Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

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54. **TÍTULO** Inhibidores de Peptido - Reformulada

51. **CLASIFICACIÓN INTERNACIONAL** A61 K 31/19

71. **SOLICITANTE** SmithKLine Beecham Corporation

DOMICILIO One Franklyne plaza, philadelphina PA 19103, E.U.A

74. **APODERADO** Carlos M Olarte

22. **BOGOTÁ, D. C.,** 01 septiembre, 2003

2020

(FORMA P-10)

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Industria y Comercio
SUPERINTENDENCIA

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Fecha (AMD) 2003-09-01 16 46 14
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE

[X]	Patente de Invencion	[ ]	Patente de Modelo de Utilidad
[ ]	Capítulo I	[X]	Capitulo II

(2) SOLICITANTE (71)

Nombre SMITHKLINE BEECHAM CORPORATION
Dirección One Franklin Plaza, Philadelphia, PA 19103 E U A
Nacionalidad o Domicilio ESTADOUNIDENSE
Lugar de Constitución Philadelphia
Teléfono Fax
E Mail

IDENTIFICACION
C C [ ] NIT [ ]
C E [ ] Otro [ ]
Cual
Número

(3) REPRESENTANTE O APODERADO

Nombre CARLOS R OLARTE
Dirección World Trade Center Torre C Calle 100 No 8A 55 Piso 10
Teléfono 638 6200 Fax 638-6201
E Mail office@olarteraisbeck com

IDENTIFICACION
C C [X] NIT [ ]
C E [ ] Otro [ ]
Cual
Numero 79 782 747 Bta TP 74 295

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Nacionalidad o Domicilio (1) CHINA (2) ESTADOUNIDENSE, (3) KOREANA (4) ESTADOUNIDENSE

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US	Marzo 1 2001	60/272 570

(9) Comprobante de pago No 61 685 **Fecha Septiembre 1, 2003**

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

(10) **ANEXOS**

2

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional (Resumen descripción reivindicaciones dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen descripción reivindicaciones dibujos)
- [X] 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 12 x 12
- [ ] De ser el caso información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso modificaciones efectuadas a la solicitud internacional
- [X] Otros Busqueda Internacional

(11) **FIGURA CARATERISTICA**

(12) Solicito la concesión de la patente

NOMBRE CARLOS R. OLARTE

FIRMA

C C 79 782 747 de Btá T P 74295

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

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NIT 800176089-2

RECIBO OFICIAL DE CAJA 03 - 61 685

FECHA SEPTIEMBRE 1 DE 2003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	14578066	29/08/2003	3 870 000 00

***** C O N C E P T O *****

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

RESPONSABLE _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SMITHKLINE BEECHAM CORPORATION

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español certificando que Peter John Giddings es apoderado de Smithkline Beecham Corporation, firmado por James Kerr Milligan.

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   - Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229470
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA COINCIDE CON EL FOTOCOPIA QUE HE TENIDO A LA VISTA

28 AGO 2003

Marlen Neira C

BOGOTA, D.C. - MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
NOTARIA ONCE (11) Español - Ingles
Resolución No. 2117 del 7 Oct 1987

Yo, el infrascrito, **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

C E R T I F I C O:

QUE es auténtica la firma "P. Giddings" suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la corporación denominada **"SMITHKLINE BEECHAM CORPORATION"**, corporación legalmente constituída y existente de acuerdo con las leyes del Estado de Pensilvania, Estados Unidos de América, con domicilio social en 1, Franklin Plaza, Philadelphia, Pensilvania 19101, Estados Unidos de América;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debida y suficientemente autorizado para firmar documentos de esta clase, en virtud del Poder otorgado en su favor por la referida Sociedad fechado el 11 de julio de 2002, copia del cual he tenido a la vista.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy rece de agosto del año dos mil tres.

SCRIVENER NOTARIES

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.

28 AGO 2003

BOGOTA, D.C. - COLOMBIA
NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

DE PINNA
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APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par **James Kerr Milligan**

3. Acting in the capacity of / agissant en qualité de **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

5. at London/à Londres — Certified/Attesté

6. the/le **14 August 2003**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs / par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G229470**

9. Stamp: / timbre:

10. Signature: **J. Garbrah**

FOREIGN AND COMMONWEALTH OFFICE LONDON

NOTARIO CHICÓ DE ESTE DOCUMENTO COPIA QUE ESTA COPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
28 AGO 2003
D.C. - COