

Se prefiere un compuesto de Fórmula I



I

en la cual

X^1 es $-\text{NHC}(\text{R}^1)(\text{R}^2)\text{X}^3$ o $-\text{NHCH}(\text{R}^{19})\text{C}(\text{O})\text{R}^{20}$,

X^2 es $-\text{OH}$, $-\text{OC}(\text{O})\text{NR}^{12}\text{R}^{12}$ o $-\text{OC}(\text{O})\text{R}^{14}$, en cuyas fórmulas R^{12} y R^{14} son como se define más adelante,

X^3 es ciano, $-\text{C}(\text{R}^7)(\text{R}^8)\text{R}^{16}$, $-\text{C}(\text{R}^6)(\text{OR}^6)_2$, $-\text{CH}_2\text{C}(\text{O})\text{R}^{16}$, $-\text{CH}=\text{CH}-\text{S}(\text{O})_2\text{R}^5$, $-\text{C}(\text{O})\text{CF}_2\text{C}(\text{O})\text{NR}^5\text{R}^5$, $-\text{C}(\text{O})\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{C}(\text{O})\text{C}(\text{O})\text{OR}^5$, $-\text{C}(\text{O})\text{CH}_2\text{OR}^5$, $-\text{C}(\text{O})\text{CH}_2\text{N}(\text{R}^6)\text{SO}_2\text{R}^5$ o $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^5$, en cuyas fórmulas R^5 es hidrógeno, (C_{1-4}) alquilo, (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo, R^6 es hidrógeno, hidroxilo o (C_{1-6}) alquilo, o donde X^3 contiene un grupo $-\text{NR}^5\text{R}^6$, R^5 y R^6 junto con el átomo de nitrógeno al cual están unidos ambos, forman hetero (C_{3-10}) cicloalquilo, hetero (C_{5-10}) arilo o hetero (C_{8-10}) bicicloarilo, R^7 es hidrógeno o (C_{1-4}) alquilo y R^8 es hidroxilo o R^7 y R^8 forman juntos oxo, R^{16} es hidrógeno, $-\text{X}^4$, $-\text{CF}_3$, $-\text{CF}_2\text{CF}_2\text{R}^9$ o $-\text{N}(\text{R}^6)\text{OR}^6$, R^9 es hidrógeno, halo, (C_{1-4}) alquilo, (C_{5-10}) aril (C_{0-6}) alquilo o (C_{5-10}) heteroaril (C_{0-6}) alquilo,

X^4 comprende un anillo heteromonocíclico que contiene 4 a 7 átomos miembros de anillo o un sistema de anillos heterobícíclico condensado que contiene 8 a 14 átomos miembros de anillo y cualquier derivado carbocíclico cetona, iminocetona o tiocetona de los mismos,

en la cual dentro de R^5 , X^3 o X^4 cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13} es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil, (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil, (C_{0-3}) alquilo, (C_{6-10}) aril, (C_{0-6}) alquilo, hetero (C_{5-10}) aril, (C_{0-6}) alquilo, (C_{9-10}) bicicloaril, (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril, (C_{0-6}) alquilo,

R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 se selecciona de un grupo constituido por hidrógeno, ciano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-8}) cicloalquileno o (C_{3-8}) heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$,

$-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13} son como se define arriba,

R^3 es $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y X^6 se selecciona de $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, y

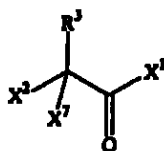
R^{19} y R^{20} , junto con los átomos a los cuales están unidos R^{19} y R^{20} , forman (C_{4-8}) heterocicloalquileno, en el cual no más de uno de los átomos miembros de anillo que comprende el anillo es un heteroátomo seleccionado de $-NR^{21}-$ o $-O-$, donde el anillo está insustituido o sustituido con R^1 , donde R^1 es como se define arriba, y R^{21} es hidrógeno, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ y $-S(O)_2NR^{14}R^{12}$, en cuyas fórmulas R^{12} , R^{13} y R^{14} son como se define arriba,

en la cual dentro de R^3 , R^4 , R^{15} , R^{17} y R^{18} cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, y dentro de R^3 y R^4 cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se describe arriba, con la condición de que sólo está presente una estructura de anillo bicíclica en R^3 , R^4 o R^{15} , y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y

261
162

mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

Se prefiere un compuesto de Fórmula I



I

en la cual

X^1 es $-NHC(R^1)(R^2)C(O)C(O)NR^5R^6$, en cuya fórmula R^5 es hidrógeno, (C_{1-4}) alquilo, (C_{3-10}) cicloalquil, (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil, (C_{0-3}) alquilo, (C_{6-10}) aril, (C_{0-6}) alquilo, hetero (C_{5-10}) aril, (C_{0-6}) alquilo, (C_{9-10}) bicicloaril, (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril, (C_{0-6}) alquilo y R^6 es hidrógeno, hidroxilo o (C_{1-6}) alquilo, o R^5 y R^6 , junto con el átomo de nitrógeno al cual están unidos ambos forman hetero (C_{3-10}) cicloalquilo, hetero (C_{5-10}) arilo o hetero (C_{8-10}) bicicloarilo,

X^2 es hidrógeno,

en la cual dentro de X^1 cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)N-R^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13} es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil, (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil, (C_{0-3}) alquilo, (C_{6-10}) aril, (C_{0-6}) alquilo, hetero (C_{5-10}) aril, (C_{0-6}) alquilo, (C_{9-10}) bicicloaril, (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril, (C_{0-6}) alquilo,

R^1 es hidrógeno y R^2 es (C_{1-6}) alquilo, y

R^3 es $-CH_2X^6$, en cuya fórmula X^6 es $-X^5NR^{12}S(O)_2R^{12}$ o $-X^5S(O)_2R^{14}$, en cuyas fórmulas X^5 , R^{12} y R^{14} son como se define arriba,

162
163

en la cual dentro de R^3 cualquier sistema de anillo alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5N-R^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y dentro de R^3 cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se describe arriba, con la salvedad de que sólo está presente una estructura de anillo bicíclica en R^3 , y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

Se prefieren los compuestos de la invención en los cuales X^1 es $-NHC(R^1)(R^2)X^3$ o $-NHCH(R^{19})C(O)R^{20}$, en cuyas fórmulas R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 es hidrógeno, (C_{1-6}) alquilo, $-X^5OR^{12}$, $-X^5S(O)R^{13}$, $-X^5OR^{14}$, (C_{6-10}) aril (C_{0-6}) alquilo o hetero (C_{3-10}) aril (C_{0-6}) alquilo, o R^1 o R^2 considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-6}) cicloalquileno o (C_{3-6}) heterocicloalquileno, en los cuales dentro de dicho R^2 , cualquier heteroarilo, arilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con (C_{1-6}) alquilo o hidroxilo, particularmente en los cuales X^3 es ciano, $-C(O)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH=CHS(O)_2R^5$, $-CH_2C(O)R^{16}$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ o $-C(O)C(O)R^5$, en cuyas fórmulas R^5 , R^6 y R^{16} son como se describe arriba, y R^{19} y R^{20} junto con los átomos a los cuales están unidos R^{19} y R^{20} forman (C_{4-8}) heterocicloalquileno, en cuya fórmula no más de uno de los átomos miembros del anillo que comprende el anillo es un heteroátomo seleccionado de $-NR^{21}-$ u $-O-$, particularmente en el cual el anillo está insustituido o sustituido con (C_{1-6}) alquilo o $-X^5C(O)OR^{12}$ y R^{21} es hidrógeno, (C_{1-6}) alquilo, $-X^5C(O)R^{12}$, $-X^5C(O)OR^{12}$, $-R^{14}$, $-X^5C(O)R^{14}$ o $-C(O)OR^{14}$

Son particularmente preferidos los compuestos de la invención en los cuales X^3 es ciano, $-C(O)X^4$, $-C(O)H$, $-C(O)N(CH_3)OCH_3$, $-CH(OCH_3)_2$, $-C(O)CF_3$, $-C(O)CF_2CF_3$, $-CH_2C(O)R^{16}$, (E)-2-bencenosulfonilvinilo, 2-dimetilcarbamoil-2,2-difluoroacetilo,

2-oxo-2-pirrolidin-1-il-acetilo, 2-morfolin-4-il-2-oxoacetilo, 2-oxo-2-piperazin-1-il-acetilo, 2-(4-metanosulfonil-piperazin-1-il)-2-oxoacetilo, 2-(1,1-dioxo-1 λ^6 -tioformolin-4-il)-2-oxoacetilo, dimetilaminooxalilo, tetrahidropiran-4-ilaminooxalilo, 2-morfolin-4-il-etilaminooxalilo, ciclopentil-etil-aminooxalilo, piridin-3-ilaminooxalilo, fenilaminoxalilo, 1-benzoil-piperidin-4-ilaminooxalilo, 1-bencil-carbamoyl-metanoilo, 1-benciloxi(oxalilo), 2-benciloxi-acetilo, 2-bencenosulfonilamino-etanoilo, 2-oxo-2-fenil-etanoilo, 3*H*-oxazol-2-carbonilo, 5-trifluorometil-oxazol-2-carbonilo, 3-trifluorometil-[1,2,4]-oxadiazol-5-carbonilo, 2,2,3,3,3-pentafluoro-propionilo, hidroxiaminooxalilo, oxalilo, 2-(1,3-dihidro-isoindol-2-il)-2-oxoacetilo, benzotiazol-2-ilaminooxalilo, 2-oxo-etilo, 2-oxazol-2-il-2-oxo-etilo o 2-benzooxazol-2-il-2-oxo-etilo, particularmente en los cuales X⁴ es 1*H*-benzoimidazol-2-ilo, pirimidin-2-ilo, benzooxazol-2-ilo, benzotiazol-2-ilo, piridazin-3-ilo, 3-fenil-[1,2,4]-oxadiazol-5-ilo o 3-etil-[1,2,4]oxadiazol-5-ilo, y R¹⁹ y R²⁰, junto con los átomos a los cuales están unidos R¹⁹ y R²⁰, forman 1-benzoil-3-oxo-piperidin-4-ilo, 1-benzoil-3-oxo-azepan-4-ilo, 2-metil-4-oxo-tetrahydro-furan-3-ilo, 2-etil-4-oxo-tetrahydro-furan-3-ilo, 4-oxo-1-(1-fenilmetanoil)-pirrolidin-3-ilo o (S)-2-acetoxi-4-oxo-azetidín-3-ilo

Son muy particularmente preferidos los compuestos de la invención en los cuales X³ es -C(O)X⁴, en particular 1*H*-benzoimidazol-2-ilcarbonilo, pirimidin-2-ilcarbonilo, benzooxazol-2-ilcarbonilo, benzotiazol-2-ilcarbonilo, piridazin-3-ilcarbonilo, 3-fenil-[1,2,4]oxadiazol-5-ilcarbonilo o 3-etil-[1,2,4]oxadiazol-5-ilcarbonilo, o -C(O)C(O)NR⁵R⁶, en particular 2-oxo-2-pirrolidin-1-ilacetilo, 2-morfolin-4-il-2-oxoacetilo, 2-oxo-2-piperazin-1-il-acetilo, 2-(4-metanosulfonil-piperazin-1-il)-2-oxo-acetilo, 2-(1,1-dioxo-1 λ^6 -tiomorfolin-4-il)-2-oxo-acetilo, dimetilaminooxalilo, tetrahidropiran-4-ilamino-oxalilo, 2-morfolin-4-il-etilaminooxalilo, ciclopentil-etil-aminooxalilo, piridin-3-ilaminooxalilo, fenilaminoxalilo o 1-benzoil-piperidin-4-ilaminooxalilo

Se prefieren los compuestos de la invención en los cuales X² es -OH o -OC(O)NR¹²R¹², particularmente en los cuales cada R¹² representa independientemente hidrógeno o (C₁₋₆)alquilo, donde dicho alquilo está insustituido o sustituido con hidroxilo o metoxilo, o X² es -OC(O)NHR¹⁴, en cuya fórmula R¹⁴ es (C₃₋₁₀)cicloalquil(C₀₋₆)alquilo o hetero(C₃₋₁₀)cicloalquil(C₁₋₃)alquilo, o X² es -OC(O)R¹⁴, en cuya fórmula R¹⁴ es -NR²²R²³ y R²² y R²³ junto con el átomo de nitrógeno al cual están unidos R²² y R²³ forman un anillo hetero(C₄₋₆)cicloalquilo, anillo que puede estar insustituido o sustituido con hidroxilo, particularmente en el cual X² se selecciona de -OH, dimetilcarbamoiloxi, morfolin-4-ilcarboniloxi, piperidin-1-ilcarboniloxi, pirrolidin-1-il-carboniloxi, pirimidin-2-ilamino, tetrahidropiran-4-ilamino, 1-metil-piperidin-4-ilamino, *N*-(2-metoxietil)-*N*-(tetrahidropiran-4-il)amino, isopropil-amino y ciclohexilamino,

4-*terc*-butoxycarbonilpiperazin-1-ilcarboniloxi, *N*-bencil-carbamoiłoxi, pirrolidin-1-il-carboniloxi, *N,N*-dimetil-carbamoiłoxi, piperidin-1-il-carboniloxi, 4-metanosulfonil-piperazin-1-il-carboniloxi, 4-etoxycarbonilpiperazin-1-il-carboniloxi, *N*-ciclohexil-carbamoiłoxi, *N*-fenil-carbamoiłoxi, *N*-(5,6,7,8-tetrahidro-naftalen-1-il)-carbamoiłoxi, *N*-butil-*N*-metil-carbamoiłoxi, *N*-piridin-3-il-carbamoiłoxi, *N*-isopropil-carbamoiłoxi, *N*-piridin-4-il-carbamoiłoxi, *N*-cianometil-*N*-metil-carbamoiłoxi, *N,N*-bis-(2-metoxi-etil)-carbamoił-oxi, *N*-fenetil-carbamoiłoxi, piperazina-carboniloxi, *N*-naftalen-2-il-carbamoiłoxi, 4-bencil-piperazina-1-carbamoiłoxi, 4-(1-furan-2-il-carbonil)-piperazina-1-carbamoiłoxi, tiomorfolin-4-il-carboniloxi, 1,1-dioxo-1λ⁶-tiomorfolin-4-il)carboniloxi, bis-(2-metoxi-etil)-carbamoiłoxi, morfolin-4-ilcarboniloxi, 2-metoxi-etilcarbamoiłoxi, dietilcarbamoiłoxi, pirrolidin-1-ilcarboniloxi, 2-hidroxietilcarbamoiłoxi, tetrahidro-furan-2-ilmetilcarbamoiłoxi, ciclopropilcarbamoiłoxi, *terc*-butilcarbamoiłoxi, 3-hidroxipirrolidin-1-il-carboniloxi y carbamoiłoxi, más particularmente morfolin-4-ilcarboniloxi, 2-metoxietilcarbamoiłoxi, dietilcarbamoiłoxi, pirrolidin-1-ilcarboniloxi, 2-hidroxietilcarbamoiłoxi, tetrahidro-furan-2-ilmetilcarbamoiłoxi, ciclopropilcarbamoiłoxi, *terc*-butilcarbamoiłoxi, 3-hidroxipirrolidin-1-il-carboniloxi y carbamoiłoxi

Se prefieren los compuestos de la invención en los cuales X² es -NHR¹⁵, en cuya fórmula R¹⁵ es (C₆₋₁₀)arilo, hetero(C₅₋₁₀)arilo, (C₉₋₁₀)bícicloarilo o hetero(C₈₋₁₀)-bícicloarilo, o -NR¹⁷R¹⁸, en cuya fórmula R¹⁷ es hetero(C₃₋₁₀)cicloalquilo y R¹⁸ es hidrógeno o R¹⁷ y R¹⁸ son independientemente (C₆₋₁₀)aril(C₁₋₆)alquilo o hetero(C₅₋₁₀)aril(C₁₋₆)alquilo, en los cuales dentro de R¹⁵, R¹⁷ y R¹⁸ cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C₁₋₆)-alquilo, ciano, halo, nitro, (C₁₋₄)alquilo sustituido con halo, -X⁵OR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹³, -X⁵C(O)NR¹²R¹², -X⁵N-R¹²S(O)₂R¹² y/o 1 radical seleccionado de -R¹⁴, -X⁵OR¹⁴ y -X⁵C(O)NR¹⁴R¹², en particular en los cuales X² se selecciona de 5-nitrotiazol-2-ilamino, 2-nitrofenilamino, pirimidin-2-ilamino, tetrahidropiran-4-ilamino, *N*-(2-metoxietil)-*N*-(tetrahidropiran-4-il)amino, 1-metil-piperidin-4-ilamino, isopropilamino, di(tien-2-ilmetil)-amino o di(bencil)amino

Se prefieren los compuestos de la invención en los cuales X² es -OR⁴ en cuya fórmula R⁴ es 4-metoxi-fenilo, 4'-hidroximetil-fenilo, metoximetilo, fenilmetanoilo, 1-(4-fenoxi-fenil)-metanoilo, 3-bifenilo, 4-bifenilo, 1-bifenil-4-il-metanoilo, naftalen-2-il-metanoilo, benzo-[1,3]dioxol-5-il-metanoilo, (4-metanosulfonilaminofenil)-metanoilo, benzo[*b*]tien-2-il-metanoilo, 4'-cloro-4-bi-fenilo, 4-hidroxifenilmetanoilo, 3-cloro-benzo[*b*]tien-2-il-metanoilo, tien-2-il-metanoilo,

tien-3-il-metanollo, 3-cloro-tien-2-il-metanollo, 5-metil-tien-2-il-metanollo, 4-metoxi-fenilmetanollo, 4-trifluorometoxi-fenilmetanollo, 4-cloro-fenilmetanollo, 3-bromofenilo, ciclohexilmetilo, 3,4-dimetoxi-fenilmetanollo, 3,4-difluorofenilmetanollo, 3-fluoro,4-metoxi-fenilmetanollo, 4-fluorofenilmetanollo, 4-trifluorometil-fenilmetanollo, 4-formil-fenil-formulo, 3-formil-fenil-formulo, 4-metil-pentanollo, tetrahidropiran-4-ilmetil-2-morfolin-4-il-2-oxo-metilo

Son muy particularmente preferidos compuestos de la invención en los cuales X^2 se selecciona de -OH, dimetilcarbamoiloxi, morfolin-4-ilcarbamoiloxi, piperidin-1-ilcarbamoiloxi, pirrolidin-1-il-carbamoiloxi, pirimidin-2-ilamino, tetrahidropiran-4-ilamino, 1-metilpiperidin-4-ilamino, *N*-(2-metoxietil)-*N*-(tetrahidropiran-4-il)-amino, isopropilamino y ciclohexilamino

Se prefieren los compuestos de la invención en los cuales R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 es hidrógeno, $-X^5OR^{12}$, $-X^5R^{12}$, (C_{5-10}) heteroaril (C_{0-6}) alquilo, (C_{5-10}) aril (C_{0-6}) alquilo, (C_{5-10}) cicloalquil (C_{0-6}) alquilo, (C_{5-10}) heterocicloalquil (C_{0-6}) alquilo o (C_{1-6}) alquilo, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 forman (C_{3-8}) cicloalquileno o (C_{3-8}) heterocicloalquileno, en los cuales dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está sustituido opcionalmente con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo e hidroxil, particularmente en los cuales R^1 es hidrógeno o metilo y R^2 es hidrógeno, metoximetilo, (C_{1-6}) alquilo, fenetilo, tien-2-ilo o 5-metil-furan-2-ilo, o R^1 y R^2 considerados junto con el átomo de carbono al cual están unidos R^1 y R^2 forman ciclopropileno, tetrahidropiran-4-ileno o metil-piperidin-4-ileno

Se prefieren los compuestos de la invención en los cuales R^3 es $-CH_2X^6$, en cuya fórmula X^6 se selecciona de $-X^5SR^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2R^{13}$, $-X^5C(O)R^{13}$, $-X^5OR^{12}$, $-X^5SR^{14}$, $-X^5R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, particularmente en las cuales R^3 es tufeno-2-sulfonil-metilo, 3-cloro-2-fluoro-fenilmetano-sulfonil-metilo, benceno-sulfonil-metilo, fenilmetano-sulfonil-metilo, 2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil-metilo, 2-bencenosulfonil-etilo, 2-(piridina-2-sulfonil)-etilo, 2-(piridina-4-sulfonil)-etilo, 2-fenilmetano-sulfonil-etilo, oxipiridin-2-il-metano-sulfonil-metilo, prop-2-eno-1-sulfonil-metilo, 4-metoxi-fenilmetano-sulfonil-metilo, *p*-tolil-metano-sulfonil-metilo, 4-cloro-fenilmetano-sulfonil-metilo, *o*-tolil-metano-sulfonil-metilo, 3,5-dimetil-fenilmetano-sulfonil-metilo, 4-tri-fluoro-metil-fenilmetano-sulfonil-metilo, 4-trifluoro-metoxi-fenilmetano-sulfonil-metilo, 2-bromo-fenilmetano-sulfonil-metilo, piridin-2-il-metano-sulfonil-metilo, piridin-3-il-metano-sulfonil-metilo, piridin-4-il-metano-sulfonil-metilo,

naftalen-2-il-metano-sulfonil-metilo, 3-metil-fenilmetano-sulfonil-metilo,
3-tri-fluorometil-fenilmetano-sulfonil-metilo, 3-trifluoro-metoxi-fenilmetano-sulfonil-metilo,
4-fluoro-2-tri-fluorometoxi-fenilmetano-sulfonil-metilo,
2-fluoro-6-trifluorometil-fenilmetanosulfonilmetilo, 3-cloro-fenilmetanosulfonilmetilo,
2-fluoro-fenilmetanosulfonilmetilo, 2-trifluoro-fenilmetanosulfonilmetilo,
2-ciano-fenilmetanosulfonilmetilo, 4-*terc*-butil-fenilmetanosulfonil-metilo,
2-fluoro-3-fenil-fenilmetano-sulfonil-metilo, 3-fluoro-fenilmetanosulfonilmetilo,
4-fluoro-fenilmetano-sulfonilmetilo, 2-cloro-fenilmetanosulfonilmetilo,
2,5-difluoro-fenilmetanosulfonilmetilo, 2,6-difluoro-fenilmetanosulfonilmetilo,
2,5-dicloro-fenilmetano-sulfonil-metilo, 3,4-dicloro-fenilmetanosulfonilmetilo,
2-(1,1-di-fluoro-metoxi)-fenilmetanosulfonilmetilo, 2-ciano-fenilmetano-sulfonil-metilo,
3-ciano-fenilmetanosulfonil-metilo, 2-trifluoro-metoxi-fenilmetano-sulfonilmetilo,
2,3-difluoro-fenilmetanosulfonilmetilo, 2,5-difluoro-fenilmetanosulfonilmetilo,
bifenil-2-ilmetanosulfonil-metilo, ciclohexilmetilo, 3-fluoro-fenilmetanosulfonil-metilo,
3,4-difluoro-fenilmetanosulfonilmetilo, 2,4-difluoro-fenilmetanosulfonilmetilo,
2,4,6-trifluoro-fenilmetanosulfonilmetilo, 2,4,5-trifluoro-fenilmetano-sulfonilmetilo,
2,3,4-trifluoro-fenilmetanosulfonil-metilo, 2,3,5-trifluoro-fenilmetano-sulfonilmetilo,
2,5,6-trifluoro-fenilmetanosulfonilmetilo, 2-cloro-5-tri-fluoro-metilfenilmetanosulfonilmetilo,
2-metil-propano-1-sulfonilo, 2-fluoro-3-trifluoro-metilfenilmetanosulfonilmetilo,
2-fluoro-4-trifluoro-metilfenilmetanosulfonilmetilo,
2-fluoro-5-trifluoro-metil-fenilmetano-sulfonilmetilo,
4-fluoro-3-trifluoro-metilfenilmetanosulfonilmetilo, 2-metoxi-fenilmetanosulfonilmetilo,
3,5-bis-trifluorometil-fenilmetanosulfonilmetilo,
4-difluoro-metoxi-fenilmetanosulfonilmetilo, 2-difluoro-metoxi-fenilmetanosulfonilmetilo,
3-difluorometoxi-fenilmetano-sulfonilmetilo, 2,6-dicloro-fenilmetanosulfonilmetilo,
bifenil-4-ilmetanosulfonilmetilo, 3,5-dimetil-isoxazol-4-ilmetanosulfonilmetilo,
5-cloro-tien-2-il-metano-sulfon-ilmetilo, 2-[4-(1,1-difluoro-metoxi)-bencenosulfonil]-etilo,
2-[2-(1,1-difluoro-metoxi)-bencenosulfonil]-etilo,
2-[3-(1,1-difluoro-metoxi)-bencenosulfonil]-etilo, 2-(4-trifluorometoxi-bencenosulfonil)-etilo,
2-(3-trifluoro-metoxi-bencenosulfonil)-etilo, 2-(2-trifluoro-metoxi-benceno-sulfonil)-etilo,
(cianometil-metil-carbamoi)-metilo, bifenil-3-ilmetilo, 2-oxo-2-pirrohidin-1-il-etilo,
2-bencenosulfonil-etilo, isobutilsulfanilmetilo, 2-fenilsulfanil-etilo,
ciclohexilmetanosulfonilmetilo, 2-ciclohexil-etanosulfonilo, bencilo, naftalen-2-ilo,
bencilsulfanilmetilo, 2-trifluorometil-bencilsulfanil-metilo, fenilsulfaniletilo,
ciclopropil-metanosulfonil-metilo, 5-bromo-tien-2-ilmetilo, 3-fenil-propilo,
2,2-difluoro-3-fenil-propilo, 3,4,5-trimetoxi-fenilmetano-sulfonilmetilo,

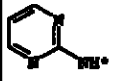
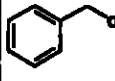
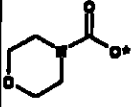
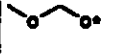
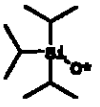
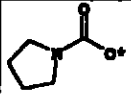
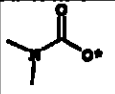
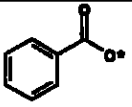
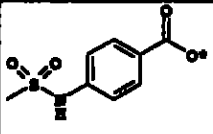
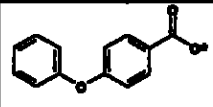
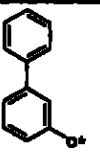
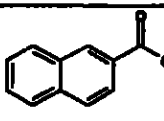
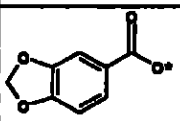
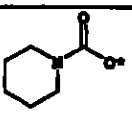
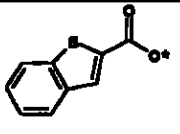
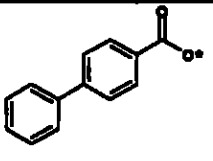
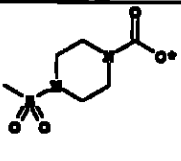
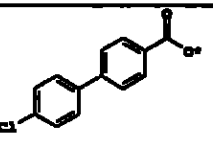
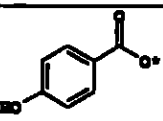
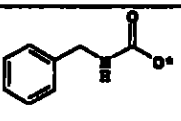
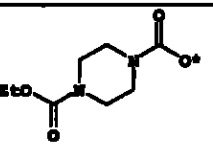
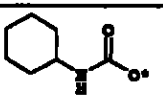
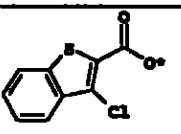
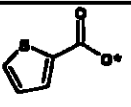
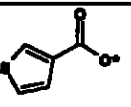
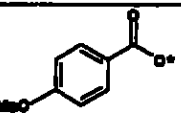
2,2-difluoro-3-tien-2-il-propilo, ciclo-hexiletilo, ciclohexilmetilo, *terc*-butilmetilo, 1-metilciclohexilmetilo, 1-metilciclopentilmetilo, 2,2-difluoro-3-fenilpropilo, 2,2-dimetil-3-fenilpropilo, 1-bencilciclopropilmetilo, $-X^5S(O)_2R^{13}$ y $-X^5S(O)_2R^{14}$, en cuyas fórmulas R^{13} es alquilo y R^{14} es fenilo, pudiendo estar dicho fenilo insustituido o sustituido

Se prefieren los compuestos de la invención en los cuales R^3 es ciclohexiletilo, ciclohexilmetilo, *terc*-butilmetilo, 1-metilciclohexilmetilo, 1-metilciclo-pentilmetilo, 2,2-difluoro-3-fenilpropilo, 2,2-dimetil-3-fenilpropilo, 1-bencilciclopropilmetilo, $-X^5S(O)_2R^{13}$ o $-X^5S(O)_2R^{14}$, en cuyas fórmulas R^{13} es alquilo y R^{14} es fenilo, pudiendo estar dicho fenilo insustituido o sustituido

Las tablas siguientes tienen por objeto proporcionar orientación en cuanto a la mejor realización de la presente invención Sin embargo, las mismas no limitan el alcance de la invención Las personas con experiencia ordinaria pueden preparar selectivamente compuestos particulares uniendo O^* , NH^* o H^* de uno de los fragmentos (A1 a A62) que se muestran en la Tabla 1 al átomo de carbono de metino ($*CH^*$) de uno de los fragmentos (B1 a B93) que se muestran en la Tabla 2, y uniendo el átomo de carbono de metino ($*CH^*$ o $*CF^*$) de uno de los fragmentos (B1 a B93) que se muestran en la Tabla 2 al átomo de carbono de acilo (C^*) de uno de los fragmentos (C1 a C91) representados en la Tabla 3

TABLA 1

TABLE 1

A1		A2		A3	
A4		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	
A16		A17		A18	
A19		A20		A21	
A22		A23		A24	
A25		A26		A27	

168
170

A28		A29		A30	
A31		A32		A33	
A34		A35		A36	
A37		A38		A39	
A40		A41		A42	
A43		A44		A45	
A46		A47		A48	
A49		A50		A51	
A52		A53		A54	
A55		A56		A57	

270
171

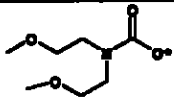
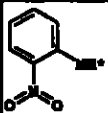
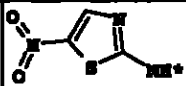
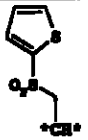
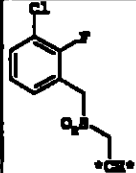
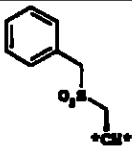
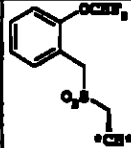
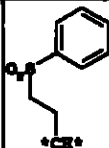
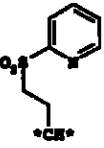
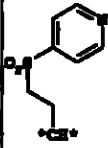
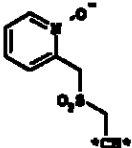
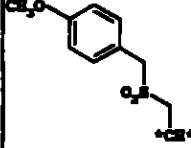
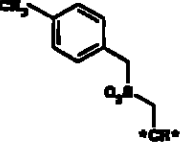
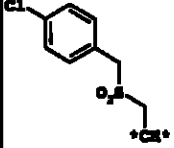
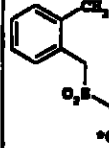
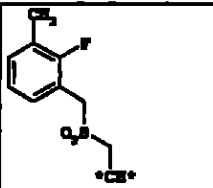
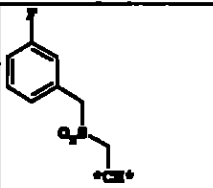
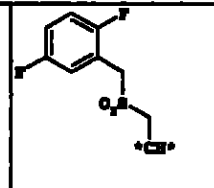
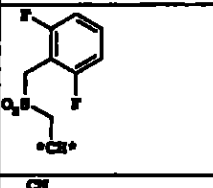
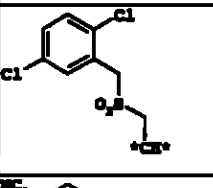
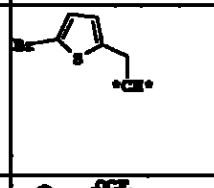
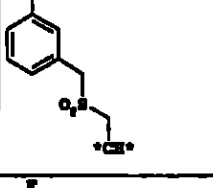
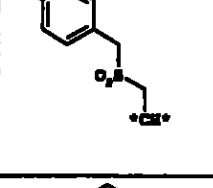
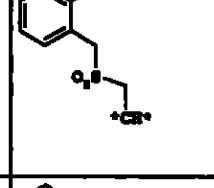
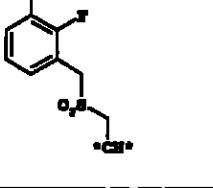
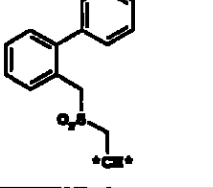
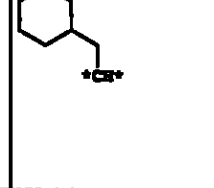
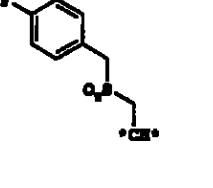
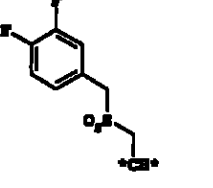
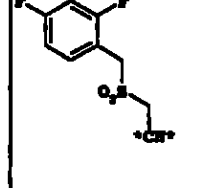
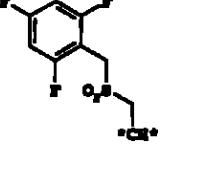
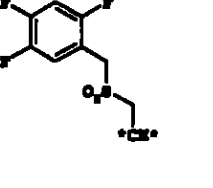
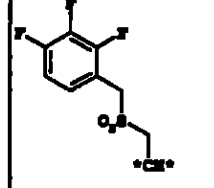
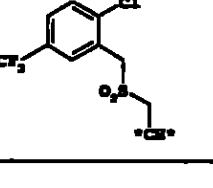
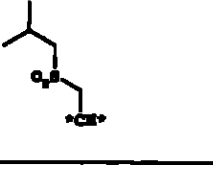
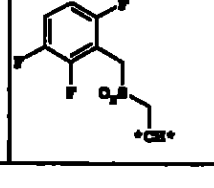
A58		A59		A60	
A61	H ⁺	A62	F ⁺		

TABLA 2

B1		B2		B3	
B4		B5		B6	
B7		B8		B9	
B10		B11		B12	
B13		B14		B15	

177
172

B16		B17		B18	
B19		B20		B21	
B22		B23		B24	
B25		B26		B27	
B28		B29		B30	
B31		B32		B33	

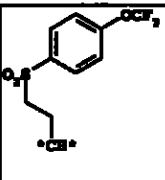
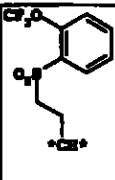
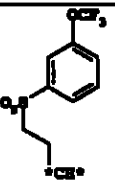
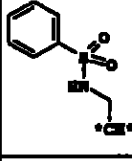
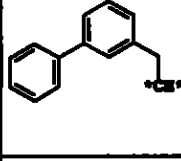
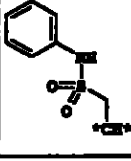
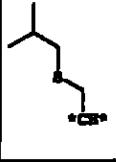
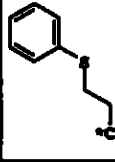
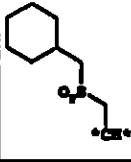
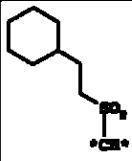
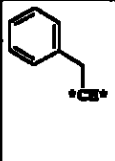
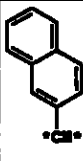
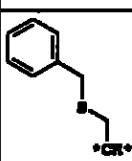
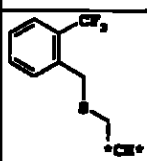
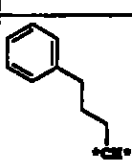
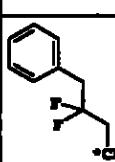
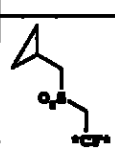
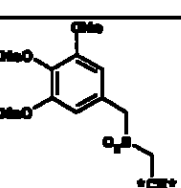
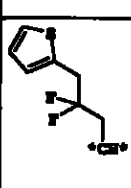
B34	 <chem>COP(=O)(C)c1ccccc1F</chem>	B35	 <chem>COP(=O)(C)c1ccc(F)cc1</chem>	B36	 <chem>COP(=O)(C)c1cc(F)c(F)cc1</chem>
B37	 <chem>COP(=O)(C)c1cc(F)c(F)cc1</chem>	B38	 <chem>COP(=O)(C)c1cc(Cl)c(Cl)cc1</chem>	B39	 <chem>COP(=O)(C)Cc1ccsc1</chem>
B40	 <chem>COP(=O)(C)Cc1cccc(C)c1</chem>	B41	 <chem>COP(=O)(C)Cc1ccc(C)cc1</chem>	B42	 <chem>COP(=O)(C)Cc1ccccc1OC</chem>
B43	 <chem>COP(=O)(C)Cc1cc(F)c(F)cc1</chem>	B44	 <chem>COP(=O)(C)Cc1ccccc1-c2ccccc2</chem>	B45	 <chem>COP(=O)(C)Cc1ccccc1</chem>
B46	 <chem>COP(=O)(C)Cc1ccc(F)cc1</chem>	B47	 <chem>COP(=O)(C)Cc1cc(F)c(F)cc1</chem>	B48	 <chem>COP(=O)(C)Cc1cc(F)c(F)c(F)c1</chem>
B49	 <chem>COP(=O)(C)Cc1c(F)c(F)c(F)cc1</chem>	B50	 <chem>COP(=O)(C)Cc1cc(F)c(F)c(F)c1</chem>	B51	 <chem>COP(=O)(C)Cc1cc(F)c(F)c(F)c1</chem>
B52	 <chem>COP(=O)(C)Cc1cc(C)ccc1Cl</chem>	B53	 <chem>COP(=O)(C)CC(C)C</chem>	B54	 <chem>COP(=O)(C)Cc1cc(F)c(F)c(F)c1</chem>

173

174

B55		B56		B57	
B58		B59		B60	
B61		B62		B63	
B64		B65		B66	
B67		B68		B69	
B70		B71		B72	

174
175

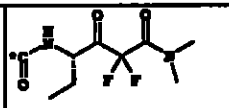
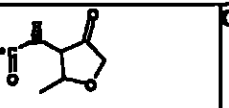
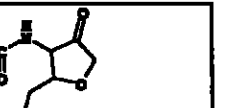
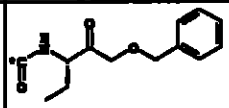
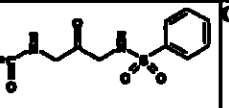
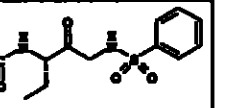
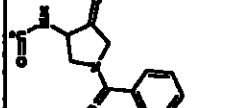
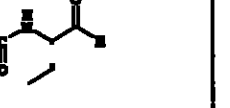
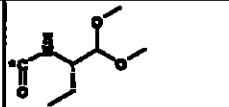
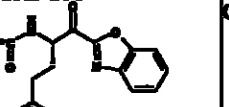
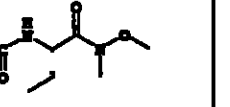
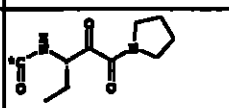
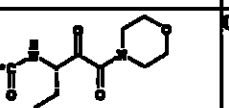
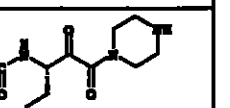
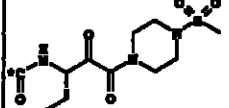
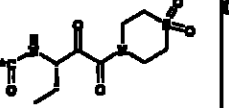
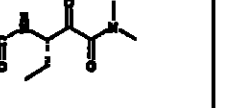
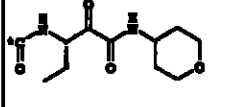
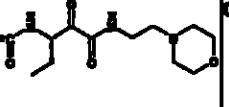
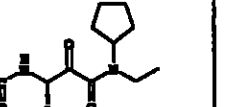
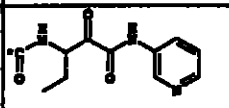
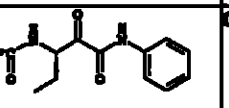
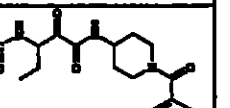
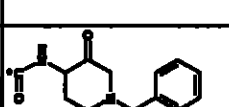
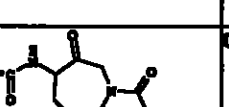
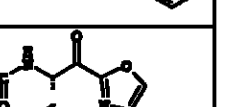
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B76		B77		B78	
B79		B80		B81	
B82		B83		B84	
B85		B86		B87	
B88		B89		B90	
B91		B92		B93	

~~175~~
176

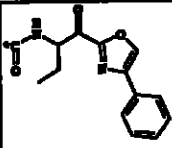
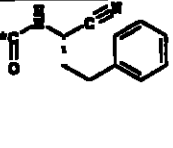
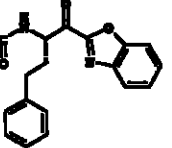
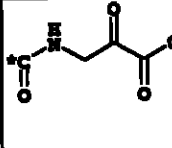
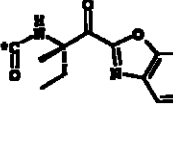
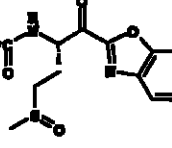
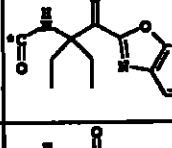
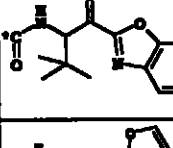
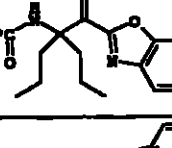
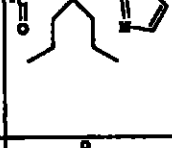
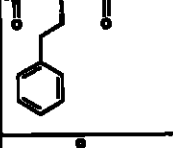
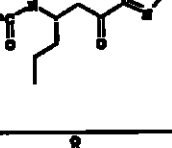
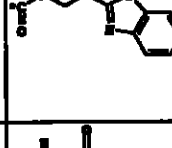
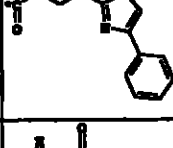
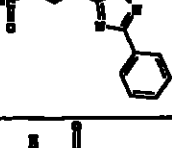
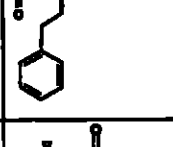
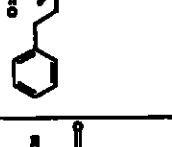
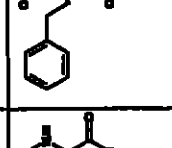
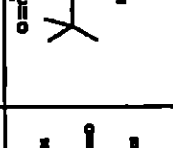
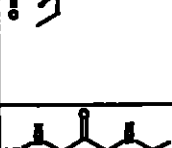
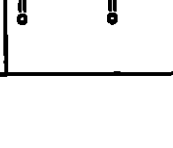
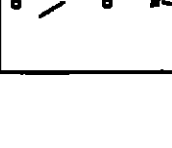
TABLA 3

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

176
177

C25		C26		C27	
C28		C29		C30	
C31		C32		C33	
C34		C35		C36	
C37		C38		C39	
C40		C41		C42	
C43		C44		C45	
C46		C47		C48	
C49		C50		C51	

~~177~~
178

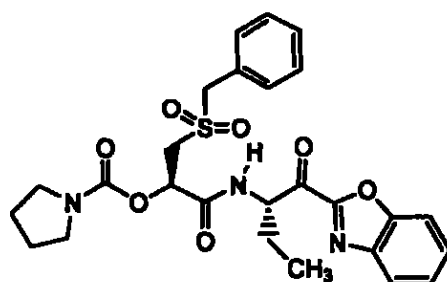
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C55		C56		C57	
C58		C59		C60	
C61		C62		C63	
C64		C65		C66	
C67		C68		C69	
C70		C71		C72	
C73		C74		C75	

178
179

C76		C77		C78	
C79		C80		C81	
C82		C83		C84	
C85		C86		C87	
C88		C89		C90	
C91					

Por conveniencia, puede hacerse referencia a los compuestos de la presente invención por sus combinaciones de fragmentos "A", "B", y "C" Así, por ejemplo, el compuesto al que se hace referencia como A7-B4-C13 es producto de la combinación del grupo A7 en la Tabla 1 y B4 en la Tabla 2 y C13 en la Tabla 3, es decir el ácido pirrolidina-1-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-fenil metanosulfonil-etil-éster

179
180



Compuestos preferidos adicionales de la Fórmula I se proporcionan a continuación

(*R*)-*N*-cianometil-2-hidroxi-3-fenilmetanosulfonyl-propionamida,
(*R*)-*N*-(1-ciano-1-tiofen-2-il-metil)-2-hidroxi-3-fenilmetanosulfonyl-propionamida,
(*R*)-*N*-(1-ciano-1-tiofen-2-il-metil)-3-[2-(1,1-difluoro-metoxi)fenilmetanosulfonyl]-2-hidroxi-propionamida,
(*R*)-*N*-(cianometil-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-2-hidroxi-propionamida,
ácido morfolina-4-carboxílico-(*R*)-1-(cianometil-carbamoyl)-2-fenilmetanosulfonyl-etil-éster,
ácido morfolina-4-carboxílico-(*R*)-1-(cianometil-carbamoyl)-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-etil-éster,
ácido (*R*)-(2-metoxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-fenilmetano-sulfonyl-etil-éster,
ácido (*S*)-dietil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-pirrolidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-morfolina-4-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-4-etil-piperazina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-2-hidroxi-metil-pirrolidina-1-carboxílico-(*S*)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-(2,2,2-trifluoro-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-(2-hidroxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (tetrahydrofuran-2-il-metil)-carbámico-(*S*)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-azetidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-ciclopropil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-piperidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-(2-metoxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*R*)-3-hidroxi-pirrolidina-1-carboxílico-(*S*)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
ácido (*S*)-3-hidroxi-pirrolidina-1-carboxílico-(*S*)-1-(cianometil-carbamoyl)-2-ciclohexil-

120
131

etil-éster;

ácido (S)-morfolina-4-carboxílico-1-(cianometil-carbamoyl)-3-ciclohexil-propil-éster,

ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzo-oxazol-2-il-metanoil)-

propilcarbamoyl]-2-fenilmetano-sulfonil-etil-éster,

ácido morfolina-4-carboxílico(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoyl]-2-

[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster;

ácido morfolina-4-carboxílico(R)-1-[(S)-1-(1-benzotiazol-2-il-metanoil)-propil-

carbamoyl]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster;

ácido pirrolidina-1-carboxílico(R)-1-[(S)-1-(1-benzo-oxazol-2-il-metanoil)-

propilcarbamoyl]-2-fenilmetano-sulfonil-etil-éster;

ácido dimetil-carbámico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-

propilcarbamoyl]-2-fenilmetanosulfonil-etil-éster;

ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-bencil-carbamoyl-metanoil)-

propilcarbamoyl]-2-fenilmetano-sulfonil-etil-éster,

ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(oxazol[4,5-b]piridina-2-carbonil)-

propilcarbamoyl]-2-fenilmetano-sulfonil-etil-éster,

ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-

propilcarbamoyl]-2-fenilmetanosulfonil-etil-éster;

(S)-2-[(R)-3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-2-hidroxi-

propanoilamino]-N-metoxi-N-metil-butiramida,

(R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-N-[(S)-1-formil-propil]-2-hidroxi-

propionamida,

(R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-

propionamida,

ácido (S)-3-{3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-

propanoilamino}-2-oxopentanoico-bencilamida,

N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetano-

sulfonil]-propionamida,

N-[(S)-1-(1-benzooxazol-2-il-metanoil)-3-fenil-propil]-3-p-tolilmetanosulfonil-propionamida,

3-(2-difluorometoxi-fenilmetanosulfonil)-N-(1-etil-2,3-dioxo-3-pirrolidin-1-il-propil)-

propionamida,

3-(2-difluorometoxi-fenilmetanosulfonil)-N-(1-etil-3-morfolin-4-il-2,3-dioxo-propil)-

propionamida,

3-(2-difluorometoxi-fenilmetanosulfonil)-N-(1-etil-2,3-dioxo-3-piperazin-1-il-propil)-

propionamida,

3-(2-difluorometoxi-fenilmetanosulfonil)-N-[3-(1,1-

181
182

dioxo-1,6-tiomorfolin-4-il)-1-etil-2,3-dioxo-propil]-propionamida,
 3-(2-difluorometoxi-fenilmetanosulfonil)-N-[1-etil-3-(4-metil-sulfonil-piperazin-1-il)-2,3-dioxo-propil]-propionamida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-dimetilamida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-ciclopentil-etilamida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-fenilamida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-piridin-3-ilamida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-(tetrahidropiran-4-il)-amida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-(1-benzoil-piperidin-4-il)-amida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-(2-morfolin-4-il-etil)-amida,
 (R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-(2-nitro-fenilamino)-3-fenilmetanosulfonil-propionamida,
 N-[1-(benzooxazol-2-carbonil)-propil]-3-fenilmetanosulfonil-2-(pirimidin-2-ilamino)propionamida,
 (R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-(5-nitro-tiazol-2-ilamino)-3-fenilmetanosulfonil-propionamida,
 ácido (2S)(4,4-difluoro-2-hidroxi-5-fenilpentanoico-(1(S)-ciano-3-fenil-propil)-amida,
 N-(1(S)-ciano-3-fenil-propil)-2-(S)-(2-morfolin-4-il-2-oxo-etoxi)-4-fenil-butiramida,
 N-(1(S)-ciano-3-fenil-propil)-2-(S)-fluoro-4-fenil-butiramida,
 N-(1(S)-ciano-3-fenil-propil)-2,2-difluoro-4-fenil-butiramida,
 N-(1(S)-ciano-3-fenil-propil)-2-(S)-hidroxi-4-fenil-butiramida,
 N-(1(S)-ciano-3-fenil-propil)-2-(R)-hidroxi-4-fenil-butiramida,
 N-(1(S)-ciano-3-fenil-propil)-2-(R)-metoxi-4-fenil-butiramida,
 ácido 2,2-difluoro-5-fenil-pentanoico-(1-ciano-ciclo-propil)-amida,
 N-(1(S)-ciano-3-fenil-propil)-4-fenil-butiramida,
 ácido 2,2-difluoro-5-fenil-pentanoico-((S)-1-ciano-3-fenil-propil)-amida,
 N-(4-ciano-1-etil-piperidin-4-il)-3-ciclohexil-propionamida,
 N-(4-ciano-1-etil-piperidin-4-il)-3-(2-difluorometoxi-fenilmetanosulfonil)-propionamida,
 ácido (S)-*tert*-butil-carbámico-1-(cianometil-carbamoil)-2-ciclohexil-etil-éster,

ácido (R)-carbámico-1-(cianometil-carbamoil)-2-(2-difluorometoxi-fenilmetanosulfonil)-etil-éster;
ácido (S)-carbámico-1-(cianometil-carbamoil)-2-ciclo-hexil-etil-éster,
ácido (R)-morfolina-4-carboxílico-1-(1-ciano-ciclopropil-carbamoil)-2-fenilmetanosulfonil-etil-éster,
ácido (R)-morfolina-4-carboxílico-1-(4-ciano-tetrahidropiran-4-ilcarbamoil)-2-fenilmetanosulfonil-etil-éster,
3-ciclohexil-2-hidroxí-*N*-[1-(oxazolo[4,5-*b*]piridina-2-carbonil)-2-propil]-propionamida,
(R)-*N*-[1-(benzotiazol-2-carbonil)-butil]-2-isopropil-amino-3-fenilmetanosulfonil-propionamida,
(R)-*N*-[1-(benzotiazol-2-carbonil)-butil]-3-fenilmetano-sulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-*N*-[1-(benzotiazol-2-carbonil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida,
(R)-*N*-[1-(benzotiazol-2-carbonil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida,
(R)-*N*-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-*N*-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(1-metil-piperidín-4-ilamino)-3-fenilmetanosulfonil-propionamida,
(R)-*N*-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida,
(R)-*N*-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(dibencil-amino-3-fenilmetanosulfonil-propionamida,
(S)-*N*-[(S)-1-benzoxazol-2-carbonil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-propionamida,
(S)-*N*[(S)-1-(benzoxazol-2-carbonil)-butil]-2-isopropil-amino-3-tiofen-2-il-propionamida,
(R)-*N*-[1-(benzotiazol-2-carbonil)-butil]-3-fenilmetano-sulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-*N*-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-*N*-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-[(2-metoxi-etil)-tetrahidropiran-4-il-amino]-3-fenilmetano-sulfonil-propionamida,
(R)-*N*-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-ciclohexil-amino-3-fenilmetanosulfonil-propionamida,

(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-dimetil-amino-3-fenilmetanosulfonil-propionamida,
(1S)-N-[1-(benzooxazol-2-carbonil)-butil]-2-(S)-fluoro-4-fenil-butiramida,
ácido 2,2-difluoro-5-fenil-pentanoico-[(S)-1-(benzoxazol-2-carbonil)-butil]-amida,
ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(benzooxazol-2-carbonil)-propilcarbamoil]-2-ciclohexil-etil-éster,
ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(oxazolo[4,5-b]piridina-2-carbonil)-propilcarbamoil]-etil-éster,
ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-etil-éster,
ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(5-fenil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-etil-éster,
ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(benzooxazol-2-carbonil-propilcarbamoil)-3-ciclohexil-propil-éster,
ácido 4-[4,4-dimetil-2-(morfolina-4-carboniloxi)-pentanoil-amino]-3-oxo-azepan-1-carboxílico-bencil-éster,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-ciclo-propilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-ciclohexil-amino-3-ciclopropilmetanosulfonil-propionamida,
(R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-cicloheptil-amino-3-ciclopropilmetanosulfonil-propionamida,
(R)-3-fenilmetanosulfonil-N-[(S)-3-fenil-1-(tiazol-2-carbonil)-propil]-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-3-fenil-propil]-3-ciclopropil-metanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-3-ciclopropilmetanosulfonil-N-[1-(5-etil-1,2,4-oxadiazol-3-carbonil)-propil]-2-(tetrahidropiran-4-il-amino)-propionamida,
(R)-3-fenilmetanosulfonil-N-[1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propil]-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-il-amino)-propionamida,
ácido {(R)-1-[1-(benzotiazol-2-il-hidroxí-metil)-butil-carbamoil]-3-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxí-metil)-butilcarbamoil]-3-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,

124
185

ácido {(S)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-
butilcarbamoil]-2-tiofen-2-il-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[1-(benzotiazol-2-il-hidroxi-metil)-butil-
carbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-
butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-
butilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido (R)-1-{1-[hidroxi-(3-fenil-1,2,4-oxadiazol-5-il-metil)-
propilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido ((R)-2-ciclopropilmetanosulfonil-1-{(S)-1-[(5-etil-
1,2,4-oxadiazol-3-il)-hidroxi-metil]-propilcarbamoil}-etil)-carbámico-*terc*-butil-éster,
ácido {(R)-1-[1-(benzoxazol-2-il-hidroxi-metil)-butil-
carbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-
propilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(hidroxi-tiazol-2-il-metil)-3-fenil-
propilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-
butilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido (R)-1-{1-[hidroxi-(3-fenil-1,2,4-oxadiazol-5-il)-
metil]-propilcarbamoil}-3-fenilmetanosulfonil-etil)-carbámico-*terc*-butil-éster,
ácido ((R)-2-ciclopropilmetanosulfonil-1-{(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-
propilcarbamoil}-etil)-carbámico-*terc*-butil-éster,
ácido {(R)-1-[1-(benzoxazol-2-il-hidroxi-metil)-butil-
carbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-
propilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(hidroxi-tiazol-2-il-metil)-3-fenil-
propilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido (R)-2-fenilmetanosulfonil-1-{(S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroxi-metil]-
propilcarbamoil}-etil)-carbámico-*terc*-butil-éster,
(R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-[ciclopropil-metil-(tetrahidropirran-4-il-metil)-
amino]-3-fenilmetano-sulfonil-propionamida,
(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-
propionamida,

(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-iso-propilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(1-metil-piperidin-4-ilamino)-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida,
(S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-propionamida,
(S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-tiofen-2-il-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-[2-metoxi-etil]-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-ciclohexilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida,
N-cianometil-3-ciclohexil-propionamida,
N-cianometil-3-(2-difluorometoxi-fenilmetanosulfonil)-propionamida,
ácido 3-(3-ciclohexil-propionilamino)-2-oxo-5-fenil-pentanoico-tiazol-2-ilamida,
3-ciclohexil-N-(1-formil-3-fenil-propil)-propionamida,

126
187

3-(2-difluorometoxi-fenilmetanosulfonil)-*N*-[(*S*)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propil]-propionamida,
N-[(*S*)-1-(benzooxazol-2-carbonil)-propil]-2-(2-ciano-fenilamino)-3-ciclohexil-propionamida,
N-cianometil-3-ciclohexil-2-(4-metoxi-fenoxi)-propionamida,
2-benciloxi-*N*-cianometil-3-ciclohexil-propionamida,
(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-benciloxi-3-fenilmetanosulfonil-propionamida,
(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-metoximetoxi-3-fenilmetanosulfonil-propionamida,
(*S*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-hidroxí-3-fenil-propionamida,
(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propil]-3-fenilmetanosulfonil-2-trisopropilsilaniloxi-propionamida,
(*R*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxí-3-fenilmetanosulfonil-propionamida,
(*R*)-2-hidroxí-3-fenilmetanosulfonil-*N*-[(*S*)-1-(1-piridazin-3-il-metanoil)-butil]-propionamida,
ácido (*S*)-3-((*R*)-2-hidroxí-3-fenilmetanosulfonil-propanoil-amino)-2-oxo-pentanoico-bencilamida,
(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxí-propionamida,
(*R*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxí-propionamida,
(2*R*,5*S*)-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil-metil]-6-etoxi-5-etil-morfolin-3-ona,
y sus *N*-óxidos correspondientes, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos (v g. hidratos) farmacéuticamente aceptables de tales compuestos y sus *N*-óxidos y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

Farmacología y Utilidad

Los compuestos de la invención son inhibidores selectivos de la catepsina S y, como tales, son útiles para tratar enfermedades en las cuales 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 en el tratamiento de trastornos autoinmunes, con inclusión, pero sin carácter limitante, de diabetes de aparición juvenil, esclerosis múltiple, pénfigo vulgar, enfermedad de Graves, miastenia grave, lupus eritematoso sistémico, artritis reumatoide y tiroiditis de Hashimoto, trastornos alérgicos, con inclusión, pero sin carácter limitante, del asma, y respuestas alogénicas inmunes, con inclusión, pero sin carácter limitante, de trasplantes de órganos o injertos de tejidos.

187
188

La catepsina S está implicada también en trastornos que implican elastólisis excesiva, tales como enfermedad pulmonar obstructiva crónica (v g , enfisema), bronquiolitis, elastólisis excesiva de las vías aéreas en el asma y la bronquitis, neumonitis y enfermedad cardiovascular tal como rotura de la placa y ateroma La catepsina S está implicada en la formación de fibrillas y, por consiguiente, los inhibidores de la catepsina S son útiles en el tratamiento de la amiloidosis sistémica

Las actividades inhibidoras de las cisteína-proteasas de los compuestos de la invención se pueden determinar por métodos conocidos por quienes poseen una experiencia ordinaria en la técnica. Se conocen ensayos *in vitro* adecuados para medir la actividad de las proteasas y la inhibición de la misma por los compuestos de ensayo Típicamente, el ensayo mide la hidrólisis inducida por las proteasas de un sustrato de base peptídica Detalles de los ensayos para medir la actividad inhibidora de las proteasas se exponen en EJEMPLOS DE ENSAYOS ENZIMÁTICOS, más adelante

Administración y Composiciones Farmacéuticas

En general, los compuestos de Fórmula I se administrarán en cantidades terapéuticamente eficaces por la vía de cualquiera de los modos usuales y aceptables conocidos en la técnica, sea aisladamente o en combinación con uno o más agentes terapéuticos Una cantidad terapéuticamente eficaz puede variar ampliamente dependiendo de la gravedad de la enfermedad, la edad y la salud relativa del individuo, la potencia del compuesto utilizado y otros factores Por ejemplo, cantidades terapéuticamente eficaces de un compuesto de Fórmula I pueden variar desde aproximadamente 1 microgramo por kilogramo de peso corporal ($\mu\text{g/kg}$) por día a aproximadamente 60 miligramos por kilogramo de peso corporal (mg/kg) por día, como valores típicos desde aproximadamente 1 $\mu\text{g/kg/día}$ a aproximadamente 20 mg/kg/día . Por consiguiente, una cantidad terapéutica-mente eficaz para un paciente humano de 80 kg puede variar desde aproximadamente 80 $\mu\text{g/día}$ a aproximadamente 4,8 g/día, como valor típico desde aproximadamente 80 $\mu\text{g/día}$ a aproximadamente 1,6 g/día En general, una persona con experiencia ordinaria en la técnica, basándose en su conocimiento personal y la descripción de esta Solicitud, podrá determinar una cantidad terapéuticamente eficaz de un compuesto de Fórmula I para tratar una enfermedad dada

Los compuestos de la Fórmula I se pueden administrar como composiciones farmacéuticas por una de las rutas siguientes oral, sistémica, (v g., transdérmica, intranasal o mediante supositorio) o parenteral (v g , intramuscular, intravenosa o subcutánea) Las composiciones pueden presentarse en forma de tabletas, píldoras, cápsulas, semisólidos, polvos, formulaciones de liberación sostenida, soluciones, suspensiones, elixires, aerosoles, o cualquier otra composición apropiada y están constituidas, en general, por un compuesto de la

Fórmula I en combinación con al menos un excipiente farmacéuticamente aceptable. Los excipientes aceptables son atóxicos, favorecen la administración, y no afectan desfavorablemente al beneficio terapéutico del ingrediente activo. Un excipiente de este tipo puede ser cualquier excipiente sólido, líquido, semisólido o, en el caso de una composición aerosol, gaseoso que está disponible generalmente para una persona con experiencia en la técnica.

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 desecada, y análogos. Los excipientes líquidos y semisólidos se pueden seleccionar de agua, etanol, glicerol, propilenglicol y diversos aceites, con inclusión de aceites de origen petrolífero, animal, vegetal o sintético (v.g., aceite de cacahuete, aceite de soja, aceite mineral, aceite de sésamo, y análogos). Vehículos líquidos preferidos, particularmente para soluciones inyectables, incluyen agua, solución salina, dextrosa acuosa y glicoles.

La cantidad de un compuesto de Fórmula I en la composición puede variar ampliamente dependiendo del tipo de formulación, el volumen de una unidad de dosificación, la clase de excipientes y otros factores conocidos por quienes poseen experiencia en la técnica de las ciencias farmacéuticas. En general, una composición de un compuesto de Fórmula I para tratar una enfermedad dada comprenderá desde 0,01% p a 10% p, preferiblemente desde 0,3% p a 1% p, de ingrediente activo, siendo el resto el excipiente o excipientes. Preferiblemente, la composición farmacéutica se administra en una forma de dosificación unitaria simple para tratamiento continuo o en una forma de dosificación unitaria simple ad libitum cuando se requiere específicamente alivio de los síntomas. Formulaciones farmacéuticas representativas que contienen un compuesto de Fórmula I se describen en el Ejemplo 15 más adelante.

Química

Procesos para Preparación de los Compuestos de Fórmula I

Los compuestos de la invención se pueden preparar por la aplicación o adaptación de métodos conocidos, por los cuales se entienden métodos utilizados hasta ahora o descritos en la bibliografía, por ejemplo los descritos por R. C. Larock en *Comprehensive Organic Transformations*, VCH Publishers, 1989.

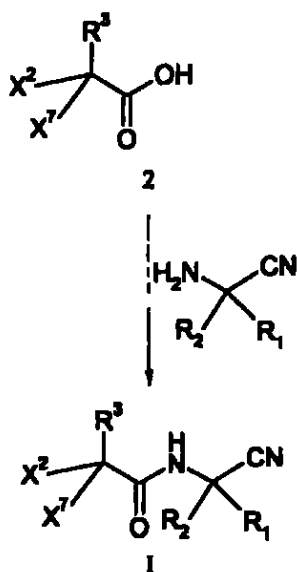
En las reacciones que se describen más adelante, puede ser necesario proteger grupos funcionales reactivos, por ejemplo grupos hidroxilo, amino, imino, tio o carboxilo, cuando se desean éstos en el producto final, a fin de evitar su participación indeseable en las reacciones. Pueden utilizarse grupos protectores convencionales de acuerdo con la práctica estándar, por ejemplo véase T. W. Greene y P. G. Wuts en *"Protective Groups in Organic Chemistry"*, John

189
190

Wiley and Sons, 1991

Los compuestos de Fórmula I, en la cual X^1 es $-NHC-(R^1)(R^2)X^3$, se pueden preparar procediendo de acuerdo con el esquema de reacción 1 siguiente

Esquema de Reacción 1



en el cual cada uno de X^2 , X^3 , X^7 , R^1 , R^2 y R^3 son como se define para la Fórmula I en el Sumario de la Invención

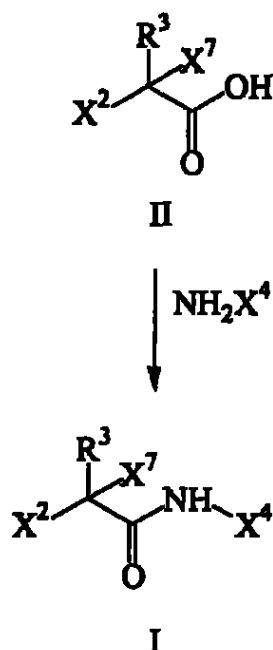
Los compuestos de Fórmula I se pueden preparar por condensación de un ácido de Fórmula II con un compuesto amínico de fórmula $NH_2CR^1R^2X^3$. La reacción de condensación puede efectuarse con un agente de copulación apropiado (v g, hexafluorofosfato de benzotriazol-1-iloxitris-pirrolidinofosfomio (PyBOP®), hexafluorofosfato de tetrametiluronio (HATU), hidrocloreuro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI), hexafluorofosfato de *O*-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio (HBTU), 1,3-diciclohexilcarbodiimida (DCC), *N*-ciclo-hexilcarbodiimida, *N'*-metilpoliestireno, o análogos) y opcionalmente un catalizador apropiado (v g, 1-hidroxibenzotriazol (HOBt), 1-hidroxí-7-azabenzotriazol (HOAt), *O*-(7-azabenzotriazol-1-il)-1,1,3,3, , [sic] o análogos) y una base no nucleófila (v g. trietilamina, *N*-metilmorfolina, y análogas, o cualquier combinación adecuada de las mismas) a la temperatura ambiente, y requiere 5 a 10 horas para completarse

Un Paso de oxidación, en caso requerido, puede llevarse a cabo con un agente oxidante (v g, Oxone®, ácido metacloroperbenzoico o análogos) en un disolvente adecuado (v g, metanol, agua, o análogos, o cualquier combinación adecuada de los mismos) a la temperatura ambiente y requiere 16 a 24 horas para completarse. Descripciones detalladas

para la síntesis de un compuesto de Fórmula I por los procesos del esquema de reacción 1 se exponen en los Ejemplos 1 a 10, más adelante

Los compuestos de Fórmula I, en la cual X^1 es $-NHX^4$, se pueden preparar procediendo de acuerdo con el esquema de reacción 2 siguiente

Esquema de Reacción 2



en el cual cada uno de X^2 , X^4 , X^7 , y R^3 son como se define para la Fórmula I en el Sumario de la Invención

Los compuestos de Fórmula I se pueden preparar por condensación de un ácido de Fórmula II con un compuesto amínico de fórmula NH_2X^4 . La reacción de condensación puede efectuarse con un agente de copulación apropiado (v g, hexafluorofosfato de benzotriazol-1-iloxitrispirrolidino fosfonio (PyBOP®), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio (HATU), hidrocloreuro de 1-(3-dimetilaminopropil)3-etilcarbodiimida (EDCI), hexafluorofosfato de *O*-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio (HBTU), 1,3-diciclohexilcarbodiimida (DCC), *N*-ciclohexilcarbodiimida, *N'*-metilpoliestireno, o análogos) y opcionalmente un catalizador apropiado (v g, 1-hidroxibenzotriazol (HOBt), 1-hidroxi-7-azabenzotriazol (HOAt), o análogos) y una base no nucleófila (v g, trietilamina, *N*-metilmorfolina, y análogos, o cualquier combinación adecuada de las mismas) a la temperatura ambiente, y requiere 5 a 10 horas para completarse

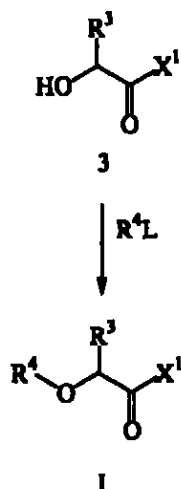
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192

Un Paso de oxidación, en caso requerido, puede llevarse a cabo con un agente oxidante (v g , Oxone®, ácido metacloroperbenzoico o análogos) en un disolvente adecuado (v g , metanol, agua, o análogos, o cualquier combinación adecuada de los mismos) a la temperatura ambiente y requiere 16 a 24 horas para completarse

Los compuestos de Fórmula I en la cual X^2 es $-OR^4$, se pueden preparar por reacción de un compuesto de Fórmula 3 con un compuesto de Fórmula R^4L de acuerdo con el esquema de reacción siguiente

Esquema de Reacción 3

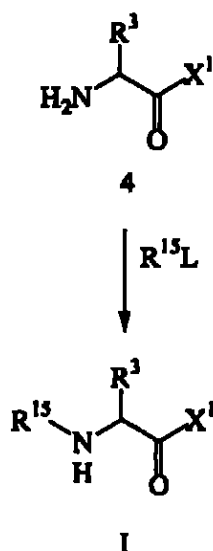


en el cual L es un grupo lábil y X^1 , R^3 y R^4 son como se define en el Sumario de la Invención. Una descripción detallada para la síntesis de un compuesto de Fórmula I por el proceso arriba descrito se expone en el Ejemplo 4, más adelante

Los compuestos de Fórmula I en la cual X^2 es $-NHR^{15}$, se pueden preparar por reacción de un compuesto de Fórmula 4 con un compuesto de fórmula $R^{15}L$ de acuerdo con el esquema de reacción siguiente

192
193

Esquema de Reacción 4



en el cual L es un grupo lábil y X^1 , R^3 y R^{15} son como se define en el Sumario de la Invención. Una descripción detallada para la síntesis de un compuesto de Fórmula I por el proceso arriba descrito se expone en [versión actualizada], más adelante

Procesos Adicionales para Preparación de los Compuestos de Fórmula I

Un compuesto de Fórmula I se puede preparar como una sal de adición de ácido farmacéuticamente aceptable por reacción de la forma de base libre del compuesto con un ácido inorgánico u orgánico farmacéuticamente aceptable. Alternativamente, una sal de adición de base farmacéuticamente aceptable de un compuesto de Fórmula I se puede preparar por reacción de la forma de ácido libre del compuesto con una base inorgánica u orgánica farmacéuticamente aceptable. Ácidos y bases inorgánicos y orgánicos adecuados para la preparación de las sales farmacéuticamente aceptables de los compuestos de Fórmula I se exponen en la sección de definiciones de esta Solicitud. Alternativamente, las formas de sal de los compuestos de Fórmula I se pueden preparar utilizando sales de los materiales de partida o compuestos intermedios.

Las formas de ácido libre o base libre de los compuestos de Fórmula I se pueden preparar a partir de la sal de adición de base o sal de adición de ácido correspondiente. Por ejemplo, un compuesto de Fórmula I en una forma de sal de adición de ácido se puede convertir en la base libre correspondiente por tratamiento con una base adecuada (v.g. solución de hidróxido de amonio, hidróxido de sodio, y análogos). Un compuesto de Fórmula I en una forma de sal de adición de base se puede convertir en el ácido libre correspondiente por tratamiento con un ácido adecuado (v.g. ácido clorhídrico, etc).

Los N-óxidos de los compuestos de Fórmula I se pueden preparar por métodos conocidos por quienes poseen una experiencia ordinaria en la técnica. Por ejemplo, los N-óxidos se pueden preparar por tratamiento de una forma no oxidada del compuesto de Fórmula I con un agente oxidante (v g, ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido *meta*-cloroperoxibenzoico, o análogos) en un disolvente orgánico inerte adecuado (v g, un hidrocarburo halogenado tal como diclorometano) a aproximadamente 0°C. Alternativamente, los N-óxidos de los compuestos de Fórmula I se pueden preparar a partir del N-óxido de un material de partida apropiado.

Los compuestos de Fórmula I en forma no oxidada se pueden preparar a partir de los N-óxidos de los compuestos de Fórmula I por tratamiento con un agente reductor (v g., azufre, dióxido de azufre, trifenilfosfina, borohidruro de litio, borohidruro de sodio, tricloruro o tribromuro de fósforo, o análogos) en un disolvente orgánico inerte adecuado (v g, acetonitrilo, etanol, dioxano acuoso, o análogos) a 0 hasta 80°C.

Los derivados profármaco de los compuestos de Fórmula I se pueden preparar por métodos conocidos por quienes poseen una experiencia ordinaria en la técnica (v g, para detalles adicionales véase Saulnier *et al* (1994, *Bioorganic and Medicinal Chemistry Letters*, Vol 4, p 1995). Por ejemplo, se pueden preparar profármacos apropiados por reacción de un compuesto no derivatizado de Fórmula I con un agente de carbamilación adecuado (v g, 1,1-aciloxialquilcarbonoclorurato, carbonato de *para*-nitrofenilo, o análogos).

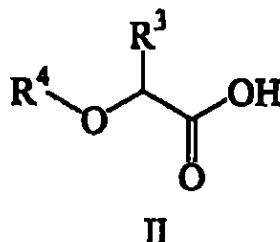
Los derivados protegidos de los compuestos de Fórmula I se pueden preparar por medios conocidos por quienes poseen una experiencia ordinaria en la técnica. Una descripción detallada de los métodos aplicables para la creación de grupos protectores y su eliminación puede encontrarse en T W Greene, *Protecting Groups in Organic Synthesis*, 3ª edición, John Wiley & Sons, Inc 1999. Los compuestos de la presente invención se pueden preparar convenientemente, o pueden formarse durante el proceso de la invención, como solvatos (v g. hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar convenientemente por recristalización a partir de una mezcla disolvente acuoso/orgánica, utilizando disolventes orgánicos tales como dioxina, tetrahydrofurano o metanol. Los compuestos de Fórmula I se pueden preparar como sus estereoisómeros individuales por reacción de una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diastereoisómeros, separación de los diastereoisómeros y recuperación del enantiómero ópticamente puro. Si bien la resolución de los enantiómeros se puede llevar a cabo utilizando derivados diastereoisómeros covalentes de los compuestos de Fórmula I, se prefieren los complejos dissociables (v g, sales diastereoisómeras cristalinas). Los diastereoisómeros tienen propiedades físicas diferentes (v g, puntos de fusión, puntos de ebullición, solubilidades, reactividad, y análogos) y se

188
195

pueden separar fácilmente aprovechando estas diferencias. Los diastereoisómeros se pueden separar por cromatografía o, preferiblemente, por técnicas de separación/resolución basadas en las diferencias de solubilidad. El enantiómero ópticamente puro se recupera luego, junto con el agente de resolución, por cualquier medio práctico que no conduzca a racemización. Una descripción más detallada de las técnicas aplicables para la resolución de estereoisómeros de compuestos a partir de su mezcla racémica puede encontrarse en Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc (1981).

En resumen, los compuestos de Fórmula I se preparan por un proceso que comprende

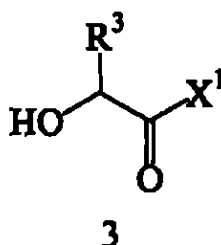
(A) hacer reaccionar un compuesto de Fórmula II



con un compuesto de la fórmula $\text{NH}_2\text{CR}^1\text{R}^2\text{X}^3$, en la cual X^3 , R^1 , R^2 , R^3 y R^4 son como se define en el Sumario de la Invención para la Fórmula I, o

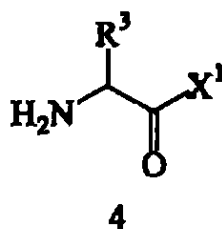
(B) hacer reaccionar un compuesto de Fórmula II con un compuesto de la fórmula NH_2X^4 , en la cual X^4 , R^3 y R^4 son como se define en el Sumario de la Invención para la Fórmula I, o

(C) hacer reaccionar un compuesto de Fórmula III



con un compuesto de fórmula R^4L , en el cual X^1 , R^3 y R^4 son como se define en el Sumario de la Invención y L es un grupo lábil, o

(D) hacer reaccionar un compuesto de Fórmula IV



con un compuesto de fórmula R^{15}L , en el cual X^1 , R^3 y R^4 son como se define en el Sumario de la Invención y L es un grupo lábil, y

- (E) convertir opcionalmente un compuesto de Fórmula I en una sal farmacéuticamente aceptable,
- (F) convertir opcionalmente una forma de sal de un compuesto de Fórmula I en una forma no salina,
- (G) convertir opcionalmente una forma no oxidada de un compuesto de Fórmula I en un *N*-óxido farmacéuticamente aceptable,
- (H) convertir opcionalmente una forma de *N*-óxido de un compuesto de Fórmula I en su forma no oxidada,
- (I) resolver opcionalmente un isómero individual de un compuesto de Fórmula I a partir de una mezcla de isómeros,
- (J) convertir opcionalmente un compuesto no derivatizado de Fórmula I en un derivado profármaco farmacéuticamente aceptable, y
- (K) convertir opcionalmente un derivado profármaco de un compuesto de Fórmula I en su forma no derivatizada

Ejemplos

La presente invención se ilustra adicionalmente, pero sin carácter limitante, por los ejemplos siguientes que ilustran la preparación de compuestos de Fórmula I y II (Ejemplos) y compuestos intermedios (Referencias) de acuerdo con la invención

Procedimientos de LC/MS

LC/MS (método A)

Espectrómetro de Masas (MS9 - Tiempo de Vuelo LCT (Micromass UK Ltd) No de Serie KA014

Modo de Ionización Pulverización Electrónica (Ion Positivo)

Barrido ToF MS (barrido total m/z 100-¹²00, suma para 0,4 s @ 50us/barrido)

Centroid Mode Liquid Chromatograph (LC) Hewlett Packard HP1100 Series Binary Pump (Serial # US80301343) & Degasser (serial # JP73008973)

Fase móvil

A = agua + tampón de 0,05% TFA (ácido tri-fluoro-acético)

B = acetonitrilo + tampón de TFA al 0,05%

Gradiente 5% B a 100% B en 5 minutos

Columna Hypersil BDS C-18, 3u, 4,6 mm x 50 mm,

Fase Inversa

Volumen de inyección 5 µl

Caudal 1 ml/min a la columna & al detector UV, división del flujo después del detector UV de tal modo que 0,75 ml/min van al detector ELS y 0,25 ml/min van al espectrómetro de masas

Detectores Auxiliares (i) Hewlett Packard Modelo HP1100 Series UV detector (serial # JP73704703)

Longitud de onda = 220 nm

(ii) Sedere (Francia) Modelo SEDEX 75 Evaporative Light Scattering (ELS) detector (serial # 9970002A)

Temperatura = 46°C, presión de nitrógeno = 4 bares

Tomador de muestras automático/Inyector Gilson Modelo 215 Liquid Handler con válvula de inyección Modelo 819 (serial # 259E8280)

LC/MS (método B)

Igual que el método A, pero con un gradiente diferente 5%B hasta 90%B en 3 minutos, 90%B hasta 100%B en 2 minutos

LC/MS (método C)

Espectrómetro de Masas (MS - Tiempo de Vuelo LCT (Micromass UK Ltd) Serial No KA014

Modo de ionización Pulverización Electrónica (Ion Positivo)

Barrido Tof MS (barrido total m/z 100-1200, suma para 0,4 s @ 50us/barrido)

Centroid Mode Liquid Chromatograph (LC) Hewlett Packard HP1100 Series Binary Pump (Serial # US80301343) & Degasser (serial # JP73008973)

Fase móvil

A = agua + tampón de ácido fórmico al 0,1%

B = acetonitrilo + tampón de ácido fórmico al 0,1%

Gradiente 5%B a 90%B en 3 minutos, 90%B a 100%B en 2 mm.

Columna. Phenomenex Synergi C-18, 2u, 4 mm x 20 mm, Fase Inversa

Volumen de inyección 5 μ l

Caudal 1 ml/min a la columna & al detector UV, con división del flujo después del detector UV de tal modo que 0,75 ml/min van al detector ELS y 0,25 ml/min van al espectrómetro de masas

Detectores Auxiliares (i) Hewlett Packard Modelo HP1100 Series UV detector (serial # JP73704703)

Longitud de onda = 220 nm

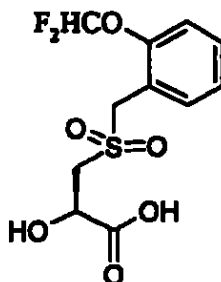
(ii) Sedere (Francia) Modelo SEDEX 75 Evaporative Light Scattering (ELS) detector (serial # 9970002A)

Temperatura = 46°C, presión de nitrógeno = 4 bares

Tomador de muestras automático/Inyector Gilson Modelo 215 Liquid Handler con válvula de inyección Modelo 819 (serial # 259E8280)

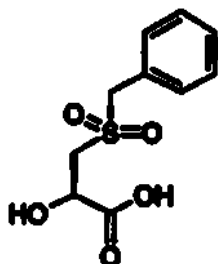
EJEMPLO DE REFERENCIA 1

(a) Ácido (R)-3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonyl]-2-hidroxi-propiónico



Una solución de ácido (R)-2-*terc*-butoxicarbonil-amino-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-propiónico (5,19 g) en CH_2Cl_2 (20 ml), se trató con ácido trifluoroacético (20 ml) a la temperatura ambiente. Después de dos horas, la mezcla de reacción se concentró a presión reducida. El sólido blanco obtenido se disolvió en H_2SO_4 1M (100 ml) y dioxano (30 ml). La solución se enfrió a 0°C y se añadió NaNO_2 (1,95 g en 50 ml de agua) con agitación durante 1 hora. La mezcla de reacción se agitó durante una noche a la temperatura ambiente. El producto se concentró luego y se extrajo con acetato de etilo, se secó con MgSO_4 anhidro, se filtró, se concentró y se recristalizó en acetato de etilo para dar ácido (R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-2-hidroxi-propiónico (2,36 g).

b) Acido (R) 2 hidroxi 3 fenilmetanosulfoni propionico



Procediendo de una manera similar al Ejemplo de Referencia 1(a) anterior pero utilizando acido (R) 2 *tert* butoxi carbonilamino 3 [(fenilmetanosulfoni) propionico se preparo acido (R) 2 hidroxi 3 fenilmetano-sulfoni propionico

EJEMPLO DE REFERENCIA 2

(R) 2-Amino-N metoxi-N-metil butiramida

A una solucion de acido [(R) 1 (metoxi metil carbamoi) propil] carbamico *tert* butil ester (4.92 g, 20 mmol) en CH₂Cl₂ (20 ml) se afadio TFA (10 ml) a la temperatura ambiente. Despues de agitar durante dos horas, la mezcla de reaccion se concentro a sequedad a presion reducida para producir (R) 2 amino N metoxi N-metil butiramida sal de TFA (5.4 g)

EJEMPLO DE REFERENCIA 3

Acido (R) 3 [2 (1,1 difluoro metoxi)-fenilmetanosulfoni] 2 trisopropilaminoxipropionico

Se hizo reaccionar acido (R) 3 [2 (1,1 difluoro metoxi) fenilmetanosulfoni] 2-hidroxi propionico (7.0 g, 22.58 mmol), en CH₂Cl₂ (50 ml) con 2,6 lutidina (12.09 g, 111.9 mmol) y trisopropilamilo trifluoro metanosulfonato (20.75 g, 67.74 mmol) a 78°C durante 1 hora. Se deajo calentar la mezcla de reaccion a la temperatura ambiente antes de enfriarla rapidamente por adiccion de solucion saturada de cloruro de amonio. El producto se extrajo con acetato de etilo, se elimino el disolvente a presion reducida y el residuo aceitoso se disolvio luego en EtOH THF H₂O (3:1:1, 60 ml). Se afadio K₂CO₃ solido (24 g) a la temperatura ambiente y la mezcla se agito durante 1 hora. se filtro se extrajo con acetato de etilo se seco con MgSO₄ anhidro, se filtro y se concentro para dar acido (R) 3 [2 (1,1-difluoro metoxi) fenilmetanosulfoni]-2 trisopropilaminoxipropionico (8.58 g)

Seguendo como en la referencia 3, se proporcionó el compuesto intermedio siguiente
Ácido (R)-3-fenilmetanosulfonyl-2-trisopropylsilyloxy-propionic

EJEMPLO DE REFERENCIA 4

Ácido 3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-propionico

Una mezcla de [2-(1,1-difluoro-metoxi)-fenil]-metanotiol (190 mg, 1,0 mmol), ácido acrílico (69 μ l, 1,0 mmol), diisopropiletilamina (440 μ l, 1,1 mmol) y 0,5 ml de dimetilformamida se agitó a 45°C durante cuatro horas. Se añadieron dietil-éter (5 ml) y HCl 1N (2 ml). Se separaron las capas y la capa orgánica se lavó con HCl 1N (2 ml), se secó sobre $MgSO_4$ y se concentró. El aceite resultante se disolvió en metanol (5 ml), se trató con una solución acuosa (5 ml) de Oxone® (921 mg, 1,5 mmol), y se agitó durante 1 hora. Se eliminó el metanol a presión reducida y se añadieron 20 ml de agua. La mezcla se extrajo con dos porciones de 60 ml de acetato de etilo, se secó sobre $MgSO_4$ y se concentró para dar ácido 3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-propionico (160 mg, 0,54 mmol, rendimiento 54%)

EJEMPLO DE REFERENCIA 5

Ácido 3-bencilsulfanyl-2-(2-nitro-fenilamino)-propionico

Se combinaron S-bencilcisteína (1,06 g, 5,0 mmol), 2-fluoronitrobenceno (1,05 ml, 10,0 mmol), carbonato de potasio (1,38 g, 10,0 mmol) y dimetilformamida (3 ml), y se agitaron a 100°C durante cuatro horas. La mezcla se diluyó con 40 ml de agua y se lavó con dos porciones de 15 ml de dietil-éter. La capa acuosa se acidificó a pH 4 con HCl 6N y se extrajo con dos porciones de 30 ml de acetato de etilo. La capa de acetato de etilo se secó sobre $MgSO_4$, y se concentró. Se añadió dietil-éter y se decantó luego para dar ácido 3-bencilsulfanyl-2-(2-nitro-fenilamino)-propionico (541 mg, 1,63 mmol, rendimiento 33%)

EJEMPLO DE REFERENCIA 6

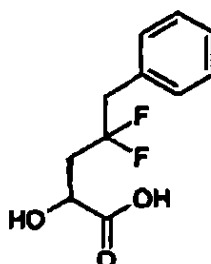
Ácido (R)-3-bencilsulfanyl-2-(5-nitro-tiazol-2-ilamino)-propionico

Se agitaron S-bencilcisteína (0,845 g, 4 mmol) y bis(trimetilsilil)acetamida (3 ml, 16 mmol) a 75°C durante 1 hora. Se añadió 2-bromo-5-nitrotiazol (837 mg, 4 mmol) y tolueno (8 ml) y la mezcla se agitó a 100°C durante 1 día. Se eliminó el tolueno a presión reducida. El residuo se agitó en 5 ml de dioxano y 5 ml de HCl 1N durante 30 minutos. Se eliminó el dioxano a presión reducida y la mezcla se basificó con $NaHCO_3$ saturado y se lavó con 50 ml

de acetato de etilo La capa acuosa se acidificó con HCl 6 N y se extrajo con dos porciones de 25 ml de acetato de etilo, se secó sobre MgSO_4 , se concentró y se cromatógrafió utilizando un gradiente de metanol al 5-10% en cloruro de metileno para dar ácido (R)-3-bencilsulfanil-2-(5-nitro-bazol-2-ilamino)-propionico (42,7 mg, 0,123 mmol, rendimiento 3%)

EJEMPLO DE REFERENCIA 7

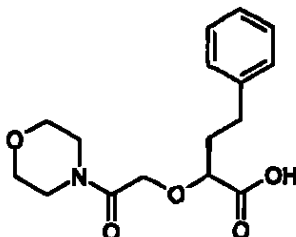
Ácido (2S)-4,4-difluoro-2-hidroxi-5-fenil-pentanoico



A una suspensión de ácido (S)-2-amino-4,4-difluoro-5-fenilpentanoico (1,0 mmol, 230 mg) en agua (3 ml) se añadió gota a gota ácido sulfúrico 2M hasta que se disolvió el sólido (aprox 3 ml) Se añadió luego gota a gota una solución de nitrito de sodio (1,5 eq, 1,5 mmol, 104 mg) en 1 ml de agua La mezcla se agitó a la temperatura ambiente durante 21 horas y se extrajo luego dos veces con éter (30 ml) Las capas orgánicas se secaron sobre MgSO_4 y se concentraron luego a vacío para proporcionar ácido (2S)-4,4-difluoro-2-hidroxi-5-fenil-pentanoico (90 mg, 39%) como un sólido blanco ^1H NMR (CDCl_3) 7,3 (m, 5H), 5,6 (b, 1H), 4,61 (dd, $J = 8,5, 2,9$ Hz, 1H), 3,3 (t, $J = 16,8$ Hz, 2H), 2,45 (m, 1H), 2,2 (m, 2H)

EJEMPLO DE REFERENCIA 8

Ácido 2-(S)-(2-morfolin-4-il-2-oxo-etoxi)-4-fenil-butírico



Paso(1) A una solución enfriada (0°C) de (2R)-2-hidroxi-4-fenilbutirato de etilo (1,81 g, 8,71 ml), ácido 4-nitro-benzoico (1,1 eq, 9,56 mmol, 1,598 g) y trifetil-fosfina (1,1 eq, 9,5

mmol, 2,50 g) en THF seco (80 ml) bajo nitrógeno se añadió lentamente azodicarboxilato de dietilo (1,1 eq , 9,56 mmol, 1,67 g) La mezcla se agitó a 0°C durante 2,5 horas y se concentró luego a vacío El residuo se trituró con una mezcla de acetato de etilo y heptano (1 3, 150 ml) y los sólidos resultantes se separaron por filtración El filtrado se concentró a vacío y se purificó sobre 110 g de gel de sílice, eluyendo con una mezcla de acetato de etilo y heptano (1 4, v/v) para proporcionar ácido 4-nitrobenzoico-(S)-1-etoxicarbonil-3-fenil-propil-éster (3,4 g, 98%)

Paso (ii) A una solución enfriada (0°C) de ácido 4-nitro-benzoico-(S)-1-etoxicarbonil-3-fenil-propil-éster (2,04 g, 5,83 mmol) en MeOH (30 ml) se añadió carbonato de potasio (1,5 eq , 8,75 mmol, 1,21 g) La mezcla se agitó a 0°C durante 5 minutos y luego a la temperatura ambiente durante 1,5 horas, y se concentró a vacío El residuo se repartió entre agua (40 ml) y acetato de etilo (40 ml) La capa orgánica se secó sobre MgSO₄ y se concentró luego a vacío El residuo se purificó sobre 35 g de gel de sílice, y se eluyó con diclorometano para proporcionar (2S)-2-hidroxi-4-fenil-butirato de metilo como un aceite incoloro (933 mg, 82%)

Paso (iii) A una solución de (2S)-2-hidroxi-4-fenil-butirato de metilo (300 mg, 1,54 mmol) en DMF seca (3 ml) bajo nitrógeno se añadió hidruro de sodio (60%, 1,5 eq , 2,32 mmol, 92,7 mg) Después de 5 min, se añadió 4-(2-cloroacetil)morfolina (1,1 eq , 1,69 mmol, 277 mg) y la mezcla se agitó a la temperatura ambiente durante 2cuatro horas, se diluyó luego con agua (60 ml) y se neutralizó después con HCl 1N La solución acuosa se extrajo dos veces con acetato de etilo (40 ml) La capa orgánica se lavó con agua (50 ml), se secó sobre MgSO₄ y se concentró luego a vacío El residuo se purificó sobre 35 g de gel de sílice, eluyendo con acetato de etilo y luego con MeOH al 5% en acetato de etilo para proporcionar ácido (S)-2-(2-morfolin-4-il-2-oxo-etoxi)-4-fenil-butírico-metil-éster (117 mg, 24%)

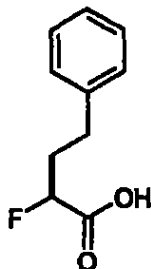
Paso (iv) A una solución de ácido (S)-2-(2-morfolin-4-il-2-oxo-etoxi)-4-fenil-butírico-metil-éster (117 mg, 0,36 mmol) en MeOH H₂O (2 1 vol, 3 ml) se añadió hidróxido de litio hidratado (2,0 eq , 0,73 mmol, 30,5 mg) La mezcla se agitó a la temperatura ambiente durante 5 horas, se diluyó luego con agua (30 ml) y se extrajo después con éter (30 ml) La capa acuosa se acidificó con HCl 1N y se extrajo dos veces con éter (30 ml) Los extractos ácidos se secaron sobre MgSO₄ y se concentraron luego a vacío para proporcionar ácido (S)-2-(2-morfolin-4-il-2-oxo-etoxi)-4-fenil-butírico (85,5 mg, 77%) como un aceite incoloro ¹H NMR (CDCl₃) 10,5 (b, 1H), 7,2 (m, 5H), 4,55 (d, J = 15,2 Hz, 1H), 4,14 (d, J = 15,2 Hz, 1H), 3,9 (dd, J = 7,6, 4,2 Hz, 1H), 4,6 (m, 6H), 3,4 (m, 2H), 2,8 (m, 2H), 2,3 (m, 1H), 2,15 (m, 1H)

LC/MS 96% (M+1) 308

202
203

EJEMPLO DE REFERENCIA 9

Ácido (2S)-2-fluoro-4-fenil-butírico

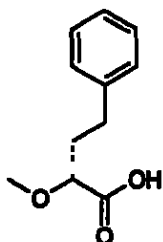


Paso(i) A una solución enfriada (0°C) de (2R)-2-hidroxi-4-fenil-butarato de metilo (1,00 g, 4,80 mmol) en diclorometano seco (3 ml) se añadió DAST (3,0 eq , 14,4 mmol, 2,32 g) La mezcla se agitó a la temperatura ambiente durante 18 horas, se diluyó luego con diclorometano (20 ml) y se enfrió con rapidez cuidadosa-mente con bicarbonato de sodio saturado (150 ml) La capa acuosa se extrajo con diclorometano (30 ml) y las capas orgánicas se secaron sobre MgSO₄ y se concentraron luego a vacío El residuo se purificó sobre 50 g de gel de sílice, eluyendo con una mezcla de diclorometano y heptano (1 2 y luego 1 1, v/v) para proporcionar 2S-fluoro-4-fenil-butarato de metilo como un aceite amarillo claro (578 mg, 57%)

Paso (ii) A una solución de 2S-fluoro-4-fenil-butarato de metilo (577 mg, 2,74 mmol) en una mezcla de MeOH H₂O (2 1 vol, 6 ml) se añadió hidróxido de litio monohidratado (1,5 eq , 4,11 mmol, 173 mg) La mezcla se agitó a la temperatura ambiente durante 5 horas y se concentró luego a vacío El residuo se diluyó con agua (30 ml) y se extrajo con éter (20 ml) La capa acuosa se acidificó con HCl y se extrajo con éter (30 ml) El extracto ácido se secó sobre MgSO₄ y se concentró luego a vacío para proporcionar ácido 2(S)-fluoro-4-fenil-butírico como un aceite amarillo (486 mg, 97%) ¹H NMR (CDCl₃) 7,5 (b, 1H), 7,3 (m, 5H), 4,95 (ddd, J = 48,9, 6,9, 5,4 Hz, 1H), 2,85 (m, 2H), 2,25 (m, 2H) MS (CI) M+1 183

EJEMPLO DE REFERENCIA 10

Ácido 2(R)-metoxi-4-fenil-butírico



Paso 1 A una solución de (2R)-2-hidroxi-4-fenil-butirato de etilo (500 mg, 2,40 mmol) en DMF seca (4 ml) bajo nitrógeno se añadió hidruro de sodio (60%, 2,0 eq , 4,80 mmol, 192 mg) seguido por yoduro de metilo (3,0 eq , 7,20 mmol, 1,02 g) La mezcla se agitó a la temperatura ambiente durante 22 horas, se diluyó luego con NH₄Cl (100 ml) y se extrajo con acetato de etilo (50 ml) La capa orgánica se secó sobre MgSO₄ y se concentró luego a vacío El residuo se purificó sobre 35 g de gel de sílice, eluyendo con acetato de etilo y heptano (1 3, v/v) para proporcionar ácido (R)-2-metoxi-4-fenil-butírico-etil-éster (480 mg, 90%)

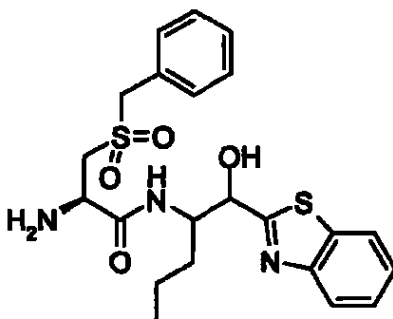
Paso 2 A una solución de ácido (R)-2-metoxi-4-fenil-butírico-etil-éster (480 mg, 2,8 mmol) en MeOH H₂O (2 1 vol, 9 ml) se añadió hidróxido de litio hidratado (2,0 eq , 4,32 mmol, 181 mg) La mezcla se agitó a la temperatura ambiente durante 2,5 horas, se diluyó luego con agua (20 ml) y se extrajo después con éter (20 ml) La capa acuosa se acidificó con HCl 1N y se extrajo luego dos veces con éter (30 ml) Los extractos reunidos se secaron sobre MgSO₄ y se concentraron luego a vacío para proporcionar ácido 2(R)-metoxi-4-fenil-butírico (426 mg, cuantitativo) como un sólido incoloro ¹H NMR (CDCl₃) 7,25 (m, 5H), 3,8 (dd, J = 6,8, 5,2 Hz, 1H), 3,48 (s, 3H), 2,78 (t, J = 7,3 Hz, 2H), 2,1 (m, 2H) MS (CI) M 194

Siguiendo como en la referencia 10, pero utilizando bromuro de bencilo en el Paso 2, se proporcionó el compuesto intermedio siguiente

Ácido 2(R)-benciloxi-4-fenil-butírico

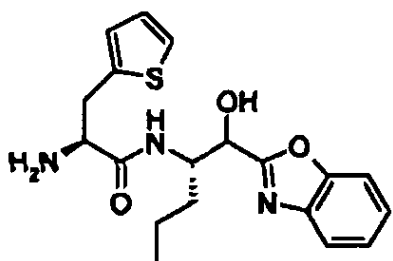
EJEMPLO DE REFERENCIA 11

(a) (R)-2-Amino-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida



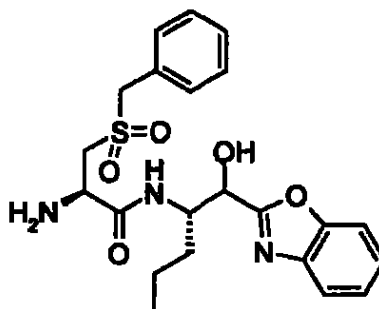
Una solución de ácido {(R)-1-[1-(benzotiazol-2-il-hidroxi-metil)-butil]carbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*butil-éster {888 mg, 1,58 mmol, Ejemplo 27(a)} en diclorometano (5 ml) se trató con ácido trifluoroacético (5 ml) La mezcla se agitó a la temperatura ambiente durante 1 hora y se evaporó luego El residuo se disolvió en diclorometano (20 ml) y esta solución se trató con Silicycle Triamine (4,3 g, 16 mmol) La mezcla se agitó a la temperatura ambiente durante dos horas y se filtró luego El filtrado se evaporó para dar el compuesto del título (692 mg, 94%) LC/MS m/z = 562 (M+H)

(b) (S)-2-Amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-tiofen-2-il-propionamida



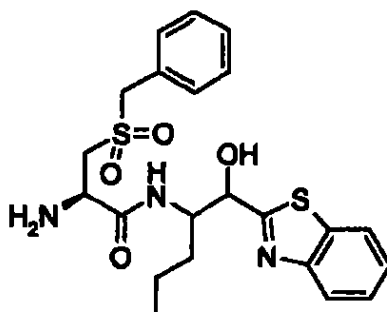
Procediendo de manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido {(S)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]carbamoil]-2-tiofen-3-il-etil}-carbámico-*terc*-butil-éster {790 mg, 1,67 mmol, Ejemplo 27(c)} y sometiendo el producto de reacción a cromatografía súbita sobre sílice eluyendo con una mezcla de acetato de etilo y metanol (9 l, v/v) se preparó (S)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-tiofen-2-il-propionamida (415 mg, 66%) LC/MS m/z = 374 (M+H)

- (c) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida



Procediendo de manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*tert*-butil-éster {908 mg, 1,66 mmol, Ejemplo 27(b)} se preparó (R)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida (726 mg, 98%) LC/MS $m/z = 446$ (M+H)

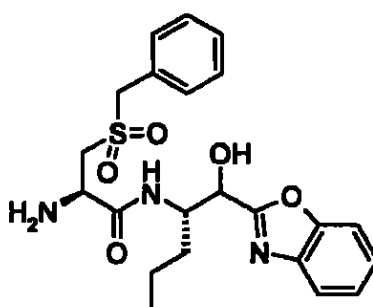
- (d) (R)-2-Amino-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida



Procediendo de manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido {(R)-1-[1-(benzotiazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*tert*-butil-éster {0,63 mmol, Ejemplo 27(d)} se preparó (R)-2-amino-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetano-sulfonil-propionamida (2¹² mg, 73%) LC/MS $m/z = 462$ (M+H)

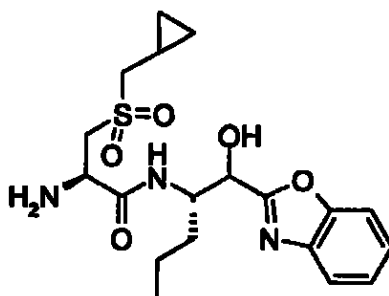
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- (e) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida



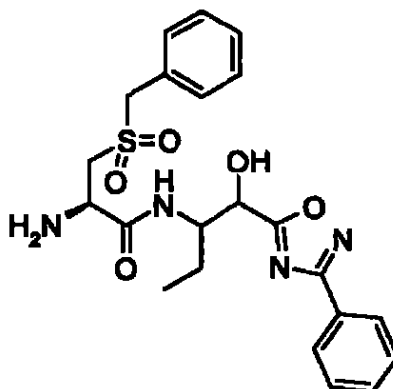
Procediendo de manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster {1,7 mmol, Ejemplo 27(e)} se preparó (R)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetano-sulfonil-propionamida (726 mg, 98%) LC/MS $m/z = 446$ (M+H)

- (f) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-ciclopropilmetanosulfonil-propionamida



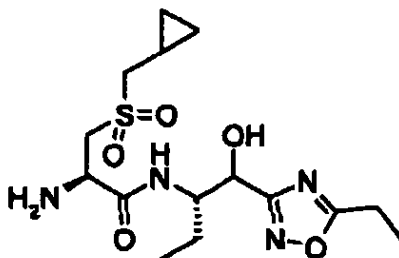
Procediendo de manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster {450 mg, 0,88 mmol, Ejemplo 27(f)} se preparó (R)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-ciclopropilmetanosulfonil-propionamida (360 mg, 0,879 mmol, 100%) LC/MS $m/z = 410$ (M+H)

- (g) (R)-2-Amino-N-{1-[hidroxí-(3-fenil-1,2,4-oxadiazol-5-il)-metil]-propil}-3-fenilmetanosulfonil-propionamida



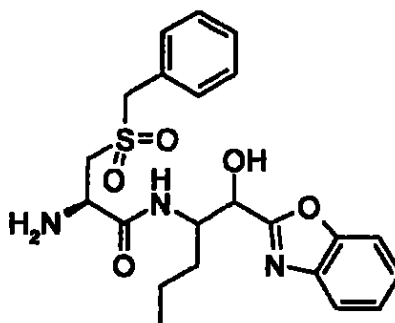
Procediendo de manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido (R)-1-{1-[hidroxí-(3-fenil-1,2,4-oxadiazol-5-il)-metil]-propil-carbamoyl}-2-fenilmetano-sulfonil-etil)-carbámico-*terc*-butil-éster {Ejemplo 27(g)} se preparó (R)-2-amino-N-{1-[hidroxí-(3-fenil-1,2,4-oxadiazol-5-il)-metil]-propil}-3-fenilmetanosulfonil-propionamida. LC/MS m/z = 481 (M+Na), 459 (M+H)

- (h) (R)-2-Amino-3-ciclopropilmetanosulfonil-N-[(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxí-metil]-propil]-propionamida



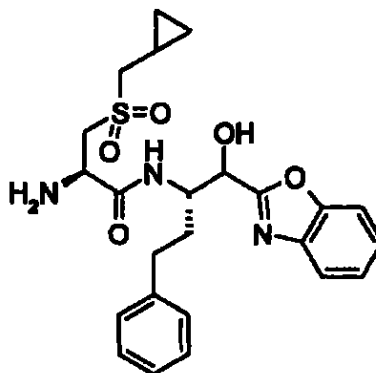
Procediendo de manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido ((R)-2-ciclopropilmetanosulfonil-1-{(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxí-metil]-propil-carbamoyl}-etil)-carbámico-*terc*-butil-éster {Ejemplo 27(i)} se preparó (R)-2-amino-3-ciclopropilmetanosulfonil-N-[(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxí-metil]-propil]-propionamida. LC/MS m/z = 375 (M+H)

- (i) (R)-2-Amino-N-[1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida



Procediendo de manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido {(R)-1-[1(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*tert*-butil-éster {Ejemplo 27(j)} se preparó (R)-2-amino-N-[1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida. LC/MS $m/z = 446$ (M+H)

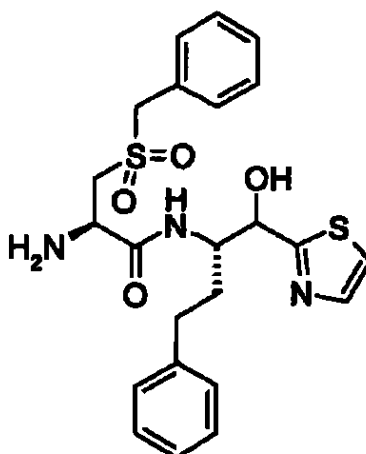
- (j) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-propil]-3-ciclopropilmetanosulfonil-propionamida



Procediendo de una manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-propilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*tert*-butil-éster {Ejemplo 27(k)} se preparó (R)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-propil]-3-ciclopropilmetanosulfonil-propionamida. LC/MS $m/z = 472$ (M+H)

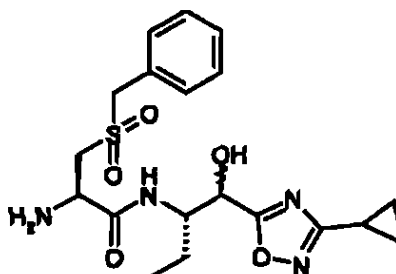
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- (k) (R)-2-Amino-N-[(S)-2-(hidroxí-tiazol-2-il-metil)-3-fenil-propil]-3-fenilmetanosulfonil-propionamida



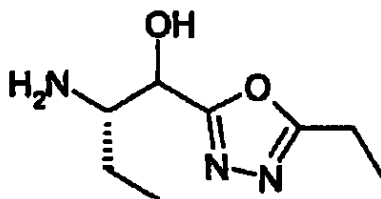
Procediendo de una manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando {(R)-1-[(S)-1-(hidroxí-tiazol-2-il-metil)-3-fenil-propilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster {Ejemplo 27(l)} se preparó (R)-2-amino-N-[(S)-1-(hidroxí-tiazol-2-il-metil)-3-fenil-propil]-3-fenilmetanosulfonil-propionamida

- (l) (R)-2-Amino-3-fenilmetanosulfonil-N-[(S)-1-[(3-ciclo-propil-1,2,4-oxadiazol-5-il)-hidroxí-metil]-propil]-propionamida



Procediendo de una manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido ((R)-2-fenilmetanosulfonil-1-[(S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroxí-metil]-propilcarbamoil]-etil)-carbámico-*terc*-butil-éster {Ejemplo 27(s)} se preparó (R)-2-amino-3-fenilmetanosulfonil-N-[(S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroxí-metil]-propil]-propionamida.

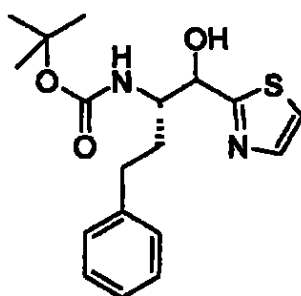
(m) 2-Amino-1-(5-etil-[1,3,4]oxadiazol-2-il)-butan-1-ol



Procediendo de una manera similar al Ejemplo de Referencia 11(a) anterior, pero utilizando ácido {1-[(5-etil-[1,2,4]oxadiazol-2-il)-hidroximetil]-propil}-carbámico *terc*-butil-éster (Ejemplo de Referencia 16) se preparó 2-amino-1-(5-etil-[1,3,4]oxadiazol-2-il)-butan-1-ol

EJEMPLO DE REFERENCIA 12

Ácido [(S)-1-(hidroxitiazol-2-il-metil)-3-fenil-propil]-carbámico-*terc*-butil-éster

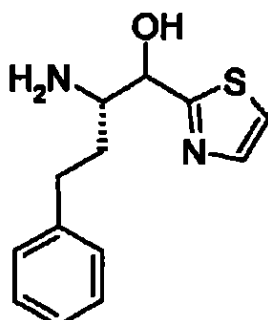


Se mezcló *n*-butil-litio (4,2 ml, 10,5 mmol, solución 2,5 M en hexanos) con 16 ml de dietil-éter y la solución resultante se enfrió a -78°C. Se disolvió 2-bromotiazol (1,64 g, 10 mmol) en una mezcla de 2 ml de dietil-éter y 1 ml de THF. Esta solución se añadió gota a gota a la solución de *n*-butil-litio. La mezcla de reacción resultante se agitó durante 15 min. Se añadió gota a gota a la mezcla de reacción una solución de ácido [(S)-1-(metoximetil-carbamoyl)-3-fenil-propil]-carbámico-*terc*-butil-éster (1,4 g, 4,3 mmol) en 20 ml de THF. Se continuó la agitación durante 1 hora y la mezcla de reacción se enfrió rápidamente por adición de 50 ml de agua. Después de calentar a la temperatura ambiente, se separaron las fases y la fase acuosa se extrajo con acetato de etilo. Las fases orgánicas reunidas se lavaron con salmuera y se secaron con sulfato de magnesio. Se evaporaron los disolventes a vacío para dar 1,4 g de ácido [(S)-3-fenil-1-(tiazol-2-carbonil)-propil]-carbámico-*terc*-butil-éster como un sólido pardo. Se disolvió el ácido [(S)-3-fenil-1-(tiazol-2-carbonil)-propil]-carbámico-*terc*-butil-éster (1,41 g, 4,1 mmol) en 50 ml de etanol y la solución se enfrió a 0°C. Se añadió borohidruro de sodio (155 mg, 4,1 mmol) y la mezcla de

reacción se agitó durante 90 minutos. Se añadió agua y la fase acuosa se acidificó por adición de ácido clorhídrico 1M. La fase acuosa se extrajo con acetato de etilo. Las fases orgánicas reunidas se lavaron con salmuera y se secaron con sulfato de magnesio. Se evaporó el disolvente a presión reducida (1,32, 3,8 mmol, 88%) LC/MS m/z = 271 (M+H-isobuteno), 249 (M+H-boc)

EJEMPLO DE REFERENCIA 13

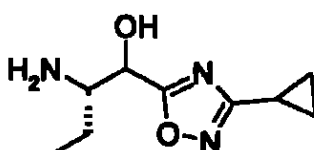
(S)-2-Amino-4-fenil-1-tiazol-2-il-butan-1-ol



Se disolvió ácido [(S)-1-(hidroxil-tiazol-2-il-metil)-3-fenil-propil]-carbámico-*tert*-butil-éster (1,32 g, 3,8 mmol, Ejemplo de Referencia ¹²) en 10 ml de diclorometano. Se añadió ácido trifluoroacético y la mezcla de reacción resultante se agitó durante dos horas. Se evaporaron los disolventes a presión reducida y se añadió solución saturada de bicarbonato de sodio. La solución se extrajo con acetato de etilo. Las fases orgánicas reunidas se lavaron con salmuera y se secaron con sulfato de magnesio. Se evaporó el disolvente y el producto bruto se purificó por cromatografía súbita (eluyendo con acetato de etilo seguido por 10% de metanol en acetato de etilo) para dar (S)-2-amino-4-fenil-1-tiazol-2-il-butan-1-ol (466 mg, 1,87 mmol, 49%) LC/MS m/z = 249 (M+H)

EJEMPLO DE REFERENCIA 14

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



Una solución de ácido boc-3-S-amino-3-hidroxi-pentanoico (2,00 g, 8,57 mmol) y 1,20 equivalentes de ciclopropanocarboxamidoxima (1, g, 10,29 mmol) en 20 ml de

diclorometano se agitó a 0°C mientras se añadían 1,25 equivalentes de N-ciclohexilcarbodiimida-N'-metil-poliestireno (1,70 mmol/g, 6,30 g, 10,72 mmol) en porciones, y la mezcla de reacción se agitó bajo nitrógeno durante tres horas, mientras se calentaba a 15°C. La mezcla de reacción se filtró y la resina se lavó con diclorometano. Se evaporó a vacío hasta sequedad [LC/MS m/z = 338 (M+H+Na)]. El residuo se disolvió en 20 ml de tetrahidrofurano y se calentó en un reactor de microondas a 160°C durante 3 minutos. Se evaporó a vacío hasta sequedad [LC/MS m/z = 320 (M+H+Na)]. El residuo se disolvió en 50 ml de diclorometano y se agitó a la temperatura ambiente mientras se añadía gota a gota una solución de 50 ml de ácido trifluoroacético al 50% en diclorometano. Después de tres horas, se evaporó la mezcla de reacción a vacío hasta sequedad y se disolvió nuevamente en 50 ml de diclorometano. Se añadieron 3 equivalentes de Silicycle-Triamine-3 y la mezcla se agitó durante una noche a la temperatura ambiente. Se filtró la mezcla y se lavó con diclorometano. Se evaporó a vacío para dar (S)-2-amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol, 1,04 g (rendimiento global 61%) [LC/MS m/z = 198 (M+H)].

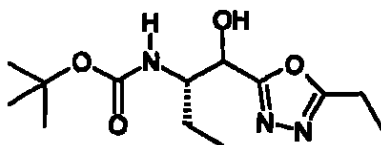
EJEMPLO DE REFERENCIA 15

Etil-1,3,4-oxadiazol

Una mezcla de la hidrazida fórmica (60 g, 1 mol), ortopropionato de trietilo (176,26 g, 1 mol) y ácido p-toluenosulfónico (950 mg) se calentó a 120°C durante 12 horas. Se eliminó el etanol a vacío y el residuo se destiló a vacío para dar 24 g de etil-1,3,4-oxadiazol. ^1H NMR (DMSO-d₆) 9,34 (1H, s), 2,86 (2H, q), 1,25 (3H, t).

EJEMPLO DE REFERENCIA 16

Ácido {1-[(5-etil-[1,3,4]oxadiazol-2-il)-hidroxil-metil]-propil}-carbámico-terc-butil-éster



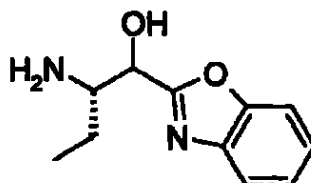
A una solución agitada de etil-1,3,4-oxadiazol (4,66 g, 48 mmol, Ejemplo de Referencia 15) en THF (50 ml) se añadió n-BuLi (solución 1,6M en 30 ml de hexano) gota a gota bajo N₂ a -78°C. Después de 1 hora, se añadió MgBr·Et₂O (12,38 g, 48 mmol) y la mezcla de reacción se dejó calentar a -45°C durante 1 hora antes de tratarla con 2-Boc-Nlu-aldehído (3,2 g, 24 mmol) en THF (20 ml). La mezcla de reacción se agitó durante 1 hora, se extinguió con NH₄Cl saturado, y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera,

213
214

se secó con MgSO_4 y se concentró. El residuo se purificó por cromatografía en columna de gel de sílice para dar ácido {1-[(5-etil-[1,3,4]oxadiazol-2-il)-hidroxi-metil]-propil}-carbámico-*tert*-butil-éster (2,13 g) ^1NMR ($\text{DMSO}-d_6$) 6,65, 6,52 (1H, d, d, $J = 9,2$ Hz, $J = 9,2$ Hz, NH, diastereoisómero), 6,14, 5,95 (1H, d, d, $J = 5,6$ Hz, $J = 5,6$ Hz, OH, diastereoisómero), 4,758, 4,467 (1H, m, diastereoisómero), 3,7-3,55 (1H, m), 2,8 (2H, q), 1,33 (^{12}H , t), 1,25-1,21 (2H, m), 0,82 (3H, m) MS 284,1 (M-1), 286 (M+1), 308 (M+Na)

EJEMPLO DE REFERENCIA 17

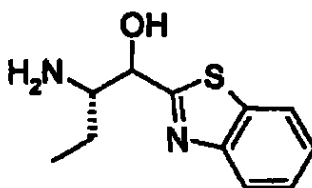
(a) (S)-2-Amino-1-benzooxazol-2-il-butan-1-ol



Paso 1 Se enfrió benzoxazol (600 mg, 5 mmol) en 20 ml de THF a -5°C y se añadió cloruro de isopropil-magnesio (2M en THF, 2,5 ml, 5 mmol). Después de agitar durante 1 hora a -5°C , se añadió ácido (S)-(1-formilpropil)-carbámico-*tert*-butil-éster {561 mg, 3 mmol, Ejemplo de Referencia 18(a)}, preparado como en la referencia 15, en 10 ml de THF. Se dejó calentar la reacción a la temperatura ambiente con agitación durante dos horas. La reacción se extinguió con solución saturada de cloruro amonio, y se eliminó el exceso de THF. El residuo se extrajo con EtOAc, se lavó con salmuera, se secó con MgSO_4 anhidro, se filtró y se concentró. El residuo bruto se purificó por cromatografía para dar 688 mg de producto (75%, LC-MS 305,2 (M-1), 307,1 (M+1)).

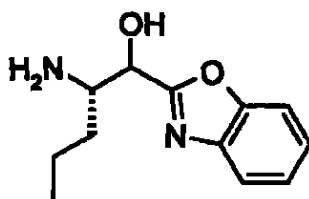
Paso 2 Se mezclaron ácido (S)-[1-(benzooxazol-2-il-hidroxi-metil)-propil]-carbámico-*tert*-butil-éster (275 mg, 0,89 mmol) y MeCl_2 (5 ml), y se añadió TFA (1 ml) a la temperatura ambiente. Después de agitar durante 1 hora, se eliminaron el disolvente y el exceso de TFA a vacío para producir 260 mg de (S)-2-amino-1-benzooxazol-2-il-butan-1-ol, sal de TFA.

(b) (S)-2-Amino-1-benzotiazol-2-il-butan-1-ol



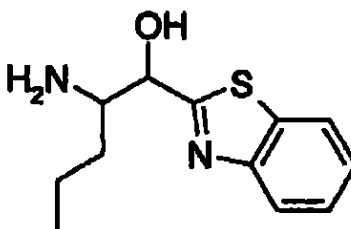
Procediendo de manera similar al Ejemplo 17(a), pero utilizando benzotiazol en el Paso 1, se preparó la sal de TFA de (S)-2-amino-1-benzotiazol-2-il-butan-1-ol

(c) (S)-2-amino-1-benzooxazol-2-il-pentan-1-ol



Procediendo de manera similar al Ejemplo 17(a), pero utilizando ácido (S)-(1-formil-butil)-carbámico-*tert*-butil-éster {561 mg, 3 mmol, Ejemplo de Referencia 18(b)} en el Paso 1, se preparó (S)-2-amino-1-benzooxazol-2-il-pentan-1-ol

(d) 2-Amino-1-benzotiazol-2-il-pentan-1-ol



Procediendo de una manera similar al Ejemplo 17(a), pero utilizando benzotiazol y ácido (S)-(1-formil-butil)-carbámico-*tert*-butil-éster {561 mg, 3 mmol, Ejemplo de Referencia 18(b)} en el Paso 1, se preparó 2-amino-1-benzotiazol-2-il-pentan-1-ol

EJEMPLO DE REFERENCIA 18

(a) Ácido (S)-(1-formil-propil)-carbámico-*tert*-butil-éster

Se enfrió (S)-(+)-2-amino-1-butanol (50 g, 561 mmol) en 200 ml de agua y 200 ml de dioxano a 0°C y se mezcló con NaOH (26,9 g, 673 mmol) y dicarbonato de di-*t*-butilo (146,96 g, 673 mmol). Después de la adición, se dejó calentar la mezcla de reacción a la temperatura ambiente. La mezcla de reacción se agitó durante dos horas. Después de eliminar el dioxano, el residuo se extrajo con EtOAc, se lavó luego con salmuera y se secó con MgSO₄ anhidro, se filtró y se concentró. Sin purificación ulterior, se utilizó el producto bruto (120 g) para el Paso de reacción siguiente.

Una solución de cloruro de oxalilo (40,39 g, 265 mmol) en 700 ml de MeCl₂ se agitó y se enfrió a -60°C. Se añadió gota a gota dimetilsulfóxido (51,7 g, 663 mmol) en 100 ml de MeCl₂. Después de 10 minutos, se añadió gota a gota a -70°C una solución de

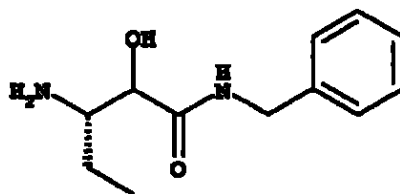
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216

(S)-2-boc-amino-1-butanol (50 g, 265 mmol) en 100 ml de MeCl₂. La mezcla de reacción se dejó calentar a -40°C durante 10 minutos y se enfrió luego nuevamente a -70°C. Se añadió una solución de trietilamina (74,9 g, 742 mmol) en 100 ml de MeCl₂. La mezcla de reacción se dejó calentar a la temperatura ambiente durante dos horas. Se añadieron 100 ml de dihidrogenofosfato de sodio saturado, y la capa orgánica se lavó luego con salmuera y se secó sobre MgSO₄. Se eliminó el disolvente para dar 45 g de ácido (S)-(1-formil-propil)-carbámico-*terc*-butil-éster; ¹H NMR (DMSO-*d*₆) 9,4 (1H, s), 7,29 (1H, br), 3,72 (1H, m), 1,69 (2H, m), 1,4-1,2 (9H, s), 0,86 (3H, t).

(b) Procediendo de una manera similar al Ejemplo de Referencia 18(a), pero utilizando (S)-(+)-2-amino-1-pentanol se preparó ácido (S)-(1-formil-butil)-carbámico-*terc*-butil-éster.

EJEMPLO DE REFERENCIA 19

Ácido (S)-3-amino-2-hidroxi-pentanoico-bencilamida



Paso 1 Se disolvió ácido (1S)-(2-ciano-1-etil-2-hidroxi-etil)carbámico-*terc*-butil-éster (10 g, 46,7 mmol) en 1,4-dioxano (100 ml). Se añadió anisol (5 ml) y luego HCl concentrado (100 ml). La mezcla se calentó a reflujo durante 2cuatro horas. Se evaporó la mezcla a sequedad a vacío y se redisolvió en 100 ml de agua. Se lavó la solución con éter y se neutralizó luego con NaHCO₃ acuoso saturado. Se añadió dicarbonato de di-*terc*-butilo (10 g, 46 mmol) con 1,4-dioxano (200 ml), y la mezcla se agitó a la temperatura ambiente durante 2cuatro horas. Se eliminó el dioxano a vacío y la solución acuosa remanente se lavó con éter. Se acidificó la solución con HCl 1N y se extrajo con acetato de etilo. Las capas orgánicas reunidas se lavaron con salmuera, se secaron con sulfato de magnesio y se evaporaron para dar ácido 3-*terc*-butoxicarbonilamino-2-hidroxi-pentanoico (4,5 g) como un aceite amarillento.

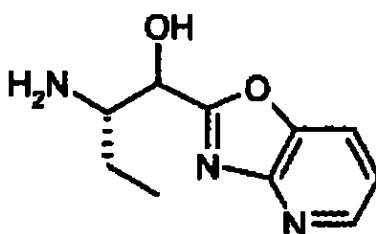
Paso 2 Se combinó ácido 3-*terc*-butoxicarbonilamino-2-hidroxi-pentanoico (300 mg, 1,29 mmol) con EDC (400 mg, 2,1 mmol) y HOBt (400 mg, 2,6 mmol). Se añadió en una sola porción una solución de bencilamina (0,22 ml) y 4-metilmorfolina (0,5 ml) en diclorometano (4 ml). La mezcla se agitó a la temperatura ambiente durante dos horas. Después de dilución

con acetato de etilo (150 ml), se lavó la solución con HCl acuoso 1N, agua, solución acuosa saturada de NaHCO₃ y salmuera. La mezcla resultante se secó con sulfato de magnesio y se evaporó a vacío para dar ácido (S)-3-amino-2-hidroxi-pentanoico-bencilamida (380 mg) como un sólido blanco

Paso 3 Se disolvió ácido (S)-3-amino-2-hidroxi-pentanoico-bencilamida en una mezcla de TFA/diclorometano (1 l, 6 ml), se agitó durante 1 hora y se evaporó a sequedad. Se obtuvo ácido (3S)-3-amino-2-hidroxi-pentanoico-bencilamida como la sal de TFA y se utilizó sin purificación ulterior

EJEMPLO DE REFERENCIA 20

(S)-2-amino-1-oxazolo[4,5-b]piridin-2-il-butan-1-ol



Paso 1 Una mezcla de 2-amino-3-hidroxipiridina (25 g, 227 mmol), ortoformiato de trietilo (75 ml) y ácido p-toluenosulfónico (61 mg) se calentó a 140°C durante 8 horas. Se eliminó a vacío el exceso de ortoformiato de trietilo. El producto se cristalizó en acetato de etilo para dar 22,5 g de piridiloxazol, ¹H NMR (DMSO-*d*₆) 9,26 (1H, s), 8,78 (1H, d), 8,45 (1H, d), 7,7 (1H, dd), MS ¹²0,8 (M+1)

Paso 2 Se enfrió piridiloxazol (600 mg, 5 mmol) en 30 ml de THF a 30°C antes de la adición de cloruro de isopropanilmagnesio (2M en THF, 2,5 ml, 5 mmol). Después de agitar durante 1 hora a 0°C, se añadió ácido (S)-(1-formil-propil)-carbámico-*tert*-butil-éster (573 mg, 3 mmol, Ejemplo de Referencia 18) en 20 ml de THF. Se retiró el baño de hielo y la mezcla de reacción se dejó calentar a la temperatura ambiente. La mezcla de reacción se agitó durante dos horas y se extinguió con solución saturada de cloruro de amonio. Se eliminó el exceso de HF y el residuo se extrajo con EtOAc, se lavó con salmuera, se secó con MgSO₄ anhidro, se filtró y se concentró. El residuo bruto se purificó por cromatografía para dar ácido [1-(hidroxioxazolo[4,5-b]piridin-2-il-metil)-propil]-carbámico-*tert*-butil-éster (383 mg) ¹H NMR (DMSO-*d*₆) 8,42 (1H, m), 8,18 (1H, m), 7,3 (1H, m), 6,8, 6,6 (1H, dd, d, OH, diastereoisómero), 6,3, 6,02 (1H, d, d, NH, diastereoisómero), 4,82, 4,5 (1H, m, m, diastereoisómero), 1,8-1,3 (2H, m), 1,2, 1,05 (9H, s, s, diastereoisómero), 0,89 (3H, m), MS

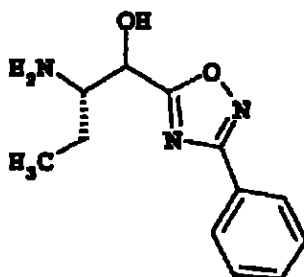
306,2 (M-1), 308,6 (M+1)

Paso 3 A una solución agitada de ácido [1-(hidroxí-oxazolo[4,5-*b*]piridin-2-il-metil)-propil]-carbámico-*terc*-butil-éster (¹² g, 100 mmol) en THF (300 ml) se añadió *n*-BuLi (solución 1,6M en 62,5 ml de hexano) gota a gota bajo N₂ a -78°C. Después de una hora, se añadió MgBr·Et₂O (25,8 g, 100 mmol) y la mezcla de reacción se dejó calentar a -45°C durante una hora antes de tratarla con 2-boc-amino-butíal-dehído (11,46 g, 60 mmol) en THF (50 ml). La mezcla de reacción se agitó durante una hora, se extinguió con NH₄Cl saturado y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó con MgSO₄ y se concentró. El residuo se purificó por cromatografía en columna de gel de sílice para dar 2-boc-amino-1-(5-piridiloxazol-2-il)-1-butanol (14,1 g).

Paso 4 Se mezclaron 2-boc-amino-1-(5-piridiloxazol-2-il)-1-butanol (311 mg, 1 mmol) y MeCl₂ (5 ml) y se añadió TFA (1 ml) a la temperatura ambiente. Después de agitar durante una hora, se eliminaron el disolvente y el exceso de TFA a vacío para producir 355 mg de 2-amino-1-oxazolo[4,5-*b*]piridin-2-il-butan-1-ol, sal de TFA.

EJEMPLO DE REFERENCIA 21

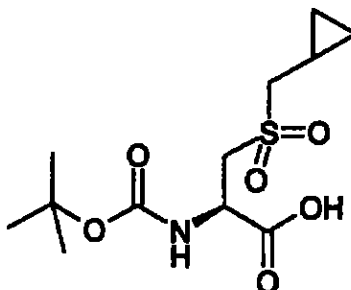
(S)-2-Amino-1-(3-fenil-[1,2,4]oxadiazol-5-il)-butan-1-ol



Se combinó ácido 3-*terc*-butoxicarbonilamino-2-hidroxi-pentanoico (500 mg, 2,14 mmol) con EDC (600 mg, 3,14 mmol), HOBt (600 mg, 3,92 mmol) y *N*-hidroxí-benzamídina (292 mg, 2,14 mmol). Se añadió diclorometano (10 ml) y a continuación 4-metilmorfolina (1 ml). La mezcla se agitó a la temperatura ambiente durante 16 horas. Después de dilución con acetato de etilo (200 ml), la solución se lavó con agua (30 ml), solución acuosa saturada de NaHCO₃ y salmuera, se secó con MgSO₄ y se evaporó a vacío. El producto bruto se disolvió en piridina (10 ml) y se calentó a 80°C durante 15 horas. Se evaporó la piridina a vacío y el residuo se purificó por cromatografía súbita sobre gel de sílice (eluyente: acetato de etilo) para dar 290 mg (0,83 mmol). Se disolvió el oxadiazol (145 mg, 0,41 mmol) en CH₂Cl₂ (4 ml) y se añadió TFA (4 ml). Después de agitar durante una hora, la mezcla se evaporó a sequedad para dar (S)-2-amino-1-(3-fenil-[1,2,4]oxadiazol-5-il)-butan-1-ol.

EJEMPLO DE REFERENCIA 22

Ácido (R)-2-*terc*-butoxicarbonilamino-3-ciclopropilmetano-sulfonil-propiónico

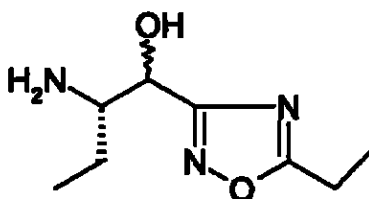


Paso 1 Se disolvió hidróxido de sodio (2,16 g, 54 mmol) en 27 ml de agua y la solución se añadió a una suspensión de ácido (R)-*terc*-butoxicarbonilamino-3-mercapto-propiónico (8,2 g, 37 mmol) en 54 ml de metanol. Después que se formó una solución clara, se añadió bromometil-ciclopropano (5 g, 37 mmol) y la mezcla de reacción resultante se agitó durante tres días. Se eliminó el metanol a presión reducida. El residuo se trató con 200 ml de ácido clorhídrico 1M y se extrajo luego tres veces con 200 ml de diclorometano. Las fases orgánicas reunidas se lavaron con salmuera y se secaron con sulfato de magnesio. El disolvente se evaporó a presión reducida para dar ácido 2-*terc*-butoxicarbonilamino-3-ciclopropil-metilsulfanil-propiónico (7,94 g).

Paso 2 Se disolvió hidróxido de sodio (2,32 g, 58 mmol) en 75 ml de agua. Se añadió ácido 2-*terc*-butoxicarbonil-amino-3-ciclopropilmetilsulfanil-propiónico (7,94 g, 29 mmol). Se añadió lentamente una solución de Oxone™ en 100 ml de agua. Se ajustó el pH a 3 por adición de bicarbonato de sodio y la mezcla de reacción se agitó durante 30 minutos. Se extrajo luego tres veces con 200 ml de acetato de etilo. Las fases orgánicas reunidas se lavaron con 100 ml de salmuera y se secaron con sulfato de magnesio. Se eliminó el disolvente para dar ácido (R)-2-*terc*-butoxicarbonilamino-3-ciclopropilmetanosulfonil-propiónico (4,64 g, 15 mmol, 31%).

EJEMPLO DE REFERENCIA 23

Sal de ácido trifluoroacético de (S)-2-amino-1-(5-etil-1,2,4-oxadiazol-3-il)-butan-1-ol



Paso 1 Una solución de ácido (2-ciano-1-etil-2-hidroxi-etil)-carbámico-*terc*-butil-éster (1, 9,53 g, 44 mmol) en metanol (80 ml) se enfrió a 0°C y se trató sucesivamente con hidrocloreuro de hidroxilamina (3,05, 44 mmol) en metanol (80 ml) y solución de metóxido de sodio al 25% en metanol (10,2 ml) Se agitó a 0°C durante 5 min, se retiró el baño frío y la mezcla de reacción se agitó a la temperatura ambiente durante 5 h Se eliminó el metanol por evaporación a presión reducida, y se repartió el producto bruto entre acetato de etilo y agua. Se separó la capa orgánica, se secó (MgSO₄) y se evaporó a presión reducida para dar un aceite amarillo Se purificó por mpic, eluyendo como una mezcla de acetato de etilo-heptano para dar ácido {(S)-1-[hidroxi-(N¹-hidroxycarbamimidoyl)-metil]-propil}-carbámico-*terc*-butil-éster [sic] como un sólido blanco (3,5 g) MS M(H⁺) 248

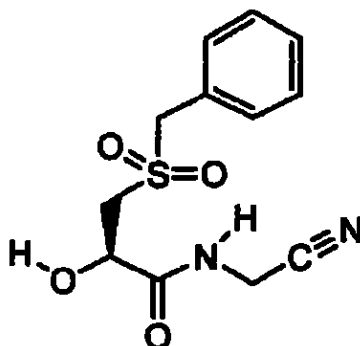
Paso 2 Una mezcla de ácido {(S)-1-[hidroxi-(N¹-hidroxycarbamimidoyl)-metil]-propil}-carbámico-*terc*-butil-éster [sic] (525 mg, 2,16 mmol), y anhídrido propiónico (0,3 ml, 2,37 mmol) en dioxano (5 ml) se calentó a 150°C en un equipo de microondas (Smith Creator, S00219) durante 35 min Se evaporó el producto bruto a presión reducida y se purificó por cromatografía súbita en columna para dar ácido {(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propil}-carbámico-*terc*-butil-éster como un sólido amarillo (0,8 g, 67%)

¹H-MNR (CDCl₃) 4,88-4,80 (2H, m), 4,01-3,84 (1H, 2 m ancho), 3,64-3,45 (1H, 2 bs), 2,95-2,86 (2H, dq, J = 4,2 Hz, 7,6 Hz), 1,73-1,62 (1H, m), 1,6-1,32 (13H, m), 1,02-0,94 (3H, q, J = 7,5 Hz) MS 304 (M+1)

Paso 3 Se trató ácido {(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propil}-carbámico-*terc*-butil-éster (214 mg, 0,75 mmol) en diclorometano (3 ml) con ácido trifluoro-acético a la temperatura ambiente durante 3 h Se evaporó el disolvente a presión reducida para dar la sal de ácido trifluoro-acético de (S)-2-amino-1-(5-etil-1,2,4-oxadiazol-3-il)-butan-1-ol como un aceite pardo (0,3 g) ¹H NMR (CDCl₃) 7,9-7,4 (3H, 2 bs), 5,07 & 5,24 (1H, 2 x d, J = 3,5 Hz & 5,5 Hz), 3,8-3,6 (1H, 2 bs), 2,96-2,87 (2H, dq, J = 2,4 Hz, 7,5 Hz), 1,8-1,4 (2H, m), 1,40-1,34 (3H, dt, J = 1,4 Hz, 7,5 Hz), 1,06-0,98 (3H, dt, J = 7,5 Hz, 10,5 Hz) MS 186 (M+1)

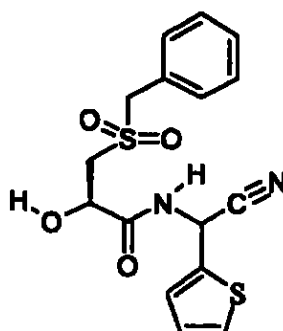
EJEMPLO 1

(a) (R)-N-Cianometil-2-hidroxi-3-fenilmetanosulfonil-propionamida (Compuesto 4)



Se añadió DMF (5 ml) a una mezcla de ácido 2-hidroxi-3-fenilmetanosulfonil-propiónico [200 mg, 0,82 mmol, Ejemplo de Referencia 1(b)], EDC (300 mg, 1,57 mmol), HOBt (300 mg, 1,96 mmol) e hidrocloreuro de aminoacetoniitrilo (200 mg, 2,1 mmol) Se añadió 4-metilmorfolina (0,5 ml) y la mezcla se agitó a la temperatura ambiente durante dos horas Se diluyó la mezcla con acetato de etilo (200 ml), se lavó con HCl 1N, salmuera, solución acuosa saturada de NaHCO₃, y salmuera, se secó con MgSO₄ y se evaporó a vacío Se cristalizó (R)-N-cianometil-2-hidroxi-3-fenilmetanosulfonil-propionamida a partir de acetato de etilo/hexano para dar 154 mg (0,55 mmol), ¹H NMR (DMSO) 8,89-8,87 (m, 1H), 7,46-7,37 (m, 5H), 6,71-6,62 (m, 1H), 4,60-4,45 (m, 3H), 4,17-4,08 (m, 2H), 3,39-3,28 (m, 2H) MS (M⁺+1) 283

(b) (R)-N-(1-ciano-1-tiofen-2-il-metil)-2-hidroxi-3-fenilmetanosulfonil-propionamida (Compuesto 7)

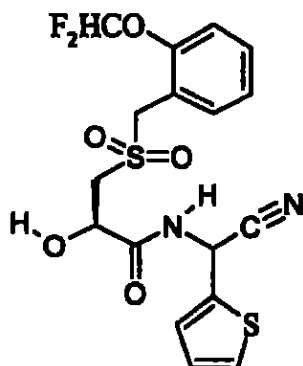


Procediendo de una manera similar al Ejemplo 1(a) anterior pero utilizando ácido (R)-2-hidroxi-3-fenilmetanosulfonil-propiónico [Ejemplo de Referencia 1(b)] y ácido DL-α-amino-3-tiofenoacético, se preparó (R)-N-(1-ciano-1-tiofen-2-il-metil)-2-hidroxi-3-fenilmetanosulfonil-propionamida ¹H NMR (DMSO) 9,55 (d, 4=6,5 Hz, 1H), 7,58 (d, J =

222

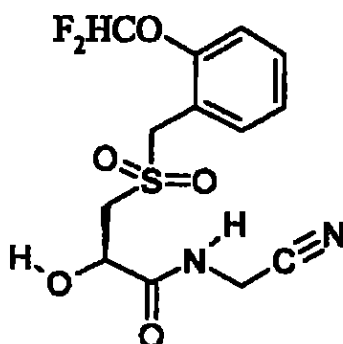
5,21 Hz, 1H), 7,42-7,39 (m, 5H), 7,23 (m, 1H), 7,05 (dd, J = 3,51 Hz, 1H), 6,58 (dd, J = 3,45 Hz, J = 6,66 Hz, 1H), 6,41 (s, 1H), 4,59-4,50 (m, 3H), 3,29 (s, 2H), MS 362,6 (M⁻), 365 (M⁺)

(c) (R)-N-(1-Ciano-1-tiofen-2-il-metil)-3-[2-(1,1-difluorometoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida, (Compuesto 8)



Procediendo de una manera similar al Ejemplo 1(a) anterior, pero utilizando ácido (R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propiónico [Ejemplo de Referencia 1(a)] y ácido DL- α -amino-2-tiofenoacético se preparó (R)-N-(1-ciano-1-tiofen-2-il-metil)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida ¹H NMR (CD₃Cl) δ 7,6-7,2 (m, 7H), 7,01 (t, J = 73,6 Hz, 1H), 6,62 (s, 1H), 6,21 (d, J = 8,15, 1H), 4,71-4,67 (m, 1H), 4,46 (s, 2H), 3,68 (s, 2H), 3,22-3,18 (m, 1H), MS 428,6 (M⁻), 453 (M+23)

(d) (R)-N-Cianometil-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida, (Compuesto 17)

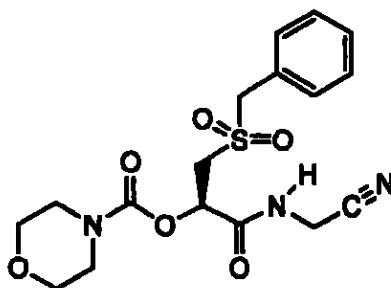


Procediendo de una manera similar al Ejemplo 1(a) anterior, pero utilizando ácido (R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propiónico [Ejemplo de Referencia 1(a)], se preparó (R)-N-cianometil-3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-2-hidroxi-propionamida ¹H NMR (DMSO) 8,81 (t, J = 5,67 Hz, 1H), 7,55-7,4 (m, 2H), 7,35-7,2 (m, 2H), 7,13 (t, J = 73,68 Hz, 1H), 6,62 (d, J = 6,67 Hz, 1H), 4,58 (s, 2H),

4,52-4,45 (m, 2H), 4, ¹² (d, J = 5,94 Hz, 2H), 3,45-3,4 (m, 2H) MS 347,4 (M-1), 371 (M+23)

EJEMPLO 2

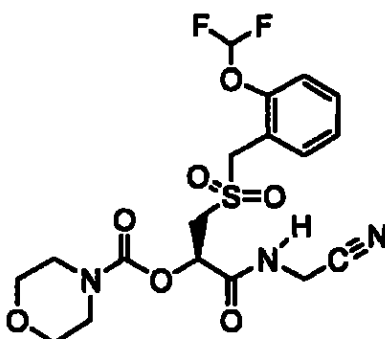
Ácido morfolina-4-carboxílico-(R)-1-(cianometil-carbamoyl)-2-fenilmetanosulfonil-etil-éster,
(Compuesto 6)



Se añadió solución de fosgeno (0,77 ml, 1,93 M en tolueno) a CH₂Cl₂ (5 ml) y se enfrió a 0°C bajo nitrógeno. Se añadió quinolina (0, ¹² ml, 1,0 mmol) seguida por (R)-N-cianometil-2-hidroxí-3-fenilmetano-sulfonil-propionamida [100 mg, 0,354 mmol, Ejemplo 1(a)]. La mezcla se agitó a la temperatura ambiente durante tres horas. Se añadió morfolina (1 mmol) y se continuó la agitación durante tres horas. Se diluyó la mezcla con acetato de etilo (200 ml) y se lavó sucesivamente con HCl 1N, salmuera, solución acuosa saturada de NaHCO₃ y salmuera. El producto se secó con MgSO₄ y se evaporó a vacío y cristalizó en una solución de acetato de etilo/hexano para dar ácido morfolina-4-carboxílico-(R)-1-(cianometil-carbamoyl)-2-fenilmetanosulfonil-etil-éster (85 mg, 0,215 mmol). ¹H NMR (DMSO) 8,99-8,88 (m, 1H), 7,46-7,37 (m, 5H), 5,42-5,32 (m, 1H), 4,60-4,45 (m, 2H), 4,20-4,13 (m, 2H), 3,70-3,28 (m, 10H) MS (M⁺+1) 396

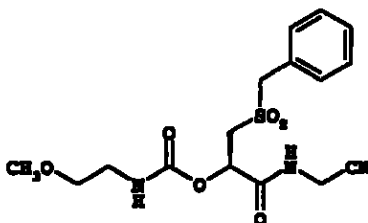
EJEMPLO 3

- (a) Ácido morfolina-4-carboxílico-(R)-1-(cianometil-carbamoyl)-2-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonyl]-etil-éster, (Compuesto 31)



Se disolvió (*R*)-*N*-cianometil-3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonyl]-2-hidroxi-propionamida [100 mg, 0,287 mmol, Ejemplo 1(d)] en CH₂Cl₂ (2 ml). Se añadieron piridina (32,4 µl, 0,4 mmol) y luego cloroformato de triclorometilo (36,2 µl, 0,3 mmol). La mezcla se agitó a la temperatura ambiente durante tres horas. Se añadió morfolina (0,5 ml) y se continuó la agitación durante tres horas. La mezcla se diluyó con acetato de etilo (200 ml), se lavó con HCl 1N, salmuera, solución acuosa saturada de NaHCO₃ y salmuera. Se secó con MgSO₄, se evaporó a vacío y se cristalizó en una solución de acetato de etilo/hexano para dar ácido morfolina-4-carboxílico-(R)-1-(cianometil-carbamoyl)-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-etil-éster (60 mg, 0,130 mmol), ¹H NMR (DMSO) δ 8,95 (t, J = 5,2 Hz, 1H), 7,51-7,44 (m, 2H), 7,32-7,22 (m, 2H), 7,14 (t, J_{H,F}=73 Hz, 1H), 5,39-5,35 (m, 1H), 4,67-4,53 (m, 2H), 4,19-4,15 (m, 2H), 3,83-3,28 (m, 10H), MS M⁺+1) 462

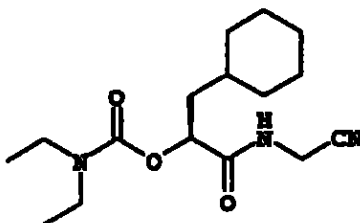
- (b) Ácido (R)-(2-metoxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-fenilmetanosulfonyl-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (*R*)-*N*-cianometil-2-hidroxi-3-fenilmetanosulfonyl-propionamida [Ejemplo 1(a)] y 2-metoxietilamina, se preparó ácido (R)-(2-metoxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-fenilmetanosulfonyl-etil-éster. ¹H NMR (DMSO) 8,91 (t, J = 5,6 Hz, 1H), 7,64 (t, J = 5,6 Hz, 1H), 7,40-7,32 (m, 5H), 5,30-5,25 (m, 1H), 4,59-4,50 (m, 2H), 4,17-4,13 (m, 2H), 3,58 (dd, J = 9,2 Hz, J = 14,8 Hz, 1H), 3,43 (d, 14,8 Hz, 1H), 3,33 (s, 3H), 3,38-3,12 (m,

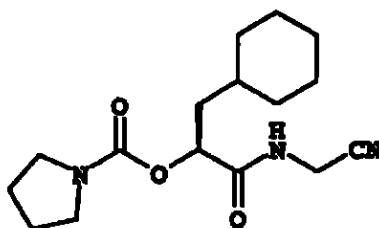
4H) MS (M+H)⁺ 384

(c) Ácido (S)-dietil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y dietilamina se preparó ácido (S)-dietil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR (DMSO) 8,62 (t, J = 5,6 Hz, 1H), 4,87-4,82 (m, 1H), 4, ¹² (d, J = 5,6, 2H), 3,42-3,10 (m, 4H), 1,72-0,82 (m, 19H) MS (M+H)⁺ 310

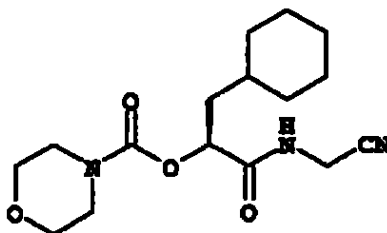
(d) Ácido (S)-pirrolidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y pirrolidina se preparó ácido (S)-pirrolidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR (DMSO) 8,59 (t, J = 4,8 Hz, 1H), 4,86-4,81 (m, 1H), 4,11 (d, J = 4,8, 2H), 3,48-3,19 (m, 4H), 1,87-0,82 (m, 17H) MS (M+H)⁺ 308

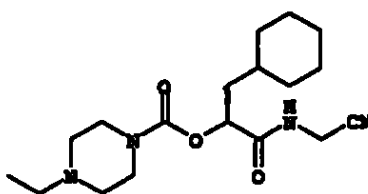
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(e) Ácido (S)-morfolina-4-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



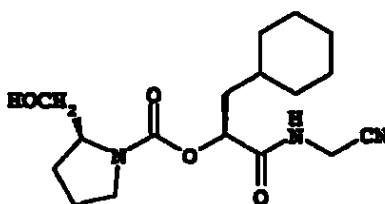
Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y morfolina se preparó ácido (S)-morfolina-4-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR (DMSO) 8,66 (t, J = 5,2 Hz, 1H), 4,88-4,83 (m, 1H), 4,13 (d, J = 4,8, 2H), 3,60-3,26 (m, 8H), 1,71-0,82 (m, 13H) MS (M+H)⁺ 324

(f) Ácido (S)-4-etil-piperazina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y 4-etil-piperazina se preparó ácido (S)-4-etil-piperazina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster LC-MS tiempo de elución 2,08 min 349,2 (M-1), 351,3 (M+1) (MS-API 150EX LC HP Agilent 1100 Series Columna Phenomenex, 5u ODS3 100A 100X3mm, caudal 2 ml/min Gradiente de dos disolventes Disolvente A, 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde t=0 a t=6 min A continuación vuelve el gradiente a 100% A, 0% B desde t=7 a t=15 min)

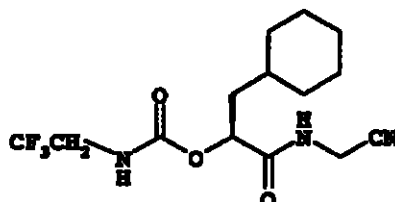
(g) Ácido (S)-2-hidroximetil-pirrolidina-1-carboxílico-(S)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



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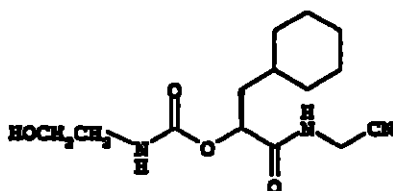
Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y (S)-2-hidroximetil-pirrolidina se preparó ácido (S)-2-hidroximetil-pirrolidina-1-carboxílico-co-(S)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster LC-MS tiempo de elución 3,73 min 336,5 (M-1), 338,2 (M+1) (MS-API 150EX LC HP Agilent 1100 Series Columna Phenomenex, 5u ODS3 100A 100X3mm, caudal 2 ml/min Gradiente de dos disolventes Disolvente A, 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde t=0 a t=6 min A continuación vuelve el gradiente a 100% A, 0% B desde t=7 a t=15 min)

(h) Ácido (S)-(2,2,2-trifluoro-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y 2,2,2-trifluoroetilamina se preparó ácido (S)-(2,2,2-trifluoro-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster LC-MS tiempo de elución 4,07 min 336,5 (M-1), 334,1 (M-1), 336,2 (M+1) (MS-API 150EX LC HP Agilent 1100 Series Columna Phenomenex, 5u ODS3 100A 100X3mm, caudal 2 ml/min Gradiente de dos disolventes Disolvente A, 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde t=0 a t=6 min A continuación vuelve el gradiente a 100% A, 0% B desde t=7 a t=15 min)

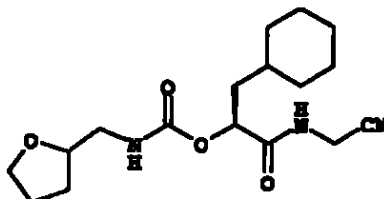
(i) Ácido (S)-(2-hidroxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y 2-hidroxi-etilamina se preparó ácido (S)-(2-hidroxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR. (DMSO) 8,65 (t, J = 5,2 Hz, 1H), 7,16 (t, J = 5,2 Hz, 1H), 4,85-4,80 (m, 1H), 4,62 (t, J = 5,6 Hz, 1H), 4, ¹² (d, J = 5,6 Hz, 2H), 3,45-3,33 (m, 2H), 3, ¹²-2,96 (m, 2H), 1,74-0,80 (m, 13H), MS (M+H)⁺ 298

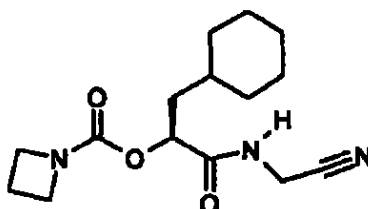
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(j) Ácido (tetrahydrofuran-2-ilmetil)-carbámico-(S)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



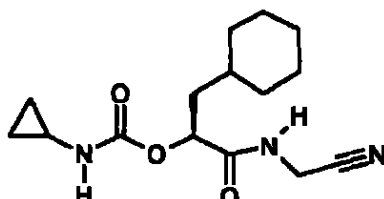
Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y tetrahydrofurfurilamina, se preparó ácido (tetrahydrofuran-2-ilmetil)-carbámico-(S)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster como una mezcla 1:1 de diastereoisómeros, ¹H NMR (DMSO) 8,66 (t, J = 5,2 Hz, 1H), 7,28 (t, J = 5,2 Hz, 1H), 4,86-4,81 (m, 1H), 4,1² (d, J = 5,2 Hz, 2H), 3,83-3,54 (m, 3H), 3,09-2,92 (m, 2H), 1,89-0,80 (m, 17H) MS (M+H)⁺ 338

(k) Ácido (S)-azetidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y azetidina, se preparó ácido (S)-azetidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR (DMSO) 8,59 (t, J = 5,2 Hz, 1H), 4,82-4,77 (m, 1H), 4,11 (dd, J = 5,2 Hz, 2H), 4,13-3,81 (m, 4H), 2,18 (quint, J = 7,6 Hz, 2H), 1,71-0,80 (m, 13H) MS (M+H)⁺ 294

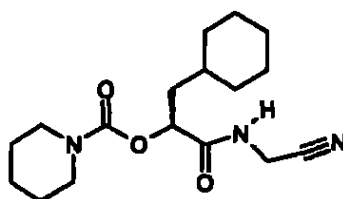
(l) Ácido (S)-ciclopropil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y ciclopropilamina se preparó ácido (S)-ciclopropil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR (DMSO) 8,64 (t, J = 5,2 Hz, 1H), 7,44 (br, 1H), 4,83-4,78 (m, 1H), 4,11 (d, J = 5,2 Hz, 2H), 2,50-2,40

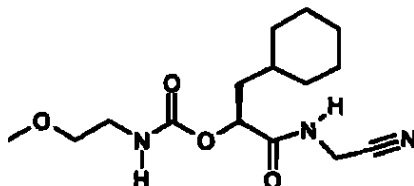
(m, 1H), 1,72-0,78 (m, 13H), 0,58-0,30 (m, 4H) MS (M+H)⁺ 294

(m) Ácido (S)-piperidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



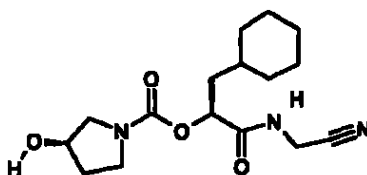
Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y piperidina se preparó ácido (S)-piperidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR (DMSO) 8,63 (t, J = 5,2 Hz, 1H), 4,86-4,81 (m, 1H), 4,11 (d, J = 5,6 Hz, 2H), 3,48-3,20 (m, 4H), 1,70-0,82 (m, 19H) MS (M+H)⁺ 322

(n) Ácido (S)-(2-metoxi-etil)carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y 2-metoxietilamina se preparó ácido (S)-(2-metoxi-etil)carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR (DMSO) 8,66 (t, J = 5,6 Hz, 1H), 7,27 (t, J = 5,6 Hz, 1H), 4,85-4,80 (m, 1H), 4,¹² (d, J = 5,6 Hz, 2H), 3,40-3,03 (m, 4H), 3,32 (s, 3H), 1,74-0,80 (m, 13H) MS (M+H)⁺ 312

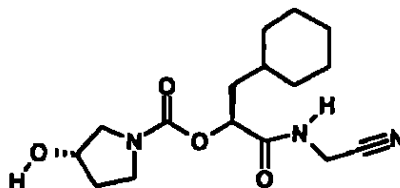
(o) Ácido (R)-3-hidroxi-pirrolidina-1-carboxílico-(S)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y (R)-3-hidroxi-pirrolidina se preparó ácido (R)-3-hidroxi-pirrolidina-1-carboxílico-(S)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR (DMSO) 8,64-8,56 (m, 1H), 4,98-4,80 (m, 2H), 4,29-4,20 (m, 1H), 4,11 (d, J = 5,2 Hz, 2H), 3,57-3,¹² (m, 4H), 1,91-0,82 (m, 15H) MS (M+H)⁺ 324

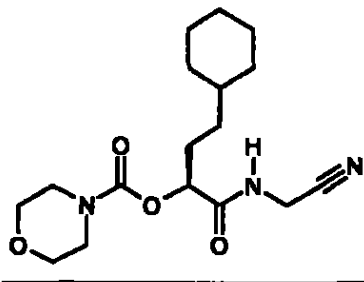
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230

(p) Ácido (S)-3-hidroxi-pirrolidina-1-carboxílico-(S)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y (S)-3-hidroxi-pirrolidina se preparó ácido (S)-3-hidroxi-pirrolidina-1-carboxílico-(S)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ^1H NMR (DMSO) 8,63-8,55 (m, 1H), 4,98-4,90 (m, 1H), 4,85-4,80 (m, 1H), 4,28-4,19 (m, 1H), 4,13-4,09 (m, 2H), 3,54-3,09 (m, 4H), 1,90-3,81 (m, 15H) MS (M+H)⁺ 324

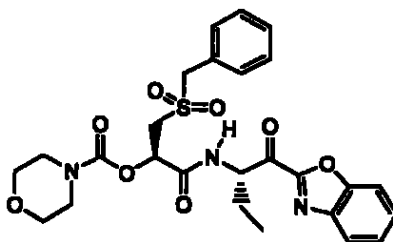
(q) Ácido (S)-morfolina-4-carboxílico-1-(cianometil-carbamoyl)-3-ciclohexil-propil-éster



Procediendo de una manera similar al Ejemplo 3(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida y morfolina se preparó ácido (S)-morfolina-4-carboxílico-1-(cianometil-carbamoyl)-3-ciclohexil-propil-éster ^1H NMR (DMSO) 8,61 (t, J = 5,6 Hz, 1H), 4,79 (t, J = 5,6 Hz, 1H), 4,13 (d, J = 5,2 Hz, 2H), 3,59-3,26 (m, 8H), 1,73-1,55 (m, 7H), 1,23-1,06 (m, 6H), 0,88-0,76 (m, 2H) MS (M+H)⁺ 338

EJEMPLO 4

(a) Ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-fenilmetanosulfonyl-etil-éster,
(Compuesto 11)



Paso 1 Se disolvió ácido (R)-2-hidroxi-3-fenilmetano-sulfonyl-propiónico {2g, 8,19 mmol, Ejemplo de Referencia 1(b)} en CH₂Cl₂ (20 ml) Se añadieron 4-metilmorfolina (3,8 ml) y luego clorometil-metil-éter (1,52 ml, 20 mmol) Después de agitar a la temperatura ambiente durante 30 minutos, la reacción se extinguió con agua (50 ml) y se extrajo con acetato de etilo Las capas orgánicas reunidas se lavaron con solución acuosa saturada de NaHCO₃ y salmuera. El producto se secó con MgSO₄, se evaporó a vacío y se cristalizó en acetato de etilo/hexano para dar el ácido 2-hidroxi-3-fenilmetano-sulfonyl-propiónico-metoximetil-éster (1,2 g, 4,16 mmol)

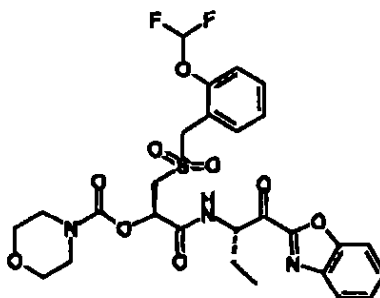
Paso 2 Se añadió solución de fosgeno (2,07 ml, 1,93 M en tolueno) a CH₂Cl₂ (10 ml) y se enfrió a 0°C bajo nitrógeno Se añadió quinolina (0,95 ml) seguida por ácido 2-hidroxi-3-fenilmetanosulfonyl-propiónico-metoxi-metil-éster (250 mg, 0,87 mmol) La mezcla se agitó a la temperatura ambiente durante tres horas Se añadió morfolina (0,35 ml, 4 mmol) y se continuó la agitación durante tres horas La mezcla se diluyó con acetato de etilo (200 ml), se lavó sucesivamente con HCl 1N, salmuera, solución acuosa saturada de NaHCO₃ y salmuera. El producto bruto se secó con MgSO₄, se evaporó a vacío y se disolvió en 1,4-dioxano (20 ml) Se añadió HCl 1N (10 ml) y la mezcla se agitó a la temperatura ambiente durante tres horas Se evaporó el dioxano a vacío y el producto se extrajo con acetato de etilo Las capas de acetato de etilo reunidas se lavaron con solución acuosa saturada de NaHCO₃ (3 x 20 ml) La solución de NaHCO₃ se acidificó con HCl 6N y se extrajo con acetato de etilo Las capas de acetato de etilo reunidas se lavaron con salmuera, se secaron con MgSO₄ y se evaporaron a vacío para dar ácido (R)-morfolina-4-carboxílico-1-carboxi-2-fenilmetano-sulfonyl-etil-éster

Paso 3 Se combinó el ácido (R)-morfolina-4-carboxílico-1-carboxi-2-fenilmetano-sulfonyl-etil-éster con EDC (250 mg, 1,3 mmol), HOBt (250 mg, 1,6 mmol) y (2S)-2-amino-1-benzooxazol-2-il-butan-1-ol {250 mg, 1,2 mmol, Ejemplo de Referencia

17(a)} Se añadieron diclorometano (4 ml) y a continuación 4-metilmorfolina (0,5 ml) La mezcla se agitó a la temperatura ambiente durante dos horas Después de dilución con acetato de etilo (150 ml), la solución se lavó con HCl acuoso 1N, agua, solución acuosa saturada de NaHCO₃ y salmuera, se secó con MgSO₄ y se evaporó a vacío El producto bruto se disolvió en diclorometano seco (10 ml), y se añadió peryodinano Dess Martin (500 mg, 1,2 mmol) Después de agitar a la temperatura ambiente durante 1 hora, la mezcla se diluyó con acetato de etilo (150 ml) y se trató con solución 0,26M de Na₂S₂O₃ en NaHCO₃ acuoso saturado La fase orgánica se lavó con NaHCO₃ acuoso saturado y salmuera, se secó con MgSO₄ y se evaporó El producto se cristalizó en acetato de etilo/hexano para dar ácido

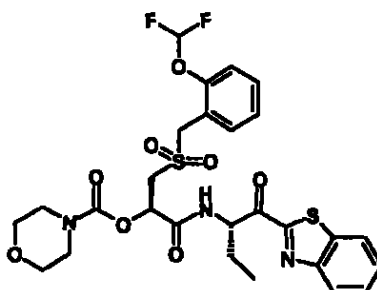
morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-fenilmetanosulfonyl-etil-éster (190 mg, 0,35 mmol), ¹H NMR (DMSO) 8,95 (d, J = 6,6 Hz, 1H), 8,01 (d, J = 7,9 Hz, 1H), 7,90 (d, J = 7,9 Hz, 1H), 7,65 (t, J = 7,5 Hz, 1H), 7,55 (t, J = 7,9 Hz, 1H), 7,40-7,34 (m, 5H), 5,44-5,35 (m, 1H), 5,26-5,16 (m, 1H), 4,60 (d, J = 13,6 Hz, 1H), 4,47 (d, J = 13,6 Hz, 1H), 3,71-3,28 (m, 10H), 2,10-1,94 (m, 1H), 1,81-1,65 (m, 1H), 0,98 (t, J = 7,2 Hz, 3H), MS (M⁺+1) 544

(b) Ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-etil-éster, (Compuesto 14)



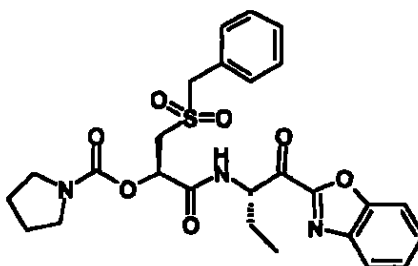
Procediendo de una manera similar al Ejemplo 4(a) anterior, pero utilizando ácido (R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-2-hidroxi-propiónico {Ejemplo de Referencia 1(a)} en el Paso 1 se preparó ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-etil-éster ¹H NMR (DMSO) 8,95 (d, J = 6,4 Hz, 1H), 8,01 (d, J = 7,9 Hz, 1H), 7,90 (d, J = 8,4 Hz, 1H), 7,65 (t, J = 7,4 Hz, 1H), 7,54 (t, J = 7,5 Hz, 1H), 7,52-7,43 (m, 2H), 7,31-7,21 (m, 2H), 7,11 (t, J_{H,F} = 73 Hz, 1H), 5,43-5,37 (m, 1H), 5,27-5,17 (m, 1H), 4,63 (d, J = 13,5 Hz, 1H), 4,54 (d, J = 13,5 Hz, 1H), 3,88-3,28 (m, 10H), 2,10-1,94 (m, 1H), 1,81-1,65 (m, 1H), 0,98 (t, J = 7,6 Hz, 3H), MS (M⁺+1) 610

(c) Ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzotiazol-2-il-metanoil)-propilcarbamoil]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster, (Compuesto 15)



Procediendo de una manera similar al Ejemplo 4(a) anterior, pero utilizando ácido (R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propiónico {Ejemplo de Referencia 1(a)} en el Paso 1 y (2S)-2-amino-1-benzotiazol-2-il-butan-1-ol {Ejemplo de Referencia 17(b)} en el Paso 3, se preparó ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzotiazol-2-il-metanoil)-propilcarbamoil]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster ¹H NMR (DMSO) 8,93 (d, J = 6,4 Hz, 1H), 8,30-8,24 (m, 2H), 7,72-7,62 (m, 2H), 7,51-7,44 (m, 2H), 7,32-7,22 (m, 2H), 7, ¹² (t, J_{H,F} = 73 Hz, 1H), 5,49-5,35 (m, 2H), 4,64 (d, J = 13,5 Hz, 1H), 4,55 (d, J = 13,5 Hz, 1H), 3,91-3,28 (m, 10H), 2,08-1,94 (m, 1H), 1,84-1,68 (m, 1H), 0,99 (t, J = 7,6 Hz, 3H) MS (M⁺+1) 626

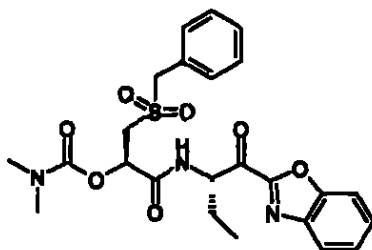
(d) Ácido pirrolidina-1-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-fenilmetanosulfonil-etil-éster, (Compuesto 19)



Procediendo de una manera similar al Ejemplo 4(a) anterior pero utilizando pirrolidina en el Paso 2, se preparó ácido pirrolidina-1-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-fenilmetanosulfonil-ésterc-éster ¹H NMR (DMSO) 8,90 (d, J = 6,4 Hz, 1H), 7,99 (d, J = 7,9 Hz, 1H), 7,89 (d, J = 8,4 Hz, 1H), 7,65 (t, J = 7,4 Hz, 1H), 7,54 (t, J = 7,5, 1H), 7,40-7,33 (m, 5H), 5,41-5,33 (m, 1H), 5,26-5,15 (m, 1H), 4,59 (d, J = 13,5 Hz, 1H), 4,47 (d, J = 13,5 Hz, 1H), 3,66-3,17 (m, 6H), 2,10-1,64 (m, 6H), 0,97 (t, J = 7,2

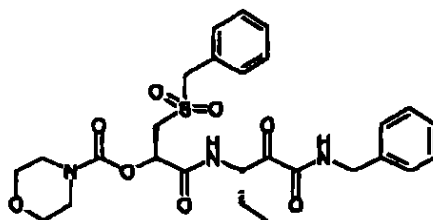
Hz, 3H), MS ($M^+ + 1$) 528

(e) Ácido dimetil-carbámico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-fenilmetano-sulfonyl-etil-éster, (Compuesto 20)



Procediendo de una manera similar al Ejemplo 4(a) anterior pero utilizando dimetilamina en el Paso 2, se preparó ácido dimetil-carbámico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-fenilmetano-sulfonyl-etil-éster ^1H NMR (DMSO) 8,91 (d, $J = 6,4$ Hz, 1H), 7,99 (d, $J = 7,9$ Hz, 1H), 7,90 (d, $J = 8,4$ Hz, 1H), 7,65 (t, $J = 7,4$ Hz, 1H), 7,54 (t, $J = 7,5$ Hz, 1H), 7,40-7,33 (m, 5H), 5,39-5,33 (m, 1H), 5,26-5,15 (m, 1H), 4,59 (d, $J = 13,5$ Hz, 1H), 4,47 (d, $J = 13,5$ Hz, 1H), 3,63 (dd, $J = 14,8$ Hz, $J = 10,6$ Hz, 1H), 3,42 (dd, $J = 14,8$ Hz, $J = 2,5$ Hz, 1H), 2,89 (s, 3H), 2,79 (s, 3H), 2,10-1,94 (m, 1H), 1,81-1,64 (m, 1H), 0,97 (t, $J = 7,2$ Hz, 3H), MS ($M^+ + 1$) 502

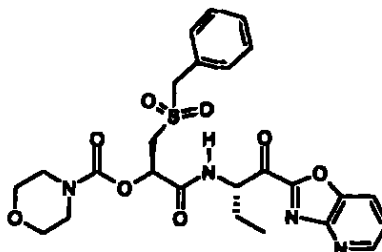
(f) Ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-bencil-carbamoil-metanoil)-propilcarbamoil]-2-fenilmetanosulfonyl-etil-éster, (Compuesto 25)



Procediendo de una manera similar al Ejemplo 4(a) anterior, pero utilizando ácido (R)-3-amino-2-hidroxi-pentanoico-bencilamina, sal de TFA (Ejemplo de Referencia 19) en el Paso 3, se preparó ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-bencil-carbamoil-metanoil)-propilcarbamoil]-2-fenilmetanosulfonyl-etil-éster ^1H NMR (DMSO) 9,27 (t, $J = 5,5$ Hz, 1H), 8,67 (d, $J = 8,1$ Hz, 1H), 7,40-7,20 (m, 10H), 5,42-5,34 (m, 1H), 4,96-4,85 (m, 1H), 4,64-4,24 (m, 4H), 3,66-3,28 (m, 10H), 1,90-1,72 (m, 1H), 1,63-1,46 (m, 1H), 0,89 (t, $J = 7,2$ Hz, 3H), MS ($M^+ + 1$) 560

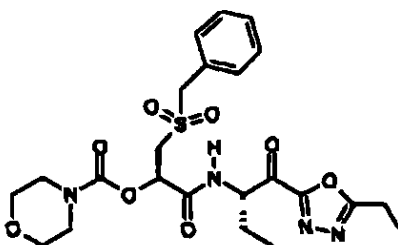
289
235

(g) Ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(oxazolo[4,5-b]piridina-2-carbonil)propil-carbamoyl]-2-fenilmetanosulfonil-etil-éster



Procediendo de una manera similar al Ejemplo 4(a) anterior, pero utilizando sal de TFA de (S)-2-amino-1-oxazolo[4,5-b]piridin-2-il-butan-1-ol (Ejemplo de Referencia 20) se preparó ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(oxazolo[4,5-b]piridina-2-carbonil)propil-carbamoyl]-2-fenilmetanosulfonil-etil-éster ^1H NMR (DMSO) 9,00 (d, J = 6,4 Hz, 1H), 8,73 (m, 1H), 8,39 (d, J = 8,4 Hz, 1H), 7,69-7,64 (m, 1H), 7,45-7,30 (m, 5H), 5,37 (d, J = 10,4 Hz, 1H), 5,19-5,13 (m, 1H), 4,57 (d, J = 13,6 Hz, 1H), 4,46 (d, J = 13,6 Hz, 1H), 3,67-3,23 (m, 10H), 2,10-1,98 (m, 1H), 1,80-1,69 (m, 1H), 0,99 (t, J = 7,0 Hz, 3H) MS (M+H)⁺ 545

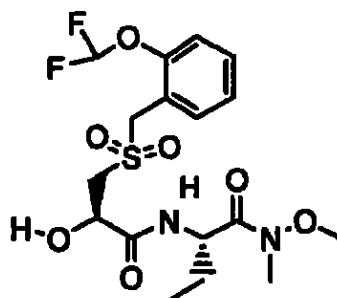
(h) Ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoyl]-2-fenilmetanosulfonil-etil-éster



Procediendo de una manera similar al Ejemplo 4(a) anterior, pero utilizando 2-amino-1-(5-etil-[1,3,4]oxadiazol-2-il-butan-1-ol {Ejemplo de Referencia 11(m)} se preparó ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propil-carbamoyl]-2-fenilmetanosulfonil-etil-éster ^1H NMR (DMSO) 8,95 (d, J = 6,0 Hz, 1H), 7,41-7,33 (m, 5H), 5,35 (d, J = 10,0 Hz, 1H), 4,97-4,91 (m, 1H), 4,63-4,45 (m, 2H), 3,64-3,23 (m, 10H), 2,96 (q, J = 7,2 Hz, 2H), 1,99-1,89 (m, 1H), 1,75-1,64 (m, 1H), 1,30 (t, J = 7,6 Hz, 3H), 0,94 (t, J = 7,2 Hz, 3H) MS (M+H)⁺ 523

EJEMPLO 5

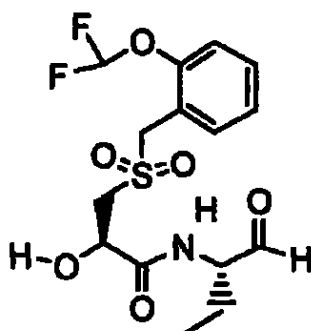
(S)-2-[(R)-3-[2-(1,1-Difluoro-metoxi)-fenilmetano-sulfonyl]-2-hidroxi-propanoilamino]-N-metoxi-N-metil-butiramida (Compuesto 32)



A una solución de ácido (R)-3-[2-(1,1-difluoro-metoxi-fenilmetanosulfonyl)-2-hidroxi-propiónico {1,24 g, 4 mmol, Ejemplo de Referencia 1(a)} en CH₂Cl₂ (20 ml) se añadió HOBt (0,74 g, 4,8 mmol), EDC (1,15 g, 6 mmol), sal de TFA de (R)-2-amino-N-metoxi-N-metil-butiramida (1,04 g, 4 mmol), preparada como en la referencia 2, y NMM (1,6 g, 16 mmol) Después de agitar durante 1 cuatro horas a la temperatura ambiente, la mezcla de reacción se diluyó con 150 ml de acetato de etilo Se lavó la mezcla con NaHCO₃ saturado y salmuera antes de secar con MgSO₄ anhidro Este producto bruto se filtró luego, se concentró y se purificó por cromatografía súbita en columna utilizando gel de sílice con hexano/acetato como eluyente para dar (S)-2-[(R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-2-hidroxi-propanoilamino]-N-metoxi-N-metil-butiramida (1,45 g), ¹H NMR (CD₃Cl) 7,6-7,5 (d, J = 7,67 Hz, 1H), 7,5-7,35 (m, 2H), 7,31-7,15 (m, 2H), 6,63 (t, J = 73,4 Hz, 1H), 5,0 (4,85 (br, 1H), 4,7-4,6 (m, 1H), 4,55-4,48 (m, 2H), 4,45-4,35 (m, 1H), 3,80 (s, 3H), 3,6-3,8 (m, 1H), 3,35-3,2 (m, 1H), 1,78 (s, 3H), 2,0-1,5 (m, 2H), 0,93 (t, J = 6,9 Hz, 3H), MS 473,4 (M-1), 439,4 (M+1)

EJEMPLO 6

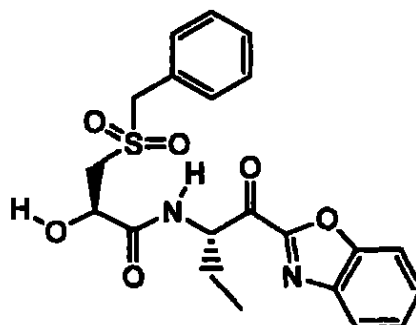
(R)-3-[2-(1,1-Difluoro-metoxi)-fenilmetanosulfonil]-N-((S)-1-formil-propil)-2-hidroxi-propionamida, (Compuesto 23)



A una solución de (S)-2-[(R)-3-[2-(1,1-difluoro-metoxi) - fenilmetanosulfonil]-2-hidroxi-propanoilamino]-N-metoxi-N-metil-butiramida (1,3 g, 3 mmol, Ejemplo 5) en etil-éter (50 ml) a 0°C bajo N₂, se añadió solución 1N de LAH en etil-éter (3 ml) Después de agitar durante tres horas a 0°C, se añadió 1 ml de acetato de etilo y solución saturada de NH₄Cl El producto bruto se extrajo luego con éter, se lavó con salmuera, se seco con MgSO₄, se filtró y se concentró El residuo se purificó por cromatografía súbita en columna utilizando gel de sílice con hexano/acetato como eluyente para dar (R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-N-((S)-1-formil-propil)-2-hidroxi-propionamida (0,66 g), ¹H NMR (DMSO) 9,43 (s, 1H), 8,42 (d, J = 7,45 Hz, 1H), 7,6-7,0 (m, 4H), 7, ¹² (t, J = 73,93 Hz, 1H), 6,52 (d, J = 6,45 Hz, 1H), 5,2-5,17 (m, 1H), 4,65-4,53 (m, 2H), 4,11-4,00 (m, 1H), 3,63-3,55 (m, 2H), 1,7-1,4 (m, 2H), 0,89 (t, J = 6,8 Hz, 3H), MS 378,2 (M-1), 380,4 (M+1)

EJEMPLO 7

(R)-N-[(S)-1-(1-Benzooxazol-2-il-metanol)-propil]-2-hidroxí-3-fenilmetanosulfonilpropionamida, (Compuesto 5)



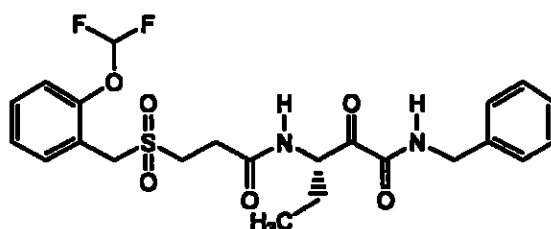
Paso 1 a una solución de ácido (R)-3-fenilmetanosulfonil-2-trisopropilsilaniloxy-propiónico {556 mg, 1 mmol, Ejemplo de Referencia 3} en CH₂Cl₂ (10 ml) a la temperatura ambiente se añadieron HOBt (183 mg, 1,2 mmol), EDC (288 mg, 15 mmol), (S)-2-amino-1-benzooxazol-2-il-butanol (206 mg, 1 mmol) y NMM (202 mg, 2 mmol) La mezcla se agitó durante una noche a la temperatura ambiente, antes de diluirla con acetato de etilo (100 ml), se lavó con NaHCO₃ acuoso saturado, salmuera, se secó con MgSO₄ anhidro, se filtró y se concentró El producto bruto se purificó luego por cromatografía súbita en columna utilizando gel de sílice con hexano/acetato como eluyente (para proporcionar 180 mg de producto) Este compuesto se disolvió en CH₂Cl₂, se añadió peryodinano Dess-Martin (196 mg, 0,46 mmol) a la temperatura ambiente y la mezcla se agitó durante dos horas Se añadió solución saturada de Na₂S₂O₃-NaHCO₃ (5 ml) y se agitó durante 30 minutos más antes de la extracción con acetato de etilo y lavado sucesivo con solución saturada de NaHCO₃ y salmuera El producto bruto se secó luego con MgSO₄ anhidro, se filtró, se concentró y se purificó por cromatografía súbita en columna utilizando gel de sílice con hexano/acetato como eluyente para dar (R)-N-[(S)-1-(1-benzooxazol-2-il-metanol)-propil]-3-fenilmetanosulfonil-2-trisopropilsilaniloxy-propionamida

Paso 2 Se mezclaron (R)-N-[(S)-1-(1-benzooxazol-2-il-metanol)-propil]-3-fenilmetanosulfonil-2-trisopropil-silaniloxy-propionamida (120 mg, 0,2 mmol) en CH₃CN (10 ml), y solución de HF al 48%/agua (1 ml) y se agitaron a la temperatura ambiente durante 16 horas Se añadió cuidadosamente solución saturada de NaHCO₃ para ajustar el pH a un valor comprendido entre 8 y 9 El producto se extrajo con acetato de etilo (100 ml), se lavó con salmuera y se secó con sulfato de magnesio Se eliminó el disolvente y el producto se cristalizó en acetato y hexano para dar (R)-N-[(S)-1-(1-benzooxazol-2-il-metanol)-propil]-2-

hidroxi-3-fenilmetanosulfonilpro-pionamida como un sólido blanco (rendimiento 85%), ^1H NMR (DMSO) 8,29 (d, $J = 7,9$ Hz, 1H), 7,74 (d, $J = 7,9$ Hz, 1H), 7,59 (t, $J = 8,1$ Hz, 1H), 7,46-7,35 (m, 7H), 6,52 (d, $J = 6,6$ Hz, 1H), 5,08-4,99 (m, 1H), 4,58-4,47 (m, 3H), 3,35-3,28 (m, 2H), 2,05-1,90 (m, 1H), 1,81-1,65 (m, 1H), 0,91 (t, $J = 7,2$ Hz, 3H), MS ($M^+ + 1$) 431

EJEMPLO 8

(a) Ácido (S)-3-{3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-propanoílamino}-2-oxo-pentanoico-bencil-amida, (Compuesto 27)



Paso 1 Una mezcla de ácido (R)-3-amino-2-hidroxi-pentanoico-bencilamida, sal de TFA (70 mg, 0,22 mmol), ácido 3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-propiónico (64 mg, 0,22 mmol, Ejemplo de Referencia 19), HOBT (33 mg, 0,22 mmol), EDC (63 mg, 0,325 mmol), 1 ml de diclorometano y N-metil-morfolina (48 μl , 0,434 mmol) La mezcla se dejó en agitación durante 16 horas El producto se extrajo en 60 ml de acetato de etilo y se lavó con dos porciones de 10 ml de HCl 1N, 10 ml de agua, y dos porciones de 10 ml de NaHCO_3 saturado, se secó sobre MgSO_4 y se concentró para dar 105 mg de ácido

(R)-3-{3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-propanoílamino}-2-hidroxi-pentanoico-bencilamida bruta (0,21 mmol, rendimiento 100%)

Paso 2 A una solución en 1 ml de diclorometano de 105 mg de ácido

(R)-3-{3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-propanoílamino}-2-hidroxi-pentanoico-bencilamida (0,21 mmol) se añadió peryodinano Dess-Martin (179 mg, 0,42 mmol) La mezcla se mantuvo en agitación durante 16 horas, se añadieron luego 10 ml de $\text{Na}_2\text{SO}_2\text{O}_3$ 0,26M en NaHCO_3 saturado y la mezcla se extrajo con dos porciones de 30 ml de acetato de etilo y se lavó con tres porciones de 15 ml de NaHCO_3 saturado La capa orgánica se secó sobre MgSO_4 y se concentró El producto se purificó por cromatografía en gel de sílice utilizando 3 l hexano acetato de etilo como eluyente y se cristalizó en dietil-éter y hexano para dar ácido

(S)-3-{3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-propanoílamino}-2-oxo-pentanoico-bencilamida (28 mg, 0,054 mmol, rendimiento 26%), ^1H NMR (CDCl_3) 7,0-7,47 (m, 9H), 6,49 (m, 1H), 6,24 (m, 1H), 5,22 (m, 1H), 4,40 (m, 2H), 4,30 (m, 3H), 3,23 (m, 2H), 2,70 (m,

239
240

2H), 2,01 (m, 1H), 1,68 (m, 1H), 0,85 (m, 3H), MS ($M^+ + 1$) 499,4, 496,53

Los compuestos siguientes se prepararon por el método del Ejemplo 8

N-[(S)-1-(1-Benzooxazol-2-il-metanoil)propil]-3-[2-

(1,1-difluoro-metoxi)-fenilmetanosulfonil]-propionamida (Compuesto 26), ^1H NMR (CDCl_3) 7,85 (d, $J = 7,6$ Hz, 1H), 7,7-7,0 (m, 7H), 6,51 (m, 2H), 5,60 (m, 1H), 4,34 (m, 3H), 3,29 (m, 2H), 2,80 (m, 2H), 2,13 (m, 1H), 1,87 (m, 1H), 0,96 (m, 3H), MS ($M^+ + 1$) 481, 480,48

N-[(S)-1-(1-Benzooxazol-2-il-metanoil)-3-fenil-propil]-3-*p*-tolilmetanosulfonil-propionamida (Compuesto 30), ^1H NMR CDCl_3) 7,9 (m, 1H), 7,62 (m, 1H), 7,56 (td, $J = 6,9, 1,2$ Hz, 1H), 7,47 (td, $J = 7,1, 1,2$ Hz, 1H), 7,3-7,1 (m, 9H), 6,47 (d, $J = 7,7$ Hz, 1H), 5,71 (m, 1H), 4,22 (s, 2H), 3,20 (m, 2H), 2,71 (m, 4H), 2,47 (m, 1H), 2,33 (s, 3H), 2,21 (m, 1H), MS ($M^+ + 1$) 505,2, 504,60

3-(2-Difluorometoxi-fenilmetanosulfonil)-N-(1-etil-2,3-dioxo-3-pirrolidin-1-il-propil)-propionamida,

3-(2-difluorometoxi-fenilmetanosulfonil)-N-(1-etil-3-morfolin-4-il-2,3-dioxo-propil)-propionamida,

3-(2-difluorometoxi-fenilmetanosulfonil)-N-(1-etil-2,3-dioxo-3-piperazin-1-il-propil)-propionamida,

3-(2-difluorometoxi-fenilmetanosulfonil)-N-[3-(1,1-dioxo-1,6-tiomorfolin-4-il)-1-etil-2,3-dioxo-propil]-propionamida,

3-(2-difluorometoxi-fenilmetanosulfonil)-N-[1-etil-3-(4-metil-sulfonil-piperazin-1-il)-2,3-dioxo-propil]-propionamida,

ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-dimetilamida,

ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-ciclopentil-etil-amida,

ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-fenilamida,

ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-piridin-3-ilamida,

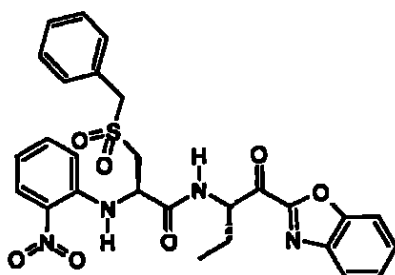
ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-(tetrahidropiran-4-il)-amida,

ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-(1-benzil-piperidin-4-il)-amida, y

ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionilamino]-2-oxo-pentanoico-(2-morfolin-4-il-etil)-amida

EJEMPLO 9

(R)-N-[(S)-1-(1-Benzooxazol-2-il-metanoil)-propil]-2-(2-nitro-fenilamino)-3-fenilmetanosulfonil-propionamida, (Compuesto 28)



Paso 1 Se disolvió ácido 3-bencilsulfanil-2-(2-nitro-fenilamino)-propiónico (350 mg, 1,05 mmol, Ejemplo de Referencia 5) en 20 ml de metanol, se trató con una solución acuosa de 20 ml de Oxone® (970 mg, 0,12 mmol) y se agitó durante 72 horas. Se añadió agua y el precipitado se filtró y se secó para dar ácido 2-(2-nitro-fenilamino)-3-fenilmetanosulfonil-propiónico (215 mg, 0,59 mmol, rendimiento 56%)

Paso 2 Una mezcla de ácido 2-(2-nitro-fenilamino)-3-fenilmetanosulfonil-propiónico (215 mg, 0,59 mmol), HOBT (136 mg, 0,148 mmol), EDC (408 mg, 2,13 mmol), (S)-2-amino-1-benzooxazol-2-il-butan-1-ol (122 mg, 0,59 mmol), {Ejemplo de Referencia 17(a)}, 2,4 ml de diclorometano y N-metil-morfolina (97 µl, 0,89 mmol) se mantuvo en agitación durante 16 horas. El producto se extrajo en 20 ml de acetato de etilo y se lavó con tres porciones de 5 ml de HCl 1N, y una sola porción de 30 ml de NaHCO₃ acuoso saturado, se secó sobre MgSO₄ y se concentró para dar (R)-N-[(S)-1-(1-benzooxazol-2-il-1-hidroximetil)-propil]-2-(2-nitro-fenilamino)-3-fenilmetano-sulfonil-propionamida (223 mg, 0,40 mmol, rendimiento 45%)

Paso 3 Se disolvió (R)-N-[(S)-1-(1-benzooxazol-2-il-1-hidroximetil)-propil]-2-(2-nitro-fenilamino)-3-fenilmetano-sulfonil-propionamida (223 mg, 0,4 mmol) en 1,6 ml de diclorometano y se trató con peryodinano Dess-Martin (342 mg, 0,80 mmol). La mezcla se mantuvo en agitación durante 16 horas, se añadieron luego 20 ml de Na₂S₂O₃ 0,26M en NaHCO₃ saturado y la mezcla se extrajo con dos porciones de 30 ml de acetato de etilo y se lavó con tres porciones de 5 ml de NaHCO₃ saturado. La capa orgánica se secó sobre MgSO₄ y se concentró. El producto bruto se disolvió en una cantidad mínima de acetato de etilo caliente y se cristalizó por adición de dietil-éter seco. Esta cristalización se repitió para dar (R)-N-[(S)-1-(1-Benzooxazol-2-il-metanoil)-propil]-2-(2-nitro-fenilamino)-3-fenilmetanosulfonil-propionamida pura (97 mg, 0,176

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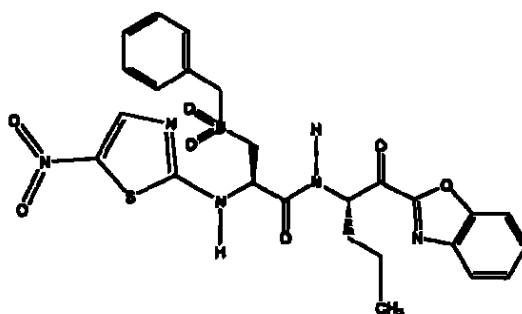
mmol, rendimiento 44%), ^1H NMR (DMSO) 8,67 (m, 1H), 8,¹² (m, 1H), 7,81 (m, 1H), 7,65-7,35 (m, 10H), 6,78 (m, 2H), 5,51 (m, 1H), 4,68 (m, 1H), 4,37 (s, 2H), 3,62 (m, 1H), 3,38 (m, 1H), 2,15 (m, 1H), 1,91 (m, 1H), 0,98 (m, 3H), MS ($\text{M}^+ + 1$) 551,0, 550,58

Se preparó el compuesto siguiente por el método del Ejemplo 9

N-[1-(Benzooxazol-2-carbonil)-propil]-3-fenilmetano-sulfonil-2-(pirimidin-2-ilamino)-propionamida

EJEMPLO 10

(R)-*N*-[(S)-1-(1-Benzooxazol-2-il-metanoil)-butil]-2-(5-nitro-tiazol-2-ilamino)-3-fenilmetanosulfonil-propionamida, (Compuesto 29)



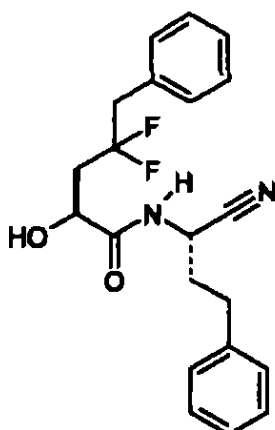
Paso 1 Una mezcla de ácido (R)-3-bencilsulfanil-2-(5-nitro-tiazol-2-ilamino)-propiónico (42 mg, 0,¹²³ mmol, Ejemplo de Referencia 6), HOBT (28 mg, 0,148 mmol), EDC (29 mg, 0,148 mmol), (S)-2-amino-1-benzooxazol-2-il-pentan-1-ol {27 mg, 0,¹²³ mmol, Ejemplo de Referencia 17(c)}, 1 ml de diclorometano y N-metil-morfolina (14 μl , 0,¹²³ mmol) se mantuvo en agitación durante 16 horas. El producto se extrajo en 60 ml de acetato de etilo y se lavó con una porción de 30 ml de HCl 1N, y una porción de 30 ml de NaHCO_3 saturado, se secó sobre MgSO_4 y se concentró para dar (R)-*N*-[(S)-1-(1-benzooxazol-2-il-1-hidroxil-metil)-butil]-3-bencilsulfanil-2-(5-nitro-tiazol-2-ilamino)-propionamida (41,8 mg, 0,077 mmol, rendimiento 63%)

Paso 2 Se disolvió (R)-*N*-[(S)-1-(1-benzooxazol-2-il-1-hidroxil-metil)-butil]-3-bencilsulfanil-2-(5-nitro-tiazol-2-ilamino)-propionamida (41,8 mg, 0,077 mmol) en 0,5 ml de metanol, se trató con una solución acuosa de 0,5 ml de Oxone[®] (43 mg, 0,069 mmol), y se agitó durante 1 hora. Se eliminó el metanol a presión reducida y se añadieron 2 ml de agua. La mezcla se extrajo con dos porciones de 10 ml de acetato de etilo, se secó sobre MgSO_4 , y se concentró. Se disolvió luego en 0,5 ml de diclorometano y se trató con peryodinano Dess-Martin (65 mg, 0,154 mmol). La mezcla se dejó en agitación durante 16 horas, se añadieron luego 5 ml de Na_2SO_3 0,26M en NaHCO_3 saturado y la mezcla se extrajo con

dos porciones de 10 ml de acetato de etilo y se lavó con tres porciones de 5 ml de NaHCO_3 saturado. La capa orgánica se secó sobre MgSO_4 y se concentró. El producto se purificó por trituración con dietil-éter para dar (R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-(5-nitro-tiazol-2-il-amino)-3-fenilmetanosulfonil-propionamida (28 mg, 0,54 mmol, rendimiento 26%), $^1\text{H NMR}$ (CDCl_3) 7,96 (s, 1H), 7,87 (m, 1H), 7,7-7,3 (m, 9H), 5,57 (m, 1H), 5,06 (m, 1H), 4,47 (m, 2H), 3,75 (m, 1H), 3,48 (m, 1H), 2,09 (m, 1H), 1,85 (m, 1H), 1,43 (m, 1H), 1,24 (m, 1H), 0,94 (m, 3H), MS ($\text{M}^+ + 1$) 572,2, 571,63

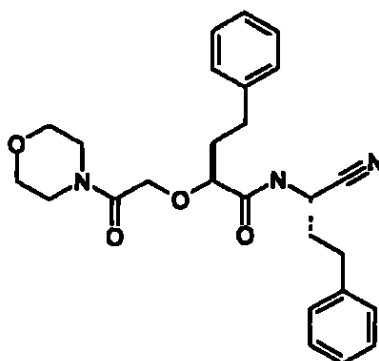
EJEMPLO 11

(a) Ácido (2S)(4,4-difluoro-2-hidroxi-5-fenil-pentan-oico-(1(S)-ciano-3-fenil-propil)-amida, (Compuesto 33)

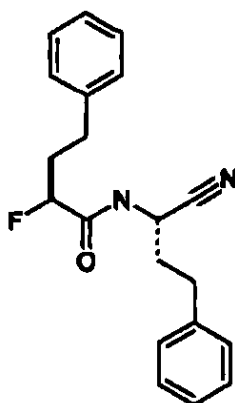


A una mezcla de hidrocloreuro de amino-acetonitrilo (0,37 mmol, 71,6 mg), ácido (2S)-4,4-difluoro-2-hidroxi-5-fenil-pentanoico (1,0 eq, 0,37 mmol, 85,0 mg, Ejemplo de Referencia 7) y N,N -diisopropiletilamina (2,2 eq, 0,81 mmol, 105,2 mg) en diclorometano seco (4 ml) bajo nitrógeno se añadió PyBOP® (1,1 eq, 0,41 mmol, 2¹² mg). La mezcla se agitó a la temperatura ambiente durante 15,5 horas y se concentró luego a vacío. El residuo se diluyó con acetato de etilo (30 ml) y la mezcla se lavó con agua (30 ml), a continuación con bicarbonato de sodio (30 ml) y finalmente con agua (30 ml). La capa orgánica se secó sobre MgSO_4 y se concentró luego a vacío. El residuo se purificó sobre 10 g de gel de sílice, eluyendo con una mezcla de acetato de etilo y heptano (1/2, v/v) para proporcionar ácido (2S)(4,4-difluoro-2-hidroxi-5-fenil-pentanoico-(1(S)-ciano-3-fenil-propil)-amida como un sólido de color canela claro (67,4 mg, 48,9%). $^1\text{H NMR}$ (CDCl_3) 7,3 (m, 10H), 7,1 (d, $J = 7$ Hz, 1H), 4,8 (q, $J = 7,4$ Hz, 1H), 4,53 (bd, $J = 9,5$ Hz, 1H), 3,2 (dt, $J = 16,2, 4,8$ Hz, 2H), 2,96 (s, 1H), 2,85 (m, 2H), 2,5 (m, 1H), 2,3-0,9 (m, 3H). LC/MS, 89% originario ($\text{M} + 1$)

- (b) N-(1(S)-Ciano-3-fenil-propil)-2-(S)-(2-morfolin-4-il-2-oxo-etoxi)-4-fenil-butiramida,
(Compuesto 34)

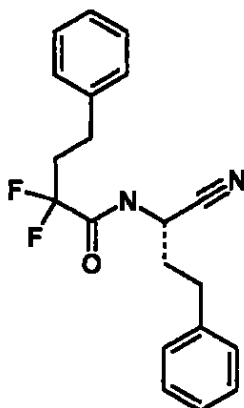


- Procediendo de una manera similar al Ejemplo 11(a) anterior, pero utilizando hidrocloreuro de (S)-2-amino-4-fenil-butironitrilo y ácido 2-(S)-(2-morfolin-4-il-2-oxo-etoxi)-4-fenil-butírico [Ejemplo de Referencia 8] se preparó N-(1(S)-ciano-3-fenil-propil)-2-(S)-(2-morfolin-4-il-2-oxo-etoxi)-4-fenil-butiramida como un aceite ^1H NMR (CDCl_3) 9,4 (d, $J = 8,2$ Hz, 1H), 7,3 (m, 10H), 4,75 (q, $J = 7,5$ Hz, 1H), 4,63 (d, $J = 15,1$ Hz, 1H), 3,95 (d, $J = 15,3$ Hz, 1H), 3,87 (dd, $J = 8,2, 3,9$ Hz, 1H), 3,7 (m, 6H), 3,32 (m, 2H), 2,85 (m, 4H), 2,1 (m, 3H), 2,05 (m, 1H) LC/MS 100% (M+1) 450
- (c) N-(1(S)-Ciano-3-fenil-propil)-2-(S)-fluoro-4-fenil-butiramida, (Compuesto 35)



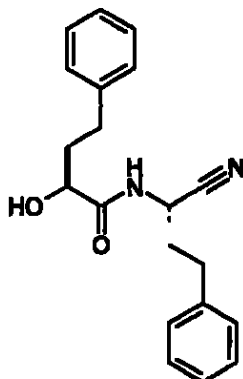
- Procediendo de una manera similar al Ejemplo 11(a) anterior, pero utilizando hidrocloreuro de (S)-2-amino-4-fenil-butironitrilo y ácido (2S)-2-fluoro-4-fenil-butírico (Ejemplo de Referencia 9) se preparó N-(1(S)-ciano-3-fenil-propil)-2-(S)-fluoro-4-fenil-butiramida como un sólido de color canela claro ^1H NMR (CDCl_3) 7,3 (m, 10H), 6,6 (bs, 1H), 4,95 (ddd, $J = 49,2, 8,2, 3,5$ Hz, 1H), 4,8 (m, 1H), 3,8 (m, 4H), 2,3 (m, 1H), 2,2 (m, 3H) MS CI (M+1) 325

(d) N-(1-(S)-Ciano-3-fenil-propil)-2,2-difluoro-4-fenil-butiramida, (Compuesto 36)



Procediendo de una manera similar al Ejemplo 11(a) anterior, pero utilizando hidrocloreuro de (S)-2-amino-4-fenil-butironitrilo y ácido 2,2-difluoro-4-fenil-butírico, se preparó N-(1-(S)-ciano-3-fenil-propil)-2,2-difluoro-4-fenil-butiramida como un sólido blanco ^1H NMR (CDCl_3) 7,3 (m, 10H), 6,6 (d, $J = 8,1$ Hz, 1H), 4,83 (q, $J = 7,4$ Hz, 1H), 2,88 (dt, $J = 7,5, 2,5$ Hz, 2H), 2,79 (t, $J = 8$ Hz, 2H), 2,4 (m, 2H), 2,2 (q, $J = 7,5$ Hz, 2H) LC/MS 50% (M+1) 343

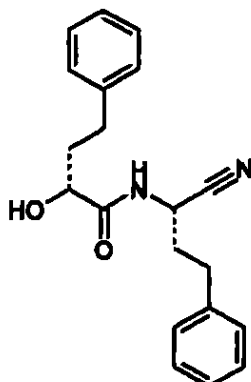
(e) N-(1-(S)-Ciano-3-fenil-propil)-2-(S)-hidroxi-4-fenil-butiramida, (Compuesto 37)



Procediendo de una manera similar al Ejemplo 11(a) anterior, pero utilizando hidrocloreuro de (S)-2-amino-4-fenil-butironitrilo y ácido (2S)-2-hidroxi-4-fenil-butírico se preparó N-(1-(S)-ciano-3-fenil-propil)-2-(S)-hidroxi-4-fenil-butiramida como un sólido blanco ^1H NMR (CDCl_3) 7,3 (m, 10H), 6,9 (d, $J = 8,4$ Hz, 1H), 4,86 (q, $J = 7,4$ Hz, 1H), 4,2 (m, 1H), 2,84 (t, $J = 7,1$ Hz, 2H), 2,77 (t, $J = 7,8$ Hz, 2H), 2,5 (d, $J = 4,7$ Hz, 1H), 2,2 (m, 3H), 1,95 (m, 1H) LC/MS 49% (M+1) 323

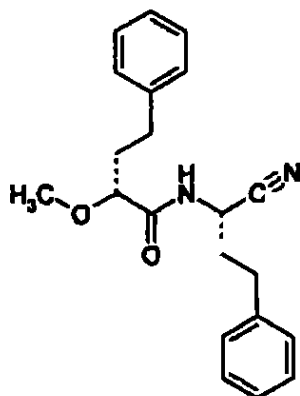
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(f) N-(1-(S)-Ciano-3-fenil-propil)-2-(R)-hidroxi-4-fenil-butiramida, (Compuesto 38)



Procediendo de una manera similar al Ejemplo 11(a) anterior, pero empleando hidrocloreuro de (S)-2-amino-4-fenil-butironitrilo y ácido (2R)-2-hidroxi-4-fenil-butírico, se preparó N-(1-(S)-ciano-3-fenil-propil)-2-(R)-hidroxi-4-fenil-butiramida como un sólido blanco ^1H NMR (CDCl_3) 7,4-7,1 (m, 10H), 6,9 (d, $J = 8,7$ Hz, 1H), 4,87 (q, $J = 7,3$ Hz, 1H), 4,1 (m, 1H), 2,85 (t, $J = 7,5$ Hz, 2H), 2,77 (t, $J = 8,4$ Hz, 2H), 2,3 (d, $J = 5,1$ Hz, 1H), 2,2 (m, 3H), 2,0 (m, 1H) LC/MS 94% ($M+1$) 323

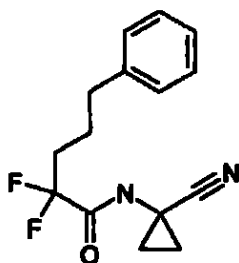
(g) N-(1-(S)-Ciano-3-fenil-propil)-2-(R)-metoxi-4-fenil-butiramida, (Compuesto 39)



Procediendo de una manera similar al Ejemplo 11(a) anterior, pero utilizando hidrocloreuro de (S)-2-amino-4-fenil-butironitrilo (0,407 mmol, 80 mg) y ácido 2(R)-metoxi-4-fenil-butírico (Ejemplo de Referencia 10) se preparó N-(1-(S)-ciano-3-fenil-propil)-2-(R)-metoxi-4-fenil-butiramida como un sólido blanco (91,8 mg, 67%) ^1H NMR (CDCl_3) 7,2 (m, 10H), 6,8 (d, $J = 8,5$ Hz, 1H), 4,86 (q, $J = 7,5$ Hz, 1H), 3,67 (dd, $J = 6,5, 4,5$ Hz, 1H), 3,35 (s, 3H), 2,85 (m, 2H), 2,68 (t, $J = 8,0$ Hz, 2H), 2,2-2,0 (m, 4H) LC/MS 84% (M^++1) 337

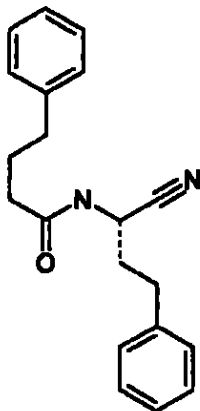
245
247

(h) Ácido 2,2-difluoro-5-fenil-pentanoico-(1-ciano-ciclopropil)-amida, (Compuesto 40)



Procediendo de una manera similar al Ejemplo 11(a) anterior, pero utilizando ácido 2,2-difluoro-5-fenil-pentanoico e hidrocloreuro de 1-amino-ciclopropanocarbó-nitrilo, se preparó ácido 2,2-difluoro-5-fenil-pentan-oico-(1-ciano-ciclopropil)-amida ^1H NMR (CDCl_3) δ 1,32 (m, 2H), 1,64 (m, 2H), 1,82 (m, 2H), 2, ^{12} (m, 2H), 2,8-2,56 (m, 2H), 6,82 (m, 1H), 7,36-7,15 (m, 5H) MS (ES-) 277

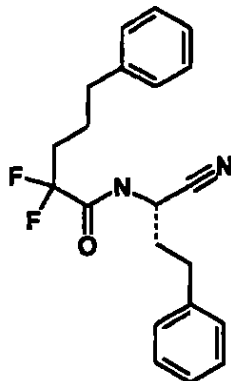
(i) N-(1-(S)-Ciano-3-fenil-propil)-4-fenil-butiramida, (Compuesto 41)



Procediendo de una manera similar al Ejemplo 11(a) anterior, pero utilizando hidrocloreuro de (S)-2-amino-4-fenil-butironitrilo y ácido 4-fenilbutírico, se preparó N-(1-(S)-ciano-3-fenil-propil)-4-fenil-butiramida como un aceite incoloro ^1H NMR (CDCl_3) δ 7,3 (m, 10H), 6,0 (d, $J = 8,3$ Hz, 1H), 4,9 (q, $J = 7,4$ Hz, 1H), 2,8 (m, 2H), 2,65 (t, $J = 7,4$ Hz, 2H), 2,15 (m, 4H), 1,95 (m, 2H) LC/MS 100% ($M+1$) 307

EJEMPLO 12

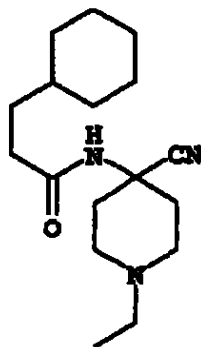
Ácido 2,2-difluoro-5-fenil-pentanoico-((S)-1-ciano-3-fenil-propil)-amida, (Compuesto 42)



Una mezcla de ácido 2,2-difluoro-5-fenil-pentanoico (109 mg, 0,509 mmol), hidrocloreuro de (S)-2-amino-4-fenil-butronitrilo (103 mg, 0,523 mmol) y HATU (206 mg, 0,542 mmol) en DMF (4 ml) se agitó a la temperatura ambiente durante 5 horas y se evaporó luego a presión reducida. El residuo se recogió en acetato de etilo y se lavó con HCl 1N, bicarbonato de sodio y finalmente con agua. El extracto orgánico se secó sobre Na₂SO₄ y se evaporó luego a vacío para dar un aceite anaranjado. El residuo se sometió a mpic, eluyendo con una mezcla de acetato de etilo y heptano (1/9, v/v) para dar ácido 2,2-difluoro-5-fenil-pentanoico-((S)-1-ciano-3-fenil-propil)-amida como un aceite incoloro (82 mg). ¹H NMR (CDCl₃) 7,3-7,1 (m, 10H), 6,9 (bs, 1H), 4,80 (q, J = 7,5 Hz, 1H), 2,80 (dt, J = 7,3, 2,7 Hz, 2H), 2,65 (t, J = 7,5 Hz, 2H), 2,2-2,0 (m, 4H), 1,8 (m, 2H). MS 357 (MH⁺), 379 (M+Na).

EJEMPLO 13

(a) N-(4-Ciano-1-etil-piperidin-4-il)-3-ciclohexil-propionamida



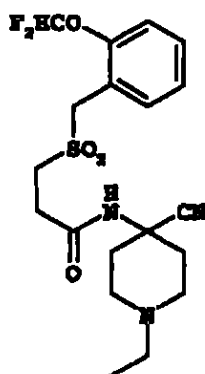
Paso 1 A una solución agitada de 1-etil-4-piperidona (25 g, 0,197 mol) en 300 ml de

dietil-éter, y NH_4Cl (22,3 g, 0,41 mol), se añadió NaCN (14,5 g, 0,295 mol, en 70 ml de agua) gota a gota a la temperatura ambiente. Después de agitar durante 24 h, se separó el dietil-éter y la fase acuosa se extrajo con $n\text{-BuOH}$, se lavó luego con salmuera y se secó. Después de la eliminación de la mayor parte del $n\text{-BuOH}$ a presión reducida, el residuo se diluyó con 50 ml de dietil-éter y se acidificó luego con HCl 2N en solución de dietil-éter a 0°C . El sólido se secó a vacío para dar 45 g de 4-amino-1-etil-piperidina-4-carbo-nitrilo, sal de HCl .

Paso 2 A una mezcla agitada de ácido 3-ciclohexil-propiónico (156 mg, 1 mmol), 4-amino-1-etil-piperidina-4-carbonitrilo, sal de HCl (227, 1 mmol, preparada como en el Paso 1 anterior), y HATU (570 mg, 1,5 mmol) en MeCl_2 (5 ml), se añadió

N,N -disopropiletilamina (516 mg, 4 mmol) a la temperatura ambiente. Después de agitar durante cuatro horas, la mezcla de reacción se extrajo con acetato de etilo. Se lavó la capa orgánica con NaHCO_3 saturado y con salmuera, se secó con MgSO_4 y se concentró para dar N -(4-ciano-1-etil-piperidin-4-il)-3-ciclohexil-propionamida (170 mg). LC-MS tiempo de elución 2,25 min 290,2 (M-1), 292,2 (M+1) (MS API 150EX LC HP Agilent 1100 series Column Phenomenex, 5u ODS3 100A 100X3 mm, caudal 2 ml/min. Gradiente de dos disolventes: disolvente A 99% agua, 1% acetonitrilo, 0,1% AcOH . Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH . Gradiente desde 100% A, 0% B, a 0% A, 100% B desde $t = 0$ a $t = 6$ min. El gradiente volvió luego a 100% A, 0% B desde $t = 7$ a $t = 15$ min).

(b) N -(4-Ciano-1-etil-piperidin-4-il)-3-(2-difluorometoxi-fenilmetanosulfonyl)-propionamida

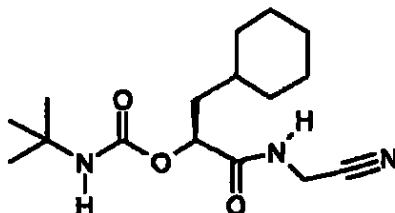


Procediendo de una manera similar al Ejemplo 13(a), pero utilizando ácido 3-(2-difluorometoxi-fenilmetano-sulfonyl)-propiónico (294 mg, 1 mmol) y 4-amino-1-etil-piperidina-4-carbonitrilo, sal de HCl (227, 1 mmol) se obtuvo N -(4-ciano-1-etil-piperidin-4-il)-3-(2-difluoro-metoxi-fenilmetanosulfonyl)-propionamida, (260 mg). LC-MS $R_T = 1,96$ min, 428,2 (M-1), 430,3 (M+1) MS API 150EX (LC Agilent 1100Series Column Phenomenex, 5u ODS3 100A 100X3 mm Caudal 2 ml/min Gradiente

de dos disolventes Disolvente A 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde $t = 0$ a $t = 6$ min El gradiente volvió luego a 100% A, 0% B desde $t = 7$ a $t = 15$ min)

EJEMPLO 14

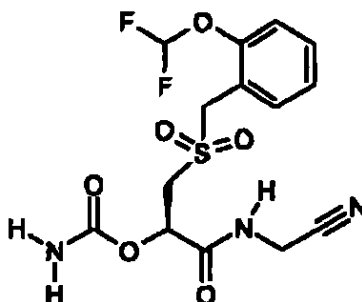
Ácido (S)-*tert*-butil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Se disolvió (S)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida (53 mg, 0,252 mmol) en diclorometano (1 ml) Se añadió trietilamina (0,1 ml) y a continuación isocianato de *tert*-butilo (0,034 ml, 0,3 mmol) La mezcla se agitó a la temperatura ambiente durante una noche Después de dilución con acetato de etilo (100 ml), la solución se lavó con HCl acuoso 1N, salmuera, NaHCO₃ acuoso saturado, y salmuera, se secó con MgSO₄ y se evaporó a vacío La cromatografía súbita sobre gel de sílice (hexano/acetato de etilo 1:1) dio ácido (S)-*tert*-butil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster (63 mg, 0,204 mmol) como un sólido blanco

EJEMPLO 15

(a) Ácido (R)-carbámico-1-(cianometil-carbamoyl)-2-(2-difluorometoxi-fenilmetanosulfonil)-etil-éster

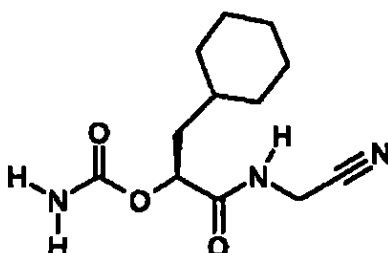


Se disolvió

(R)-N-cianometil-3-(2-(1,1-difluorometoxi)-fenilmetanosulfonil)-2-hidroxi-propionamida {100 mg, 0,287 mmol, Ejemplo 1(a)} en diclorometano (2 ml) y se añadió THF (1 ml) Se añadió isocianato de tricloroacetilo (0,051 ml, 0,43 mmol) y la mezcla se agitó durante 1 h Se

eliminaron los disolventes a vacío y el residuo se disolvió en 1,4-dioxano (10 ml) Se añadió HCl acuoso 1N (5 ml) y la mezcla se calentó a 70°C durante 4 h Después de enfriar a la temperatura ambiente, se extrajo la mezcla con acetato de etilo Las capas orgánicas reunidas se lavaron con salmuera, se secaron con MgSO₄ y se evaporaron a vacío La cromatografía súbita sobre gel de sílice (hexano/acetato de etilo 1/3) dio ácido (R)-carbámico-1-(cianometil-carbamoyl)-2-(2-difluorometoxi-fenilmetanosulfonyl)-etil-éster (35 mg, 0,089 mmol) como un sólido blanco ¹H NMR (DMSO) 8,90 (t, J = 4,8 Hz, 1H), 7,48-7,43 (m, 2H), 7,30-7,21 (m, 2H), 7,11 (t, J_{H,F} = 73,6 Hz, 1H), 6,98-6,76 (br, 2H), 5,28-5,23 (m, 1H), 4,60 (s, 2H), 4,15 (d, J = 4,8 Hz, 2H), 3,70 (dd, J = 10,0 Hz, J = 14,8 Hz, 1H), 3,54 (d, J = 14,4 Hz, 1H) MS (M+H)⁺ 392

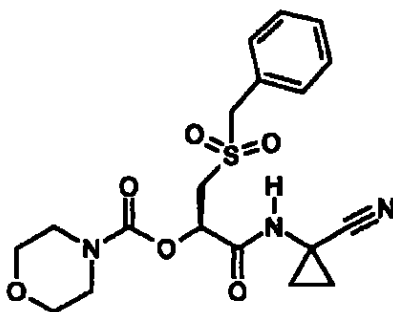
(b) Ácido (S)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster



Procediendo de una manera similar al Ejemplo 8(a) anterior, pero utilizando (R)-N-cianometil-3-ciclohexil-2-hidroxi-propionamida se preparó ácido (S)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster ¹H NMR (DMSO) 8,63 (t, J = 5,6 Hz, 1H), 6,63 (br, 2H), 4,81-4,77 (m, 1H), 4,11 (d, J = 5,2 Hz, 2H), 1,74-0,81 (m, 3H) MS (M+H)⁺ 254

EJEMPLO 16

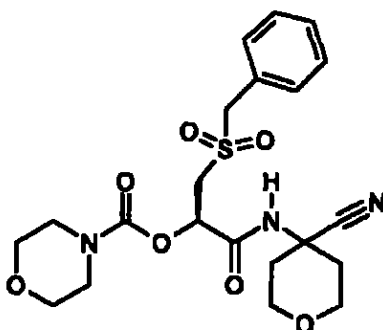
(a) Ácido (R)-morfolina-4-carboxílico-1-(1-ciano-ciclo-propilcarbamoyl)-2-fenilmetanosulfonyl-etil-éster



Se añadió DMF a una mezcla de ácido

(R)-morfolina-4-carboxílico-1-carboxi-2-fenilmetanosulfonil-etil-éster {procedente del Paso 2 en el Ejemplo 4(a)} (60 mg, 0,168 mmol), HATU (200 mg, 0,52 mmol), e hidrocloreuro de 1-amino-ciclopropanocarbonitrilo (100 mg, 0,84 mmol) Se añadió 4-metilmorfolina (0,5 ml) y la mezcla se agitó durante una noche Se diluyó la mezcla con acetato de etilo (100 ml), se lavó con HCl acuoso 1N, salmuera, NaHCO₃ acuoso saturado y salmuera, se secó con MgSO₄ y se evaporó a vacío La cromatografía súbita sobre gel de sílice (hexano/acetato de etilo 1 2) dio ácido (R)-morfolina-4-carboxílico-1-(1-ciano-ciclopropil-carbamoyl)-2-fenilmetanosulfonil-etil-éster (7 mg, 0,017 mmol) ¹H NMR (DMSO) 9,16 (s, 1H), 7,40-7,32 (m, 5H), 5,24-5,19 (m, 1H), 4,55 (d, J = 13,2 Hz, 1H), 4,48 (d, J = 13,2 Hz, 1H), 3,63-3,25 (m, 10H), 1,51-1,39 (m, 2H), 1,20-1,07 (m, 2H) MS (M+H)⁺ 422

(b) Ácido (R)-morfolina-4-carboxílico-1-(4-ciano-tetrahidropiran-4-ilcarbamoyl)-2-fenilmetanosulfonil-etil-éster

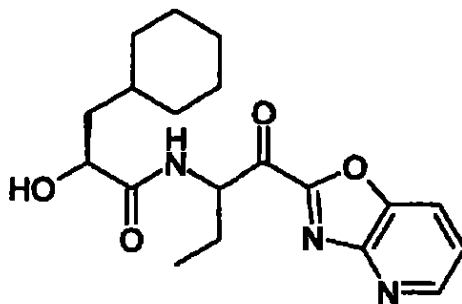


Procediendo de una manera similar al Ejemplo 16(a) anterior, pero utilizando hidrocloreuro de 4-amino-tetrahidropiran-4-carbonitrilo {preparado de acuerdo con el Ejemplo 13(a), Paso 1 , pero utilizando tetrahidropiran-4-ona} se preparó ácido (R)-morfolina-4-carboxílico-1-(4-ciano-tetrahidropiran-4-ilcarbamoyl)-2-fenilmetanosulfonil-etil-éster LC-MS tiempo de elución = 3,20 min 464,4 (M-1), 466,2 (M+1) (MS API 150EX LC HP Agilent 1100 Series Column Phenomenex, Su ODS3 100A 100X3 mm Caudal 2 ml/min Gradiente de dos disolventes Disolvente A 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde t = 0 a t = 6 min El gradiente volvió luego a 100% A, 0% B desde t = 7 a t = 15 min)

243
253

EJEMPLO 17

3-Ciclohexil-2-hidroxi-N-[1-(oxazolo[4,5-b]piridina-2-carbonil)-propil]-propionamida



Paso 1 A una solución agitada de ácido

[1-(hidroxi-oxazolo[4,5-b]piridin-2-il-metil)-propil]-carbámico-*terc*-butil-éster (3,11 g, 10 mmol, preparado como se describe en el Ejemplo de Referencia 20, Paso 2) en dioxano (4 ml) se añadió HCl (solución 4N en 5 ml de dioxano) a la temperatura ambiente. Después de dos horas, se añadió etil-éter (50 ml) y se filtró la mezcla de reacción. El sólido resultante se lavó con 20 ml adicionales de etil-éter y se secó a vacío para dar 3 g de

2-amino-1-oxazolo[4,5-b]piridin-2-il-butan-1-ol, sal de HCl

Paso 2 A una mezcla agitada de ácido 3-ciclohexil-2-hidroxi-propiónico (155 mg, 0,9 mmol), 2-amino-1-oxazolo[4,5-b]piridin-2-il-butan-1-ol, sal de HCl, y HOBt (168 mg, 1,1 mmol) en MeCN (5 ml) se añadieron EDC (270 mg, 1,4 mmol) y N-metilmorfolina (0,45 ml) a 23°C. Después de agitar durante cuatro horas, la mezcla de reacción se extrajo con acetato de etilo. La capa orgánica se lavó con NaHCO₃ saturado y con salmuera, se secó con MgSO₄ y se concentró para dar 293 g de 3-ciclohexil-2-hidroxi-N-[1-(hidroxi-oxazolo[4,5-b]piridin-2-il-metil)-propil]-propionamida, que se utilizó en el Paso 3 siguiente sin purificación ulterior. MS 360,3 (M-1), 362,3 (M+1), 384,2 (M+Na).

Paso 3 A una solución agitada de

3-ciclohexil-2-hidroxi-N-[1-(hidroxi-oxazolo[4,5-b]piridin-2-il-metil)-propil]-propionamida (300 mg, 0,83 mmol) en MeCl₂ (20 ml), se añadió MnO₂ (1,44 g, 16,6 mmol) a la temperatura ambiente. Después de agitar durante 30 min, la mezcla se filtró para eliminar el MnO₂, y se lavó con 20 ml de MeCl₂. Se eliminó el disolvente a vacío y el residuo se purificó por cromatografía en columna de gel de sílice para dar

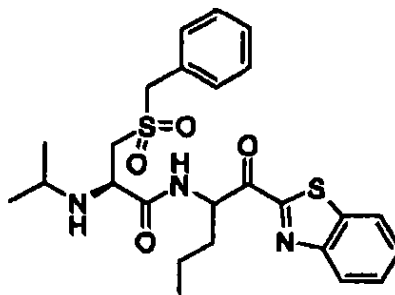
3-ciclohexil-2-hidroxi-N-[1-(oxazolo[4,5-b]piridina-2-carbonil)-propil]-propionamida (40 mg). ¹H NMR (DMSO-d₆) 8,71 (1H, dd, NH, diastereoisómero), 8,38 (1H, dd), 8,28 (1H, m), 7,7-7,6 (1H, m), 5,5-5,4 (1H, m), 5,2-5,1 (1H, m), 3,95-3,99 (1H, br, OH), 2,1-1,95 (1H, m), 1,85-1,75 (1, m), 1,7-0,8 (16H, m).

253
254

MS 358,1 (M-1), 360,1 (M+1), 382 (M+Na)

EJEMPLO 18

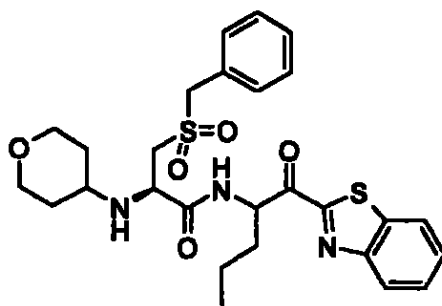
(a) (R)-N-[1-(Benzotiazol-2-carbonil)-butil]-2-isopropil-amino-3-fenilmetanosulfonyl-propionamida



Una solución de (R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-fenilmetanosulfonyl-propionamida {30 mg, 0,06 mmol, Ejemplo 30(a)} en diclorometano (10 ml) se trató con peryodinano Dess-Martin (51 mg, 0,12 mmol) Esta mezcla se agitó a la temperatura ambiente durante 45 min, se trató luego con tiosulfato fijado a Resina (400 mg, 0,6 mmol) y se continuó la agitación durante 2cuatro horas más, después de lo cual la mezcla se trató con AP-Trisamina (270 mg, 0,6 mmol) Después de agitar durante 2cuatro horas más, la mezcla de reacción se filtró y el filtrado se evaporó para dar (R)-N-[1-(benzotiazol-2-carbonil)-butil]-2-isopropil-amino-3-fenilmetanosulfonyl-propionamida (23 mg, 75%) como una mezcla de diastereoisómeros ¹H NMR (CDCl₃, 300 MHz) 8,29-8,27 (m, 1H), 8,23-8,19 (m, 1H), 8,01-7,98 (m 1H), 7,63-7,36 (m, 7H), 5,80-5,74 (m, 1H), 4,36-4,31 (m, 2H), [3,79 (dd, J = 9,5 Hz, 3Hz), 3,73 (dd, J = 9 Hz, 2,5 Hz) 1H], 3,41-3,34 (m, 1H), 3,20-3,01 (m, 1H), 2,89-2,85 (m, 1H), 2,17-2,06 (m, 1H), 1,88-1,78 (m, 1H), 1,52-1,25 (m, 3H), 1,12-1,06 (m, 6H), [0,96 (t, J = 7,5 Hz) 0,95 (t, J = 7,5 Hz) 1H] LC/MS m/z = 502 (M+H)

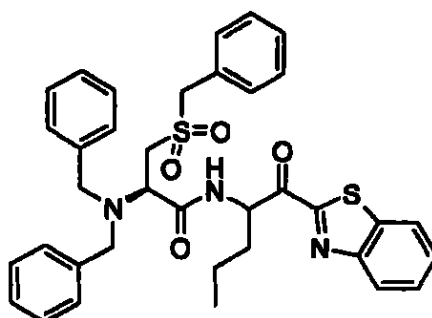
209
255

(b) (R)-N-[1-(Benzotiazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida



Procediendo de una manera similar al Ejemplo 18(a) pero utilizando (R)-N-[1-(benzotiazol-2-il-hidroximetil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)propionamida {0,11 mmol, Ejemplo 29(b)} y sometiendo el producto bruto a HPLC se preparó (R)-N-[1-(benzotiazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida (10 mg, 16%) LC/MS, tiempo de retención 2,92 min (TIC), $m/z = 544$ (M+H) (determinado por el método A)

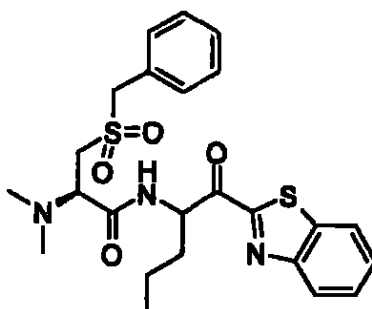
(c) (R)-N-[1-(Benzotiazol-2-carbonil)-butil]-2-dibencil-amino-3-fenilmetanosulfonil-propionamida



Procediendo de una manera similar al Ejemplo 18(a), pero utilizando (R)-N-[1-(benzotiazol-2-il-hidroximetil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida {0,11 mmol, Ejemplo 29(a)} y sometiendo el producto bruto a HPLC se preparó (R)-N-[1-(benzotiazol-2-carbonil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida (4 mg) como una mezcla de diastereoisómeros ^1H NMR (CDCl_3 , 300 MHz) 8,33-7,89 (m, 3H), 7,61-7,55 (m, 2H), 7,47-7,29 (m, 15H), 5,75 (m, 1H), [4,54 (d, $J = 14$ Hz), 4,51 (d, $J = 13,5$ Hz), 1H], [4,27 (d, $J = 14$ Hz), 4,25 (d, $J = 13,5$ Hz), 1H], 4,11-3,95 (m, 2H), [3,78 (d, $J = 13$ Hz), 3,76 (d, $J = 13$ Hz), 2H], [3,51 (d, $J = 13$ Hz), 3,50 (d, $J = 13$ Hz), 2H], 3,19-3,13 (m, 1H), 2,10-1,77 (m, 2H), 1,51-1,37 (m, 2H), 0,91-0,84 (m, 3H) LC/MS $m/z = 640$ (M+H)

250
256

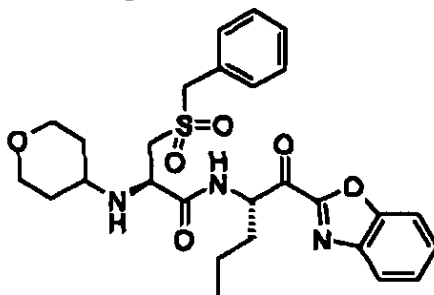
(d) (R)-N-[1-(Benzotiazol-2-carbonil)-butil]-2-dimetil-amino-3-fenilmetanosulfonyl-propionamida



Procediendo de una manera similar al Ejemplo 18(a) pero utilizando (R)-N-[1-(benzotiazol-2-il-hidroximetil)-butil]-2-dimetilamino-3-fenilmetanosulfonyl-propionamida {30 mg, 0,06 mmol, Ejemplo 30(b)}, y sometiendo el producto bruto a HPLC se preparó (R)-N-[1-(benzotiazol-2-carbonil)-butil]-2-dimetilamino-3-fenilmetanosulfonyl-propionamida (11 mg, 38%) LC/MS, tiempo de retención 2,98 min (TIC), $m/z = 488$ (M+H) (determinado por el método A)

EJEMPLO 19

(a) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonyl-2-(tetrahidropiran-4-ilamino)-propionamida



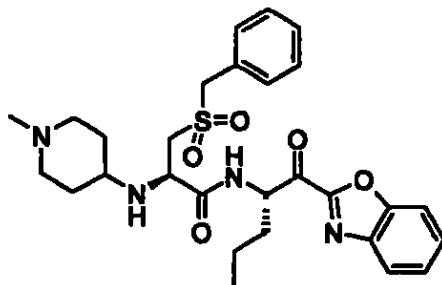
Una solución de (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonyl-2-(tetrahidropiran-4-ilamino)-propionamida {0,22 mmol, Ejemplo 31(a)} en diclorometano (10 ml) se trató con peryodinano Dess-Martin (187 mg, 0,44 mmol) Esta mezcla se agitó a la temperatura ambiente durante una noche, se trató luego con tiosulfato fijado a Resina (1,47 g, 2,2 mmol) y se continuó la agitación durante 2cuatro horas más, después de lo cual la mezcla se trató con Silicycle Triamine (611 mg, 2,2 mmol) Después de agitar durante 2cuatro horas más, la mezcla de reacción se filtró El filtrado se

258
257

evaporó y el residuo se sometió a HPLC para dar

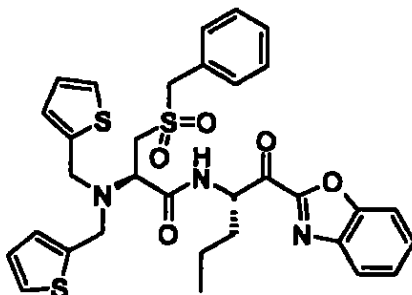
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropirán-4-ilamino)-propionamida (9 mg, 8%) LC/MS, tiempo de retención 3,0 min (TIC), $m/z = 528$ (M+H) (determinado por el método B)

(b) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-2-(1-metil-piperidin-4-ilamino)-3-fenilmetanosulfonil-propionamida



Procediendo de una manera similar al Ejemplo 19(a), pero utilizando (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(1-metil-piperidin-4-ilamino)-3-fenilmetanosulfonil-propionamida {0,22 mmol, Ejemplo 31(b)} se preparó (R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(1-metil-piperidin-4-ilamino)-3-fenilmetanosulfonil-propionamida (7 mg, 6%) LC/MS, tiempo de retención 2,7 min (TIC), $m/z = 541$ (M+H) (determinado por el método A)

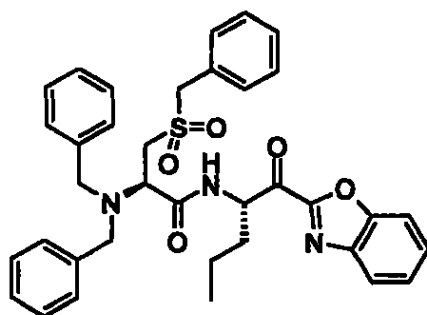
(c) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida



Procediendo de una manera similar al Ejemplo 19(a), pero utilizando (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida {0,22 mmol, Ejemplo 31(c)} se preparó (R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida (5,3 mg, 4%) LC/MS, tiempo de retención 3,7 min (TIC) $m/z = 636$ (M+H) (determinado por el método A)

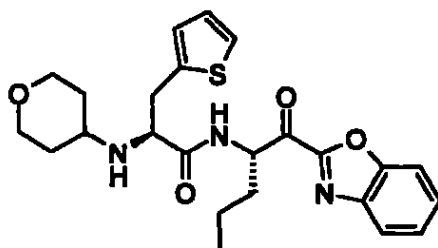
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258

(d) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-2-diben-
c-ilamino-3-fenilmetanosulfonilpropionamida



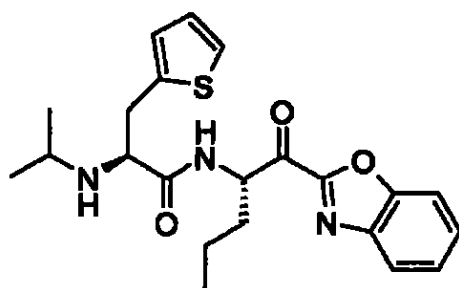
Procediendo de una manera similar al Ejemplo 19(a), pero utilizando (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonilpropionamida {0,22 mmol, Ejemplo 31(d)} se preparó (R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-dibencilamino-3-fenilmetanosulfonilpropionamida (3,8 mg, 3%) LC/MS, tiempo de retención, 4,14 min (TIC), m/z = 624 (M+H) (determinado por el método B)

(e) (S)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-propionamida



Procediendo de una manera similar al Ejemplo 19(a) pero utilizando (S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-propionamida {0,22 mmol, Ejemplo 31(e)} se preparó (S)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-propionamida (6,5 mg, 6%) LC/MS, tiempo de retención 2,92 min (TIC), m/z = 456 (M+H) (determinado por el método B)

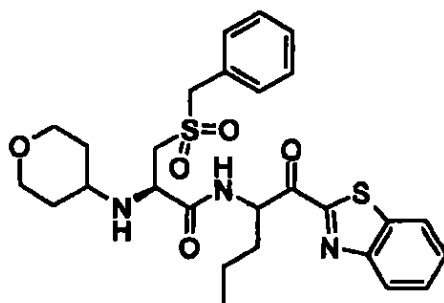
(f) (S)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-iso-propilamino-3-tiofen-2-il-propionamida



Procediendo de una manera similar al Ejemplo 19(a), pero utilizando (S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-tiofen-2-il-propionamida {0,22 mmol, Ejemplo 31(f)}, se preparó (S)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-isopropilamino-3-tiofen-2-il-propionamida (10,6 mg, 12%) LC/MS, tiempo de retención 2,99 min (TIC), $m/z = 414$ (M+H)(determinado por el método B)

EJEMPLO 20

(a) (R)-N-[1-(Benzotiazol-2-carbonil)-butil]-3-fenilmeta-nosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida de
ide



Una solución de (R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida {0,22 mmol, Ejemplo 32(a)} en diclorometano (10 ml) se trató con peryodinano Dess-Martin (187 mg, (0,44 mmol)) Después de agitar a la temperatura ambiente durante 30 minutos, la mezcla de reacción se trató con solución saturada de tiosulfato de sodio (50 ml) y solución saturada de bicarbonato de sodio (50 ml) Se separaron las fases y la fase acuosa se extrajo con diclorometano Las fases orgánicas reunidas se lavaron con salmuera, se secaron luego sobre sulfato de magnesio y se evaporaron después El residuo se sometió a cromatografía súbita utilizando un cartucho

de gel de sílice para dar (R)-N-[1-(benzotiazol-2-carbonil)-butil]-3-fenilmetano-sulfonil-2-(tetrahidropirán-4-ilamino)-propionamida (46 mg, 38%) como una mezcla de diastereoisómeros. Los dos diastereoisómeros se separaron por cromatografía en columna de gel de sílice eluyendo con una mezcla 1:1 v/v heptano/acetato de etilo.

Diastereoisómero A

¹H NMR (CDCl₃, 300 MHz) 8,23-8,20 (m, 2H), 8,00 (dd, J = 7 Hz, 2H, 1H), 7,63-7,53 (m, 2H), 7,48-7,40 (m, 5H), 5,80 (m, 1H), 4,38 (d, J = 14 Hz, 1H), 4,32 (d, J = 14 Hz, 1H), 3,97-3,90 (m, 2H), 3,80 (dd, J = 9,5 Hz, 3 Hz, 1H), 3,43-3,30 (m, 3H), 3,13 (dd, J = 14,5 Hz, 9,5 Hz, 1H), 2,70 (m, 1H), 2,27 (m, 1H), 2,09 (m, 1H), 1,91-1,76 (m, 3H), 1,52-1,37 (m, 4H), 0,95 (t, J = 7,5 Hz, 3H).

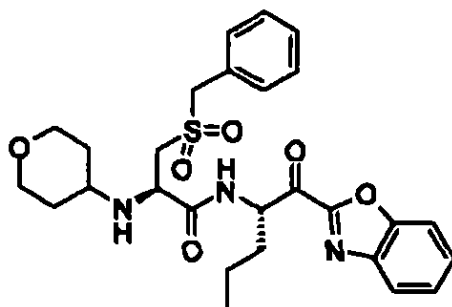
LC/MS m/z = 544 (M+H)

Diastereoisómero B

¹H NMR (CDCl₃, 300 MHz) 8,22-8,19 (m, 2H), 8,01-7,98 (m, 1H), 7,63-7,53 (m, 2H), 7,44-7,37 (m, 5H), 5,74 (m, 1H), 4,35-4,31 (m, 2H), 3,99-3,94 (m, 2H), 3,86 (dd, J = 9,5 Hz, 3 Hz, 1H), 3,49-3,33 (m, 3H), 3,08 (dd, J = 14,5 Hz, 9,5 Hz, 1H), 2,75-2,70 (m, 1H), 2,22 (m, 1H), 2,15-2,06 (m, 1H), 1,91-1,75 (m, 3H), 1,53-1,37 (m, 4H), 0,96 (t, J = 7,5 Hz, 3H).

LC/MS m/z = 544 (M+H)

(b) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropirán-4-ilamino)-propionamida

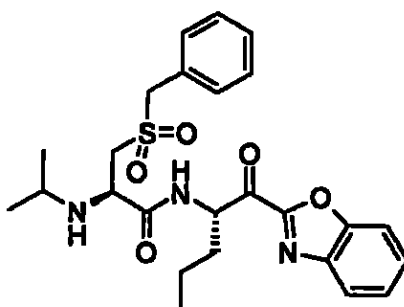


Procediendo de una manera similar al Ejemplo 20(a), pero utilizando (R)-N-[(S)-1-(benzoxazol-2-il-hidroximetil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropirán-4-ilamino)-propionamida {0,22 mmol, Ejemplo 32(b)} se preparó (R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropirán-4-ilamino)-propionamida (48 mg, 41%) ¹H NMR (CDCl₃, 300 MHz) 8,22 (d, J = 8,5 Hz, 1H), 7,92 (d, J = 8 Hz, 1H), 7,68 (d, J = 8,5 Hz, 1H), 7,60-7,40 (m, 7H), 5,68-5,61 (m, 1H), 4,37 (d, J = 14 Hz, 1H), 4,31 (d, J = 14 Hz, 1H), 3,97-3,91 (m, 2H), 3,80 (dd, J = 9,5 Hz, 3 Hz, 1H), 3,43-3,32 (m, 3H), 3,12 (dd, J = 14,5 Hz, 9,5 Hz, 1H), 2,73-2,66 (m, 1H), 2,26 (m, 1H), 2,13-2,05 (m, 1H), 1,89-1,77 (m, 3H), 1,52-1,39 (m, 4H), 0,97 (t, J = 7,5 Hz, 3H). LC/MS m/z

= 528 (M+H)

EJEMPLO 21

(a) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-2-isopropilamino-3-fenilmetanosulfonyl-propionamida

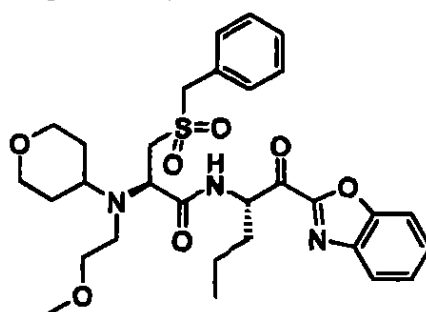


Una solución de (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-fenilmetano-sulfonyl-propionamida {30 mg, 0,063 mmol, Ejemplo 31(c)} en diclorometano (10 ml) se trató con peryodinano Dess-Martin (53 mg, 0,126 mmol) y esta mezcla se agitó a la temperatura ambiente durante 1 hora y se sometió luego a tratamiento con el manipulador de líquidos The Mettler-Toledo Allex™ como se describe a continuación

Se añadió diclorometano (15 ml) a la mezcla de reacción, seguido por una mezcla 1:1 (8 ml) de solución saturada de tiosulfato de sodio y solución saturada de bicarbonato de sodio. Se separaron las fases y la fase orgánica se lavó con 5 ml adicionales de la solución tiosulfato/bicarbonato. La fase orgánica se lavó luego con salmuera y se secó después sobre sulfato de magnesio. El producto bruto se sometió a cromatografía súbita utilizando un cartucho de gel de sílice para dar (R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-isopropilamino-3-fenilmetanosulfonyl-propionamida (6,2 mg, 20%) LC/MS tiempo de retención 2,7 min (TIC), m/z = 486 (M+H) (determinado por el método C)

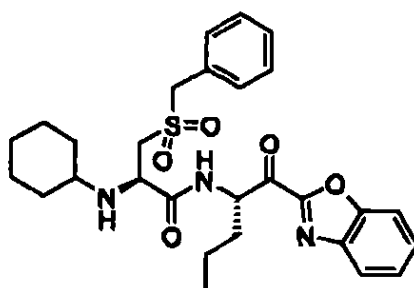
261
262

(b) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-2-[(2-metoxi-etil)-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida



Procediendo de una manera similar al Ejemplo 21(a), pero utilizando (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-[(2-metoxi-etil)-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida {80 mg, 0,136 mmol, Ejemplo 32(d)} se preparó (R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-[(2-metoxi-etil)-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida (7 mg, 9%) LC/MS tiempo de retención 3,5 min (TIC), $m/z = 586$ (M+H) (determinado por el método C)

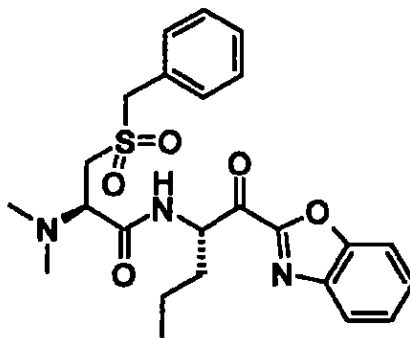
(c) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-2-ciclo-hexilamino-3-fenilmetanosulfonil-propionamida



Procediendo de una manera similar al Ejemplo 21(a), pero utilizando (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-ciclohexilamino-3-fenilmetanosulfonil-propionamida {48 mg, 0,091 mmol, Ejemplo 32(e)} se preparó (R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-ciclohexilamino-3-fenilmetanosulfonil-propionamida (7,9 mg, 16%) LC/MS, tiempo de retención 2,99-3,02 min (TIC), $m/z = 526$ (M+H) (determinado por el método C)

262
263

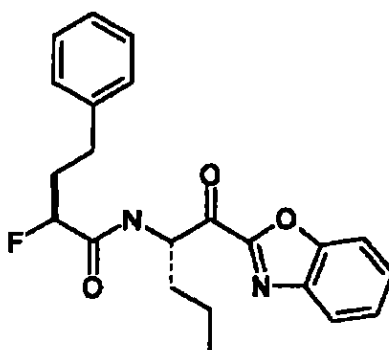
(d) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-butil]-2-dimetilamino-3-fenilmetanosulfonyl-propionamida



Procediendo de una manera similar al Ejemplo 21(a), pero utilizando (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonyl-propionamida {10 mg, 0,021 mmol, Ejemplo 32(f)}, se preparó (R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-dimetilamino-3-fenilmetanosulfonyl-propionamida (2,5 mg, 24%) LC/MS, tiempo de retención 2,82 min (TIC), $m/z = 472$ (M+H) (determinado por el método C)

EJEMPLO 22

(1S)-N-[1-(Benzoxazol-2-carbonil)-butil]-2-(S)-fluoro-4-fenil-butramida



Paso 1 a una mezcla de (S)-2-amino-1-benzoxazol-2-il-pentan-1-ol {0,549 mmol, 191 mg, Ejemplo de Referencia 17(c)}, ácido (S)-2-fluoro-4-fenilbutírico (1,0 eq , 0,549 mmol, 100 mg, Ejemplo de Referencia 9) y N,N-diisopropiletilamina (1,1 eq , 0,604 mmol, 78 mg) en diclorometano seco (5 ml) bajo nitrógeno se añadió PyBOP® (1,1 eq , 0,603 mmol, 285 mg) La mezcla se agitó a la temperatura ambiente durante 23,5 h, y se concentró luego a vacío El residuo se diluyó con acetato de etilo (20 ml) y se lavó con bicarbonato de sodio (30 ml) y luego con agua (30 ml) La capa orgánica se secó (MgSO₄) y se concentró a vacío El residuo

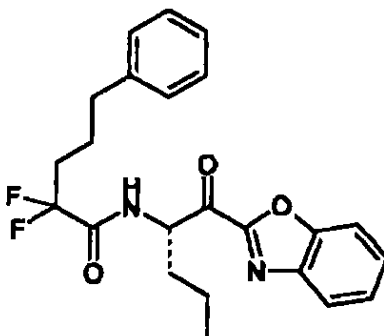
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264

se purificó por cromatografía en columna de gel de sílice, eluyendo con acetato de etilo y heptano (1 2) para proporcionar (S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-fluoro-4-fenil-butiramida como una mezcla de diastereoisómeros (167,8 mg, 79,5%)

Paso 2 A una solución de (S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-fluoro-4-fenil-butiramida en diclorometano seco (5 ml) bajo nitrógeno se añadió una solución al 15% en peso en diclorometano (2,0 eq , 0,863 mmol, 2,44 g) de 1,1,1-triacetoxi-1,1-dihidro-1,2-benzoyodioxol-3(1H)-ona (periyodinano Dess-Martin) La mezcla se agitó a la temperatura ambiente durante 2 h, y se enfrió luego rápidamente por adición de una solución de Na₂SO₂O₃ (4,0 eq , 1,73 mmol, 273 mg) en solución saturada de bicarbonato de sodio (30 ml) La capa orgánica se secó (MgSO₄) y se concentró a vacío El residuo se purificó sobre 10 g de gel de sílice, eluyendo con acetato de etilo y heptano (1 3) para proporcionar (1S)-N-[1-(benzooxazol-2-carbonil)-butil]-2-(S)-fluoro-4-fenil-butiramida como un sólido amarillo claro (156 mg, 94%) ¹H NMR (CDCl₃) 7,95 (d, J = 7,9 Hz, 1H), 7,7 (d, J = 8,2 Hz, 1H), 7,6 (t, J = 7,3 Hz, 1H), 7,51 (t, J = 7,4 Hz, 1H), 7,2 (m, 6H), 5,8 (m, 1H), 4,95 (ddd, J = 49,4, 8, 3,5 Hz, 1H), 2,8 (m, 2H), 2,4 (m, 1H), 2,2 (m, 2H), 1,85 (m, 1H), 1,5 (m, 2H), 1,0 (t, J = 7,3 Hz, 3H) LC/MS 86% (M+1) 383

EJEMPLO 23

Ácido 2,2-difluoro-5-fenil-pentanoico-[(S)-1-(benzoxazol-2-carbonil)-butil]-amida



Paso 1 Una solución de ácido 2,2-difluoro-5-fenil-pentanoico (182 mg, 0,85 mmol) en DMF (10 ml) se trató con (S)-2-amino-1-benzoxazol-2-il-pentan-1-ol (187 mg, 0,85 mmol), HATU (323 mg, 0,85 mmol) y N,N-diisopropiletilamina (0,162 ml) y se agitó a la temperatura ambiente durante 5 1/2 horas Se eliminó la DMF por evaporación, se recogió el producto bruto en acetato de etilo y se lavó con HCl 1N, NaHCO₃ saturado y salmuera Se secó sobre Na₂SO₄ y se evaporó a presión reducida para dar un aceite La purificación por cromatografía en columna, eluyendo con mezcla 1 1 de acetato de etilo y heptano dio ácido

264
265

2,2-difluoro-5-fenil-pentanoico-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-amida como un aceite anaranjado (216 mg) MS 417 (MH⁺)

Paso 2 Una solución de ácido

2,2-difluoro-5-fenil-pentanoico-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-amida (216 mg, 0,52 mmol) en diclorometano (10 ml) se trató con

1,1,1-triacetoxi-1,1-dihidro-1,2-benzoyodoxol-3(1H)-ona (periyodinano Dess-Martin) (220 mg, 0,52 mmol) durante 1 h a la temperatura ambiente. La mezcla de reacción se lavó con Na₂SO₂O₃ 0,5M, NaHCO₃ saturado, y agua, y se secó sobre Na₂SO₄. El disolvente se evaporó a presión reducida y el producto bruto se purificó por cromatografía súbita eluyendo con una mezcla de acetato de etilo y heptano para dar ácido

2,2-difluoro-5-fenil-pentanoico-[(S)-1-(benzoxazol-2-carbonil)-butil]-amida como un sólido blanquecino (90 mg)

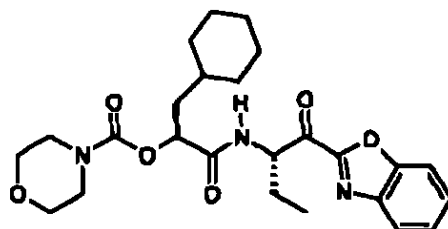
¹H NMR (CDCl₃) 7,93 (d, J = 8 Hz, 1H), 7,68 (d, J = 8 Hz, 1H), 7,59 (t, J = 8 Hz, 1H), 7,49 (t, J = 8 Hz, 1H), 7,3-7,11 (m, 5H), 5,72 (m, 1H), 2,67 (t, J = 7,5 Hz, 2H), 2,22-2,07 (m, 3H), 1,92-1,77 (m, 3H), 1,55-1,26 (m, 2H), 0,96 (t, J = 7,4 Hz, 3H)

LC/MS 415 (M+1)

EJEMPLO 24

(a) Ácido morfolina-4-carboxílico-(S)-1-

[(S)-1-(benzo-oxazol-2-carbonil)-propilcarbamoil]-2-ciclohexil-metil-éster



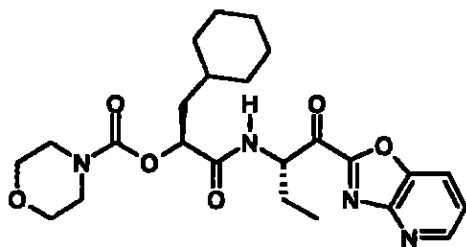
Paso 1 Se disolvió ácido (S)-3-ciclohexil-2-hidroxi-propiónico (3 g, 17,4 mmol) en metanol (30 ml). Se añadieron ortoformato de trimetilo (5 ml) y ácido p-toluenosulfónico monohidratado (10 mg). La mezcla se agitó a la temperatura ambiente durante una noche. Se añadió agua (50 ml) y se continuó la agitación durante 2 h. Se eliminó el metanol a vacío y el residuo acuoso se extrajo con acetato de etilo (3 x 50 ml). Las capas orgánicas reunidas se lavaron con NaHCO₃ acuoso saturado y salmuera, se secaron con MgSO₄ y se evaporaron. Se obtuvo ácido (S)-3-ciclohexil-2-hidroxi-propiónico-metil-éster como un líquido incoloro (3,1 g, 16,7 mmol).

Paso 2 Se disolvió ácido (S)-3-ciclohexil-2-hidroxi-propiónico-metil-éster (1 g, 5,37 mmol) en diclorometano (20 ml). Se añadió piridina (0,57 ml, 7 mmol) y la solución se enfrió a 0°C bajo nitrógeno. Se añadió cloroformiato de triclorometilo (0,66 ml, 5,5 mmol) y la mezcla se agitó durante 30 min a la temperatura ambiente. Se añadió morfolina (0,5 ml) y se continuó la agitación durante 2 h. Después de dilución con acetato de etilo (200 ml), la solución se lavó con HCl acuoso 1N y salmuera, se secó con MgSO₄ y se evaporó a vacío. El residuo se disolvió en metanol (50 ml) y se añadió solución acuosa 1N de NaOH (20 ml). La mezcla se agitó a la temperatura ambiente durante 4 h. Se eliminó el metanol a vacío y el residuo acuoso se lavó con dietil-éter. La capa acuosa se acidificó con HCl acuoso 1N y se extrajo con acetato de etilo (3 x 100 ml). Las capas orgánicas reunidas se lavaron con salmuera, se secaron con MgSO₄ y se evaporaron a vacío. El ácido (S)-morfolina-4-carboxílico-1-carboxi-2-ciclohexil-etil-éster bruto se utilizó sin purificación ulterior.

Paso 3 Procediendo de una manera similar a la descrita en el paso 3 del Ejemplo 4(a), pero utilizando ácido (S)-morfolina-4-carboxílico-1-carboxi-2-ciclohexil-etil-éster, se preparó ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(benzooxazol-2-carbonil)-propilcarbamoil]-2-ciclo-hexil-metil-éster. ¹H NMR (DMSO) 8,61 (d, J = 6,4 Hz, 1H), 7,97 (d, J = 8,0 Hz, 1H), 7,87 (d, J = 8,0 Hz, 1H), 7,61 (t, J = 8,0 Hz, 1H), 7,52 (t, J = 8,0 Hz, 1H), 5,15-5,09 (m, 1H), 4,91-4,86 (m, 1H), 3,56-3,20 (m, 8H), 2,05-1,93 (m, 1H), 1,79-0,78 (m, 14H), 0,96 (t, J = 7,2 Hz, 3H). MS (M+H)⁺ 472.

Procediendo de una manera similar al Ejemplo 24(a) se preparó

(b) Ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(oxazolo[4,5-b]piridina-2-carbonil)-propil-carbamoil]-etil-éster

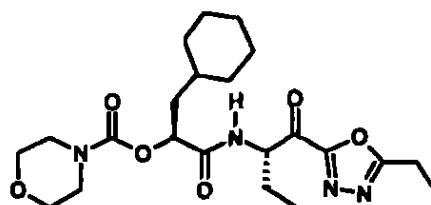


¹H NMR (DMSO) 8,73-8,69 (m, 2H), 8,38 (d, J = 8,0 Hz, 1H), 7,67-7,62 (m, 1H), 5,08-5,02 (m, 1H), 4,88-4,83 (m, 1H), 3,57-3,20 (m, 8H), 2,07-1,95 (m, 1H), 1,79-0,75 (m, 14H), 0,97 (t, J = 7,2 Hz, 3H). MS (M+H)⁺ 473.

268
269

(c) Ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-

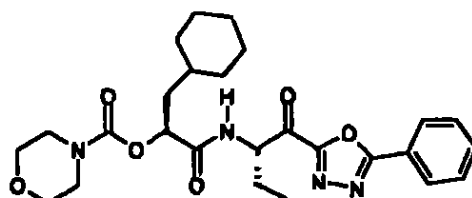
[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propil-carbamoi]-etil-éster



^1H NMR (DMSO) 8,62 (d, $J = 4,8$ Hz, 1H), 4,94-4,84 (m, 2H), 3,57-3,20 (m, 8H), 2,95 (q, $J = 7,2$ Hz, 2H), 1,98-1,87 (m, 1H), 1,74-0,82 (m, 14H), 1,29 (t, $J = 7,2$ Hz, 3H), 0,93 (t, $J = 7,2$ Hz, 3H) MS (M+H) $^+$ 451

(d) Ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-

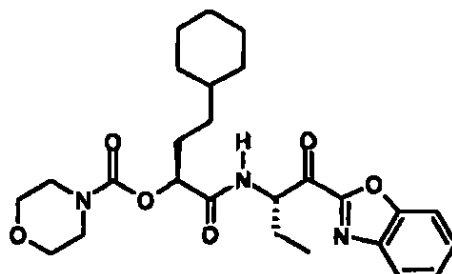
[(S)-1-(5-fenil-[1,3,4]oxadiazol-2-carbonil)-propil-carbamoi]-etil-éster



^1H NMR (DMSO) 8,69 (d, $J = 6,0$ Hz, 1H), 8,07 (d, $J = 8$ Hz, 2H), 7,70-7,59 (m, 3H), 4,99-4,92 (m, 1H), 4,88-4,83 (m, 1H), 3,57-3,20 (m, 8H), 2,03-1,92 (m, 1H), 1,77-0,77 (m, 14H), 0,96 (t, $J = 7,2$ Hz, 3H) MS (M+H) $^+$ 499

(e) Ácido morfolina-4-carboxílico-(S)-1-[(S)-1-

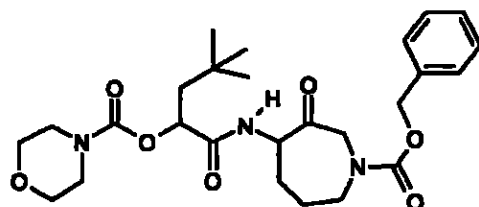
(benzo-oxazol-2-carbonil)-propilcarbamoi]-3-ciclohexil-propil-éster



^1H NMR (DMSO) 8,60 (d, $J = 6,8$ Hz, 1H), 7,97 (d, $J = 8,0$ Hz, 1H), 7,87 (d, $J = 8,0$ Hz, 1H), 7,61 (t, $J = 8,0$ Hz, 1H), 7,52 (t, $J = 8,0$ Hz, 1H), 5,13-5,06 (m, 1H), 4,81-4,76 (m, 1H), 3,56-3,21 (m, 8H), 2,05-1,93 (m, 1H), 1,79-1,46 (m, 8H), 1,19-0,90 (m, 6H), 0,96 (t, $J = 7,2$ Hz, 3H), 0,77-0,62 (m, 2H) MS (M+H) $^+$ 486

EJEMPLO 25

Ácido 4-[4,4-dimetil-2-(morfolina-4-carboniloxi)-
pentan-olamino]-3-oxo-azepan-1-carboxílico-bencil-éster



Se suspendió hidruro de sodio (60% en aceite mineral, 10 g, 250 mmol) en DMF seca. Se añadió gota a gota ácido alil-carbámico-bencil-éster (19,1 g, 100 mmol) a la temperatura ambiente. Después de agitar durante 5 min, se añadió gota a gota 5-bromo-1-penteno (25 g, 168 mmol). Se continuó la agitación a 50°C durante 1 h. Se extinguió la reacción con agua y se repartió luego entre dietil-éter y agua. La capa de éter se lavó con agua y salmuera, se secó con MgSO₄ y se evaporó a vacío. La cromatografía súbita (acetato de etilo/hexano 1/9) dio 15,5 g de ácido alil-pent-4-enil-carbámico-bencil-éster. Se disolvió el ácido alil-pent-4-enilcarbámico-bencil-éster (15,5 g, 59,8 mmol) en dicloroetano y se añadió bis(triciclohexilfosfina)bencilideno-rutenio(IV)-dicloruro (1 g). La mezcla se calentó a reflujo en atmósfera de nitrógeno hasta que el análisis por TLC indicó reacción completa. Se evaporó el disolvente a vacío y el residuo se purificó por cromatografía súbita (acetato de etilo/hexano 1/9). Rendimiento 7,8 g de ácido 2,3,4,7-tetrahidro-azepina-1-carboxílico-bencil-éster.

A una solución de ácido 2,3,4,7-tetrahidro-azepina-1-carboxílico-bencil-éster (4,5 g, 19,45 mmol) en diclorometano (50 ml) se añadió ácido m-cloroperbenzoico (60 mmol). La mezcla se agitó a la temperatura ambiente durante 16 h. Se añadió solución acuosa saturada de K₂CO₃ y la mezcla se extrajo con diclorometano. Las capas orgánicas reunidas se lavaron con NaHCO₃ acuoso saturado y salmuera, se secaron con MgSO₄ y se evaporaron a vacío. El epóxido bruto se disolvió en una mezcla 8/1 metanol/agua (100 ml). Se añadieron cloruro de amonio (3,2 g, 60 mmol) y azida de sodio (3,9 g, 60 mmol) y la mezcla se calentó a 60°C durante 48 h. Se eliminó la mayor parte del disolvente a vacío. El residuo se extrajo con acetato de etilo. Las capas orgánicas reunidas se lavaron con NaHCO₃ acuoso saturado (200 ml) y salmuera (200 ml), se secaron con MgSO₄ y se evaporaron a vacío. La cromatografía súbita del residuo (hexano/acetato de etilo 3/1) dio 3,3 g de ácido 4-azido-3-hidroxi-azepan-1-carboxílico-bencil-éster.

268

269

A una solución de ácido 4-azido-3-hidroxi-azepan-1-carboxílico-bencil-éster (3,3 g, 11,37 mmol) en metanol (50 ml) se añadieron trietilamina (5 ml) y 1,3-propanoditiol (3,42 ml, 35 mmol). La mezcla se agitó a la temperatura ambiente hasta que el análisis TLC demostró el consumo completo del material de partida. Se eliminó por filtración un precipitado blanco y el filtrado se evaporó a sequedad. El residuo se trituró con una mezcla 1:1 hexano-dietil-éter para eliminar el exceso de ditiol y se secó a vacío.

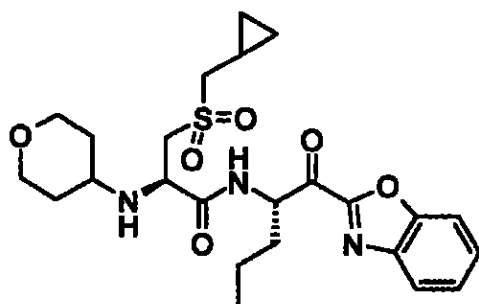
Se combinaron ácido 4-amino-3-hidroxi-azepan-1-carboxílico-bencil-éster bruto (150 mg, 0,57 mmol), ácido morfolina-4-carboxílico-1-carboxi-3,3-dimetil-butil-éster (120 mg, 0,46 mmol), EDC (400 mg, 2,1 mmol), y HOBt (400 mg, 2,5 mmol). Se añadió diclorometano (5 ml) y luego 4-metilmorfolina (0,5 ml). La mezcla se agitó a la temperatura ambiente durante 2 h. Después de dilución con acetato de etilo (100 ml) la solución se lavó con HCl 1N, NaHCO₃ acuoso saturado y salmuera, se secó con MgSO₄ y se evaporó a vacío. El residuo se disolvió en DMSO (5 ml). Se añadieron trietilamina (0,3 ml) y luego complejo SO₃-piridina (150 mg) y la mezcla se agitó a la temperatura ambiente durante 2 h. Después de dilución con acetato de etilo (100 ml), la solución se lavó con agua (50 ml) y salmuera, se secó con MgSO₄ y se evaporó a vacío. El residuo se purificó por cromatografía súbita sobre gel de sílice y dio ácido

4-[4,4-dimetil-2-(morfolina-4-carbon-iloxi)-pentanoilamino]-3-oxo-azepan-1-carboxílico-bencil-éster (95 mg, 0,189 mmol) como un sólido blanco.

Mezcla 2:1 de diastereoisómeros, ¹H NMR (DMSO) 8,14-8,08 (m, 1H), 7,40-7,25 (m, 5H), 5,18-4,89 (m, 3H), 4,51-4,33 (m, 2H), 4,01-3,76 (m, 2H), 3,60-3,25 (m, 8H), 2,95-2,79 (m, 1H), 1,84-1,54 (m, 6H), 0,92-0,91 (s, 9H). MS (M+H)⁺ 504. LC/MS m/z = 474 (M+H).

EJEMPLO 26

(a) (R)-N-[(S)-1-Benzoxazol-2-carbonil]-butil-3-ciclopropilmetanosulfonil-2-(tetrahidropirán-4-ilamino)-propionamida



Paso 1 Se disolvió (R)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-ciclopropilmetanosulfonil-propionamida {90 mg, 0,22 mmol, Ejemplo de Referencia

269

270

11(f)} en ácido acético al 5% en acetonitrilo (10 ml) Se añadió tetrahidro-4H-piran-4-ona (110 mg, 1,1 mmol), seguida por cianoborohidruro de (poliestirilmetil)-trimetilamonio (107 mg, 1,1 mmol) La mezcla de reacción resultante se agitó durante cuatro horas y se filtró luego con succión Se evaporaron los disolventes a alto vacío El residuo se disolvió en 5 ml de diclorometano, se añadió Silicycle Triamine (940 mg, 2,2 mmol) y la mezcla de reacción se agitó durante cuatro horas Se filtró con succión y el filtrado se concentró a presión reducida para dar

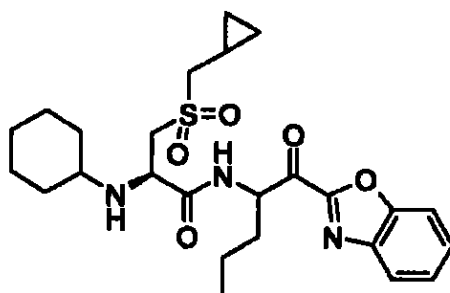
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-ciclopropilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida (89 mg, 0,18 mmol, 82%)

Paso 2 Se disolvió (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-ciclopropilmetanosulfonil-2-(te-trahidropiran-4-ilamino)-propionamida (89 mg, 0,18 mmol) en 10 ml de diclorometano Se añadió el peryodinano Dess-Martin (153 mg, 0,36 mmol) y la mezcla de reacción resultante se agitó durante dos horas La mezcla de reacción se vertió en una mezcla 1/1 de solución saturada de bicarbonato de sodio y solución saturada de tiosulfato de sodio La fase acuosa se extrajo con diclorometano Las fases orgánicas reunidas se lavaron con solución saturada de bicarbonato de sodio y salmuera La fase orgánica se secó con sulfato de magnesio y el diclorometano se evaporó a reducida. El producto bruto se purificó por cromatografía súbita (heptano/acetato de etilo 1/1 para la elución) para dar

(R)-N-[(S)-1-benzoxazol-2-carbonil)-butil]-3-ciclopropilmetanosulfon-il-2-(tetrahidropiran-4-ilamino)-propionamida (24 mg, 0,049 mmol, 27%) ¹H NMR (CDCl₃, 300 MHz) 8,29 (d, J = 8,5 Hz, 1H), 7,93 (d, J = 8 Hz, 1H), 7,68 (d, J = 8 Hz, 1H), 7,59-7,46 (m, 2H), 5,67 (m, 1H), 3,99-3,93 (m, 2H), 3,84 (dd, J = 9,5 Hz, 2,5 Hz, 1H), 3,56 (dd, J = 14,5 Hz, 2,5 Hz, 1H), 3,42-3,33 (m, 2H), 3,24 (dd, J = 14,5 Hz, 9,5 Hz, 1H), 3,02-2,99 (m, 2H), 2,78-2,71 (m, 1H), 2,13-2,07 (m, 1H), 1,95-1,78 (m, 3H), 1,55-1,41 (m, 5H), 1,23-1,16 (m, 1H), 1,00 (t, J = 7,5 Hz, 3H), 0,81-0,74 (m, 2H), 0,48-0,43 (m, 2H)

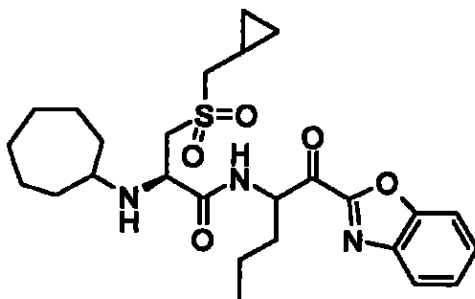
LC/MS m/z = 492 (M+H)

(b) (R)-N-[1-(Benzoxazol-2-carbonil)-butil]-2-ciclohexil-amino-3-ciclopropilmetanosulfonil-propionamida



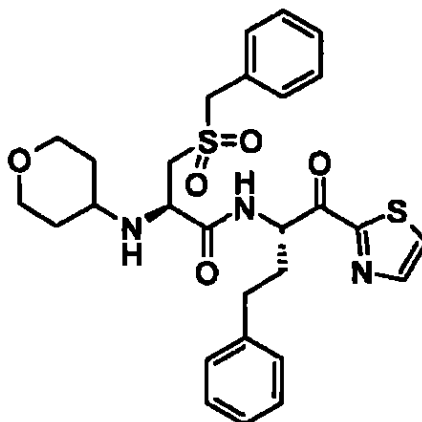
Procediendo de una manera similar al Ejemplo 26(a), pero utilizando ciclohexanona, se preparó (R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-ciclohexilamino-3-ciclopropilmetanosulfonil-propionamida (predominantemente como un solo diastereoisómero) ^1H NMR (CDCl_3 , 300 MHz) 8,37 (d, $J = 8,5$ Hz, 1H), 7,92 (d, $J = 8$ Hz, 1H), 7,67 (d, $J = 8$ Hz, 1H), 7,59-7,36 (m, 2H), 5,65 (m, 1H), 3,79 (dd, $J = 9,5$ Hz, 2,5 Hz, 1H), 3,54 (dd, $J = 14,25$ Hz, 2,5 Hz, 1H), 3,24 (dd, $J = 14,25$ Hz, 9,5 Hz, 1H), 3,02-2,95 (m, 2H), 2,49 (m, 1H), 2,12-2,07 (m, 1H), 1,96-1,17 (m, 15H), 0,98 (t, $J = 7$ Hz, 3H), 0,80-0,72 (m, 2H), 0,48-0,43 (m, 2H) LC/MS $m/z = 490$ (M+H)

(c) (R)-N-[1-(Benzoxazol-2-carbonil)-butil]-2-cicloheptilamino-3-ciclopropilmetanosulfonil-propionamida



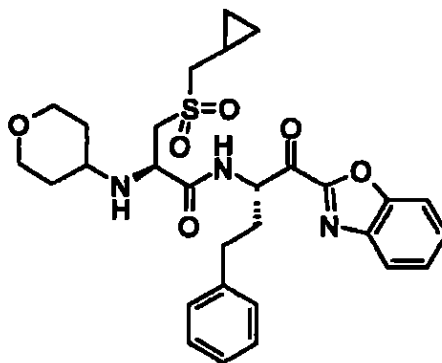
Procediendo de una manera similar al Ejemplo 24(a), pero utilizando cicloheptanona se preparó (R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-cicloheptilamino-3-ciclopropilmetanosulfonil-propionamida. ^1H NMR (CDCl_3 , 300 MHz) [8,36 (d, $J = 8,5$ Hz), 8,28 (d, $J = 8,5$ Hz), 1H], [8,5 (dd, $J = 8$ Hz, 1Hz), 7,97 (dd, $J = 8,5$ Hz, 1,5 Hz), 1H], [7,92 (d, $J = 8,5$ Hz), 7,67 (d, $J = 8$ Hz, 1H], 7,59-7,48 (m, 1H), [7,44 (ddd, $J = 8$ Hz, 7,5 Hz, 1Hz), 7,19 (ddd, $J = 8$ Hz, 7,5 Hz, 1Hz), 1H], [5,65 (m), 5,62 (m), 1H], [3,82 (dd, $J = 10$ Hz, 3 Hz), 3,75 (dd, $J = 9$ Hz, 3 Hz), 1H], [3,55 (dd, $J = 14,5$ Hz, 3 Hz), 3,49 (dd, $J = 14,5$ Hz, 3 Hz), 1H], 3,27 (dd, $J = 14,5$ Hz, 9 Hz, 1H), 3,03-2,96 (m, 2H), 2,72 (m, 1H), 2,14-2,05 (m, 1H), 1,91-1,39 (m, 16H), 1,23-1,17 (m, 1H), [0,99 (t, $J = 7,25$ Hz), 0,98 (t, $J = 7,25$ Hz), 1H], 0,79-0,7 (m, 2H), 0,48-0,44 (m, 2H) LC/MS $m/z = 504$ (M+H)

(d) (R)-3-Fenilmetanosulfonil-N-[(S)-3-fenil-1-(tiazol-2-carbonil)-propil]-2-(tetrahidropiran-4-ilamino)-propionamida



Procediendo de una manera similar al Ejemplo 26(a), pero utilizando (R)-2-amino-N-[(S)-1-(hidroxitiazol-2-il-metil)-3-fenil-propil]-3-fenilmetanosulfonil-propionamida {Ejemplo de Referencia 11(k)} se preparó (R)-3-fenilmetanosulfonil-N-[(S)-3-fenil-1-(tiazol-2-carbonil)-propil]-2-(tetrahidropiran-4-ilamino)-propionamida ¹H NMR (CDCl₃, 300 MHz) 8,27 (d, J = 9 Hz, 1H), 8,06 (d, J = 3 Hz, 1H), 7,73 (d, J = 3 Hz, 1H), 7,47-7,39 (m, 5H), 7,25-7,11 (m, 5H), 5,72 (m, 1H), 4,36 (d, J = 14 Hz, 1H), 4,31 (d, J = 14 Hz, 1H), 3,97-3,90 (m, 2H), 3,76 (dd, J = 9,5 Hz, 3 Hz, 1H), 3,40-3,31 (m, 3H), 3,01 (dd, J = 14,5 Hz, 9,5 Hz, 1H), 2,76-2,62 (m, 3H), 2,51-2,40 (m, 1H), 2,22-2,09 (m, 1H), 1,87-1,75 (m, 2H), 1,53-1,38 (m, 3H)
LC/MS m/z = 556 (M+H)

(e) (R)-N-[(S)-1-(Benzoxazol-2-carbonil)-3-fenil-propil]-3-ciclopropilmetanosulfonil-2-(tetrahidropiran-4-ilamino)propionamida



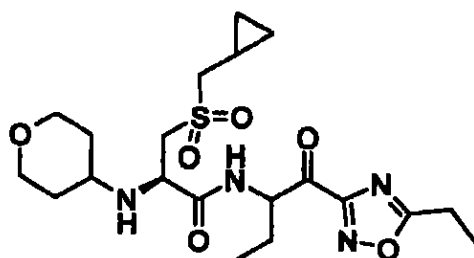
Procediendo de una manera similar al Ejemplo 26(a), pero utilizando

(R)-2-amino-N-[(S)-1-(hidroxí-tiazol-2-il-metil)-3-fenil-propil]-3-fenilmetanosulfonil-propionamida {Ejemplo de Referencia 11(j)}, se preparó

(R)-N-[(S)-1-(benzoxazol-2-carbonil)-3-fenil-propil]-3-ciclo-propilmetanosulfonil-2-(tetrahidropirán-4-ilamino)propionamida. ¹H NMR (CDCl₃, 300 MHz) 8,36 (d, J = 8,5 Hz, 1H), 7,92 (d, J = 8 Hz, 1H), 7,67 (d, J = 8 Hz, 1H), 7,60-7,46 (m, 2H), 7,25-7,16 (m, 5H), 5,72 (m, 1H), 3,99-3,93 (m, 2H), 3,81 (dd, J = 9,5 Hz, 3Hz, 1H), 3,52 (dd, J = 14 Hz, 3Hz, 1H), 3,41-3,33 (m, 2H), 3,15 (dd, J = 14 Hz, 9,5 Hz, 1H), 3,01-2,70 (m, 2H), 2,81-2,70 (m, 3H), 2,53 (m, 1H), 2,27-2,23 (m, 1H), 1,94-1,44 (m, 5H), 1,22-1,17 (m, 1H), 0,80-0,74 (m, 2H), 0,47-0,42 (m, 2H) LC/MS m/z = 554 (M+H)⁺

(f) (R)-3-Ciclopropilmetanosulfonil-N-[1-(5-etil-

1,2,4-oxadiazol-3-carbonil)-propil]-2-(tetrahidropirán-4-ilamino)-propionamida



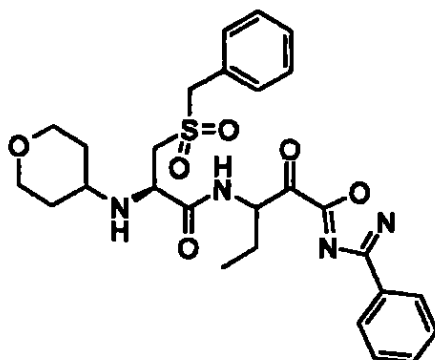
Procediendo de una manera similar al Ejemplo 26(a), pero utilizando

(R)-2-amino-3-ciclopropilmetanosulfonil-N-[(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxí-metil]-propil]-propionamida {Ejemplo de Referencia 11(h)}, se preparó

(R)-3-ciclopropilmetanosulfonil-N-[1-(5-etil-1,2,4-

oxadiazol-3-carbonil)-propil]-2-(tetrahidropirán-4-ilamino)-propionamida ¹H NMR (CDCl₃, 300 MHz) [8,28 (d, J = 8,5 Hz), 8,15 (d, J = 8 Hz), 1H], [5,40(m), 5,33(m), 1H], 3,99-3,95 (m, 2H), [3,90 (dd, J = 10 Hz, 3 Hz), 3,84 (dd, J = 9,5 Hz, 3 Hz), 1H], [3,55 (dd, J = 14 Hz, 3 Hz), 3,47 (dd, J = 14 Hz, 11 Hz), 1H], 3,45-3,33 (m, 2H), 3,23 (dd, J = 14 Hz, 10 Hz, 1H), 3,07-2,94 (m, 4H), 2,82-2,71 (m, 1H), 2,19-2,08 (m, 1H), 1,95-1,77 (m, 5H), 1,58-1,43 (m, 1H), 1,45 (t, J = 7,5 Hz, 3H), 1,23-1,14 (m, 1H), [1,00 (t, J = 7,5 Hz), 0,97 (t, J = 7,5 Hz), 3H], 0,81-0,73 (m, 2H), 0,48-0,41 (m, 2H) LC/MS m/z = 457 (M+H)

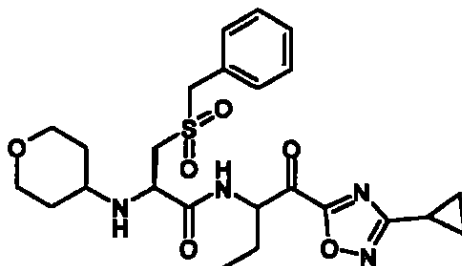
(g) (R)-3-Fenilmetanosulfonil-N-[1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propil]-2-(tetrahidropiran-4-il-amino)-propionamida



Procediendo de una manera similar al Ejemplo 26(a), pero utilizando (R)-2-amino-N-{1-[hidroxí-(3-fenil-1,2,4-oxadiazol-5-il)-metil]-propil}-3-fenilmetanosulfonil-propionamida {Ejemplo de Referencia 11(g)} se preparó

(R)-3-fenilmetanosulfonil-N-[1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propil]-2-(tetrahidropiran-4-il-amino)-propionamida ^1H NMR (CDCl_3 , 300 MHz) [8,15 (d, $J = 8$ Hz), 8,14 (d, $J = 8$ Hz), 1H], 7,61-7,39 (m, 10H), [5,46(m), 5,40(m), 1H], 4,34-4,28 (m, 2H), 4,09-3,93 (m, 2H), [3,87 (dd, $J = 9,5$ Hz, 3Hz), 3,81 (dd, $J = 9,5$ Hz, 3 Hz), 1H], 3,41-3,32 (m, 3H), [3,16 (dd, $J = 13,5$ Hz, 10 Hz), 3,11 (dd, $J = 14$ Hz, 9,5 Hz), 1H], 2,75-2,68 (m, 1H), 2,23-2,13 (m, 1H), 1,26-1,43 (m, 6H), 1,06-0,99 (m, 3H) LC/MS $m/z = 541$ (M+H)

(h) (R)-N-[1-(3-Ciclopropil-1,2,4-oxadiazol-5-carbonil)-propil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-il-amino)propionamida



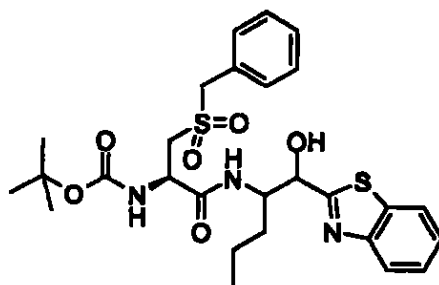
Procediendo de una manera similar al Ejemplo 26(a), pero utilizando (R)-2-amino-3-fenilmetanosulfonil-N-((S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroxí-metil]-propil)-propionamida {Ejemplo de Referencia 11(I)} se preparó (R)-N-[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbon-il)-propil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-il-amino)propionamida ^1H NMR (CDCl_3 ,

274
275

300 MHz) [8,19 (d, J = 8,5 Hz), 8,11 (d, J = 7,5 Hz), 1H], 7,46-7,40 (m, 5H), [5,33(m), 5,27(m), 1H], 4,55-4,35 (m, 2H), 3,99-3,95 (m, 2H), [3,88 (dd, J = 10 Hz, 3 Hz), 3,83 (dd, J = 9,5 Hz, 3 Hz), 1H], 3,44-3,34 (m, 3H), 3,18-3,07 (m, 1H), 2,78-2,67 (m, 1H), 2,24-2,17 (m, 1H), 2,15-2,08 (m, 1H), 1,89-1,72 (m, 3H), 1,55-1,43 (m, 2H), 1,20-1,11 (m, 4H), [0,98 (t, J = 7,5 Hz), 0,97 (t, J = 7,5 Hz), 3H]
LC/MS m/z = 505 (M+H)

EJEMPLO 27

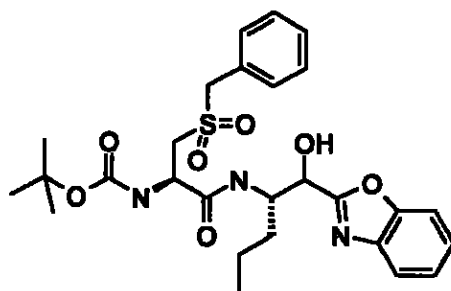
(a) Ácido {(R)-1-[1-(benzotiazol-2-il)-hidroxi-metil]-butilcarbamoil}-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster



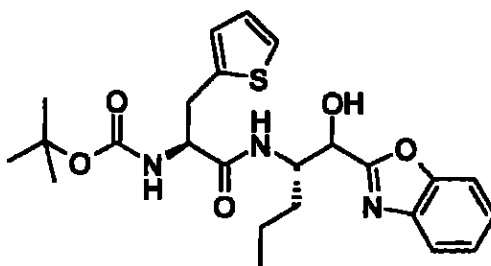
N-Ciclohexilcarbodiimida-N'-metil-poliestireno (1,74 g, 3,4 mmol) suspendido en una mezcla de diclorometano (10 ml) y dimetilformamida (2 ml) se trató con hidroxibenzotriazol (391 mg, 2,89 mmol) y L-N-boc-bencilsulfonilalanina (876 mg, 2,55 mmol) Esta mezcla se agitó a la temperatura ambiente durante 30 minutos, y se trató luego con 2-amino-1-benzotiazol-2-il-pentan-1-ol {400 mg, 1,7 mmol, Ejemplo de Referencia 17(d)} y, después de agitar durante dos horas más, la mezcla se trató luego con Silicycle-Triamune (2,36 g, 8,5 mmol) La mezcla de reacción se agitó durante dos horas y se filtró luego El filtrado se evaporó para dar el compuesto del título (888 mg, 93%) LC/MS m/z = 562

275
276

(b) Ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetano-sulfoniletil}-carbámico-*terc*-butil-éster

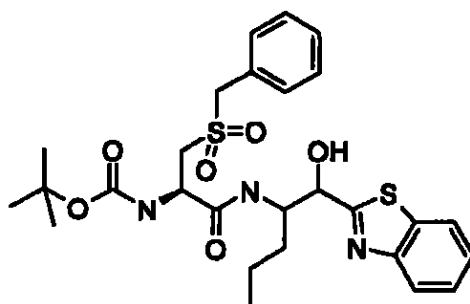


Procediendo de una manera similar al Ejemplo 27(a) anterior, pero utilizando L-N-boc-bencilsulfonilalanina (876 mg, 2,55 mol) y (2S)-2-amino-1-benzoxazol-2-il-pentan-1-ol {374 mg, 1,7 mmol, Ejemplo de Referencia 17(c)} se preparó ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-1-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster (908 mg, 98%)
(c) Ácido {(S)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-tiofen-2-il-etil}-carbámico-*terc*-butil-éster



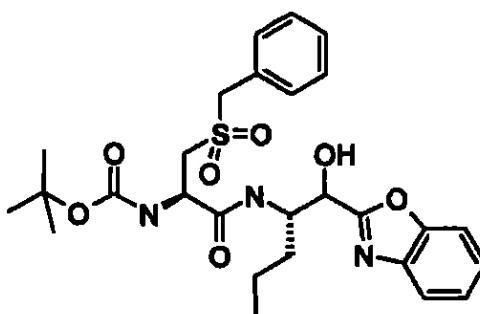
Procediendo de una manera similar al Ejemplo 27(a) anterior, pero utilizando diimida fijada a Resina (1,76 g, 3,4 mmol) suspendida en diclorometano (10 ml), hidroxibenzotriazol (391 mg, 2,89 mmol), ácido (2S)-2-*terc*-butoxicarbonilamino-3-tiofen-2-il-propiónico (692 mg, 2,55 mmol), (2S)-2-amino-1-benzoxazol-2-il-pentan-1-ol {374 mg, 1,7 mmol, Ejemplo de Referencia 17(c)} y Silicycle-Triamine (2,36 g, 8,5 mmol), se preparó ácido {(S)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-tiofen-2-il-etil}-carbámico-*terc*-butil-éster (790 mg, 1,67 mmol, 98%)
LC/MS $m/z = 562$ (M+H)

(d) Ácido {(R)-1-[1-(benzotiazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetanosulfoniletil}-carbámico-*terc*-butil-éster



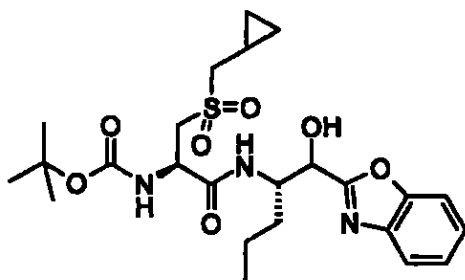
Procediendo de una manera similar al Ejemplo 27(a) anterior, pero utilizando diimida fijada a Resina (741 mg, 1,26 mmol), hidroxibenzotriazol (144 mg, 1,07 mmol), L-N-boc-bencilsulfonilalanina (326 mg, 0,95 mmol), 2-amino-1-benzotiazol-2-il-pentan-1-ol {150 mg, 0,63 mmol, Ejemplo de Referencia 17(d)} y Silicycle-Triamine (2,36 g, 8,5 mmol) se preparó ácido {(R)-1-[1-(benzotiazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster LC/MS m/z = 652 (M+H), que se utilizó sin purificación ulterior

(e) Ácido {(R)-1-[1-(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetanosulfoniletil}-carbámico-*terc*-butil-éster



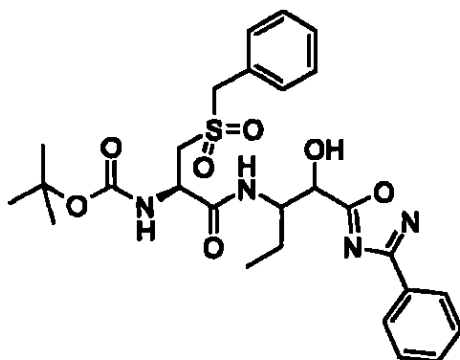
Procediendo de una manera similar al Ejemplo 27(a) anterior, pero utilizando diimida fijada a Resina (1,76 g, 3,4 mmol), hidroxibenzotriazol (391 mg, 2,89 mmol), L-N-boc-bencilsulfonilalanina (876 mg, 2,55 mmol), (2S)-2-amino-1-benzoxazol-2-il-pentan-1-ol {374 mg, 1,7 mmol, Ejemplo de Referencia 17(c)} y Silicycle-Triamine (2,36 g, 8,5 mmol) se preparó ácido {(R)-1-[1-(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster LC/MS m/z = 546 (M+H), 490 (M = H-buteno), que se utilizó directamente en la reacción siguiente

(f) Ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-ciclopropilmetano-sulfonyl-etil}-carbámico-*terc*-butil-éster



Procediendo de una manera similar al Ejemplo 27(a) anterior, pero utilizando una suspensión de diimida fijada a Resina (1,07 g, 1,82 mmol) en diclorometano (20 ml), hidroxibenzotriazol (209 mg, 1,55 mmol) y ácido (R)-2-*terc*-butoxicarbonilamino-3-ciclopropilmetanosulfonyl-propiónico (420 mg, 1,365 mmol, Ejemplo de Referencia 22), (S)-2-amino-1-benzoxazol-2-il-pentan-1-ol (200 mg, 0,91 mmol, Ejemplo de Referencia 17 (c)) y Silicycle-Triamine (2,8 g, 9,1 mmol) se preparó ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-ciclopropilmetanosulfonyl-etil}-carbámico-*terc*-butil-éster (450 mg, 97%) LC/MS m/z = 532 (M+Na), 510 (M+H), 454 (M+H-isobuteno)

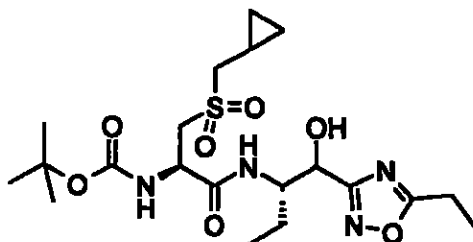
(g) Ácido (R)-1-{1-[hidroxi-3-fenil-1,2,4-oxadiazol-5-il]-metil]-propilcarbamoil}-2-fenilmetanosulfonyl-etil)-carbámico-*terc*-butil-éster



Procediendo de una manera similar al Ejemplo 27(f) anterior, pero utilizando L-N-boc-bencilsulfonylalanina y ácido (R)-2-*terc*-butoxicarbonilamino-3-fenilmetanosulfonyl-propiónico y (S)-2-amino-1-(3-fenil-[1,2,4]oxadiazol-5-il)-butan-1-ol (Ejemplo de Referencia 21) se preparó ácido (R)-1-{1-[hidroxi-3-fenil-1,2,4-oxadiazol-5-il]-metil]-propilcarbamoil}-2-fenilmetanosulfonyl-etil)-carbámico-*terc*-butil-éster, LC/MS m/z = 545 (M+Na), 467 (M+H-isobuteno), 423 (M+H-Boc)

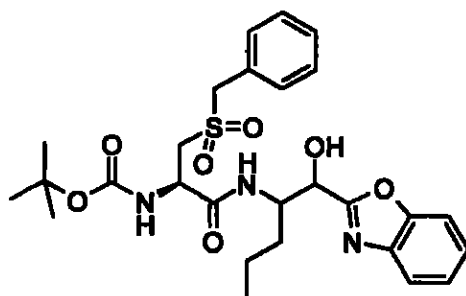
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279

(i) Ácido ((R)-2-ciclopropilmetanosulfonyl-1-((S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroximetil]-propylcarbamoil)-etil)-carbámico-*terc*-butil-éster



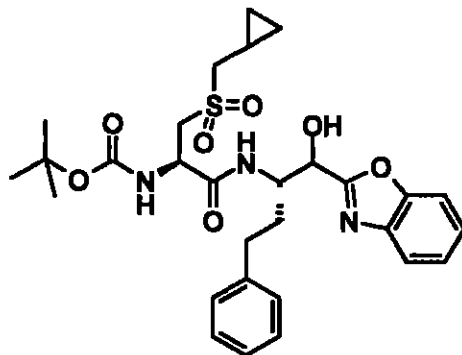
Procediendo de una manera similar al Ejemplo 27(f) anterior, pero utilizando 2-amino-1-(5-etil-[1,2,4]-oxadiazol-3-il)-butan-1-ol (Ejemplo de Referencia 23), se preparó ácido ((R)-2-ciclopropilmetanosulfonyl-1-((S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroximetil]-propylcarbamoil)-etil)-carbámico-*terc*-butil-éster LC/MS $m/z = 497$ (M+Na), 419 (M+H-isobuteno), 375 (M+H-Boc)

(j) Ácido ((R)-1-[1-(benzoxazol-2-il)-hidroximetil]-butylcarbamoil]-2-fenylmetanosulfonyl-etil)-carbámico-*terc*-butil-éster



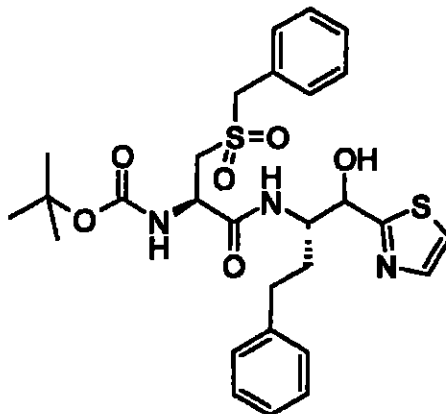
Procediendo de una manera similar al Ejemplo 27(f) anterior, pero utilizando L-N-boc-bencilsulfonilalanina y (S)-2-amino-1-benzoxazol-2-il)-pentan-1-ol {Ejemplo de Referencia 17(c)}, se preparó ácido ((R)-1-[1-(benzoxazol-2-il)-hidroximetil]-butylcarbamoil]-2-fenylmetanosulfonyl-etil)-carbámico-*terc*-butil-éster LC/MS $m/z = 546$ (M+H), 490 (M+H-isobuteno)

(k) Ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-propilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster



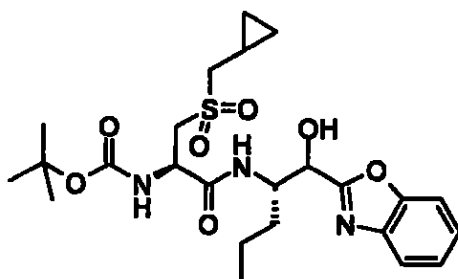
Procediendo de una manera similar al Ejemplo 27(f) anterior, pero utilizando (2S)-2-amino-4-fenil-1-benzoxazol-2-il-butan-1-ol, se preparó ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-propilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster LC/MS m/z = 572 (M+H), 516 (M+H-isobuteno)

(l) Ácido {(R)-1-[(S)-1-(hidroxi-tiazol-2-il-metil)-3-fenil-propilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster



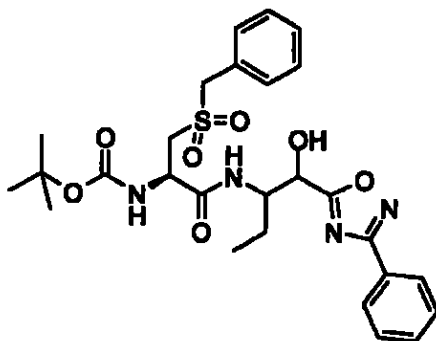
Procediendo de una manera similar al Ejemplo 27(f) anterior, pero utilizando L-N-boc-bencilulfonilalanina y (2S)-2-amino-4-fenil-1-tiazol-2-il-butan-1-ol (Ejemplo de Referencia 13) se preparó Ácido {(R)-1-[(S)-1-(hidroxi-tiazol-2-il-metil)-3-fenil-propilcarbamoil]-2-fenilmeta-nosulfonil-etil}-carbámico-*terc*-butil-éster LC/MS m/z = 574 (M+H)

(m) Ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster



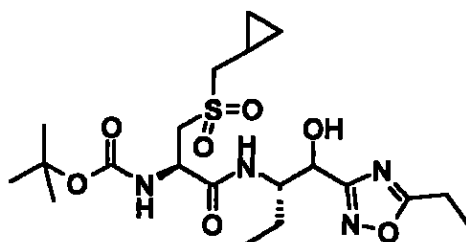
Procediendo de una manera similar al Ejemplo 27(f) anterior, pero utilizando *N*-ciclohexilcarbodiimida, *N*'-metil-poliestireno (1,07 g, 1,82 mmol) suspendido en diclorometano (20 ml), hidroxibenzotriazol (209 mg, 1,55 mmol), ácido (R)-2-*terc*-butoxicarbonilamino-3-ciclo-propilmetanosulfonil-propiónico (420 mg, 1,365 mmol, Ejemplo de Referencia 22), (S)-2-amino-1-benzoxazol-2-il-pentan-1-ol (200 mg, 0,91 mmol, Ejemplo de Referencia 17(c)) y Silicycle-Triamine (2,8 g, 9,1 mmol), se preparó ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster (450 mg, 0,88 mmol, 97%) LC/MS m/z = 532 (M+Na, 510 (M+H), 454 (M+H-isobuteno)

(n) Ácido (R)-1-{1-[hidroxí(3-fenil-1,2,4-oxadiazol-5-il)-metil]-propilcarbamoil}-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster

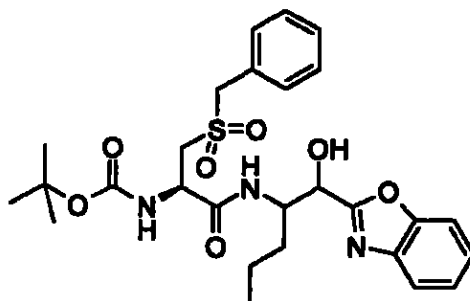


Procediendo de una manera similar al Ejemplo 27(m) anterior, pero utilizando L-N-boc-bencilsulfonilalanina y (S)-2-amino-1-(3-fenil-[1,2,4]oxadiazol-5-il)-butan-1-ol (Ejemplo de Referencia 21) se preparó ácido (R)-1-{1-[hidroxí(3-fenil-1,2,4-oxadiazol-5-il)-metil]-propilcarbamoil}-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster LC/MS m/z = 545 (M+Na), 467 (M+H-isobuteno), 423 (M+H-Boc)

- (o) Ácido {(R)-2-ciclopropilmetanosulfonil-1-[(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxil-metil]-propilcarbamoil]-etil)-carbámico-terc-butil-éster



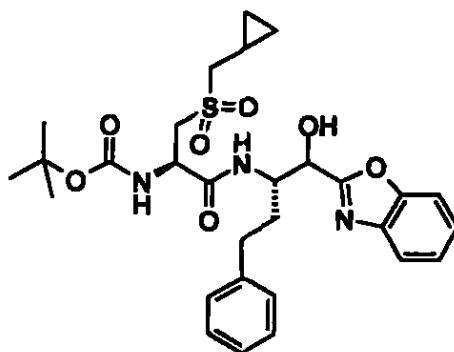
- Procediendo de una manera similar al Ejemplo 27(m) anterior, pero utilizando (S)-2-amino-1-(5-etil-[1,2,4]oxadiazol-3-il)-butan-1-ol, se preparó ácido {(R)-2-ciclopropilmetanosulfonil-1-[(S)-1-[(5-etil-1,2,4-oxa-diazol-3-il)-hidroxil-metil]-propilcarbamoil]-etil)-carbámico-terc-butil-éster LC/MS m/z = 497 (M+Na), 419 (M+H-isobuteno), 375 (M+H-Boc)
- (p) Ácido {(R)-1-[1-(benzoxazol-2-il)-hidroxil-metil]-butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-terc-butil-éster



- Procediendo de una manera similar al Ejemplo 27(m) anterior, pero utilizando L-N-boc-bencilsulfonilalanina y (S)-2-amino-1-benzoxazol-2-il-pentan-1-ol {200 mg, 0,91 mmol, Ejemplo de Referencia 17(c)} se preparó ácido {(R)-1-[1-(benzoxazol-2-il)-hidroxil-metil]-butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-terc-butil-éster LC/MS m/z = 546 (M+H), 490 (M+H-isobuteno)

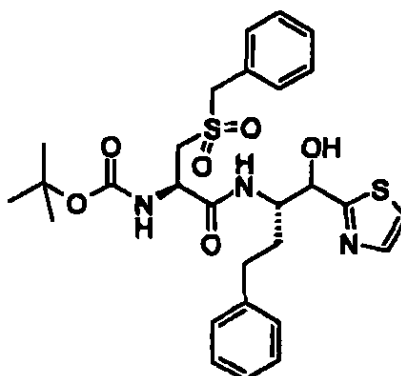
282
283

(q) Ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-propilcarbamoil]-2-ciclopropil-metanosulfon-il-etil}-carbámico-*terc*-butil-éster



Procediendo de una manera similar al Ejemplo 27(m) anterior, pero utilizando (2S)-2-amino-4-fenil-1-benzoxazol-2-il-butan-1-ol, se preparó ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-propilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster LC/MS m/z = 572 (M+H), 516 (M+H-isobuteno)

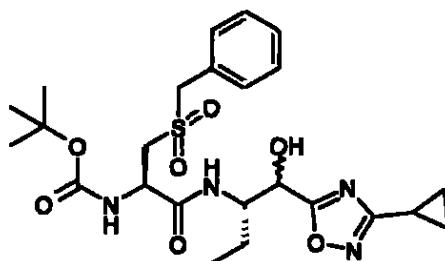
(r) Ácido {(R)-1-[(S)-1-(hidroxi-tiazol-2-il-metil)-3-fenil-propilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster



Procediendo de una manera similar al Ejemplo 27(m) anterior, pero utilizando L-N-boc-metilsulfonilalanina y (2S)-2-amino-4-fenil-1-tiazol-2-il-butan-1-ol (Ejemplo de Referencia 13) se preparó ácido {(R)-1-[(S)-1-(hidroxi-tiazol-2-il-metil)-3-fenil-propilcarbamoil]-2-fenilmeta-nosulfonil-etil}-carbámico-*terc*-butil-éster LC/MS m/z = 574 (M+H)

283
284

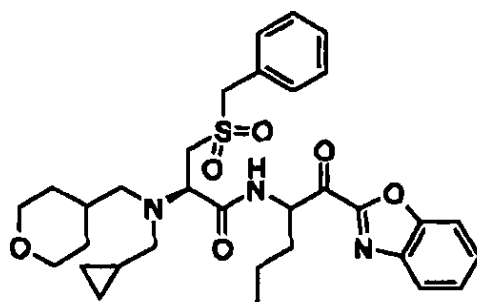
(s) Ácido ((R)-2-fenilmetanosulfonyl-1-((S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroximetil]-propilcarbamoil)-etil)-carbámico-terc-butyl-éster



Procediendo de una manera similar al Ejemplo 27(m) anterior, pero utilizando L-N-boc-bencilsulfonilalanina y (S)-2-amino-1-(3-ciclopropil-1,2,4-oxadiazol-5-il)-butan-1-ol (Ejemplo de Referencia 14) se preparó ácido ((R)-2-fenilmetanosulfonyl-1-((S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroximetil]-propilcarbamoil)-etil)-carbámico-terc-butyl-éster

EJEMPLO 28

(R)-N-[1-(Benzoxazol-2-carbonil)-butil]-2-[ciclopropilmetil-(tetrahidropiran-4-ilmetil)-amino]-3-fenilmetano-sulfonyl-propionamida



Paso 1 Se disolvió (R)-2-amino-N-[1-(benzoxazol-2-il)-hidroximetil]-butil]-3-fenilmetanosulfonyl-propionamida {200 mg, 0,448 mmol, Ejemplo de Referencia 11(i)} en ácido acético al 5% en acetonitrilo (10 ml) Se añadió tetrahidropiran-4-carbaldehído (51 mg, 0,448 mmol) y la mezcla de reacción se agitó durante 16 horas (Se añadió cianoborohidruro de (poliestirilmetil)trimetilamonio (218 mg, 0,896 mmol) y la mezcla de reacción se agitó durante tres horas Se añadió ciclopropanocarbaldéhído (157 mg, 2,24 mmol) y se continuó la agitación durante tres horas La mezcla se filtró con succión y el filtrado se concentró a alto vacío

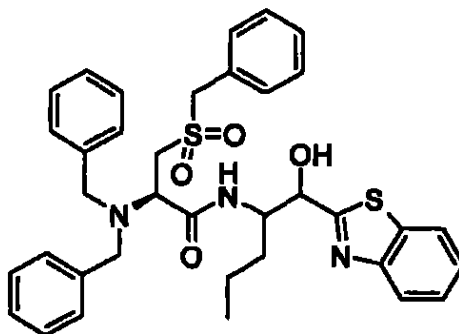
Paso 2 El residuo se disolvió en 10 ml de diclorometano Se añadió el peryodinano

284
285

Dess-Martin (380 mg, 0,896 mmol) y la mezcla de reacción resultante se agitó durante dos horas. Se vertió la mezcla de reacción en una mezcla 1/1 de solución saturada de bicarbonato de sodio y solución saturada de tiosulfato de sodio. La fase acuosa se extrajo con diclorometano. Las fases orgánicas reunidas se lavaron con solución saturada de bicarbonato de sodio y salmuera. La fase orgánica se secó con sulfato de magnesio y el diclorometano se evaporó a presión reducida. El producto bruto se purificó por cromatografía súbita (heptano/acetato de etilo 2/1, seguido por heptano/acetato de etilo 1/1 para la elución) para dar (R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-[ciclopropil-metil-(tetrahidropirán-4-ilmetil)-amino]-3-fenilmetano-sulfonil-propionamida como una mezcla de diastereo-isómeros (83 mg, 0,139 mmol, 31%) LC/MS m/z = 596 (M+H), tiempo de retención 3,84 (método C)

EJEMPLO 29

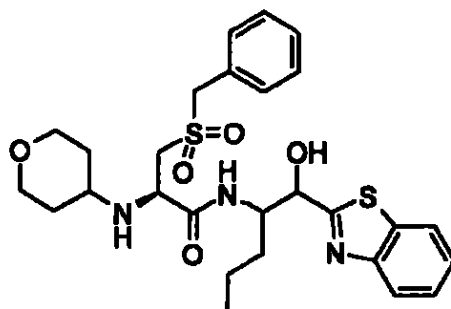
(a) (R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida



Se disolvió (R)-2-amino-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida (50 mg, 0,11 mmol, Ejemplo de Referencia 11(a)) en una mezcla de acetonitrilo (5 ml) y ácido acético (1 ml). Se añadieron benzaldehído (56 µl, 0,55 mmol, 5 equivalentes) y cianoborohidruro fijado a resina (54 mg, 0,22 mmol, 2 equivalentes). La mezcla de reacción se agitó durante una noche, se filtró con succión y el filtrado se evaporó para dar la (R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida que se utilizó sin purificación ulterior en la preparación del Ejemplo 18(c).

285
286

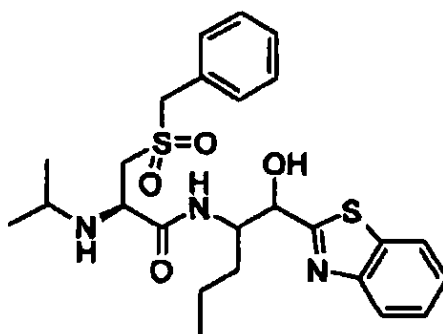
(b) (R)-N-[1-(Benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida



Procediendo de una manera similar al Ejemplo 29(a) anterior, pero utilizando tetrahidro-4H-piran-4-ona (51 μ l, 0,55 mmol, 5 equivalentes) se preparó (R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetano-sulfonil-2-(tetrahidropiran-4-ilamino)-propionamida LC/MS m/z = 546 (M+H)

EJEMPLO 30

(a) (R)-N-[1-(Benzotiazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-fenilmetanosulfonil-propionamida

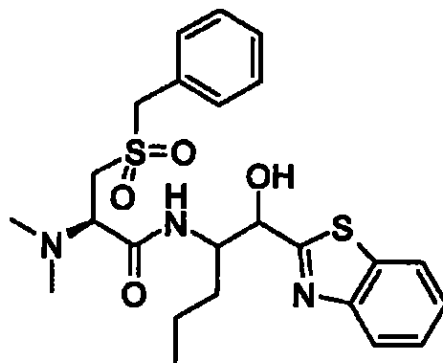


Se disolvió (R)-2-amino-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonilpropionamida {50 mg, 0,11 mmol, Ejemplo de Referencia 11(a)} se disolvió en una mezcla de acetonitrilo (5 ml) y ácido acético (1 ml) Se añadieron acetona (500 μ l) y cianoborohidruro fijado a Resina (54 mg, 0,22 mmol, 2 equivalentes) La mezcla de reacción se agitó durante una noche, se filtró con succión y se concentró a vacío El residuo se disolvió en diclorometano y se añadió AP Trisamine (Argonaut Technology) (550 mg, 1,2 mmol) La mezcla se agitó durante dos horas, se filtró con succión y el filtrado se concentró a vacío para dar

288
287

(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-fenilmetanosulfonyl-propionamida (30 mg, 0,06 mmol, 54%) LC/MS m/z = 504 (M+H)

(b) (R)-N-[1-Benzotiazol-2-il-hidroxi-metil)-butil]-2-di-metilamino-3-fenilmetanosulfonyl-propionamida

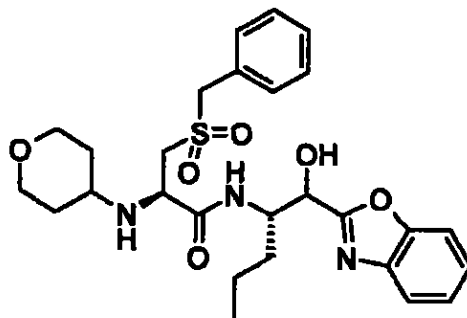


Procediendo de una manera similar al Ejemplo 30(a) anterior, pero utilizando solución de formaldehído (75 μ l, 1 mmol, solución acuosa al 37% p) se preparó

(R)-N-[1-benzotiazol-2-il-hidroxi-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonyl-propionamida (30 mg, 54%) LC/MS m/z = 490 (M+H)

EJEMPLO 31

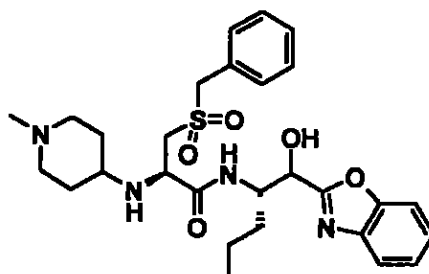
(a) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonyl-2-(tetrahidropiran-4-ilamino)-propionamida



Una solución de (R)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonyl-propionamida {100 mg, 0,22 mmol, Ejemplo de Referencia 11(c)} en una mezcla de acetonitrilo (5 ml) y ácido acético (1 ml) se trató con tetrahidro-4H-piran-4-ona (101 μ l, 1,1 mmol) Después de agitar a la temperatura ambiente durante tres horas, la mezcla se trató luego con cianoborohidruro fijado a Resina (108 mg, 0,44 mmol) y se continuó la agitación

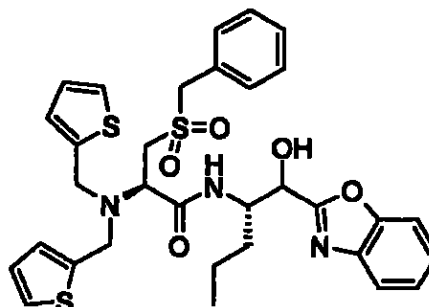
durante una noche. La mezcla de reacción se filtró y se evaporó el filtrado. El residuo se disolvió en diclorometano (10 ml) y la solución se trató con Silicycle-Triamine (611 mg, 2,2 mmol), se agitó luego durante dos horas y se filtró después. La solución de (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropirran-4-il-amino)-propionamida se utilizó directamente en la preparación del Ejemplo 20(b).

(b) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-2-(1-metil-piperidin-4-il-amino)-3-fenilmetanosulfonil-propionamida



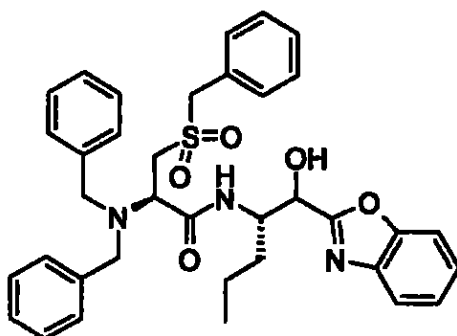
Procediendo de una manera similar al Ejemplo 31(a) anterior, pero utilizando 1-metil-4-piperidona (136 µl, 1,1 mmol) se preparó (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(1-metil-piperidin-4-il-amino)-3-fenilmetanosulfonil-propionamida que se utilizó directamente en la preparación del Ejemplo 19(b).

(c) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida



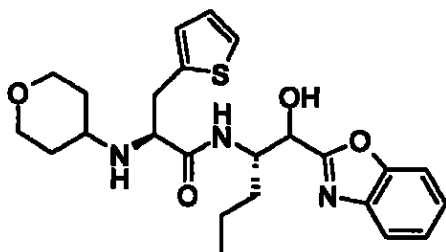
Procediendo de una manera similar al Ejemplo 31(a) anterior, pero utilizando 2-tiofenocarboxaldehído (20 µl, 0,22 mmol) se preparó (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida, que se utilizó directamente en la preparación del Ejemplo 19(c).

(d) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida



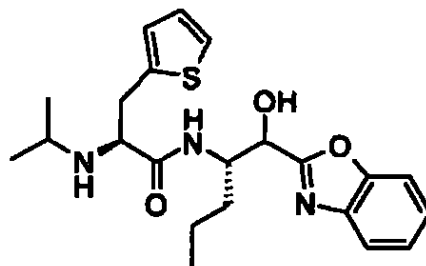
Procediendo de una manera similar al Ejemplo 31(a) anterior, pero utilizando benzaldehído (22 μ l, 0,22 mmol) se preparó (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida, que se utilizó directamente en la preparación del Ejemplo 19(d)

(e) (S)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-pro-pionamida

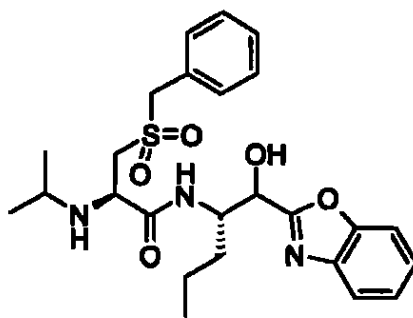


Procediendo de una manera similar al Ejemplo 317(a) [sic] anterior, pero utilizando (S)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-tiofen-2-il-propionamida {82 mg, 0,22 mmol, Ejemplo de Referencia 11(b)} y tetrahidro-4H-piran-4-ona (101 μ l, 1,1 mmol) se preparó (S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-propionamida, que se utilizó directamente en la preparación del Ejemplo 19(e)

(f) (S)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-tiofen-2-il-propionamida



Procediendo de una manera similar al Ejemplo 31(a) anterior, pero utilizando (S)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-tiofen-2-il-propionamida {82 mg, 0,22 mmol, Ejemplo de Referencia 11(b)} y acetona (100 μ l), se preparó (S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-tiofen-2-il-propionamida que se utilizó directamente en la preparación del Ejemplo 19(f)
(g) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-fenilmetano-sulfonyl-propionamida

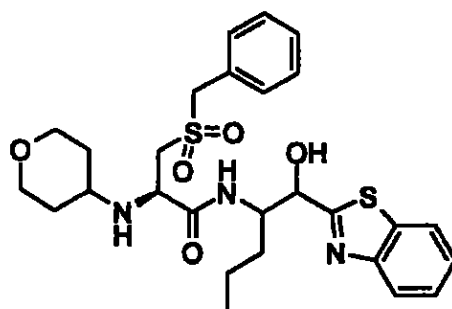


Procediendo de una manera similar al Ejemplo 31(a) anterior, pero utilizando acetona (500 μ l) se preparó (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-fenilmetanosulfonyl-propionamida (30,5 mg, 29%) LC/MS m/z = 488 (M+H)

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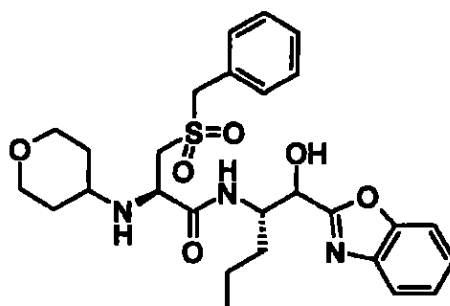
EJEMPLO 32

(a) (R)-N-[1-(Benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-il-amino)-propionamida



Una solución de (R)-2-amino-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida {100 mg, 0,22 mmol, Ejemplo de Referencia 11(a)} en una mezcla de acetonitrilo y ácido acético (10 ml, 95 5, v/v) se trató con tetrahidro-4H-piran-4-ona (101 µl, 1,1 mmol) y cianoborohidruro fijado a Resina (108 mg, 0,44 mol). Esta mezcla se agitó a la temperatura ambiente durante una noche y se evaporó luego. El residuo se disolvió en diclorometano y la solución se trató con Silicycle Triamine (611 mg, 2,2 mmol), se agitó luego a la temperatura ambiente durante dos horas y se filtró después. El filtrado se evaporó para dar (R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetano-sulfonil-2-(tetrahidropiran-4-il-amino)-propionamida. LC/MS m/z = 546 (M+H), que se utilizó directamente en la preparación del Ejemplo 18(b).

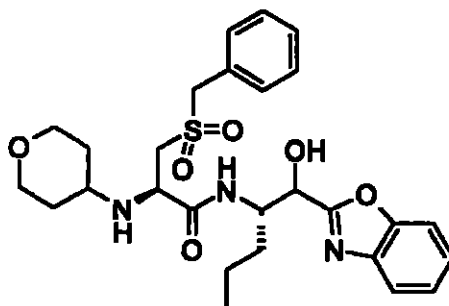
(b) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-il-amino)-propionamida



Procediendo de una manera similar al Ejemplo 32(a) anterior, pero utilizando (R)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida {98 mg, 0,22 mmol, Ejemplo de Referencia 11 8c)} se preparó (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-il-amino)-propionamida. LC/MS m/z = 530 (M+H),

que se utilizó directamente en la preparación del Ejemplo 19(a)

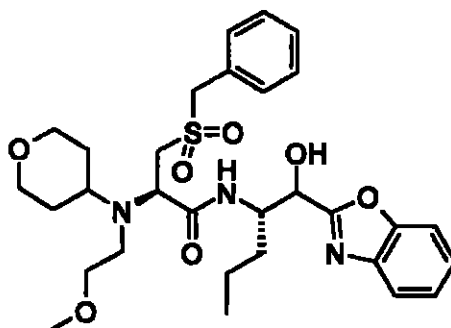
(c) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida



Procediendo de una manera similar al Ejemplo 32(a) anterior, pero utilizando (R)-2-amino-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida {Ejemplo de Referencia 11(c)} se preparó

(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida (106 mg, 91%) LC/MS m/z = 530 (M+H)

(d) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-2-[(2-metoxi-etil)-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida



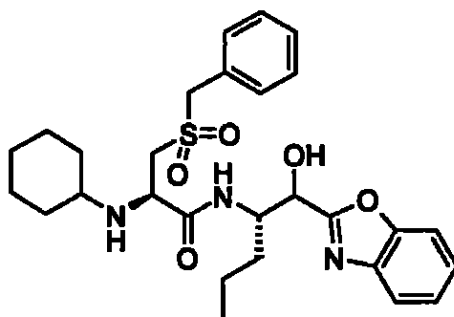
Procediendo de una manera similar al Ejemplo 32(a) anterior, pero utilizando (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida {53 mg, 0,1 mmol, Ejemplo de Referencia 32(c)} y 2-metoxietanal (53 mg, 0,55 mmol) se preparó

(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-[(2-metoxi-etil)-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida (56 mg, 95%)

LC/MS m/z = 588 (M+H)

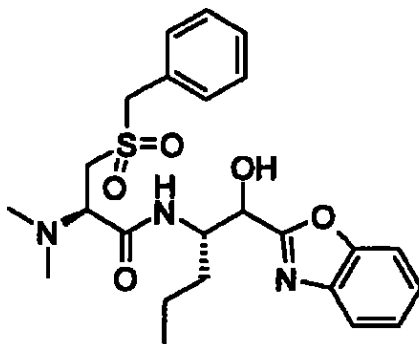
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293

(e) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-2-ciclohexilamino-3-fenilmetanosulfonil-propionamida



Procediendo de una manera similar al Ejemplo 32(a) anterior, pero utilizando (R)-2-amino-N-[(S)-1-(benz-oxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-propionamida {49 mg, 0,11 mmol, Ejemplo de Referencia 11(c)} y ciclohexanona (52 μ l, 0,5 mmol) se preparó (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-ciclo-hexilamino-3-fenilmetanosulfonil-propionamida (48 mg, 83%)

(f) (R)-N-[(S)-1-(Benzoxazol-2-il-hidroxi-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida

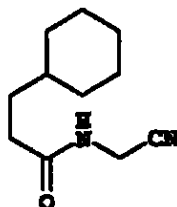


Procediendo de una manera similar al Ejemplo 32(a) anterior, pero utilizando (R)-2-amino-N-[(S)-1-(benz-oxazol-2-il-hidroxi-metil)-butil]3-fenilmetanosulfonil-propionamida {49 mg, 0,11 mmol, Ejemplo de Referencia 11(d)} y formaldehído (75 μ l, 1 mmol, 37% p en agua), se preparó (R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida (10 mg, 19%) LC/MS m/z = 474 (M+H)

EJEMPLO 33

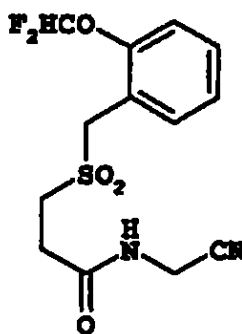
Los compuestos siguientes de Fórmula I se proporcionaron por los métodos descritos en la Solicitud

(a) N-Cianometil-3-ciclohexil-propionamida



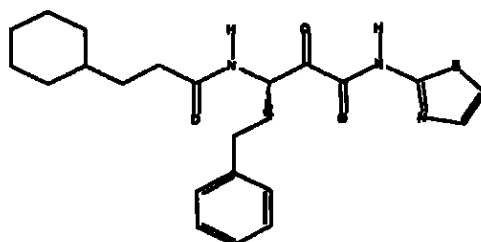
^1H NMR (CDCl_3) 6,22 (br s, 1H), 4,20 (s, 2H), 2,23 (m, 2H), 1,65 (m, 5H), 1,50 (m, 2H), 1,10-1,30 (m, 4H), 0,90 (m, 2H), LC-MS $t = 3,67$ min, 193,0 (M-1), 195,1 (M+1) MS API 150EX (LC Agilent 1100Series Columna Phenomenex, 5u ODS3 100A 100X3mm Caudal 2 ml/min Gradiente de dos disolventes Disolvente A 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde $t = 0$ a $t = 6$ min El gradiente volvió luego a 100% A, 0% B desde $t = 7$ a $t = 15$ min)

(b) N-Cianometil-3-(2-difluorometoxi-fenilmetanosulfonyl)-propionamida



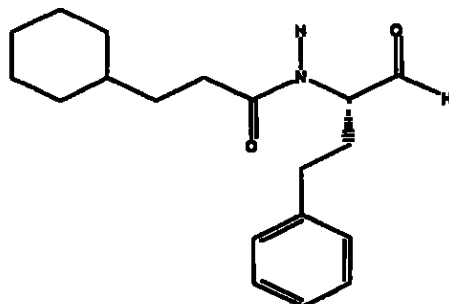
^1H NMR (CDCl_3) 7,52 (d, 1H, $J = 8$ Hz), 7,43 (t, 1H, $J = 8$ Hz), 7,29 (d, 1H, $J = 8$ Hz), 7,20 (d, 1H, $J = 8$ Hz), 6,40 (m, 1H), 4,41 (s, 2H), 4,16 (d, 2H, $J = 6$ Hz), 3,72 (s, 1H), 3,34 (t, 2H, $J = 8$ Hz), 2,77 (t, 2H, $J = 8$ Hz), LC-MS $t = 3,02$ min, 331,1 (M-1), 333,1 (M+1) MS API 150EX (LC Agilent 1100Series Columna Phenomenex, 5u ODS3 100A 100X3mm Caudal 2 ml/min Gradiente de dos disolventes Disolvente A 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde $t = 0$ a $t = 6$ min El gradiente volvió luego a 100% A, 0% B desde $t = 7$ a $t = 15$ min)

(c) Ácido 3-(3-ciclohexil-propionilamino)-2-oxo-5-fenil-pentanoico-tiazol-2-ilamida



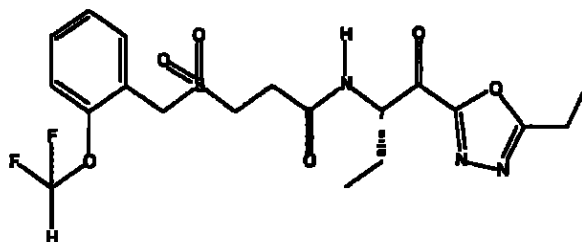
Datos [sic] para el compuesto tal como se representa y para sus formas de enol e hidrato
LC-MS t = 4,74 min, 426,4 (M-1), 428,2 (M+1), 4,97 min, 426,2 (M-1), 428,2 (M+1), 5,57 min, 426,3 (M-1), 427,9 (M+1) MS API 150EX (LC Agilent 1100Series Columna Phenomenex, 5u ODS3 100A 100X3mm Caudal 2 ml/min Gradiente de dos disolventes Disolvente A 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde t = 0 a t = 6 min El gradiente volvió luego a 100% A, 0% B desde t = 7 a t = 15 min)

(d) 3-Ciclohexil-N-(1-formil-3-fenil-propil)-propionamida



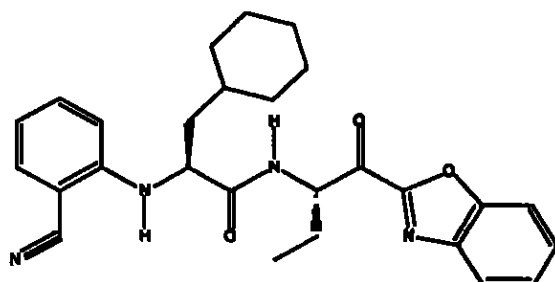
LC-MS t = 4,57 min, 300,4 (M-1), 302,3 (M+1) MS API 150EX (LC Agilent 1100Series Columna Phenomenex, 5u ODS3 100A 100X3mm Caudal 2 ml/min Gradiente de dos disolventes Disolvente A 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde t = 0 a t = 6 min El gradiente volvió luego a 100% A, 0% B desde t = 7 a t = 15 min)

(f) [sic] 3-(2-Difluorometoxi-fenilmetanosulfonil)-N-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propil]-propionamida



LC-MS $R_T = 2,32$ min, 480,3 (M+1), 482,2 (M+23) MS API 150EX (LC Agilent 1100Series Columna Phenomenex, 5u ODS3 100A 100X3mm Caudal 2 ml/min Gradiente de dos disolventes Disolvente A 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde $t = 0$ a $t = 2,5$ min El gradiente volvió luego a 100% A, 0% B desde $t = 3,0$ a $t = 3,5$ min)

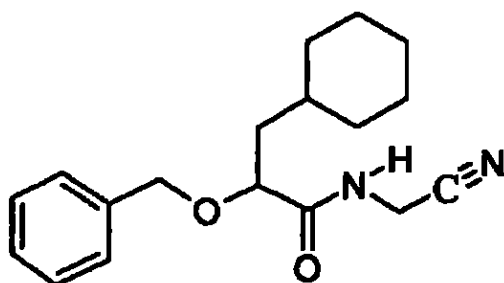
(g) N-[(S)-1-(Benzooxazol-2-carbonil-propil)-2-(2-ciano-fenilamino)-3-ciclohexil-propionamida



$^1\text{H NMR}$ (CDCl_3) 7,83 (d, 1H, $J = 8$ Hz), 7,59 (d, 1H, $J = 8$ Hz), 7,43-7,58 (m, 2H), 7,02-7,25 (m, 4H), 6,59 (t, 1H, $J = 8$ Hz), 6,49 (d, 1H, $J = 8$ Hz), 5,40-5,47 (m, 1H), 4,77 (m, 1H), 3,83-3,88 (m, 1H), 2,12-2,22 (m, 1H), 1,85-2,00 (m, 2H), 1,55-1,83 (m, 8H), 1,12-1,35 (m, 4H), 0,95-1,10 (m, 3H), LC-MS $t = 2,97$ min, 457,5 (M-1), 459,3 (M+1), 481,4 (M+23) MS API 150EX (LC Agilent 1100Series Columna Phenomenex, 5u ODS3 100A 100X3mm Caudal 2 ml/min Gradiente de dos disolventes Disolvente A 99% agua, 1% acetonitrilo, 0,1% AcOH Disolvente B, 99% acetonitrilo, 1% agua, 0,1% AcOH Gradiente desde 100% A, 0% B a 0% A, 100% B desde $t = 0$ a $t = 2,5$ min El gradiente volvió luego a 100% A, 0% B desde $t = 3,0$ a $t = 3,5$ min El gradiente se mantuvo después a 100% A, 0% B desde $t = 3,5$ a 5 min)

(h) N-Cianometil-3-ciclohexil-2-(4-metoxi-fenoxi)-propionamida (Compuesto 1), $^1\text{H NMR}$ (CDCl_3) 7,42-7,36 (m, 5H), 6,90 (t, 1H), 4,55 (d, 1H), 4,51 (d, 1H), 4,22 (dd, 1H), 4,16 (dd, 1H), 4,00 (t, 1H), 1,70-0,80 (m, 13H), MS ($M^+ + 1$) 301

(i) 2-Benciloxi-N-cianometil-3-ciclohexil-propionamida (Compuesto 2)



utilizando [sic] ácido 2(R)-benciloxi-4-fenil-butírico como material de partida. ^1H NMR (CDCl_3) δ 6,84-6,80 (m, 4H), 6,75 (t, 1H), 4,55 (dd, 1H), 4,24 (dd, 1H), 4,12 (dd, 1H), 3,78 (s, 3H), 1,80-0,85 (m, 13H), MS (M-1) 315

(j) (R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-

benciloxi-3-fenilmetanosulfonilpropionamida (Compuesto 3), ^1H NMR (CDCl_3) 7,89 (d, 1H), 7,68 (d, 1H), 7,60-7,32 (m, 13H), 5,70 (m, 1H), 4,79 (d, 1H), 4,77 (d, 1H), 4,53 (dd, 1H), 4,33 (d, 1H), 4,30 (d, 1H), 3,38 (dd, 1H), 3,25 (dd, 1H), 2,15-2,05 (m, 1H), 1,84-1,75 (m, 1H), 1,45-1,30 (m, 2H), 0,93 (t, 3H), MS (M^+ +1) 535, (M-1) 533,

(k) (R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-

metoximetoxi-3-fenilmetanosulfonil-propionamida (Compuesto 9), ^1H NMR (DMSO) 8,87 (dd, J = 6,91 Hz, 1H), 7,99 (d, J = 7,91 Hz, 1H), 7,89 (d, J = 8,15 Hz, 1H), 7,64 (t, J = 8,1 Hz, 1H), 7,54 (t, J = 8,1 Hz, 1H), 7,4-7,3 (m, 5H), 5,3-5,2 (m, 1H), 4,7-4,65 (m, 1H), 4,65-4,63 (m, 2H), 4,55-4,50 (m, 2H), 3,53-3,26 (m, 2H), 3,34 (s, 3H), 2,11-1,98 (m, 1H), 1,89-1,69 (m, 1H), 0,97 (t, J = 7,15 Hz, 3H), MS 473 (M+1), 497 (M+23),

(l) (S)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-hidroxi-3-fenil-propionamida (Compuesto 10),

(m) (R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-3-

fenilmetanosulfonil-2-trisopropilsilani-oxi-propionamida (Compuesto 12), ^1H NMR (CD_3Cl) 7,93 (d, J = 8,15 Hz, 1H), 7,6 (d, J = 8,1 Hz, 1H), 7,6-7,4 (m, 3H), 7,4-7,3 (m, 5H), 5,85-5,73 (m, 1H), 4,85-4,74 (m, 1H), 4,5-4,3 (m, 2H), 3,47-3,35 (m, 2H), 2,35-2,15 (m, 1H), 2,15-1,95 (m, 1H), 1,3-0,8 (m, 24H), MS 609,4 (M+23),

(n) (R)-N-[(S)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-

propionamida (Compuesto 13), ^1H NMR (CD_3Cl) 8,21 (d, J = 8,67 Hz, 1H), 7,98 (d, J = 8,6 Hz, 1H), 7,7-7,55 (m, 3H), 7,45-7,3 (m, 5H), 5,8-5,7 (m, 1H), 4,75-4,6 (m, 1H), 4,4-4,3 (m, 2H), 4,08 (br, 1H), 3,62-3,5 (m, 1H), 3,3-3,1 (m, 1H), 2,3-2,15 (m, 1H), 2,05-1,9 (m, 1H), 0,997 (t, J = 7,4 Hz, 3H), MS 469,2 (M+23),

(o) (R)-2-hidroxi-3-fenilmetanosulfonil-N-[(S)-1-(1-piridazin-3-il-metanoil)-butil]-

propionamida (Compuesto 16), ^1H NMR (CD_3Cl) 9,35 (dd, J = 4,93 Hz, J = 1,72 Hz, 1H), 8,14 (dd, J = 1,72 Hz, J = 8,39 Hz, 1H), 7,69 (dd, J = 4,93 Hz, J = 8,39 Hz, 1H), 7,65 (d, J = 7,6 Hz, 1H), 7,5-7,36 (m, 5H), 6,04-5,96 (m, 1H), 4,75-4,63 (m, 1H), 4,45-4,3 (m, 3H), 3,53 (dd, J = 2,48 Hz, J = 14,85 Hz, 1H), 3,22 (dd, J = 14,82 Hz, J = 2,48 Hz, 1H), 2,2-2,07 (m, 1H), 1,85-1,65 (m, 1H), 1,6-1,2 (m, 2H), 0,93 (t, J = 7,18 Hz, 3H), MS 403,6 (M-1), 428 (M+23),

(p) ácido (S)-3-((R)-2-hidroxi-3-fenilmetanosulfonil-

propanoilamino)-2-oxo-pentanoico-bencilamida (Compuesto 18), ^1H NMR (CD_3Cl)

7,45-7,25 (m, 10H), 5,34-5,26 (m, 1H), 4,7-4,6 (m, 1H), 4,47 (d, J = 6,18 Hz, 2H), 4,4-4,3 (m,

2H), 4,15-4,05 (m, 1H), 3,55-3,45 (m, 1H), 3,25-3,13 (m, 1H), 2,2-2,0 (m, 1H), 1,8-1,6 (m, 1H), 1,61 (s, 2H), 0,95 (J = 6,91 Hz, 3H), MS 469,2 (M+23),

(q) (R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida (Compuesto 21), ¹H NMR (CD₃Cl) 7,91 (d, J = 7,91 Hz, 1H), 7,75 (d, J = 7,9 Hz, 1H), 7,7-7,2 (m, 6H), 6,63 (t, J = 73,41 Hz, 1H), 5,7-5,58 (m, 1H), 5,4-5,29 (m, 1H), 4,7-4,6 (m, 1H), 4,51 (s, 2H), 4,19 (br, 1H), 3,72-3,63 (m, 1H), 3,35-3,2 (m, 1H), 2,3-2,0 (m, 1H), 2,0-1,7 (m, 1H), 0,99 (t, J = 6,9 Hz, 3H), MS 495,5 (M-1), 497,2 (M+1),

(r) (R)-N-[(S)-1-(1-benzotiazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida (Compuesto 22), ¹H NMR (CD₃Cl) 8,21 (d, J = 8,15 Hz, 1H), 7,99 (d, J = 8,1 Hz, 1H), 7,73-7,2 (m, 6H), 6,63 (t, J = 73,4 Hz, 1H), 5,85-5,75 (m, 1H), 5,3 (s, 1H), 4,78-4,7 (m, 1H), 4,56-4,4 (m, 2H), 4,19-4,09 (m, 1H), 3,7-3,6 (m, 1H), 3,35-3,2 (m, 1H), 2,28 (s, 2H), 1,27 (t, J = 6,9 Hz, 3H), MS 511,4 (M-1), 513,6 (M+1), y

(s) (2R,5S)-2-[(1,1-difluoro-metoxi)-fenilmetanosulfonilmetil]-6-etoxi-5-etil-morfolin-3-ona (Compuesto 24)

EJEMPLO DE ENSAYO ENZIMÁTICO

Ensayo de la Catepsina S

Se prepararon soluciones de los compuestos de ensayo en diversas concentraciones en 10 µl de dimetil-sulfóxido (DMSO) y se diluyeron luego en tampón de ensayo (40 µl, que comprendía MES, 50 mM (pH 6,5), EDTA, 2,5 mM, y NaCl, 100 mM) Se añadió a las diluciones catepsina S humana (0,158 pMoles en 25 µl de tampón de ensayo) Las soluciones de ensayo se mezclaron durante 5-10 segundos EN un plato de sacudidas, se taparon y se incubaron durante 30 minutos a la temperatura ambiente Se añadió a las soluciones de ensayo Z-Val-Val-Arg-AMC (9 nMoles en 25 µl de tampón de ensayo) y se siguió espectrofotométricamente la hidrólisis a (λ460 nm) durante 5 minutos Se calcularon las constantes de inhibición aparentes (K_i) a partir de las curvas enzimáticas de progreso utilizando modelos matemáticos estándar

EJEMPLO DE ENSAYO ENZIMÁTICO

Ensayo de la Catepsina B

Se prepararon soluciones de los compuestos de ensayo en diversas concentraciones en 10 µl de dimetil-sulfóxido (DMSO) y se diluyeron luego en tampón de ensayo (40 µl, que comprendía ácido N,N-bis(2-hidroxi-etil)-2-aminoetanosulfónico (BES), 50 mM (pH 6), monolaurato de polioxietilensorbitán, 0,05%, y ditiotretol (DTT), 2,5 mM) Se añadió a las

diluciones cathepsina B humana (0,025 pMoles en 25 μ l de tampón de ensayo) Las soluciones de ensayo se mezclaron durante 5-10 segundos en un plato de sacudidas, se taparon y se incubaron durante 30 minutos a la temperatura ambiente Se añadió a las soluciones de ensayo Z-FR-AMC (20 nMoles en 25 μ l de tampón de ensayo) y se siguió la hidrólisis espectrofotométricamente a (λ 460 nm) durante 5 minutos Se calcularon las constantes de inhibición aparentes (K_i) a partir de las curvas enzimáticas de progreso utilizando modelos matemáticos estándar

EJEMPLO DE ENSAYO ENZIMÁTICO

Ensayo de la Cathepsina K

Se prepararon soluciones de los compuestos de ensayo en diversas concentraciones en 10 μ l de dimetil-sulfóxido (DMSO) y se diluyeron luego en tampón de ensayo (40 μ l, que comprendía MES, 50 mM (pH 5,5), EDTA, 2,5 mM, y DTT, 2,5 mM) Se añadió a las diluciones cathepsina K humana (0,0906 pMoles en 25 μ l de tampón de ensayo) Las soluciones de ensayo se mezclaron durante 5-10 segundos en un plato de sacudidas, se taparon y se incubaron durante 30 minutos a la temperatura ambiente Se añadió a las soluciones de ensayo Z-Phe-Arg-AMC (4 nMoles en 25 μ l de tampón de ensayo) y se siguió la hidrólisis espectrofotométricamente a (λ 460 nm) durante 5 minutos Se calcularon las constantes de inhibición aparentes (K_i) a partir de las curvas enzimáticas de progreso utilizando modelos matemáticos estándar

EJEMPLO DE ENSAYO ENZIMÁTICO

Ensayo de la Cathepsina L

Se prepararon soluciones de los compuestos de ensayo en diversas concentraciones en 10 μ l de dimetil-sulfóxido (DMSO) y se diluyeron luego en tampón de ensayo (40 μ l, que comprendía MES, 50 mM (pH 5,5), EDTA, 2,5 mM, y DTT, 2,5 mM) Se añadió a las diluciones cathepsina L humana (0,05 pMoles en 25 μ l de tampón de ensayo) Se mezclaron las soluciones de ensayo durante 5-10 segundos en un plato de sacudidas, se taparon y se incubaron durante 30 minutos a la temperatura ambiente Se añadió a las soluciones de ensayo Z-Phe-Arg-AMC (1 nMol) en 25 μ l de tampón de ensayo) y se siguió la hidrólisis espectrofotométricamente a (λ 460 nm) durante 5 minutos Se calcularon las constantes de inhibición aparentes (K_i) a partir de las curvas enzimáticas de progreso utilizando modelos matemáticos estándar

De acuerdo con los ensayos de los solicitantes realizados como se ha descrito anteriormente, las constantes de inhibición aparentes (K_i) para los compuestos de la invención enumerados a continuación contra Cathepsina S, eran aproximadamente iguales o inferiores a

0,01 μ M,

ácido morfolina-4-carboxílico-(R)-1-(cianometil-carbamoyl)-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster, (Compuesto 31),
Ejemplo 3(a),

ácido

morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzo-oxazol-2-il-metanoil)-propilcarbamoyl]-2-fenilmetano-sulfonil-etil-éster, (Compuesto 11), Ejemplo 4(a),

ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzo-oxazol-2-il-metanoil)-propilcarbamoyl]-2-[2-(1,1-di-fluoro-metoxi)-fenilmetanosulfonil]-etil-éster, (Compuesto 14), Ejemplo 4(b),

ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzo-tiazol-2-il-metanoil)-propilcarbamoyl]-2-[2-(1,1-di-fluoro-metoxi)-fenilmetanosulfonil]-etil-éster, (Compuesto 15), Ejemplo 4(c),

ácido

pirrolidina-1-carboxílico-(R)-1-[(S)-1-(1-benzo-oxazol-2-il-metanoil)-propilcarbamoyl]-2-fenilmetano-sulfonil-etil-éster, (Compuesto 19), Ejemplo 4(d),

ácido

dimetil-carbámico-(R)-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoyl]-2-fenilmetanosulfonil-etil-éster, (Compuesto 20), Ejemplo 4(e),

ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-bencil-carbamoyl-metanoil)-propilcarbamoyl]-2-fenilmetano-sulfonil-etil-éster, (Compuesto 25),
Ejemplo 4(f),

ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(oxazolo[4,5-b]-piridina-2-carbonil)-propilcarbamoyl]-2-fenilmetano-sulfonil-etil-éster, Ejemplo 4(g),

ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(5-etil-[1,3,4]-oxadiazol-2-carbonil)-propilcarbamoyl]-2-fenilmetanosulfonil-etil-éster, Ejemplo 4(h),
(R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-N-((S)-1-formil-propil)-2-hidroxi-propionamida, (Compuesto 23), Ejemplo 6,

(R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida, (Compuesto 5), Ejemplo 7,

ácido

(S)-3-{3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-propanoílamino}-2-oxo-pentanoico-bencilamida, (Compuesto 27), Ejemplo 8(a),

(R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-(2-nitro-fenilamino)-3-fenilmetanosulfonil-propionamida, (Compuesto 28), Ejemplo 9,

(R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-

260
301

(5-nitro-tiazol-2-ilamino)-3-fenilmetanosulfonyl-propionamida, (Compuesto 29), Ejemplo 10,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-fenil-
meta-nosulfonyl-2-(tetrahidropiran-4-ilamino)-propionamida, Ejemplo 19(a),
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-isopropil-amino-3-fenilmetanosulfonyl-
propionamida, Ejemplo 21(a),
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-[(2-
metoxi-etil)-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonyl-propionamida, Ejemplo
21(b),
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-ciclohexil-amino-3-fenilmetanosulfonyl-
propionamida, Ejemplo 21(c),
ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(1-
oxazolo[4,5-b]piridina-2-carbonil)propilcarbamoyl]-etil-éster, Ejemplo 24(b),
3-(2-difluorometoxi-fenilmetanosulfonyl)-N-[(S)-1-
(oxazolo[4,5-b]piridina-2-carbonil)-propil]-propionamida, Ejemplo 33(e),
ácido (S)-3-((R)-2-hidroxi-3-fenilmetanosulfonyl-propan-
oilamino)-2-oxo-pentanoico-bencilamida (Compuesto 18), Ejemplo 33(p),
(R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil-2-
[2-(1,1-difluoro-metoxi)-fenilmetanosulfonyl]-2-hidroxi-propionamida (Compuesto 21),
Ejemplo 33(q)

Además, se ha observado que los compuestos de la presente invención tienen diversos
grados de acción inhibidora selectiva sobre la proteasa catepsina S. Por ejemplo, se ha
encontrado que los 22 compuestos arriba enumerados inhiben la actividad de la proteasa
catepsina S a concentraciones que son más de 75 veces menores que las concentraciones
requeridas para producir una inhibición equiactiva sobre la proteasa catepsina K.

EJEMPLO

Formulaciones Farmacéuticas Representativas que Contienen un Compuesto de Fórmula I

FORMULACIÓN ORAL

Compuesto de Fórmula I	10-100 mg
Ácido cítrico monohidratado	105 mg
Hidróxido de sodio	18 mg
Saborizante	
Agua	c s hasta 100 ml

FORMULACION INTRAVENOSA

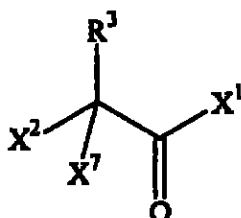
Compuesto de Fórmula I	0,1-10 mg
Dextrosa monohidratada	c s hasta isotonicidad
Ácido cítrico monohidratado	1,05 mg
Hidróxido de sodio	0,18 mg
Agua para inyección	c s hasta 1,0 ml

FORMULACION DE TABLETA

Compuesto de Fórmula I	1%
Celulosa microcristalina	73%
Ácido esteárico	25%
Sílice coloidal	1%

REIVINDICACIONES

1 Un compuesto de Fórmula I



I

en la cual

X¹ es -NHC(R¹)(R²)X³ o -NHX⁴,

X² es hidrógeno, fluoro, -OH, -OR⁴, -NHR¹⁵ o -NR¹⁷R¹⁸ y X⁷ es hidrógeno o X² y X⁷ representan ambos fluoro,

X³ es ciano, -C(R⁷)(R⁸)R¹⁶, -C(R⁶)(OR⁶)₂, -CH₂C(O)R¹⁶, -CH=CHS(O)₂R⁵, -C(O)CF₂C(O)NR⁵R⁵, -C(O)C(O)NR⁵R⁶, -C(O)C(O)OR⁵, -C(O)CH₂OR⁵, -C(O)CH₂N(R⁶)SO₂R⁵ o -C(O)C(O)R⁵, en cuyas fórmulas R⁵ es hidrógeno, (C₁-₄)alquilo, (C₃-₁₀)cicloalquil(C₀-₆)alquilo, hetero(C₃-₁₀)cicloalquil(C₀-₃)alquilo, (C₆-₁₀)aril(C₀-₆)alquilo, hetero(C₅-₁₀)aril(C₀-₆)alquilo, (C₃-₁₀)bicicloaril(C₀-₆)alquilo o hetero(C₈-₁₀)-bicicloaril(C₀-₆)alquilo, R⁶ es hidrógeno, hidroxí o (C₁-₄)alquilo, o donde X³ contiene un grupo -NR⁵R⁶, R⁵ y R⁶ junto con el átomo de nitrógeno al cual están unidos ambos, forman hetero(C₃-₁₀)cicloalquilo, hetero(C₅-₁₀)arilo o hetero(C₈-₁₀)bicicloarilo, R⁷ es hidrógeno o (C₁-₄)alquilo y R⁸ es hidroxí o R⁷ y R⁸ forman juntos oxo, R¹⁶ es hidrógeno, -X⁴, -CF₃, -CF₂CF₂R⁹ o -N(R⁶)OR⁶, R⁹ es hidrógeno, halo, (C₁-₄)alquilo, (C₃-₁₀)aril(C₀-₆)alquilo o (C₅-₁₀)heteroaril(C₀-₆)alquilo, con la salvedad de que cuando X³ es ciano, entonces X² es hidrógeno, fluoro, -OH, -OR⁴ o -NR¹⁷R¹⁸ y X⁷ es hidrógeno o X² y X⁷ representan ambos fluoro,

X⁴ comprende un anillo heteromonocíclico que contiene 4 a 7 átomos miembros de anillo o un sistema de anillos heterobicíclico condensado que contiene 8 a 14 átomos miembros de anillo y cualquier derivado carbocíclico cetona, iminocetona o tiocetona de los mismos, con la salvedad de que cuando -X⁴ es distinto de un anillo heteromonocíclico que contiene 5 átomos miembros de anillo, en el cual no más de dos de los átomos miembros de anillo que comprende el anillo son heteroátomos, entonces X² es fluoro, -OH, -OR⁴, -NHR¹⁵ o -NR¹⁷R¹⁸ y X⁷ es hidrógeno o X² y X⁷ representan ambos fluoro,

en la cual dentro de R^5 , X^3 o X^4 cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)O-R^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13} es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero- (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{3-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo,

R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 se selecciona de un grupo constituido por hidrógeno, ciano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5N-R^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-8}) cicloalquileno o (C_{3-8}) heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13} son como se define arriba,

R^3 es (C_{1-6}) alquilo o $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y X^6 se selecciona de $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$,

$-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)-R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^4 se selecciona de $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8N-R^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8O-R^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ y $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas x^8 es (C_{1-6}) alquileo y X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, con la salvedad de que cuando X^3 es ciano y X^2 es $-OR^4$, donde R^4 se define como $-R^{14}$, entonces R^{14} es (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-3}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{5-10}) aril (C_{1-6}) alquilo, (C_{9-10}) bicicloaril (C_{1-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo,

R^{15} es (C_{6-10}) arilo, hetero (C_{5-10}) arilo, (C_{9-10}) biciclo-arilo o hetero (C_{8-10}) bicicloarilo,

R^{17} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo, con la salvedad de que cuando X^3 es ciano, entonces R^{17} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-6}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{5-10}) aril (C_{1-6}) alquilo, (C_{9-10}) bicicloaril (C_{1-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo,

R^{18} es hidrógeno, (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-6}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo, con la salvedad de que cuando X^3 es ciano, entonces R^{18} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-6}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{5-10}) aril (C_{1-6}) alquilo, (C_{9-10}) bicicloaril (C_{1-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo, y

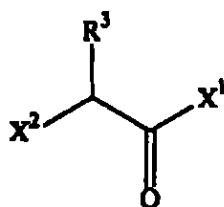
en la cual dentro de R^3 , R^4 , R^{15} , R^{17} y R^{18} cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$,

365

306

-X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵C(O)R¹³ y -X⁵S(O)₂R¹³ y/o 1 radical seleccionado de -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² y -X⁵NR¹²C(NR¹²)NR¹⁴R¹², y dentro de R³ y R⁴ cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, -NR¹²R¹², -NR¹²C(O)R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹², -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)R¹², -OC(O)R¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -NR¹²S(O)₂R¹², -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹³, -S(O)R¹³ y -S(O)₂R¹³, en cuyas fórmulas X⁵, R¹², R¹³ y R¹⁴ son como se describe arriba, con la salvedad de que cuando X³ es ciano y X² es -OR⁴, donde R⁴ se define como -R¹⁴, o -NHR¹⁸, entonces cualquier sistema aromático de anillos presente dentro de R¹⁴ o R¹⁸ no está sustituido adicionalmente con halo, (C₃₋₁₀)cicloalquilo, hetero(C₃₋₁₀)cicloalquilo, (C₆₋₁₀)arilo, hetero(C₅₋₁₀)arilo, (C₉₋₁₀)-bícicloarilo o hetero(C₈₋₁₀)bícicloarilo, con la salvedad de que solamente está presente una estructura bicíclica de anillos dentro de R³, R⁴ o R¹⁵, y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y sus derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

2 Un compuesto de la reivindicación 1, que tiene la fórmula siguiente



en la cual X² es hidrógeno, fluoro, -OH, -OR⁴, -NHR¹⁵, R³, R⁴, R¹⁵ y X¹ son igual que se define en la reivindicación 1

3 Un compuesto de la reivindicación 1 o la reivindicación 2, en el cual X¹ es -NHC(R¹)(R²)X³ o -NHCH(R¹⁹)C(O)R²⁰,

X² es hidrógeno, fluoro, -OH, -OR⁴, -NHR¹⁵ o -NR¹⁷R¹⁸ y X⁷ es hidrógeno o X² y X⁷ representan ambos fluoro,

X³ es ciano, -C(R⁷)(R⁸)R¹⁶, -C(R⁶)(OR⁶)₂, -CH₂C(O)R¹⁶, -CH=CHS(O)₂R⁵,

306
307

$-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,
 $-C(O)CH_2N(R^6)SO_2R^5$ o $-C(O)C(O)R^5$, en cuyas fórmulas R^5 es hidrógeno, (C_{1-4}) alquilo,
 (C_{3-10}) cicloalquil(C_{0-6})alquilo, hetero($C_{3-10})$ cicloalquil(C_{0-3})alquilo, (C_{6-10}) aril(C_{0-6})alquilo,
hetero($C_{5-10})$ aril(C_{0-6})alquilo, (C_{9-10}) bicicloaril(C_{0-6})alquilo o hetero($C_{8-10})$ -
bicicloaril(C_{0-6})alquilo, R^6 es hidrógeno, hidroxilo o (C_{1-6}) alquilo, o donde X^3 contiene un
grupo $-NR^5R^6$, R^5 y R^6 junto con el átomo de nitrógeno al cual están unidos ambos, forman
hetero($C_{3-10})$ cicloalquilo, hetero($C_{5-10})$ arilo o hetero($C_{8-10})$ bicicloarilo, R^7 es hidrógeno o
 (C_{1-4}) alquilo y R^8 es hidroxilo o R^7 y R^8 forman juntos oxo, R^{16} es hidrógeno, $-X^4$, $-CF_3$,
 $-CF_2CF_2R^9$ o $-N(R^6)OR^6$, R^9 es hidrógeno, halo, (C_{1-4}) alquilo, (C_{5-10}) aril(C_{0-6})alquilo o
 (C_{5-10}) heteroaril(C_{0-6})alquilo, con la salvedad de que cuando X^3 es ciano, entonces X^2 es
hidrógeno, fluoro, $-OH$, $-OR^4$ o $-NR^{17}R^{18}$ y X^7 es hidrógeno o X^2 y X^7 representan ambos
fluoro,

X^4 comprende un anillo heteromonocíclico que contiene 4 a 7 átomos miembros de
anillo o un sistema de anillos heterobícíclico condensado que contiene 8 a 14 átomos
miembros de anillo y cualquier derivado carbocíclico cetona, iminocetona o tiocetona de los
mismos, con la salvedad de que cuando $-X^4$ es distinto de un anillo heteromonocíclico que
contiene 5 átomos miembros de anillo, en el cual no más de dos de los átomos miembros de
anillo que comprende el anillo son heteroátomos, entonces X^2 es fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ o
 $-NR^{17}R^{18}$ y X^7 es hidrógeno o X^2 y X^7 representan ambos fluoro,

en el cual dentro de R^5 , X^3 o X^4 cualquier sistema de anillos alicíclico o aromático está
insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente
de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro,
 $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$,
 $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$,
 $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$,
 $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical
seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$,
 $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$,
 $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y
 $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada
aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13}
es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil(C_{0-6})alquilo,
hetero($C_{3-10})$ cicloalquil(C_{0-3})alquilo, (C_{6-10}) aril(C_{0-6})alquilo, hetero($C_{5-10})$ aril(C_{0-6})alquilo,
 (C_{9-10}) bicicloaril(C_{0-6})alquilo o hetero($C_{8-10})$ bicicloaril(C_{0-6})alquilo,

R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 se selecciona de un grupo constituido por
hidrógeno, ciano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$,

$-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2N-R^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-9}) cicloalquileno o (C_{3-9}) heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-6}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13} son como se define arriba,

R^3 es (C_{1-6}) alquilo o $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y X^6 se selecciona de $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^4 se selecciona de $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8N-R^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ y $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas x^8 es (C_{1-6}) alquileno y X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, con la salvedad de que cuando X^3 es ciano y X^2 es $-OR^4$, donde R^4 se define como $-R^{14}$, entonces R^{14} es (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-3}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo,

hetero(C₅₋₁₀)aril(C₁₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₁₋₆)alquilo o

hetero(C₈₋₁₀)bícicloaril(C₁₋₆)alquilo,

R¹⁵ es (C₆₋₁₀)arilo, hetero(C₅₋₁₀)arilo, (C₉₋₁₀)bícicloarilo o hetero(C₈₋₁₀)bícicloarilo,

R¹⁷ es (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, (C₆₋₁₀)aril(C₀₋₆)alquilo, hetero(C₅₋₁₀)aril(C₀₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₀₋₆)alquilo o hetero(C₈₋₁₀)bícicloaril(C₀₋₆)alquilo, con la salvedad de que cuando X³ es ciano, entonces R¹⁷ es (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, (C₆₋₁₀)aril(C₁₋₆)alquilo, hetero(C₅₋₁₀)aril(C₁₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₁₋₆)alquilo o hetero(C₈₋₁₀)bícicloaril(C₁₋₆)alquilo,

R¹⁸ es hidrógeno, (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₀₋₆)alquilo, (C₆₋₁₀)aril(C₀₋₆)alquilo, hetero(C₅₋₁₀)aril(C₀₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₀₋₆)alquilo o hetero(C₈₋₁₀)bícicloaril(C₀₋₆)alquilo, con la salvedad de que cuando X³ es ciano, entonces R¹⁸ es (C₁₋₆)alquilo, (C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, hetero(C₃₋₁₀)cicloalquil(C₁₋₆)alquilo, (C₆₋₁₀)aril(C₁₋₆)alquilo, hetero(C₅₋₁₀)aril(C₁₋₆)alquilo, (C₉₋₁₀)bícicloaril(C₁₋₆)alquilo o hetero(C₈₋₁₀)bícicloaril(C₁₋₆)alquilo, y

R¹⁹ y R²⁰, junto con los átomos a los cuales están unidos R¹⁹ y R²⁰, forman (C₄₋₈)heterocicloalquileno, en el cual no más de uno de los átomos miembros de anillo que comprende el anillo es un heteroátomo seleccionado de -NR²¹ - u -O-, donde el anillo está insustituido o sustituido con R², donde R² es como se define arriba, y R²¹ es hidrógeno, -C(O)OR¹², -C(O)R¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -S(O)R¹³ y -S(O)₂R¹³, -S(O)R¹⁴, -S(O)₂R¹⁴, -C(O)R¹⁴, -C(O)OR¹⁴, -C(O)N-R¹²R¹² y -S(O)₂NR¹⁴R¹², en cuyas fórmulas R¹², R¹³ y R¹⁴ son como se define arriba,

en el cual dentro de R³, R⁴, R¹⁵, R¹⁷ y R¹⁸ cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C₁₋₆)alquilo, (C₁₋₆)alquilideno, ciano, halo, (C₁₋₄)alquilo sustituido con halo, nitro, -X⁵NR¹²R¹², -X⁵NR¹²C(O)R¹², -X⁵NR¹²C(O)OR¹², -X⁵NR¹²C(O)NR¹²R¹², -X⁵NR¹²C(NR¹²)NR¹²R¹², -X⁵OR¹², -X⁵SR¹², -X⁵C(O)OR¹², -X⁵C(O)R¹², -X⁵OC(O)R¹², -X⁵C(O)NR¹²R¹², -X⁵S(O)₂NR¹²R¹², -X⁵NR¹²S(O)₂R¹², -X⁵P(O)-(OR¹²)OR¹², -X⁵OP(O)(OR¹²)OR¹², -X⁵NR¹²C(O)R¹³, -X⁵S(O)R¹³, -X⁵C(O)R¹³ y -X⁵S(O)₂R¹³ y/o 1 radical seleccionado de -R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵S(O)R¹⁴, -X⁵S(O)₂R¹⁴, -X⁵C(O)R¹⁴, -X⁵C(O)OR¹⁴, -X⁵OC(O)R¹⁴, -X⁵NR¹⁴R¹², -X⁵NR¹²C(O)R¹⁴, -X⁵NR¹²C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹², -X⁵S(O)₂NR¹⁴R¹², -X⁵NR¹²S(O)₂R¹⁴, -X⁵NR¹²C(O)NR¹⁴R¹² y -X⁵NR¹²C(NR¹²)NR¹⁴R¹², y dentro de R³ y R⁴ cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, -NR¹²R¹², -NR¹²C(O)R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹², -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)R¹², -OC(O)R¹², -C(O)NR¹²R¹²,

$-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se describe arriba, con la salvedad de que cuando X^3 es ciano y X^2 es $-OR^4$, donde R^4 se define como $-R^{14}$, o $-NHR^{18}$, entonces cualquier sistema aromático de anillos presente dentro de R^{14} o R^{18} no está sustituido adicionalmente con halo, (C_{3-10}) cicloalquilo, hetero (C_{3-10}) cicloalquilo, (C_{6-10}) arilo, hetero (C_{5-10}) arilo, (C_{9-10}) -bícicloarilo o hetero (C_{8-10}) bícicloarilo, con la salvedad de que solamente está presente una estructura bicíclica de anillos dentro de R^3 , R^4 o R^{15} , y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y sus derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

4 El compuesto de la reivindicación 1 o la reivindicación 2, en el cual

X^1 es $-NHC(R^1)(R^2)X^3$ o $-NHCH(R^{19})C(O)R^{20}$,

X^2 es hidrógeno, fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ o $-NR^{17}R^{18}$ y X^7 es hidrógeno o X^2 y X^7

representan ambos fluoro,

X^3 es $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CH-S(O)_2R^5$,

$-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,

$-C(O)CH_2N(R^6)SO_2R^5$ o $-C(O)C(O)R^5$, en cuyas fórmulas R^5 es hidrógeno, (C_{1-4}) alquilo,

(C_{3-10}) cicloalquilo, hetero (C_{3-10}) cicloalquilo, (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquilo, (C_{6-10}) arilo, (C_{0-6}) alquilo,

hetero (C_{5-10}) arilo, (C_{0-6}) alquilo, (C_{9-10}) bícicloarilo, (C_{0-6}) alquilo o hetero (C_{8-10}) bícicloarilo-

(C_{0-6}) alquilo, R^6 es hidrógeno, hidroxilo o (C_{1-6}) alquilo, o donde X^3 contiene un grupo $-NR^5R^6$,

R^5 y R^6 junto con el átomo de nitrógeno al cual están unidos ambos, forman

hetero (C_{3-10}) cicloalquilo, hetero (C_{5-10}) arilo o hetero- (C_{8-10}) bícicloarilo, R^7 es hidrógeno o

(C_{1-4}) alquilo y R^8 es hidroxilo o R^7 y R^8 forman juntos oxo, R^{16} es hidrógeno, $-X^4$, $-CF_3$,

$-CF_2CF_2R^9$ o $-N(R^6)OR^6$, R^9 es hidrógeno, halo, (C_{1-4}) alquilo, (C_{5-10}) arilo, (C_{0-6}) alquilo o

(C_{5-10}) heteroarilo, (C_{0-6}) alquilo,

X^4 comprende un anillo heteromonocíclico que contiene 4 a 7 átomos miembros de anillo o un sistema de anillos heterobícíclico condensado que contiene 8 a 14 átomos miembros de anillo y cualquier derivado carbocíclico cetona, iminocetona o tiocetona de los

mismos, con la salvedad de que cuando $-X^4$ es distinto de un anillo heteromonocíclico que contiene 5 átomos miembros de anillo, en el cual no más de dos de los átomos miembros de

anillo que comprende el anillo son heteroátomos, entonces X^2 es fluoro, $-OH$, $-OR^4$, $-NHR^{15}$ o $-NR^{17}R^{18}$, y X^7 es hidrógeno o X^2 y X^7 representan ambos fluoro,

en el cual dentro de R^5 , X^3 o X^4 cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro,

$-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$,
 $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)O-R^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$,
 $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$,
 $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical
seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$,
 $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$,
 $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y
 $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileo, R^{12} es en cada
aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13}
es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil (C_{0-6}) alquilo,
hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{3-10}) aril (C_{0-6}) alquilo,
 (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{9-10}) bicicloaril (C_{0-6}) alquilo,

R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 se selecciona de un grupo constituido por
hidrógeno, ciano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$,
 $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$,
 $-X^5C(O)-R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$,
 $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$,
 $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$,
 $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$,
 $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 ,
 R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto con el átomo de
carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-8}) cicloalquileno o
 (C_{3-8}) heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroarilo, arilo,
cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituido o
sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo,
 (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$,
 $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$,
 $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$,
 $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$,
 $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13}
son como se define arriba,

R^3 es (C_{1-6}) alquilo o $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y
 X^6 se selecciona de $-X^5NR^{12}-R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$,
 $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5N-R^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$,
 $-X^5C(O)R^{12}$, $-X^5OC(O)-R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$,
 $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$,

$-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^4 se selecciona de $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8O-R^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ y $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas x^8 es (C_{1-6}) alquileo y X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^{15} es (C_{6-10}) arilo, hetero (C_{5-10}) arilo, (C_{9-10}) biciclo-arilo o hetero (C_{8-10}) bicicloarilo,

R^{17} es hidrógeno, (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-6}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo,

R^{18} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-6}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo, y

R^{19} y R^{20} , junto con los átomos a los cuales están unidos R^{19} y R^{20} , forman (C_{4-6}) heterocicloalquileo, en el cual no más de uno de los átomos miembros de anillo que comprende el anillo es un heteroátomo seleccionado de $-NR^{21}-u-O-$, donde el anillo está insustituido o sustituido con R^2 , donde R^2 es como se define arriba, y R^{21} es hidrógeno, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ y $-S(O)_2NR^{14}R^{12}$, en cuyas fórmulas R^{12} , R^{13} y R^{14} son como se define arriba,

en el cual dentro de R^3 , R^4 , R^{15} , R^{17} y R^{18} cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y

$-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, y dentro de R^3 y R^4 cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, $-NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se describe arriba, con la salvedad de que sólo está presente una estructura de anillo bicíclica en R^3 , R^4 o R^{15} , y sus derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos y sus derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

5 Un compuesto de la reivindicación 1 o la reivindicación 2, en el cual

X^1 es $-NHC(R^1)(R^2)X^3$ o $-NHCH(R^{19})C(O)R^{20}$,

X^2 es hidrógeno, fluoro, $-OH$, $-OR^4$, o $-NR^{17}R^{18}$ y X^7 es hidrógeno o X^2 y X^7

representan ambos fluoro,

X^3 es ciano,

en el cual dentro de X^3 [sic] cualquier sistema de anillo alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquil-ideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13} es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo,

R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 se selecciona de un grupo constituido por hidrógeno, ciano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$,

$-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-8}) cicloalquileno o (C_{3-8}) heterocicloalquileno, en los cuales dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituído o sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13} son como se define arriba,

R^3 es (C_{1-6}) alquilo o $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y X^6 se selecciona de $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba,

R^4 se selecciona de $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8N-R^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8O-R^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8N-R^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ y $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^8 es (C_{1-6}) alquileno y X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, con la salvedad de que cuando X^3 es ciano y X^2 es $-OR^4$, donde R^4 se define como $-R^{14}$, entonces R^{14} es (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-3}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{5-10}) aril (C_{1-6}) alquilo, (C_{9-10}) bicicloaril (C_{1-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo,

R^{15} es (C_{6-10}) arilo, hetero (C_{3-10}) arilo, (C_{9-10}) biciclo-arilo o hetero (C_{8-10}) bicicloarilo, R^{17} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-6}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{3-10}) aril (C_{1-6}) alquilo, (C_{9-10}) biciclo-aril (C_{1-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo, R^{18} es (C_{1-6}) alquilo, (C_{3-10}) cicloalquil (C_{1-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{1-6}) alquilo, (C_{6-10}) aril (C_{1-6}) alquilo, hetero (C_{3-10}) aril (C_{1-6}) alquilo, (C_{9-10}) bicicloaril (C_{1-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{1-6}) alquilo, y

R^{19} y R^{20} , junto con los átomos a los cuales están unidos R^{19} y R^{20} , forman (C_{4-8}) heterocicloalquileno, en el cual no más de uno de los átomos miembros de anillo que comprende el anillo es un heteroátomo seleccionado de $-NR^{21}-$ u $-O-$, donde el anillo está insustituido o sustituido con R^2 , donde R^2 es como se define arriba, y R^{21} es hidrógeno, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N-R^{12}R^{12}$ y $-S(O)_2NR^{14}R^{12}$, en cuyas fórmulas R^{12} , R^{13} y R^{14} son como se define arriba,

en el cual dentro de R^3 , R^4 , R^{15} , R^{17} y R^{18} cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, y dentro de R^3 y R^4 cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)-R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})-NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se describe arriba, con la salvedad de que cuando X^2 es $-OR^4$, donde R^4 se define como $-R^{14}$, o $-NHR^{18}$, entonces cualquier sistema de anillos aromático presente dentro de R^{14} o R^{18} no está sustituido adicionalmente con halo, (C_{3-10}) cicloalquilo, hetero (C_{3-10}) cicloalquilo, (C_{6-10}) arilo, hetero (C_{3-10}) arilo, (C_{9-10}) bicicloarilo o hetero (C_{8-10}) bicicloarilo, con la salvedad de que sólo está presente una estructura bicíclica de anillos en R^3 , R^4 o R^{15} , y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los

3/5
3/6

derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

6 Un compuesto de la reivindicación 1 ó 2, en el cual

X^1 es $-NHC(R^1)(R^2)X^3$ o $-NHCH(R^{15})C(O)R^{20}$,

X^2 es $-OH$, $-OC(O)NR^{12}R^{12}$ o $-OC(O)R^{14}$, en cuyas fórmulas R^{12} y R^{14} son como se define más adelante,

X^3 es ciano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ o $-C(O)C(O)R^5$, en cuyas fórmulas R^5 es hidrógeno, (C_{1-4}) alquilo, (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) -bicicloaril (C_{0-6}) alquilo, R^6 es hidrógeno, hidroxilo o (C_{1-6}) alquilo, o donde X^3 contiene un grupo $-NR^5R^6$, R^5 y R^6 junto con el átomo de nitrógeno al cual están unidos ambos, forman hetero (C_{3-10}) cicloalquilo, hetero (C_{5-10}) arilo o hetero (C_{8-10}) bicicloarilo, R^7 es hidrógeno o (C_{1-4}) alquilo y R^8 es hidroxilo o R^7 y R^8 forman juntos oxo, R^{16} es hidrógeno, $-X^4$, $-CF_3$, $-CF_2CF_2R^9$ o $-N(R^6)OR^6$, R^9 es hidrógeno, halo, (C_{1-4}) alquilo, (C_{5-10}) aril (C_{0-6}) alquilo o (C_{5-10}) heteroaril (C_{0-6}) alquilo,

X^4 comprende un anillo heteromonocíclico que contiene 4 a 7 átomos miembros de anillo o un sistema de anillos heterobicíclico condensado que contiene 8 a 14 átomos miembros de anillo y cualquier derivado carbocíclico cetona, iminocetona o tiocetona de los mismos,

en el cual dentro de R^5 , X^3 o X^4 cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13} es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{5-10}) aril (C_{0-6}) alquilo, (C_{9-10}) bicicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril (C_{0-6}) alquilo,

R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 se selecciona de un grupo constituido por hidrógeno, ciano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)-R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-9}) cicloalquileno o (C_{3-9}) heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroanillo, anillo, cicloalquilo, heterocicloalquilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con 1 a 3 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ y $-X^5C(O)R^{13}$, en cuyas fórmulas X^5 , R^{12} y R^{13} son como se define arriba,

R^3 es (C_{1-6}) alquilo o $-C(R^6)(R^6)X^6$, en cuya fórmula R^6 es hidrógeno o (C_{1-6}) alquilo y X^6 se selecciona de $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)-R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se define arriba, y

R^{19} y R^{20} , junto con los átomos a los cuales están unidos R^{19} y R^{20} , forman (C_{4-9}) heterocicloalquileno, en el cual no más de uno de los átomos miembros de anillo que comprende el anillo es un heteroátomo seleccionado de $-NR^{21}-u-O-$, donde el anillo está insustituido o sustituido con R^2 , donde R^2 es como se define arriba, y R^{21} es hidrógeno, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ y $-S(O)_2NR^{14}R^{12}$, en cuyas fórmulas R^{12} , R^{13} y R^{14} son como se define arriba,

en el cual dentro de R^3 , R^4 , R^{15} , R^{17} y R^{18} cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, y dentro de R^3 y R^4 cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se describe arriba, con la salvedad de que sólo está presente una estructura de anillo bicíclica en R^3 , R^4 o R^{15} , y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

7 El compuesto de la reivindicación 1 o la reivindicación 2, en el cual

X^1 es $-NHC(R^1)(R^2)C(O)C(O)NR^5R^6$, en cuya fórmula R^5 es hidrógeno, (C_{1-4}) alquilo, (C_{3-10}) cicloalquil, (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil, (C_{0-3}) alquilo, (C_{6-10}) aril, (C_{0-6}) alquilo, hetero (C_{5-10}) aril, (C_{0-6}) alquilo, (C_{8-10}) bicicloaril, (C_{0-6}) alquilo o hetero (C_{8-10}) bicicloaril, (C_{0-6}) alquilo y R^6 es hidrógeno, hidróxilo o (C_{1-6}) alquilo, o R^5 y R^6 , junto con el átomo de nitrógeno al cual están unidos ambos, forman hetero (C_{3-10}) cicloalquilo, hetero (C_{5-10}) arilo o hetero (C_{8-10}) bicicloarilo,

X^2 es hidrógeno,

en el cual dentro de X^1 cualquier sistema de anillos alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5N-R^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y/o 1 radical

seleccionado de $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5N-R^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ y $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, en cuyas fórmulas X^5 es un enlace o (C_{1-6}) alquileno, R^{12} es en cada aparición independientemente hidrógeno, (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, R^{13} es (C_{1-6}) alquilo o (C_{1-6}) alquilo sustituido con halo, y R^{14} es (C_{3-10}) cicloalquil (C_{0-6}) alquilo, hetero (C_{3-10}) cicloalquil (C_{0-3}) alquilo, (C_{6-10}) aril (C_{0-6}) alquilo, hetero (C_{3-10}) aril (C_{0-6}) alquilo, (C_{9-10}) -bícicloaril (C_{0-6}) alquilo o hetero (C_{8-10}) bícicloaril (C_{0-6}) alquilo,

R^1 es hidrógeno y R^2 es (C_{1-6}) alquilo, y

R^3 es $-CH_2X^6$, en cuya fórmula X^6 es $-X^5NR^{12}S(O)_2R^{12}$ o $-X^5S(O)_2R^{14}$, en cuyas fórmulas X^5 , R^{12} y R^{14} son como se define arriba,

en el cual dentro de R^3 cualquier sistema de anillo alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, (C_{1-6}) alquilideno, ciano, halo, (C_{1-4}) alquilo sustituido con halo, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ y $-X^5S(O)_2R^{13}$ y dentro de R^3 cualquier resto alifático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de ciano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$, en cuyas fórmulas X^5 , R^{12} , R^{13} y R^{14} son como se describe arriba, con la salvedad de que sólo está presente una estructura de anillo bicíclica en R^3 , y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

8 El compuesto de la reivindicación 3, en el cual

X^1 es $-NHC(R^1)(R^2)X^3$ o $-NHCH(R^{19})C(O)R^{20}$, en cuyas fórmulas R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 es hidrógeno, (C_{1-6}) alquilo, $-X^5OR^{12}$, $-X^5S(O)R^{13}$, $-X^5OR^{14}$, (C_{6-10}) aril (C_{0-6}) alquilo o hetero (C_{3-10}) aril (C_{0-6}) alquilo, o R^1 o R^2 considerados junto con el átomo de carbono al cual están unidos a la vez R^1 y R^2 , forman (C_{3-6}) cicloalquileno o (C_{3-6}) heterociclo-alquileno, en los cuales dentro de dicho R^2 , cualquier heteroarilo, arilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con (C_{1-6}) alquilo o hidroxí,

en los cuales X^3 es ciano, $-C(O)-R^{16}$, $-C(R^6)(OR^6)_2$, $-CH=CHS(O)_2R^5$, $-CH_2C(O)R^{16}$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ o $-C(O)C(O)R^5$, y R^{19} y R^{20} junto con los átomos a los cuales están unidos R^{19} y R^{20} forman (C_{4-8}) heterocicloalquileno, en cuya fórmula no más de uno de los átomos miembros del anillo que comprende el anillo es un heteroátomo seleccionado de $-NR^{21}$ - u -O-, en el cual el anillo está insustituido o sustituido con (C_{1-6}) alquilo o $-X^5C(O)OR^{12}$ y R^{21} es hidrógeno, (C_{1-6}) alquilo, $-X^5C(O)R^{12}$, $-X^5C(O)OR^{12}$, $-R^{14}$, $-X^5C(O)R^{14}$ o $-C(O)OR^{14}$,

X^2 es $-OH$ o $-OC(O)NR^{12}R^{12}$, en cuya fórmula cada R^{12} representa independientemente hidrógeno o (C_{1-6}) alquilo, donde dicho alquilo está insustituido o sustituido con hidroxilo o metoxilo, o X^2 es $-OC(O)NHR^{14}$, en cuya fórmula R^{14} es (C_{3-10}) cicloalquil (C_{0-6}) alquilo o hetero (C_{3-10}) cicloalquil (C_{1-3}) alquilo, o X^2 es $-OC(O)R^{14}$, en cuya fórmula R^{14} es $-NR^{22}R^{23}$ y R^{22} y R^{23} junto con el átomo de nitrógeno al cual están unidos R^{22} y R^{23} forman un anillo hetero (C_{4-6}) cicloalquilo, anillo que puede estar insustituido o sustituido con hidroxilo, y

R^3 es $-CH_2X^6$, en cuya fórmula X^6 se selecciona de $-X^4SR^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2R^{13}$, $-X^5C(O)R^{13}$, $-X^5OR^{12}$, $-X^5SR^{14}$, $-X^5R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)NR^{14}R^{12}$, y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

9 El compuesto de la reivindicación 8, en el cual

X^3 es ciano, $-C(O)X^4$, $-C(O)H$, $-C(O)N(CH_3)OCH_3$, $-CH(OCH_3)_2$, $-C(O)CF_3$, $-C(O)CF_2CF_3$, $-CH_2C(O)R^{16}$, (E)-2-bencenosulfonil-vinilo, 2-dimetilcarbamoyl-2,2-difluoro-acetilo, 2-oxo-2-pirrolidin-1-il-acetilo, 2-morfolin-4-il-2-oxo-acetilo, 2-oxo-2-piperazin-1-il-acetilo, 2-(4-metanosulfonil-piperazin-1-il)-2-oxo-acetilo, 2-(1,1-di-oxo-1 λ^6 -tioformolin-4-il)-2-oxoacetilo, dimetilamino-oxalilo, tetrahidropirran-4-ilaminooxalilo, 2-morfolin-4-il-etilaminooxalilo, ciclopentil-etil-aminooxalilo, piridin-3-ilaminooxalilo, fenilamino-oxalilo, 1-benzoyl-piperidin-4-ilaminooxalilo, 1-bencil-carbamoyl-metanoílo, 1-benciloxi(oxalilo), 2-benciloxi-acetilo, 2-benceno-sulfonilamino-etanoílo, 2-oxo-2-fenil-etanoílo, 3H-oxazol-2-carbonilo, 5-trifluorometil-oxazol-2-carbonilo, 3-trifluorometil-[1,2,4]oxadiazol-5-carbonilo, 2,2,3,3,3-pentafluoro-propionilo, hidroxil-aminooxalilo, oxalilo, 2-(1,3-dihidro-isoindol-2-il)-2-oxo-acetilo, benzotiazol-2-ilaminooxalilo, 2-oxo-etilo, 2-oxazol-2-il-2-oxo-etilo o

2-benzooxazol-2-il-2-oxo-etilo,

X² se selecciona de -OH, dimetilcarbamoilo, morfolin-4-ilcarbamoilo, piperidin-1-ilcarbamoilo, pirrolidin-1-il-carbamoilo, pirimidin-2-ilamino, tetrahidropiran-4-ilamino, 1-metil-piperidin-4-ilamino, N-(2-metoxietil)-N-(tetrahidropiran-4-il)amino, isopropil-amino y ciclohexilamino, 4-*terc*-butoxicarbonilpiperazin-1-ilcarbamoilo, N-bencil-carbamoilo, pirrolidin-1-il-carbamoilo, N,N-dimetil-carbamoilo, piperidin-1-il-carbamoilo, 4-metanosulfonil-piperazin-1-il-carbamoilo, 4-etoxicarbonilpiperazin-1-il-carbamoilo, N-ciclohexil-carbamoilo, N-fenil-carbamoilo, N-(5,6,7,8-tetrahydro-naftalen-1-il)-carbamoilo, N-butil-N-metil-carbamoilo, N-piridin-3-il-carbamoilo, N-isopropil-carbamoilo, N-piridin-4-il-carbamoilo, N-cianometil-N-metil-carbamoilo, N,N-bis-(2-metoxi-etil)-carbamoilo, N-fenil-carbamoilo, piperazina-carbamoilo, N-naftalen-2-il-carbamoilo, 4-bencil-piperazina-1-carbamoilo, 4-(1-furan-2-il-carbonil)-piperazina-1-carbamoilo, tuomorfolin-4-il-carbamoilo, 1,1-dioxo-1λ⁶-tuomorfolin-4-il)carbamoilo, bis-(2-metoxi-etil)-carbamoilo, morfolin-4-ilcarbamoilo, 2-metoxi-etil-carbamoilo, dietilcarbamoilo, pirrolidin-1-il-carbon-ilo, 2-hidroxietilcarbamoilo, tetrahidro-furan-2-il-metilcarbamoilo, ciclopropilcarbamoilo, *terc*-butil-carbamoilo, 3-hidroxi-pirrolidin-1-il-carbamoilo y carbamoilo, y

R³ es tiofeno-2-sulfonil-metilo, 3-cloro-2-fluoro-fenilmetano-sulfonil-metilo, benceno-sulfonil-metilo, fenilmetano-sulfonil-metilo, 2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil-metilo, 2-bencenosulfonil-etilo, 2-(piridina-2-sulfonil)-etilo, 2-(piridina-4-sulfonil)-etilo, 2-fenilmetano-sulfonil-etilo, oxipiridin-2-il-metano-sulfonil-metilo, prop-2-eno-1-sulfonil-metilo, 4-metoxi-fenilmetano-sulfonil-metilo, *p*-tolil-metano-sulfonil-metilo, 4-cloro-fenilmetano-sulfonil-metilo, *o*-tolil-metano-sulfonil-metilo, 3,5-dimetil-fenilmetano-sulfonil-metilo, 4-trifluoro-metil-fenilmetano-sulfonil-metilo, 4-trifluoro-metoxi-fenilmetano-sulfonil-metilo, 2-bromo-fenilmetano-sulfonil-metilo, piridin-2-il-metano-sulfonil-metilo, piridin-3-il-metano-sulfonil-metilo, piridin-4-il-metano-sulfonil-metilo, naftalen-2-il-metano-sulfonil-metilo, 3-metil-fenilmetano-sulfonil-metilo, 3-trifluorometil-fenilmetano-sulfonil-metilo, 3-trifluoro-metoxi-fenilmetano-sulfonil-metilo, 4-fluoro-2-trifluorometoxi-fenilmetano-sulfonil-metilo, 2-fluoro-6-trifluorometil-fenilmetanosulfonilmetilo, 3-cloro-fenilmetanosulfonilmetilo, 2-fluoro-fenilmetanosulfonil-metilo, 2-trifluoro-fenilmetanosulfonilmetilo, 2-ciano-fenilmetanosulfonilmetilo, 4-*terc*-butil-fenilmetano-sulfonilmetilo,

2-fluoro-3-fenil-fenilmetano-sulfonil-metilo, 3-fluoro-fenilmetanosulfonilmetilo, 4-fluoro-fenilmetano-sulfonilmetilo, 2-cloro-fenilmetanosulfonilmetilo, 2,5-difluoro-fenilmetanosulfonilmetilo, 2,6-difluoro-fenilmetanosulfonilmetilo, 2,5-dicloro-fenilmetano-sulfonil-metilo, 3,4-dicloro-fenilmetanosulfonil-metilo, 2-(1,1-difluoro-metoxi)-fenilmetanosulfonil-metilo, 2-ciano-fenilmetano-sulfonil-metilo, 3-ciano-fenilmetanosulfonilmetilo, 2-trifluoro-metoxi-fenilmetano-sulfonilmetilo, 2,3-difluoro-fenilmetanosulfonil-metilo, 2,5-difluoro-fenilmetanosulfonilmetilo, bifenil-2-ilmetanosulfonilmetilo, ciclohexilmetilo, 3-fluoro-fenilmetanosulfonilmetilo, 3,4-difluoro-fenilmetano-sulfonilmetilo, 2,4-difluoro-fenilmetanosulfonilmetilo, 2,4,6-trifluoro-fenilmetanosulfonilmetilo, 2,4,5-tri-fluoro-fenilmetanosulfonilmetilo, 2,3,4-trifluoro-fenilmetanosulfonilmetilo, 2,3,5-trifluoro-fenilmetano-sulfonilmetilo, 2,5,6-trifluoro-fenilmetanosulfonil-metilo, 2-cloro-5-trifluoro-metilfenilmetanosulfonil-metilo, 2-metil-propano-1-sulfonilo, 2-fluoro-3-tri-fluoro-metilfenilmetanosulfonilmetilo, 2-fluoro-4-tri-fluoro-metilfenilmetanosulfonilmetilo, 2-fluoro-5-tri-fluoro-metil-fenilmetano-sulfonil-metilo, 4-fluoro-3-trifluoro-metilfenilmetanosulfonil-metilo, 2-metoxi-fenilmetanosulfonilmetilo, 3,5-bis-trifluorometil-fenilmetanosulfonilmetilo, 4-difluorometoxi-fenilmetanosulfonilmetilo, 2-difluoro-metoxi-fenilmetanosulfonilmetilo, 3-difluorometoxi-fenilmetanosulfonilmetilo, 2,6-dicloro-fenilmetanosulfonilmetilo, bifenil-4-ilmetanosulfonil-metilo, 3,5-dimetil-isoxazol-4-ilmetanosulfonilmetilo, 5-cloro-tien-2-il-metanosulfonilmetilo, 2-[4-(1,1-difluoro-metoxi)-bencenosulfonil]-etilo, 2-[2-(1,1-difluoro-metoxi)-bencenosulfonil]-etilo, 2-[3-(1,1-difluoro-metoxi)-bencenosulfonil]-etilo, 2-(4-trifluorometoxi-bencenosulfonil)-etilo, 2-(3-trifluoro-metoxi-benceno-sulfonil)-etilo, 2-(2-trifluoro-metoxi-benceno-sulfonil)-etilo, (cianometil-metil-carbamoil)-metilo, bifenil-3-ilmetilo, 2-oxo-2-pirrolidin-1-il-etilo, 2-benceno-sulfonil-etilo, isobutilsulfanilmetilo, 2-fenilsulfanil-etilo, ciclohexilmetanosulfonilmetilo, 2-ciclohexil-etanosulfonilo, bencilo, naftalen-2-ilo, bencilsulfanil-metilo, 2-trifluorometil-bencilsulfanil-metilo, fenil-sulfaniletilo, ciclopropil-metanosulfonilmetilo, 5-bromo-tien-2-ilmetilo, 3-fenil-propilo, 2,2-difluoro-3-fenil-propilo, 3,4,5-trimetoxi-fenilmetanosulfonilmetilo, 2,2-difluoro-3-tien-2-il-propilo, ciclohexiletilo, ciclo-hexilmetilo, *terc*-butilmetilo, 1-metilciclohexilmetilo, 1-metilciclopentilmetilo, 2,2-difluoro-3-fenilpropilo, 2,2-dimetil-3-fenilpropilo, 1-bencilciclopropilmetilo, $-X^3S(O)_2R^{13}$ y $-X^3S(O)_2R^{14}$, en cuyas fórmulas R^{13} es alquilo y R^{14} es fenilo, pudiendo estar dicho fenilo insustituido o sustituido, y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y

mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

10 Un compuesto de la reivindicación 9, en el cual

X^3 es 1*H*-benzoimidazol-2-ilcarbonilo, pirimidin-2-ilcarbonilo, benzooxazol-2-ilcarbonilo, benzotiazol-2-ilcarbonilo, piridazin-3-ilcarbonilo, 3-fenil-[1,2,4]oxadiazol-5-ilcarbonilo o 3-etil-[1,2,4]-oxadiazol-5-ilcarbonilo, 2-oxo-2-pirrolidin-1-il-acetilo, 2-morfolin-4-il-2-oxo-acetilo, 2-oxo-2-piperazin-1-il-acetilo, 2-(4-metanosulfonyl-piperazin-1-il)-2-oxo-acetilo, 2-(1,1-dioxo-1 λ^6 -tiomorfolin-4-il)-2-oxo-acetilo, dimetilaminooxalilo, tetrahidropiran-4-ilamino-oxalilo, 2-morfolin-4-il-etilaminooxalilo, ciclopentil-etil-aminooxalilo, piridin-3-ilaminooxalilo, fenilamino-oxalilo o 1-benzoil-piperidin-4-ilaminooxalilo,

X^2 se selecciona de -OH, dimetilcarbamoiloxi, morfolin-4-ilcarboniloxi, piperidin-1-il-carboniloxi, pirrolidin-1-il-carboniloxi, pirimidin-2-ilamino, tetrahidropiran-4-ilamino, 1-metil-piperidin-4-ilamino, *N*-(2-metoxietil)-*N*-(tetrahidropiran-4-il)amino, isopropil-amino y ciclohexilamino,

R^3 es ciclohexiletilo, ciclohexilmetilo, *tert*-butilmetilo, 1-metilciclohexilmetilo, 1-metilciclopentil-metilo, 2,2-difluoro-3-fenilpropilo, 2,2-dimetil-3-fenilpropilo, 1-bencilciclopropilmetilo, $-X^5S(O)_2R^{13}$ o $-X^5S(O)_2R^{14}$, donde R^{13} es alquilo y R^{14} es fenilo, pudiendo estar dicho fenilo insustituido o sustituido, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

11 El compuesto de la reivindicación 3, en el cual

X^1 es $-NHC(R^1)(R^2)X^3$ o $-NHCH(R^{19})C(O)R^{20}$, en cuyas fórmulas R^1 es hidrógeno o (C_{1-6}) alquilo y R^2 es hidrógeno, (C_{1-6}) alquilo, $-X^5OR^{12}$, $-X^5S(O)R^{13}$, $-X^5OR^{14}$, (C_{6-10}) aril (C_{0-6}) alquilo o hetero (C_{5-10}) aril (C_{0-6}) alquilo, o R^1 y R^2 , considerados junto con el átomo de carbono al cual están unidos R^1 y R^2 , forman (C_{3-6}) cicloalquileno o (C_{3-6}) -heterocicloalquileno, en cuyas fórmulas dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquileno o heterocicloalquileno está insustituido o sustituido con (C_{1-6}) alquilo o hidroxil, donde X^3 es ciano, $-C(O)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH=CHS(O)_2R^5$, $-CH_2C(O)R^{16}$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ o $-C(O)C(O)R^5$, y R^{19} y R^{20} , junto con los átomos a los cuales están unidos R^{19} y R^{20} , forman (C_{4-8}) -heterocicloalquileno, donde no más de uno de los átomos miembros de anillo que comprende el anillo es un heteroátomo seleccionado de $-NR^{21}$ - u -O-, donde el anillo está insustituido o sustituido con (C_{1-6}) alquilo o $-X^5C(O)OR^{12}$ y R^{21} es

323

324

hidrógeno, (C_{1-6}) alquilo, $-X^5C(O)R^{12}$, $-X^5C(O)OR^{12}$, $-R^{14}$, $-X^5C(O)R^{14}$ o $-C(O)OR^{14}$,

X^2 es $-NHR^{15}$, en cuya fórmula R^{15} es (C_{6-10}) arilo, hetero (C_{5-10}) arilo, (C_{9-10}) bicicloarilo o hetero (C_{8-10}) bicicloarilo, o $-NR^{17}R^{18}$, donde R^{17} es hetero (C_{3-10}) cicloalquilo y R^{18} es hidrógeno, o R^{17} y R^{18} son independientemente (C_{6-10}) aril (C_{1-6}) alquilo o hetero (C_{5-10}) -aril (C_{1-6}) alquilo, donde dentro de R^{15} , R^{17} y R^{18} cualquier sistema de anillo alicíclico o aromático está insustituido o sustituido adicionalmente con 1 a 5 radicales seleccionados independientemente de (C_{1-6}) alquilo, ciano, halo, nitro, (C_{1-4}) alquilo sustituido con halo, $-X^5OR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{13}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5N-R^{12}S(O)_2R^{12}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^5OR^{14}$ y $-X^5C(O)NR^{14}R^{12}$, y

R^3 es $-CH_2X^6$, en cuya fórmula X^6 se selecciona de $-X^5SR^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2R^{13}$, $-X^5C(O)R^{13}$, $-X^5OR^{12}$, $-X^5SR^{14}$, $-X^5R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)NR^{14}R^{12}$, y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

12 El compuesto de la reivindicación 11, en el cual

X^3 es ciano, $-C(O)X^4$, $-C(O)H$, $-C(O)N(CH_3)OCH_3$, $-CH(OCH_3)_2$, $-C(O)CF_3$, $-C(O)CF_2CF_3$, $-CH_2C(O)R^{16}$, (E)-2-bencenosulfonil-vinilo, 2-dimetilcarbamoil-2,2-difluoro-acetilo, 2-oxo-2-pirrolidin-1-il-acetilo, 2-morfolin-4-il-2-oxo-acetilo, 2-oxo-2-piperazin-1-il-acetilo, 2-(4-metanosulfonil-piperazin-1-il)-2-oxo-acetilo, 2-(1,1-dioxo-1λ⁶-tiomorfolin-4-il)-2-oxo-acetilo, dimetilamino-oxalilo, tetrahidropiran-4-ilaminooxalilo, 2-morfolin-4-il-etilaminooxalilo, ciclopentil-etil-aminooxalilo, piridin-3-ilaminooxalilo, fenilaminooxalilo, 1-benzoil-piperidin-4-ilaminooxalilo, 1-bencilcarbamoil-metanoilo, 1-benciloxi(oxalilo), 2-benciloxi-acetilo, 2-benceno-sulfonilamino-etanoilo, 2-oxo-2-fenil-etanoilo, 3H-oxazol-2-carbonilo, 5-trifluorometil-oxazol-2-carbonilo, 3-trifluorometil-[1,2,4]oxadiazol-5-carbonilo, 2,2,3,3,3-pentafluoro-propionilo, hidroxiamidooxalilo, oxalilo, 2-(1,3-dihidro-isoindol-2-il)-2-oxo-acetilo, benzotiazol-2-ilaminooxalilo, 2-oxo-etilo, 2-oxazol-2-il-2-oxo-etilo o 2-benzooxazol-2-il-2-oxo-etilo,

X^2 se selecciona de 5-nitrotiazol-2-ilamino, 2-nitrofenilamino, pirimidin-2-ilamino, tetrahidropiran-4-ilamino, *N*-(2-metoxietil)-*N*-(tetrahidropiran-4-il)amino, 1-metil-piperidin-4-ilamino, isopropilamino, di(tien-2-ilmetil)amino o di(bencil)amino, y

R^3 es tiofeno-2-sulfonil-metilo, 3-cloro-2-fluoro-fenilmetano-sulfonil-metilo, benceno-sulfonil-metilo, fenilmetano-sulfonil-metilo, 2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil-metilo, 2-bencenosulfonil-etilo, 2-(piridina-2-sulfonil)-etilo, 2-(piridina-4-sulfonil)-etilo, 2-fenilmetanosulfonil-etilo, oxipiridin-2-il-metano-sulfonil-metilo, prop-2-eno-1-sulfonil-metilo, 4-metoxi-fenilmetano-sulfonil-metilo, *p*-tolil-metano-sulfonil-metilo, 4-cloro-fenilmetano-sulfonil-metilo, *o*-tolil-metano-sulfonil-metilo, 3,5-dimetil-fenilmetano-sulfonil-metilo, 4-trifluoro-metil-fenilmetano-sulfonil-metilo, 4-trifluoro-metoxi-fenilmetano-sulfonil-metilo, 2-bromo-fenilmetano-sulfonil-metilo, piridin-2-il-metano-sulfonil-metilo, piridin-3-il-metano-sulfonil-metilo, piridin-4-il-metano-sulfonil-metilo, naftalen-2-il-metano-sulfonil-metilo, 3-metil-fenilmetano-sulfonil-metilo, 3-trifluoro-metil-fenilmetano-sulfonil-metilo, 3-trifluoro-metoxi-fenilmetano-sulfonil-metilo, 4-fluoro-2-trifluorometoxi-fenilmetano-sulfonil-metilo, 2-fluoro-6-trifluorometil-fenilmetanosulfonilmetilo, 3-cloro-fenilmetanosulfonilmetilo, 2-fluoro-fenilmetano-sulfonil-metilo, 2-trifluoro-fenilmetanosulfonilmetilo, 2-ciano-fenilmetanosulfonilmetilo, 4-*tert*-butil-fenilmetanosulfonilmetilo, 2-fluoro-3-fenil-fenilmetano-sulfonil-metilo, 3-fluoro-fenilmetanosulfonilmetilo, 4-fluoro-fenilmetano-sulfonilmetilo, 2-cloro-fenilmetano-sulfonilmetilo, 2,5-difluoro-fenilmetanosulfonilmetilo, 2,6-difluoro-fenilmetanosulfonilmetilo, 2,5-dicloro-fenilmetano-sulfonilmetilo, 3,4-dicloro-fenilmetano-sulfonilmetilo, 2-(1,1-difluoro-metoxi)-fenilmetano-sulfonilmetilo, 2-ciano-fenilmetano-sulfonil-metilo, 3-ciano-fenilmetanosulfonilmetilo, 2-trifluoro-metoxi-fenilmetano-sulfonilmetilo, 2,3-difluoro-fenilmetano-sulfonil-metilo, 2,5-difluoro-fenilmetanosulfonilmetilo, bifenil-2-ilmetanosulfonilmetilo, ciclohexilmetilo, 3-fluoro-fenilmetanosulfonilmetilo, 3,4-difluoro-fenilmetanosulfonilmetilo, 2,4-difluoro-fenilmetanosulfonil-metilo, 2,4,6-trifluoro-fenilmetanosulfonilmetilo, 2,4,5-trifluoro-fenilmetanosulfonilmetilo, 2,3,4-trifluoro-fenilmetanosulfonilmetilo, 2,3,5-trifluoro-fenilmetano-sulfonilmetilo, 2,5,6-trifluoro-fenilmetanosulfonil-metilo, 2-cloro-5-trifluoro-metilfenilmetanosulfonil-metilo, 2-metil-propano-1-sulfonilo, 2-fluoro-3-tri-fluoro-metilfenilmetanosulfonilmetilo, 2-fluoro-4-tri-fluoro-metilfenilmetanosulfonilmetilo, 2-fluoro-5-tri-fluoro-metil-fenilmetanosulfonilmetilo, 4-fluoro-3-trifluoro-metilfenilmetanosulfonilmetilo, 2-metoxi-fenilmetanosulfonilmetilo, 3,5-bis-trifluorometil-fenilmetanosulfonilmetilo, 4-difluorometoxi-fenilmetanosulfonilmetilo, 2-difluoro-metoxi-fenilmetanosulfonilmetilo, 3-difluorometoxi-fenilmetanosulfonilmetilo,

320

326

2,6-dicloro-fenilmetanosulfonilmetilo, bifenil-4-ilmetanosulfonil-metilo, 3,5-dimetil-isoxazol-4-ilmetanosulfonilmetilo, 5-cloro-tien-2-il-metanosulfonilmetilo, 2-[4-(1,1-difluoro-metoxi)-bencenosulfonil]-etilo, 2-[2-(1,1-difluoro-metoxi)-bencenosulfonil]-etilo, 2-[3-(1,1-difluoro-metoxi)-bencenosulfonil]-etilo, 2-(4-trifluorometoxi-bencenosulfonil)-etilo, 2-(3-trifluorometoxi-benceno-sulfonil)-etilo, 2-(2-trifluoro-metoxi-benceno-sulfonil)-etilo, (cianometil-metil-carbamoil)-metilo, bifenil-3-ilmetilo, 2-oxo-2-pirrolidin-1-il)-etilo, 2-benceno-sulfonil-etilo, isobutilsulfanilmetilo, 2-fenilsulfanil-etilo, ciclohexilmetanosulfonilmetilo, 2-ciclohexil-etanosulfonilo, bencilo, naftalen-2-ilo, bencilsulfanil-metilo, 2-trifluorometil-bencilsulfanil-metilo, fenil-sulfaniletilo, ciclopropil-metanosulfonilmetilo, 5-bromo-tien-2-ilmetilo, 3-fenil-propilo, 2,2-difluoro-3-fenil-propilo, 3,4,5-trimetoxi-fenilmetanosulfonilmetilo, 2,2-difluoro-3-tien-2-il-propilo, ciclohexiletilo, ciclo-hexilmetilo, *terc*-butilmetilo, 1-metilciclohexilmetilo, 1-metilciclopentilmetilo, 2,2-difluoro-3-fenilpropilo, 2,2-dimetil-3-fenilpropilo, 1-bencilciclopropilmetilo, $-X^5S(O)_2R^{13}$ y $-X^5S(O)_2R^{14}$, en cuyas fórmulas R^{13} es alquilo y R^{14} es fenilo, pudiendo estar dicho fenilo insustituido o sustituido, y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

13 Un compuesto de la reivindicación ¹², en el cual

X^3 es 1*H*-benzoimidazol-2-ilcarbonilo, pirimidin-2-ilcarbonilo, benzooxazol-2-ilcarbonilo, benzotiazol-2-ilcarbonilo, piridazin-3-ilcarbonilo, 3-fenil-[1,2,4-oxadiazol-5-ilcarbonilo o 3-etil-[1,2,4]oxadiazol-5-il-carbonilo, 2-oxo-2-pirrolidin-1-il-acetilo, 2-morfolin-4-il-2-oxo-acetilo, 2-oxo-piperazin-1-il-acetilo, 2-(4-metanosulfonil-piperazin-1-il)-2-oxo-acetilo, 2-(1,1-di-oxo-1□⁶-tiomorfolin-4-il)-2-oxo-acetilo, dimetilamino-oxalilo, tetrahidropiran-4-ilaminooxalilo, 2-morfolin-4-il-etilaminooxalilo, ciclopentil-etil-aminooxalilo, piridin-3-ilaminooxalilo, fenilaminooxalilo o 1-benzoil-piperidin-4-ilaminooxalilo,

X^2 se selecciona de -OH, dimetilcarbamoiloxi, morfolin-4-ilcarboniloxi, piperidin-1-il-carboniloxi, pirrolidin-1-il-carboniloxi, pirimidin-2-ilamino, tetrahidropiran-4-ilamino, 1-metil-piperidin-4-ilamino,

N-(2-metoxietil)-*N*-(tetrahidropiran-4-il)amino, isopropil-amino y ciclohexilamino,

R^3 es ciclohexiletilo, ciclohexilmetilo, *terc*-butilmetilo, 1-metilciclohexilmetilo, 1-metilciclo-pentilmetilo, 2,2-difluoro-3-fenilpropilo, 2,2-dimetil-3-fenilpropilo,

328

1-bencilciclopropilmetilo, $-X^5S(O)_2R^{13}$ o $X^5S(O)_2R^{14}$, en cuyas fórmulas R^{13} es alquilo y R^{14} es fenilo, pudiendo estar dicho fenilo insustituido o sustituido, y las sales y solvatos farmacéuticamente aceptables de tales compuestos y los derivados N-óxido, derivados profármaco, derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos

14 Un compuesto de la reivindicación 1, seleccionado del grupo constituido por
(R)-N-cianometil-2-hidroxi-3-fenilmetanosulfonil-propionamida,
(R)-N-(1-ciano-1-tiofen-2-il-metil)-2-hidroxi-3-fenilmetanosulfonil-propionamida,
(R)-N-(1-ciano-1-tiofen-2-il-metil)-3-[2-(1,1-difluoro-metoxi)fenilmetanosulfonil]-2-hidroxi-propionamida,
(R)-N-(cianometil-3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-2-hidroxi-propionamida,
 ácido morfolina-4-carboxílico-(*R*)-1-(cianometil-carbamoyl)-2-fenilmetanosulfonil-etil-éster;
 ácido morfolina-4-carboxílico-(*R*)-1-(cianometil-carbamoyl)-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster;
 ácido (*R*)-(2-metoxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-fenilmetanosulfonil-etil-éster;
 ácido (*S*)-dietil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
 ácido (*S*)-pirrolidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster;
 ácido (*S*)-morfolina-4-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
 ácido (*S*)-4-etil-piperazina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster;
 ácido (*S*)-2-hidroximetil-pirrolidina-1-carboxílico-(*S*)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster;
 ácido (*S*)-(2,2,2-trifluoro-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
 ácido (*S*)-(2-hidroxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
 ácido (tetrahidrofuran-2-ilmetil)-carbámico-(*S*)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster;
 ácido (*S*)-azetidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster;
 ácido (*S*)-ciclopropil-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster;
 ácido (*S*)-piperidina-1-carboxílico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
 ácido (*S*)-(2-metoxi-etil)-carbámico-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
 ácido (*R*)-3-hidroxi-pirrolidina-1-carboxílico-(*S*)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster;
 ácido (*S*)-3-hidroxi-pirrolidina-1-carboxílico-(*S*)-1-(cianometil-carbamoyl)-2-ciclohexil-etil-éster,
 ácido (*S*)-morfolina-4-carboxílico-1-(cianometil-carbamoyl)-3-ciclohexil-propil-éster;
 ácido morfolina-4-carboxílico-(*R*)-1-[(*S*)-1-(1-benzo-

oxazol-2-il-metanoil)-propilcarbamoil]-2-fenilmetano-sulfonil-etil-éster;
 ácido morfolina-4-carboxílico(*R*)-1-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster;
 ácido morfolina-4-carboxílico(*R*)-1-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propilcarbamoil]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster;
 ácido pirrolidina-1-carboxílico(*R*)-1-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-fenilmetano-sulfonil-etil-éster;
 ácido dimetil-carbámico-(*R*)-1-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoil]-2-fenilmetanosulfonil-etil-éster;
 ácido morfolina-4-carboxílico-(*R*)-1-[(*S*)-1-(1-bencil-carbamoil-metanoil)-propilcarbamoil]-2-fenilmetano-sulfonil-etil-éster;
 ácido morfolina-4-carboxílico-(*S*)-1-[(*S*)-1-(oxazolo-[4,5-*b*]piridina-2-carbonil)-propilcarbamoil]-2-fenilmetano-sulfonil-etil-éster;
 ácido morfolina-4-carboxílico-(*S*)-1-[(*S*)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-2-fenilmetanosulfonil-etil-éster;
 (*S*)-2-[(*R*)-3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-2-hidroxi-propanoílamino]-*N*-metoxi-*N*-metil-butiramida,
 (*R*)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-*N*-[(*S*)-1-formil-propil]-2-hidroxi-propionamida,
 (*R*)-(*N*)[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida,
 ácido (*S*)-3-{3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-propanoílamino}-2-oxopentanoico-bencilamida,
N-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-propionamida,
N-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-3-fenil-propil]-3-*p*-tolilmetanosulfonil-propionamida,
 3-(2-difluorometoxi-fenilmetanosulfonil)-*N*-(1-etil-2,3-dioxo-3-pirrolidin-1-il-propil)-propionamida,
 3-(2-difluorometoxi-fenilmetanosulfonil)-*N*-(1-etil-3-morfolin-4-il-2,3-dioxo-propil)-propionamida,
 3-(2-difluorometoxi-fenilmetanosulfonil)-*N*-(1-etil-2,3-dioxo-3-piperazin-1-il-propil)-propionamida,
 3-(2-difluorometoxi-fenilmetanosulfonil)-*N*-[3-(1,1-dioxo-1,6-tiomorfolin-4-il)-1-etil-2,3-dioxo-propil]-propionamida,
 3-(2-difluorometoxi-fenilmetanosulfonil)-*N*-[1-etil-3-

(4-metil-sulfonil-piperazin-1-il)-2,3-dioxo-propil)-propionamida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
 propionilamino]-2-oxo-pentanoico-dimetilamida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
 propionilamino]-2-oxo-pentanoico-ciclopentil-etil-amida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
 propionilamino]-2-oxo-pentanoico-fenilamida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
 propionilamino]-2-oxo-pentanoico-piridin-3-ilamida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-propionil-
 amino]-2-oxo-pentanoico-(tetrahidropiran-4-il)-amida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
 propionilamino]-2-oxo-pentanoico-(1-benzoil-piperidin-4-il)-amida,
 ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
 propionilamino]-2-oxo-pentanoico-(2-morfolin-4-il-etil)-amida,
 (R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-
 (2-nitro-fenilamino)-3-fenilmetanosulfonil-propionamida,
 N-[1-(benzooxazol-2-carbonil)-propil]-3-fenilmetano-
 sulfonil-2-(pirimidin-2-ilamino)propionamida,
 (R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-
 (5-nitro-tiazol-2-ilamino)-3-fenilmetanosulfonil-propionamida,
 ácido (2S)(4,4-difluoro-2-hidroxi-5-fenil-pentanoico-(1(S)-ciano-3-fenil-propil)-amida,
 N-(1(S)-ciano-3-fenil-propil)-2-(S)-(2-morfolin-4-il-oxo-etoxi)-4-fenil-butiramida,
 N-(1(S)-ciano-3-fenil-propil)-2-(S)-fluoro-4-fenil-butiramida,
 N-(1(S)-ciano-3-fenil-propil)-2,2-difluoro-4-fenilbutiramida,
 N-(1(S)-ciano-3-fenil-propil)-2-(S)-hidroxi-4-fenil-butiramida,
 N-(1(S)-ciano-3-fenil-propil)-2-(R)-hidroxi-4-fenil-butiramida,
 N-(1(S)-ciano-3-fenil-propil)-2-(R)-metoxi-4-fenil-butiramida,
 ácido 2,2-difluoro-5-fenil-pentanoico-(1-ciano-ciclo-propil)-amida,
 N-(1(S)-ciano-3-fenil-propil)-4-fenil-butiramida,
 ácido 2,2-difluoro-5-fenil-pentanoico-((S)-1-ciano-3-fenil-propil)-amida,
 N-(4-ciano-1-etil-piperidin-4-il)-3-ciclohexil-propionamida,
 N-(4-ciano-1-etil-piperidin-4-il)-3-(2-difluorometoxi-fenilmetanosulfonil)-propionamida,
 ácido (S)-*tert*-butil-carbámico-1-(cianometil-carbamoil)-2-ciclohexil-etil-éster,
 ácido (R)-carbámico-1-(cianometil-carbamoil)-2-(2-di-
 fluorometoxi-fenilmetanosulfonil)-etil-éster,

ácido (S)-carbámico-1-(cianometil-carbamoil)-2-ciclo-hexil-etil-éster;
ácido (R)-morfolina-4-carboxílico-1-(1-ciano-ciclopropil-carbamoil)-2-fenilmetanosulfonil-etil-éster;
ácido (R)-morfolina-4-carboxílico-1-(4-ciano-tetrahidropiran-4-ilcarbamoil)-2-fenilmetanosulfonil-etil-éster;
3-ciclohexil-2-hidroxi-N-[1-(oxazolo[4,5-b]piridina-2-carbonil)-2-propil]-propionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-2-isopropil-amino-3-fenilmetanosulfonilpropionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-3-fenilmetano-sulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(1-metil-piperidin-4-ilamino)-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(dibencil-amino-3-fenilmetanosulfonil-propionamida,
(S)-N-[(S)-1-benzoxazol-2-carbonil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-propionamida,
(S)-N[(S)-1-(benzoxazol-2-carbonil)-butil]-2-isopropil-amino-3-tiofen-2-il-propionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-3-fenilmetano-sulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-[(2-metoxi-etil)-tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-ciclohexil-amino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-dimetil-amino-3-fenilmetanosulfonil-propionamida,

(1S)-N-[1-(benzooxazol-2-carbonil)-butil]-2-(S)-fluoro-4-fenil-butiramida,
 ácido 2,2-difluoro-5-fenil-pentanoico-[(S)-1-(benzoxazol-2-carbonil)-butil]-amida,
 ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(benzooxazol-2-carbonil)-propilcarbamoil]-2-ciclohexil-etil-éster,
 ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(oxazolo[4,5-b]piridina-2-carbonil)-propilcarbamoil]-etil-éster,
 ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-etil-éster,
 ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(5-fenil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-etil-éster,
 ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(benzooxazol-2-carbonil)-propilcarbamoil]-3-ciclohexil-propil-éster,
 ácido 4-[4,4-dimetil-2-(morfolina-4-carboniloxi)-pentanoil-amino]-3-oxo-azepan-1-carboxílico-bencil-éster,
 (R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-ciclopropilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
 (R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-ciclohexil-amino-3-ciclopropilmetanosulfonil-propionamida,
 (R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-cicloheptil-amino-3-ciclopropilmetanosulfonil-propionamida,
 (R)-3-fenilmetanosulfonil-N-[(S)-3-fenil-1-(tiazol-2-carbonil)-propil]-2-(tetrahidropiran-4-ilamino)-propionamida,
 (R)-N-[(S)-1-(benzoxazol-2-carbonil)-3-fenil-propil]-3-ciclopropilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
 (R)-3-ciclopropilmetanosulfonil-N-[1-(5-etil-1,2,4-oxadiazol-3-carbonil)-propil]-2-(tetrahidropiran-4-il-amino)-propionamida,
 (R)-3-fenilmetanosulfonil-N-[1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propil]-2-(tetrahidropiran-4-ilamino)-propionamida,
 (R)-N-[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-il-amino)-propionamida,
 ácido {(R)-1-[1-(benzotiazol-2-il-hidroxil-metil)-butilcarbamoil]-3-fenilmetanosulfonil-etil}-carbámico-*tert*-butil-éster,
 ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxil-metil)-butilcarbamoil]-3-fenilmetanosulfonil-etil}-carbámico-*tert*-butil-éster,
 ácido {(S)-1-[(S)-1-(benzoxazol-2-il-hidroxil-metil)-butilcarbamoil]-2-tiofen-2-il-etil}-carbámico-*tert*-butil-éster,

231
332

ácido {(R)-1-[1-(benzotiazol-2-il-hidroxi-metil)-butil-carbamoi]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoi]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoi]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido (R)-1-[1-[hidroxi-(3-fenil-1,2,4-oxadiazol-5-il-metil)-propilcarbamoi]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido ((R)-2-ciclopropilmetanosulfonil-1-[(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propilcarbamoi]-etil)-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[1-(benzoxazol-2-il-hidroxi-metil)-butil-carbamoi]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-propilcarbamoi]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[(S)-1-(hidroxi-tiazol-2-il-metil)-3-fenil-propilcarbamoi]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoi]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido (R)-1-[1-[hidroxi-(3-fenil-1,2,4-oxadiazol-5-il-metil)-propilcarbamoi]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido ((R)-2-ciclopropilmetanosulfonil-1-[(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxi-metil]-propilcarbamoi]-etil)-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[1-(benzoxazol-2-il-hidroxi-metil)-butil-carbamoi]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-3-fenil-propilcarbamoi]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[(S)-1-(hidroxi-tiazol-2-il-metil)-3-fenil-propilcarbamoi]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
 ácido (R)-2-fenilmetanosulfonil-1-[(S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroxi-metil]-propilcarbamoi]-etil)-carbámico-*terc*-butil-éster,
 (R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-[ciclopropil-metil-(tetrahidropiran-4-ilmetil)-amino]-3-fenilmetano-sulfonil-propionamida,
 (R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida,
 (R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,

(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-iso-propilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(1-metil-piperidin-4-ilamino)-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida,
(S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-propionamida,
(S)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-tiofen-2-il-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-isopropilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-[2-metoxi-etil)-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-ciclohexilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida,
N-cianometil-3-ciclohexil-propionamida,
N-cianometil-3-(2-difluorometoxi-fenilmetanosulfonil)-propionamida,
ácido 3-(3-ciclohexil-propionilamino)-2-oxo-5-fenil-pentanoico-tiazol-2-ilamida,
3-ciclohexil-N-(1-formil-3-fenil-propil)-propionamida,
3-(2-difluorometoxi-fenilmetanosulfonil)-N-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propil]-propionamida,

N-[(*S*)-1-(benzooxazol-2-carbonil)-propil]-2-(2-ciano-fenilamino)-3-ciclohexil-propionamida,
N-cianometil-3-ciclohexil-2-(4-metoxi-fenoxi)-propionamida,
 2-benciloxi-*N*-cianometil-3-ciclohexil-propionamida,
 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-benciloxi-3-fenilmetanosulfonil-propionamida,
 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-metoximetoxi-3-fenilmetanosulfonil-propionamida,
 (*S*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-butil]-2-hidroxi-3-fenil-propionamida,
 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propil]-3-fenilmetanosulfonil-2-trisopropilsilaniloxi-propionamida,
 (*R*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida,
 (*R*)-2-hidroxi-3-fenilmetanosulfonil-*N*-[(*S*)-1-(1-piridazin-3-il-metanoil)-butil]-propionamida,
 ácido (*S*)-3-((*R*)-2-hidroxi-3-fenilmetanosulfonil-propanoíl-amino)-2-oxo-pentanoico-bencilamida,
 (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida,
 (*R*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida,
 (2*R*,5*S*)-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil-metil]-6-etoxi-5-etil-morfolin-3-ona,
 y sus *N*-óxidos correspondientes, y sus profármacos, y sus derivados protegidos, isómeros individuales y mezclas de isómeros de los mismos, y las sales y solvatos (v g hidratos) farmacéuticamente aceptables de tales compuestos 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 reivindicación 14, seleccionado del grupo constituido por
 (*R*)-*N*-cianometil-2-hidroxi-3-fenilmetanosulfonil-propionamida,
 (*R*)-*N*-(1-ciano-1-tiofen-2-il-metil)-2-hidroxi-3-fenilmetanosulfonil-propionamida,
 (*R*)-*N*-(1-ciano-1-tiofen-2-il-metil)-3-[2-(1,1-difluoro-metoxi)fenilmetanosulfonil]-2-hidroxi-propionamida,
 (*R*)-*N*-(cianometil-3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-2-hidroxi-propionamida,
 ácido morfolina-4-carboxílico-(*R*)-1-(cianometil-carbamoil)-2-fenilmetanosulfonil-etil-éster;
 ácido morfolina-4-carboxílico-(*R*)-1-(cianometil-carbamoil)-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster;
 ácido (*R*)-(2-metoxi-etil)-carbámico-1-(cianometil-carbamoil)-2-fenilmetanosulfonil-etil-éster,
 ácido (*S*)-dietil-carbámico-1-(cianometil-carbamoil)-2-ciclohexil-etil-éster;

ácido (S)-pirrolidina-1-carboxílico-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster;
 ácido (S)-morfolina-4-carboxílico-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster,
 ácido (S)-4-etil-piperazina-1-carboxílico-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster;
 ácido (S)-2-hidroxi-metil-pirrolidina-1-carboxílico-(S)-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster;
 ácido (S)-(2,2,2-trifluoro-etil)-carbámico-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster,
 ácido (S)-(2-hidroxi-etil)-carbámico-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster,
 ácido (tetrahydrofuran-2-il-metil)-carbámico-(S)-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster,
 ácido (S)-azetidina-1-carboxílico-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster,
 ácido (S)-ciclopropil-carbámico-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster;
 ácido (S)-piperidina-1-carboxílico-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster,
 ácido (S)-(2-metoxi-etil)-carbámico-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster,
 ácido (R)-3-hidroxi-pirrolidina-1-carboxílico-(S)-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster,
 ácido (S)-3-hidroxi-pirrolidina-1-carboxílico-(S)-1-(cianometil-carbamoi)-2-ciclohexil-etil-éster,
 ácido (S)-morfolina-4-carboxílico-1-(cianometil-carbamoi)-3-ciclohexil-propil-éster,
 ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoi]-2-fenilmetano-sulfonil-etil-éster,
 ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoi]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster;
 ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-benzotiazol-2-il-metanoil)-propilcarbamoi]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster;
 ácido pirrolidina-1-carboxílico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoi]-2-fenilmetano-sulfonil-etil-éster,
 ácido dimetil-carbámico-(R)-1-[(S)-1-(1-benzooxazol-2-il-metanoil)-propilcarbamoi]-2-fenilmetanosulfonil-etil-éster,
 ácido morfolina-4-carboxílico-(R)-1-[(S)-1-(1-bencil-carbamoi-metanoil)-propilcarbamoi]-2-fenilmetano-sulfonil-etil-éster;
 ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(oxazolo-[4,5-b]piridina-2-carbonil)-propilcarbamoi]-2-fenilmetano-sulfonil-etil-éster;
 ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoi]-2-fenilmetanosulfonil-etil-éster,
 (S)-2-[(R)-3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-2-hidroxi-propanoilamino]-N-metoxi-N-metil-butiramida,

(R)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-N-
((S)-1-formil-propil)-2-hidroxi-propionamida,
(R)-N[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-
propionamida,
ácido (S)-3-{3-[2-(1,1-difluoro-metoxi)-fenilmetano-
sulfonil]-propanoilamino}-2-oxopentanoico-bencilamida,
N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-3-[2-
(1,1-difluoro-metoxi)-fenilmetanosulfonil]-propionamida,
N-[(S)-1-(1-benzooxazol-2-il-metanoil)-3-fenil-propil]-3-*p*-tolilmetanosulfonil-propionamida,
3-(2-difluorometoxi-fenilmetanosulfonil)-N-(1-etil-2,3-dioxo-3-pirrolidin-1-il-propil)-
propionamida,
3-(2-difluorometoxi-fenilmetanosulfonil)-N-(1-etil-3-morfolin-4-il-2,3-dioxo-propil)-
propionamida,
3-(2-difluorometoxi-fenilmetanosulfonil)-N-(1-etil-2,3-dioxo-3-piperazin-1-il-propil)-
propionamida,
3-(2-difluorometoxi-fenilmetanosulfonil)-N-[3-(1,1-
dioxo-1,6-tiomorfolin-4-il)-1-etil-2,3-dioxo-propil]-propionamida,
3-(2-difluorometoxi-fenilmetanosulfonil)-N-[1-etil-3-
(4-metil-sulfonil-piperazin-1-il)-2,3-dioxo-propil]-propionamida,
ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
propionilamino]-2-oxo-pentanoico-dimetilamida,
ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
propionilamino]-2-oxo-pentanoico-ciclopentil-etil-amida,
ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
propionilamino]-2-oxo-pentanoico-fenilamida,
ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
propionilamino]-2-oxo-pentanoico-piridin-3-ilamida,
ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
propionilamino]-2-oxo-pentanoico-(tetrahidropiran-4-il)-amida,
ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
propionilamino]-2-oxo-pentanoico-(1-benzoil-piperidin-4-il)-amida,
ácido 3-[3-(2-difluorometoxi-fenilmetanosulfonil)-
propionilamino]-2-oxo-pentanoico-(2-morfolin-4-il-etil)-amida,
(R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil]-2-
(2-nitro-fenilamino)-3-fenilmetanosulfonil-propionamida,
N-[1-(benzooxazol-2-carbonil)-propil]-3-fenilmetano-

sulfonil-2-(pirimidin-2-ilamino)propionamida,
(R)-N-[(S)-1-(1-benzoxazol-2-il-metanoil)-butil]-2-(5-nitro-tiazol-2-ilamino)-3-fenilmetanosulfonil-propionamida,
ácido (2S)(4,4-difluoro-2-hidroxi-5-fenil-pentanoico-(1(S)-ciano-3-fenil-propil)-amida,
N-(1(S)-ciano-3-fenil-propil)-2-(S)-(2-morfolin-4-il-2-oxo-etoxi)-4-fenil-butiramida,
N-(1(S)-ciano-3-fenil-propil)-2-(S)-fluoro-4-fenil-butiramida,
N-(1-(S)-ciano-3-fenil-propil)-2,2-difluoro-4-fenilbutiramida,
N-(1-(S)-ciano-3-fenil-propil)-2-(S)-hidroxi-4-fenilbutiramida,
N-(1-(S)-ciano-3-fenil-propil)-2-(R)-hidroxi-4-fenilbutiramida,
N-(1-(S)-ciano-3-fenil-propil)-2-(R)-metoxi-4-fenilbutiramida,
ácido 2,2-difluoro-5-fenil-pentanoico-(1-ciano-ciclo-propil)-amida,
N-(1-(S)-ciano-3-fenil-propil)-4-fenil-butiramida,
ácido 2,2-difluoro-5-fenil-pentanoico-((S)-1-ciano-3-fenil-propil)-amida,
N-(4-ciano-1-etil-piperidin-4-il)-3-ciclohexil-propionamida,
N-(4-ciano-1-etil-piperidin-4-il)-3-(2-difluorometoxi-fenilmetanosulfonil)-propionamida,
ácido (S)-*terc*-butil-carbámico-1-(cianometil-carbamoil)-2-ciclohexil-etil-éster,
ácido (R)-carbámico-1-(cianometil-carbamoil)-2-(2-di-fluorometoxi-fenilmetanosulfonil)-etil-éster;
ácido (S)-carbámico-1-(cianometil-carbamoil)-2-ciclo-hexil-etil-éster;
ácido (R)-morfolina-4-carboxílico-1-(1-ciano-ciclopropil-carbamoil)-2-fenilmetanosulfonil-etil-éster,
ácido (R)-morfolina-4-carboxílico-1-(4-ciano-tetrahidropiran-4-ilcarbamoil)-2-fenilmetanosulfonil-etil-éster,
3-ciclohexil-2-hidroxi-N-[1-(oxazolo[4,5-*b*]piridina-2-carbonil)-2-propil]-propionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-2-isopropil-amino-3-fenilmetanolsulfonilpropionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-3-fenilmetano-sulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(1-metil-piperidin-4-ilamino)-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(bis-

tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-(dibencil-amino-3-fenilmetanosulfonil-propionamida,
(S)-N-[(S)-1-benzoxazol-2-carbonil)-butil]-2-(tetrahidropiran-4-ilamino)-3-tiofen-2-il-propionamida,
(S)-N[(S)-1-(benzoxazol-2-carbonil)-butil]-2-isopropil-amino-3-tiofen-2-il-propionamida,
(R)-N-[1-(benzotiazol-2-carbonil)-butil]-3-fenilmetano-sulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-isopropil-amino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-[(2-metoxi-etil)-tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-ciclohexil-amino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-dimetil-amino-3-fenilmetanosulfonil-propionamida,
(1S)-N-[1-(benzooxazol-2-carbonil)-butil]-2-(S)-fluoro-4-fenil-butiramida,
ácido 2,2-difluoro-5-fenil-pentanoico-[(S)-1-(benzoxazol-2-carbonil)-butil]-amida,
ácido morfolina-4-carboxílico-(S)-1-[(S)-1-(benzooxazol-2-carbonil)-propilcarbamoil]-2-ciclohexil-etil-éster,
ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(oxazolo[4,5-b]piridina-2-carbonil)-propilcarbamoil]-etil-éster,
ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-etil-éster,
ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(5-fenil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoil]-etil-éster,
ácido morfolina-4-carboxílico-(S)-1-[(S)-1 (benzooxazol-2-carbonil-propilcarbamoil]-3-ciclohexil-propil-éster,
ácido 4-[4,4-dimetil-2-(morfolina-4-carboniloxi)-pentanoilamino]-3-oxo-azepan-1-carboxílico-bencil-éster,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-3-ciclopropilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-ciclohexil-amino-3-ciclopropilmetanosulfonil-propionamida,

(R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-cicloheptil-amino-3-ciclopropilmetanosulfonil-propionamida,
(R)-3-fenilmetanosulfonil-N-[(S)-3-fenil-1-(tiazol-2-carbonil)-propil]-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-carbonil)-3-fenil-propil]-3-ciclopropilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-3-ciclopropilmetanosulfonil-N-[1-(5-etil-1,2,4-oxa-diazol-3-carbonil)-propil]-2-(tetrahidropiran-4-il-amino)-propionamida,
(R)-3-fenilmetanosulfonil-N-[1-(3-fenil-1,2,4-oxadiazol-5-carbonil)-propil]-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[1-(3-ciclopropil-1,2,4-oxadiazol-5-carbonil)-propil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-il-amino)-propionamida,
ácido {(R)-1-[1-(benzotiazol-2-il-hidroxi-metil)-butil-carbamoil]-3-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-3-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(S)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-tiofen-2-il-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[1-(benzotiazol-2-il-hidroxi-metil)-butil-carbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido (R)-1-[1-[hidroxil-(3-fenil-1,2,4-oxadiazol-5-il-metil)]-propilcarbamoil]-2-fenilmetanosulfonil-etil)-carbámico-*terc*-butil-éster,
ácido ((R)-2-ciclopropilmetanosulfonil-1-[(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxil-metil]-propilcarbamoil]-etil)-carbámico-*terc*-butil-éster,
ácido {(R)-1-[1-(benzoxazol-2-il-hidroxi-metil)-butil-carbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-fenil-propilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(hidroxil-tiazol-2-il-metil)-3-fenil-propilcarbamoil]-2-fenilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,
ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butilcarbamoil]-2-ciclopropilmetanosulfonil-etil}-carbámico-*terc*-butil-éster,

ácido (R)-1-{1-[hidroxí-(3-fenil-1,2,4-oxadiazol-5-il)-metil]-propilcarbamoil}-2-fenilmetanosulfonil-etil)-carbámico-*terc*-butil-éster,
 ácido ((R)-2-ciclopropilmetanosulfonil-1-[(S)-1-[(5-etil-1,2,4-oxadiazol-3-il)-hidroxí-metil]-propilcarbamoil]-etil)-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[1-(benzoxazol-2-il-hidroxí-metil)-butil-carbamoil]-2-fenilmetanosulfonil-etil)-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[(S)-1-(benzoxazol-2-il-hidroxí-metil)-3-fenil-propilcarbamoil]-2-ciclopropilmetanosulfonil-etil)-carbámico-*terc*-butil-éster,
 ácido {(R)-1-[(S)-1-(hidroxí-tiazol-2-il-metil)-3-fenil-propilcarbamoil]-2-fenilmetanosulfonil-etil)-carbámico-*terc*-butil-éster,
 ácido (R)-2-fenilmetanosulfonil-1-[(S)-1-[(3-ciclopropil-1,2,4-oxadiazol-5-il)-hidroxí-metil]-propilcarbamoil]-etil)-carbámico-*terc*-butil-éster,
 (R)-N-[1-(benzoxazol-2-carbonil)-butil]-2-[ciclopropil-metil-(tetrahidropirán-4-ilmetil)-amino]-3-fenilmetano-sulfonil-propionamida,
 (R)-N-[1-(benzotiazol-2-il-hidroxí-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida,
 (R)-N-[1-(benzotiazol-2-il-hidroxí-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropirán-4-ilamino)-propionamida,
 (R)-N-[1-(benzotiazol-2-il-hidroxí-metil)-butil]-2-iso-propilamino-3-fenilmetanosulfonil-propionamida,
 (R)-N-[1-(benzotiazol-2-il-hidroxí-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida,
 (R)-N-[(S)-1-(benzoxazol-2-il-hidroxí-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropirán-4-ilamino)-propionamida,
 (R)-N-[(S)-1-(benzoxazol-2-il-hidroxí-metil)-butil]-2-(1-metil-piperidín-4-ilamino)-3-fenilmetanosulfonil-propionamida,
 (R)-N-[(S)-1-(benzoxazol-2-il-hidroxí-metil)-butil]-2-(bis-tiofen-2-ilmetil-amino)-3-fenilmetanosulfonil-propionamida,
 (R)-N-[(S)-1-(benzoxazol-2-il-hidroxí-metil)-butil]-2-dibencilamino-3-fenilmetanosulfonil-propionamida,
 (S)-N-[(S)-1-(benzoxazol-2-il-hidroxí-metil)-butil]-2-(tetrahidropirán-4-ilamino)-3-tiofen-2-il-propionamida,
 (S)-N-[(S)-1-(benzoxazol-2-il-hidroxí-metil)-butil]-2-isopropilamino-3-tiofen-2-il-propionamida,
 (R)-N-[(S)-1-(benzoxazol-2-il-hidroxí-metil)-butil]-2-isopropilamino-3-fenilmetanosulfonil-propionamida,

(R)-N-[1-(benzotiazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-3-fenilmetanosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-[2-metoxi-etil]-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-ciclohexilamino-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(benzoxazol-2-il-hidroxi-metil)-butil]-2-dimetilamino-3-fenilmetanosulfonil-propionamida,
N-cianometil-3-ciclohexil-propionamida,
N-cianometil-3-(2-difluorometoxi-fenilmetanosulfonil)-propionamida,
ácido 3-(3-ciclohexil-propionilamino)-2-oxo-5-fenil-pentanoico-tiazol-2-ilamida,
3-ciclohexil-N-(1-formil-3-fenil-propil)-propionamida,
3-(2-difluorometoxi-fenilmetanosulfonil)-N-[(S)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propil]-propionamida,
N-[(S)-1-(benzoxazol-2-carbonil)-propil]-2-(2-ciano-fenilamino)-3-ciclohexil-propionamida,
N-cianometil-3-ciclohexil-2-(4-metoxi-fenoxi)-propionamida,
2-benciloxi-N-cianometil-3-ciclohexil-propionamida,
(R)-N-[(S)-1-(1-benzoxazol-2-il-metanoil)-butil]-2-benciloxi-3-fenilmetanosulfonil-propionamida,
(R)-N-[(S)-1-(1-benzoxazol-2-il-metanoil)-propil]-2-metoximetoxi-3-fenilmetanosulfonil-propionamida,
(S)-N-[(S)-1-(1-benzoxazol-2-il-metanoil)-butil]-2-hidroxi-3-fenil-propionamida,
(R)-N-[(S)-1-(1-benzoxazol-2-il-metanoil)-propil]-3-fenilmetanosulfonil-2-trisopropilsilani-oxi-propionamida,
(R)-N-[(S)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida,
(R)-2-hidroxi-3-fenilmetanosulfonil-N-[(S)-1-(1-pirid-azin-3-il-metanoil)-butil]-propionamida,
ácido (S)-3-((R)-2-hidroxi-3-fenilmetanosulfonil-propanoilamino)-2-oxo-pentanoico-bencilamida,
(R)-N-[(S)-1-(1-benzoxazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida,

(*R*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida, y
(2*R*,5*S*)-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil-metil]-6-etoxi-5-etil-morfolin-3-ona
16 Un compuesto de la reivindicación 15, seleccionado del grupo constituido por
ácido morfolina-4-carboxílico-(*R*)-1-(cianometil-carbamoi)-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster, (Compuesto 31),
ácido morfolina-4-carboxílico-(*R*)-1-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propilcarbamoi]-2-fenilmetano-sulfonil-etil-éster, (Compuesto 11),
ácido morfolina-4-carboxílico-(*R*)-1-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propilcarbamoi]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster, (Compuesto 14),
ácido morfolina-4-carboxílico-(*R*)-1-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propilcarbamoi]-2-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-etil-éster, (Compuesto 15),
ácido pirrolidina-1-carboxílico-(*R*)-1-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propilcarbamoi]-2-fenilmetano-sulfonil-etil-éster, (Compuesto 19),
ácido dimetil-carbámico-(*R*)-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propilcarbamoi]-2-fenilmetanosulfonil-etil-éster, (Compuesto 20),
ácido morfolina-4-carboxílico-(*R*)-1-[(*S*)-1-(1-bencil-carbamoi)-metanoil]-propilcarbamoi]-2-fenilmetano-sulfonil-etil-éster, (Compuesto 25),
ácido morfolina-4-carboxílico-(*S*)-1-[(*S*)-1-(oxazolo[4,5-*b*]piridina-2-carbonil)-propilcarbamoi]-2-fenilmetano-sulfonil-etil-éster;
ácido morfolina-4-carboxílico-(*S*)-1-[(*S*)-1-(5-etil-[1,3,4]oxadiazol-2-carbonil)-propilcarbamoi]-2-fenilmetanosulfonil-etil-éster;
(*R*)-3-[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-*N*-[(*S*)-1-formil-propil]-2-hidroxi-propionamida,
(*R*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-hidroxi-3-fenilmetanosulfonil-propionamida,
ácido (*S*)-3-{3-[2-(1,1-difluoro-metoxi)-fenilmetano-sulfonil]-propanoílamino}-2-oxo-pentanoico-bencilamida,
(*R*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-propil]-2-(2-nitro-fenilamino)-3-fenilmetanosulfonil-propionamida,
(*R*)-*N*-[(*S*)-1-(1-benzotiazol-2-il-metanoil)-butil]-2-(5-nitro-tiazol-2-ilamino)-3-fenilmetanosulfonil-propionamida,
(*R*)-*N*-[(*S*)-1-(benzotiazol-2-carbonil)-butil]-3-fenilmeta-nosulfonil-2-(tetrahidropiran-4-ilamino)-propionamida,

(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-isopropil-amino-3-fenilmetanosulfonil-propionamida,

(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-[(2-metoxi-etil)-(tetrahidropiran-4-il)-amino]-3-fenilmetanosulfonil-propionamida,

(R)-N-[(S)-1-(benzoxazol-2-carbonil)-butil]-2-ciclohexil-amino-3-fenilmetanosulfonil-propionamida,

ácido morfolina-4-carboxílico-(S)-2-ciclohexil-1-[(S)-1-(1-oxazolo[4,5-b]piridina-2-carbonil)propilcarbamoil]-etil-éster;

ácido (S)-3-((R)-2-hidroxi-3-fenilmetanosulfonil-propanoilamino)-2-oxo-pentanoico-bencilamida,

(R)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-propil-2-

[2-(1,1-difluoro-metoxi)-fenilmetanosulfonil]-2-hidroxi-propionamida

17 Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1 en combinación con un excipiente farmacéuticamente aceptable

18 Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 2, en combinación con un excipiente farmacéuticamente aceptable

19 Un método para tratar una enfermedad en un animal, en el cual la inhibición de la Catepsina S puede prevenir, inhibir o mejorar la patología y/o la sintomatología de la enfermedad, método que comprende administrar al animal una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1 o la reivindicación 2

20 El uso de un compuesto de la reivindicación 1 o la reivindicación 2 en la fabricación de un medicamento para tratar una enfermedad en un animal en el cual la actividad de la Catepsina S contribuye a la patología y/o sintomatología de la enfermedad

RESUMEN

La presente invención se refiere a nuevos inhibidores selectivos de la catepsina S, sus sales y *N*-óxidos farmacéuticamente aceptables, sus usos como agentes terapéuticos y los métodos para su fabricación

NUEVOS COMPUESTOS Y COMPOSICIONES

PCT REQUEST

US2001/0082

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0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	US2001/0082
I	Title of invention	NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	AXYS PHARMACEUTICALS, INC.
II-5	Address	180 Kimball Way South San Francisco, CA 94080 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	650-866-6636
II-9	Facsimile No.	650-866-6651
II-10	e-mail	george.wang@aventis.com
III-1	Applicant and/or Inventor	
III-1-1	This person is	applicant only
III-1-2	Applicant for	all designated States except US
III-1-4	Name	AVENTIS PHARMACEUTICALS INC.
III-1-5	Address	300 Somerset Corporate Blvd. Bridgewater, NJ 08807-2854 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

PCT REQUEST

2/6

US2001/0082

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III-2	Applicant and/or inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	GRAUPE, Michael
III-2-5	Address	1131 Banyan Way Pacifica, CA 94044 United States of America
III-2-6	State of nationality	AT
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	LI, Jiayao
III-3-5	Address	888 Foster City Blvd. Foster City, CA 94404 United States of America
III-3-6	State of nationality	CN
III-3-7	State of residence	US
III-4	Applicant and/or inventor	
III-4-1	This person is	applicant only
III-4-2	Applicant for	all designated States except US
III-4-4	Name (LAST, First)	LINK, John, O.
III-4-5	Address	12 Prospect Ave. San Francisco, CA 94110 United States of America
III-4-6	State of nationality	US
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	ZIPFEL, Sheila
III-5-5	Address	c/o Ayys Pharmaceuticals Inc. 180 Kimball Way South San Francisco, CA 94080 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US

PCT REQUEST

3/8

US2001/0082

Original (for SUBMISSION) - printed on 03 06.2002 04 57 45 PM

III-8	Applicant and/or inventor	
III-8-1	This person is:	applicant only
III-8-2	Applicant for	all designated States except US
III-8-4	Name (LAST, First)	TIMM, Andreas, P.
III-8-5	Address	43 Ford Avenue Apartment 4 Morristown, NJ 07960 United States of America
III-8-6	State of nationality	DE
III-8-7	State of residence	US
III-7	Applicant and/or inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	ALDOUS, David, J.
III-7-5	Address	31 Dunbridge Lane Gillette, NJ 07933 United States of America
III-7-6	State of nationality	US
III-7-7	State of residence	US
III-8	Applicant and/or inventor	
III-8-1	This person is	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	THURAIRATNAM, Sukanthini
III-8-5	Address.	6 Smoke Rise Lane Bedminster, NJ 07921 United States of America
III-8-6	State of nationality	LK
III-8-7	State of residence	US
IV-1	Agent or common representative, or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as	agent
IV-1-1	Name (LAST, First)	WANG, George, G.
IV-1-2	Address.	Aventis Pharmaceuticals Inc. Route 202-206 PO Box 6800 Bridgewater, NJ 08807-0800 United States of America
IV-1-3	Telephone No	908-231-2843
IV-1-4	Facsimile No	908-231-2626
IV-1-5	e-mail	george.wang@aventis.com
IV-1-5	Agent's registration No.	41,419

247

PCT REQUEST

4/6

US2001/0082

348

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IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	BARNEY, Charlotte, L.(35,060); BOLSCAK, James, W.(39,912); COPPOLA, William, C.(41,686); DAHLING, Gerald, V.(29,632); DARKES, Paul, R.(33,862); DOLAN, Peter, L.(46,307); DUBBERLEY, Aaron, F.(41,001); GUPTA, Balaram(40,009); KIRK, Joseph, P.(36,844); KNIGHT, Julie, Anne(48,867); KRUPEN, Karen, I.(34,647); KURYS, Barbara, E.(34,650); LIN, Jiang(51,065); MARTIN, Lawrence, L.(46,902); MOON, Carolyn, D.(33,022); NELLIGAN, Mark, C.(36,389); NEWMAN, Irving(22,638); OEHLER, Ross, J.(33,270); ORT, Ronald, G.(26,969); PARKER, Raymond, S. III(34,893); SCHMELZER, Michael(43,093); STRUPCZEWSKI, Joseph(50,903); WALSH, Andrea(34,988); WILLE, Louis, J.(32,954)
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Prot col and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and f the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

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5/6

US2001/0082

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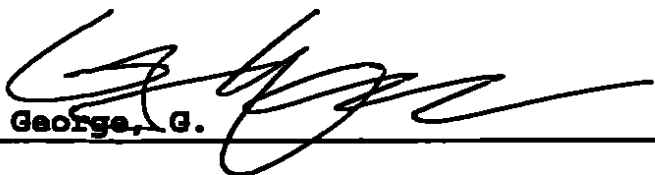
V-5	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4 9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	01 June 2001 (01.06.2001)	
VI-1-2	Number	60/295,301	
VI-1-3	Country	US	
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	-
IX-2	Description	152	-
IX-3	Claims	43	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	202	

PCT REQUEST

6/6

US2001/0082

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	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Unexecuted Declaration	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	WANG, George, G.	

FOR RECEIVING OFFICE USE ONLY

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

FOR INTERNATIONAL BUREAU USE ONLY

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

US2001/0082

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

0	For receiving Office use only			
0-1	International Application No			
0-2	Date stamp of the receiving Office			
0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet			
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2002)		
0-9	Applicant's or agent's file reference	US2001/0082		
2	Applicant	AXYS PHARMACEUTICALS, INC., et al.		
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee T	⇒	240	
12-2-1	Search fee S	⇒	866	
12-2-2	International search to be carried out by	EP		
12-3	International fee			
	Basic fee			
	(first 30 sheets) b1	407		
12-4	Remaining sheets	172		
12-5	Additional amount (X)	9		
12-6	Total additional amount b2	1,548		
12-7	b1 + b2 = B	1,955		
12-8	Designation fees			
	Number of designations contained in international application	93		
12-9	Number of designation fees payable (maximum 5)	5		
12-10	Amount of designation fee (X)	88		
12-11	Total designation fees D	440		
12-12	PCT-EASY fee reduction R	-125		
12-13	Total international fee (B+D-R) I	⇒	2,270	
12-14	Fee for priority document			
	Number of priority documents requested	1		
12-15	Fee per document (X)	15		
12-16	Total priority document fee P	⇒	15	
12-17	TOTAL FEES PAYABLE (T+S++P)	⇒	3,391	
12-19	Mode of payment	authorization to charge deposit account		
12-20	Deposit account instructions			
	The receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above	✓		

PCT (ANNEX - FEE CALCULATION SHEET)

US2001/0082

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12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	✓
12-20-3	Authorization to charge the fee for priority document	✓
12-21	Deposit account No.	18-1982
12-22	Date	03 June 2002 (03.06.2002)
12-23	Name and signature	WANG, George, G. 

VALIDATION LOG AND REMARKS

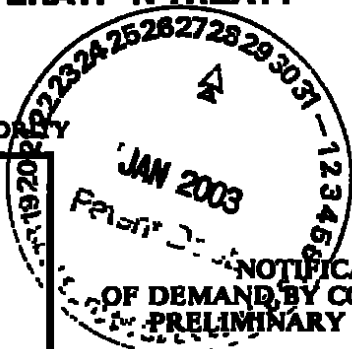
13-2-4	Validation messages Priority	Yellow! Priority 1: The twelve-month time limit for claiming priority would appear to have expired. Please verify.
13-2-7	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
		Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

PATENT COOPERATION TREATY

51-253

3-F/✓
353

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



PCT

To

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

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

21-01-2003

Applicant's or agent's file reference
US2001/0082

IMPORTANT NOTIFICATION

International application No.

PCT/US 02/ 17411

International filing date (day/month/year)

03/06/2002

Priority date (day/month/year)

01/06/2001

Applicant

AXYS 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.

31/12/2002

2 This date of receipt is:

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

3 ☐ ATTENTION: That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the PCT Applicant's Guide, Volume II.

☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on.

No ACTION DUE

DUE DATE
DKTD BY
ATTY

file

Jan 1/28/03
G. WANG

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

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx 523656 epmu d
Fax. (+49-89) 2399-4465

Authorized officer

CHURCHER G

Tel. (+49-89) 2399-2545



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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

Applicant's or agent's file reference US2001/0082	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US 02/ 17411	International filing date (day/month/year) 03/06/2002	Priority date (day/month/year) 01/06/2001
International Patent Classification (IPC) or national classification and IPC C07C317/46		
Applicant AXYS PHARMACEUTICALS, INC.		

- 1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36
- 2 This REPORT consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70 16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

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

Date of submission of the demand 31/12/2002	Date of completion of this report 18/03/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel (+49-89) 2399-0, Tx 523656 epmu d Fax (+49-89) 2399-4465	Authorized officer VERHULST W Tel (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)



I. Basis of the report

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

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66 1(e) PCT), see also international search report).

V. Reasoned statement under Rule 66 2(a)(II) with regard to novelty, inventive step or industrial applicability

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

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

TRATADO DE COOPERACION EN PATENTES

PCT

REPORTE DEL EXAMEN INTERNACIONAL PRELIMINAR

(Artículo 36 y Norma 70 PCT)

(Reporte fundamentado conforme a la Notificación del Presidente de la Oficina Europea de Patentes publicado en el OJ11/2001)

Referencia del solicitante o abogado. US2001/0082

PROCEDIMIENTO ADICIONAL: Ver Comunicación sobre el envío del reporte de examen internacional provisional (Formato PCT/IPEA/416)

No. de referencia internacional: PCT/US 02/17411

Fecha de solicitud internacional: 03/06/2002

Fecha de prioridad: 01/06/2001

Clasificación Internacional de Patentes (IPC) o Clasificación Nacional e IPC: C07C 317/46

Solicitante: AXYS PHARMACEUTICALS, INC.

1. La autoridad encargada del examen internacional provisional elaboró el reporte del examen internacional provisional y lo envió al solicitante de conformidad con el Artículo 36.

2. Este REPORTE comprende en total 2 hojas incluyendo esta hoja de cubierta

— Además se adjuntan a este reporte ANEXOS; se trata de hojas con descripciones, reivindicaciones y/o dibujos que fueron modificados y son fundamento de este reporte, y/u hojas con correcciones efectuadas por esta autoridad (ver Norma 70.16 y Sección 607 de las Pautas Administrativas del PCT).

Estos Anexos comprenden en total hojas.

3. Este reporte contiene informaciones y las correspondientes páginas respecto a los siguientes puntos:

I X Base del reporte

II Prioridad

III X Ninguna elaboración de un reporte sobre la novedad, la actividad inventiva y la aplicabilidad industrial

IV Falta de unidad de la invención

V X Verificación fundamentada conforme el artículo 35(2) respecto a la novedad, la actividad inventiva y la

aplicabilidad industrial; documentos y explicaciones
para apoyar dicha verificación

- VI _ Determinados documentos citados
- VII _ Determinadas deficiencias de la solicitud internacional
- VIII _ Determinadas observaciones a la solicitud internacional

Fecha de entrega de la solicitud:

31/12/2002

Fecha de elaboración de este reporte:

18/03/2003

Nombre y dirección postal de la autoridad encargada del examen
internacional de provisional:

Oficina Europea de Patentes
D-80298 Munich

Funcionario autorizado:

VERHULST W

REPORTE DEL EXAMEN INTERNACIONAL PROVISIONAL

No. de referencia internacional PCT/US 02/17411

I. Base del reporte

La base del examen preliminar internacional es la solicitud tal cual ella fue presentada originalmente.

III. Ninguna elaboración de opinión respecto a novedad, actividad inventiva y aplicabilidad industrial

La cuestión de si la invención reivindicada parece ser nueva, si parece involucrar una actividad inventiva o si parece ser aplicable industrialmente no ha sido el sujeto del examen preliminar internacional respecto a las reivindicaciones que no han sido sometidas a búsqueda (Artículo 17(2)(a) y Norma 66.1(e) PCT); ver también el Reporte de Búsqueda Internacional.

V. Verificación fundamentada conforme el artículo 35(2) respecto a la novedad, la actividad inventiva y la aplicabilidad industrial

Se señala lo siguiente en la medida en que se llevó a cabo el examen preliminar internacional (ver punto III arriba):

A la luz de los documentos citados en el reporte de búsqueda internacional, se considera que la invención tal cual ella está definida en las reivindicaciones independientes que han sido sujeto de un reporte de búsqueda internacional, cumple con los criterios mencionados en el Artículo 33(1) PCT, es decir parece ser novedosa, involucrar actividad inventiva y ser industrialmente aplicable.

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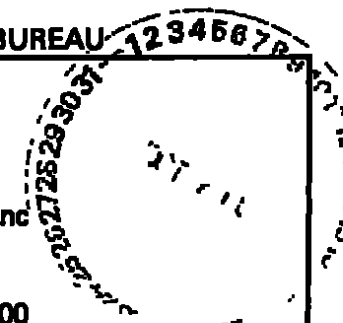
NOTIFICATION OF THE RECORDING
OF A CHANGE

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

From the INTERNATIONAL BUREAU

To

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



Date of mailing (day/month/year) 23 September 2002 (23 09 02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference US2001/0082	
International application No. PCT/US02/17411	International filing date (day/month/year) 03 June 2002 (03 06 02)

1. The following indications appeared on record concerning
☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address TIMM, Andreas, P 97 Bonney Court Bridgewater, NJ 08807 United States of America	State of Nationality DE	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning
☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address TIMM, Andreas, P 97 Bonney Court Bridgewater, NJ 08807 United States of America	State of Nationality DE	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary
 Please note applicant's new status: applicant and inventor for US only *file USA2001/0082-WO*

NO ACTION DUE

4. A copy of this notification has been sent to
☒ the receiving Office
☒ the International Searching Authority
☐ the International Preliminary Examining Authority

DUE DATE
DKTD BY
ATTY

☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other *G. Wang*

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Céline Faust (Fax 338-8995) Telephone No. (41-22) 338.83 38
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PATENT COOPERATION TREATY

PCT

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

From the INTERNATIONAL BUREAU 3456789

To

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

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360
OCT 21 2002
12 23 24 25 26 27 28 29 30 31

Date of mailing (day/month/year) 23 September 2002 (23 09 02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference US2001/0082	
International application No. PCT/US02/17411	International filing date (day/month/year) 03 June 2002 (03 06 02)

1. The following indications appeared on record concerning		
☒ the applicant	☒ the inventor	☐ the agent ☐ the common representative
Name and Address LINK, John, O 12 Prospect Ave San Francisco, CA 94110 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning		
☐ the person	☐ the name	☐ the address ☐ the nationality ☐ the residence
Name and Address LINK, John, O 12 Prospect Ave San Francisco, CA 94110 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary Please note applicant's new status: <u>applicant and inventor for US only.</u> <u>file USA2001/0082-WO</u>		
4. A copy of this notification has been sent to		
☒ the receiving Office	DUE DATE DKTD BY ATTY	☐ the designated Offices concerned
☒ the International Searching Authority		☐ the elected Office concerned
☐ the International Preliminary Examining Authority		☐ other

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Céline Faust (Fax 338-8995)
Facsimile No. (41-22) 740 14.25	Telephone No (41-22) 338.83.38

PATENT COOPERATION TREATY

COMPUTER ENTERED

PCT W 10/8/02 From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING OF A CHANGE

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

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

Date of mailing (day/month/year) 19 September 2002 (19 09 02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference US2001/0082	International filing date (day/month/year) 03 June 2002 (03 06 02)
International application No. PCT/US02/17411	

1. The following indications appeared on record concerning

☒ the applicant
 ☒ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address THURAIRATNAM, Sukanthini 6 Smoke Rise Lane Bedminster, NJ 07921 United States of America	State of Nationality LK	State of Residence US
Telephone No.		
Facsimile No.		
Teleprinter No.		

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

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

Name and Address THURAIRATNAM, Sukanthini 6 Smoke Rise Lane Bedminster, NJ 07921 United States of America	State of Nationality GB	State of Residence US
Telephone No.		
Facsimile No.		
Teleprinter No.		

3. Further observations, if necessary

4. A copy of this notification has been sent to

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

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740 14.35	Authorized officer Marie-Josée DEVILLARD (Fax 338-8995) Telephone No (41 22) 338.83.38
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PATENT COOPERATION TREATY

PCT/US02/17411

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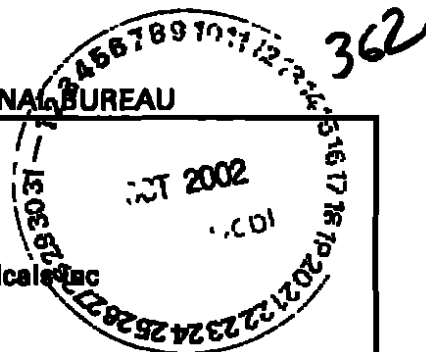
NOTIFICATION OF THE RECORDING OF A CHANGE

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

From the INTERNATIONAL BUREAU

To

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



Date of mailing (day/month/year) 19 September 2002 (19 09 02)	
Applicant's or agent's file reference US2001/0082	IMPORTANT NOTIFICATION
International application No. PCT/US02/17411	International filing date (day/month/year) 03 June 2002 (03 06 02)

1. The following indications appeared on record concerning ☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative		
Name and Address TIMM, Andreas, P. 43 Ford Avenue Apartment 4 Morristown, NJ 07960 United States of America	State of Nationality DE	State of Residence US
Telephone No.		
Facsimile No.		
Teleprinter No.		
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning ☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence		
Name and Address TIMM, Andreas, P 97 Bonney Court Bridgewater, NJ 08807 United States of America	State of Nationality DE	State of Residence US
Telephone No		
Facsimile No.		
Teleprinter No.		
3. Further observations, if necessary		
4. A copy of this notification has been sent to ☒ the receiving Office ☒ the International Searching Authority ☐ the International Preliminary Examining Authority ☐ the designated Offices concerned ☐ the elected Offices concerned ☐ other		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No (41-22) 740.14.35	Authorized officer Marie-José DEVILLARD (Fax 338-8995) Telephone No (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

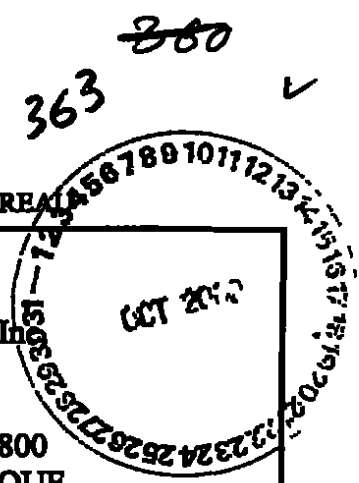
NOTIFICATION RELATING TO DECLARATION MADE UNDER PCT RULE 4 17

(PCT Rules 26ter 2(b), 47 1(a-ter) and 48 2(a)(x)
and Administrative Instructions, Section 419)

From the INTERNATIONAL BUREAU

To.

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



Date of mailing (day/month/year)
19 September 2002 (19 09 02)

Applicant's or agent's file reference
US2001/0082

IMPORTANT NOTIFICATION

International application No.
PCT/US02/17411

International filing date (day/month/year)
03 June 2002 (03 06 02)

Applicant
AXYS PHARMACEUTICALS, INC.

- 1 The applicant is hereby notified of the following regarding the declaration indicated below in respect of (name(s) indicated in the declaration) _____
 - (i) ☐ declaration as to the identity of the inventor (Rules 4 17(i) and 51bis 1(a)(i) and Section 211)
 - (ii) ☐ declaration as to the applicant's entitlement, as at the international filing date, to apply for or be granted a patent (Rules 4 17(ii) and 51bis 1(a)(ii) and Section 212)
 - (iii) ☐ declaration as to the applicant's entitlement, as at the international filing date, to claim priority of the earlier application (Rules 4.17(iii) and 51bis 1(a)(iii) and Section 213)
 - (iv) ☒ declaration of inventorship (for the purposes of the designation of the United States of America) (Rules 4 17(iv) and 51bis 1(a)(iv) and Section 214)
 - (v) ☐ declaration as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4 17(v) and 51bis 1(a)(v) and Section 215)
- 2 ☒ Addition or correction of the declaration within the time limit under Rule 26ter 1

 The added or corrected declaration was received on (date), 13 September 2002 (13 09 2002), which was received within the time limit under Rule 26ter 1

 Any declaration referred to under items 1(i) to (iv) whether or not the declaration complies with Rule 4 17, will be communicated to the designated Offices concerned pursuant to Rule 47 1(a-ter) and any declaration referred to under item 1(v) will be published as part of the pamphlet pursuant to Rule 48.2(a)(x).
- 3 ☐ Failure to add or correct the declaration within the time limit under Rule 26ter 1

 The declaration, was received on (date) _____, which was after the expiration of the time limit under Rule 26ter 1, therefore, any such declaration referred to under items 1(i) to (iv) will not be communicated to the designated Offices concerned, any such declaration referred to under item 1(v) will not be published as part of the pamphlet, and any signed declaration referred to under item 1(iv) is attached. Such declaration should be submitted by the applicant directly to the designated Offices concerned.
- 4 The applicant's attention is drawn to Rule 51bis 2 which provides that the designated Office shall not, unless it may reasonably doubt the veracity of the declaration concerned, require any document or evidence relating to the subject matter of any declaration complying with Rule 4.17(i) to (iv) which is contained in the request or submitted to the International Bureau or directly to the designated Office. Note, however, that Rule 51bis 2 may not apply in respect of certain States. For further information, see Notes to the request form, Box No. VIII
- 5 A copy of this notification is being sent to the receiving Office and the International Searching Authority

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

Authorized officer
Marie-José DEVILLARD (Fax 338-8995)

Facsimile No. (41-22) 740 14 35

Telephone No. (41-22) 338.83 38

From the INTERNATIONAL BUREAU

PCT

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

To

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

(PCT Rule 47 1(c), first sentence)

NO ACTION DUE comments

Date of mailing(day/month/year) 12 December 2002 (12 12 02)			
Applicant's or agent's file reference US2001/0082		IMPORTANT NOTICE	
International application No. PCT/US02/017411	ATTY	International filing date(day/month/year) 06 June 2002 (03 06 02)	Priority date(day/month/year) 01 June 2001 (01 06 01)
Applicant AXYS PHARMACEUTICALS, INC , et al			

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

KP, KR, US

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

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

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

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49 1(a-bis)).

- 3 Enclosed with this notice is a copy of the international application as published by the International Bureau on 12 December 2002 (12 12 02) under No. WO 02/098850

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

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

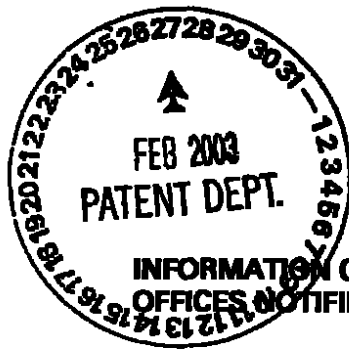
For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at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

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

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Judith Zahra
Facsimile No (41-22) 740 14.35	Telephone No.(41-22) 338.91 11

✓ 365

PATENT COOPERATION TREATY



PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To

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

Date of mailing (day/month/year) 12 February 2003 (12 02 03)		
Applicant's or agent's file reference US2001/0082		IMPORTANT INFORMATION
International application No. PCT/US02/17411	International filing date (day/month/year) 03 June 2002 (03 06 02)	
Priority date (day/month/year) 01 June 2001 (01 06 01)		
Applicant AXYS PHARMACEUTICALS, INC et al		

1 The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election
EP AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
National AU,BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK,US

2 The following Offices have waived the requirement for the notification of their election, the notification will be sent to them by the International Bureau only upon their request
AP GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
EA AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
OA BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National AE,AG,AL,AM,AT,AZ,BA,BB,BR,BY,BZ,CH,CO,CR,CU,CZ,DK,DM,DZ,EC,EE,ES,FI,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MW,MX,MZ,NZ,OM,PH,PT,SD,SE,SG,SI,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZM,ZW

3 The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the International preliminary examination report (Article 38(3)(b) and Rule 74.1)

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

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

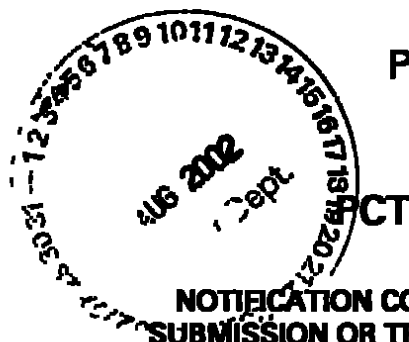
NO ACTION DUE file USA2001/0082-wo

DUE DATE 2/27/03

DKTD BY ATTY

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: <u>G. WANG</u> Serge RUBY (Fax 338-8995)
Facsimile No. (41-22) 338 89 95	Telephone No. (41-22) 338 8154

PATENT COOPERATION TREATY



NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To

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

Date of mailing (day/month/year) 29 July 2002 (29 07 02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference US2001/0082 USAV2001/0082-WO	
International application No PCT/US02/17411	
International filing date (day/month/year) 03 June 2002 (03 06 02) ✓	
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 01 June 2001 (01 06 01) ✓
Applicant AXYS PHARMACEUTICALS, INC et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17 1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17 1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17 1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
01 June 2001 (01 06 01)	60/295,301	US	18 July 2002 (18 07 02)

No ACTION DUE file

DUE DATE —

DKTD BY J. 8/8/02

ATTY G. WANG

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer <u>G. WANG</u> David BOUVERET (338-8995)
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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

Firma Responsable

Edual Nacano
28-11-2003
Fecha



2020
Bogotá, D.C.,

368

Doctor:
GUSTAVO HOLLMANN RESTREPO
Apoderado
AXYS PHARMACEUTICALS, IN. Y AVENTIS PHARMACEUTICALS, INC.

Oficio N° 11392

ASUNTO:	Radicación N°	03-104808
	Solicitud Internacional	PCT/US2002/17411
	Fecha inicio fase nacional	01/01/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).
- ☐ La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.
- ☐ La fecha de prioridad relacionada en el petitorio de la solicitud nacional difiere de la relacionada en la solicitud internacional.

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

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


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

El anterior requerimiento fue notificado por fijación en lista de fecha, 26 DIC 2020.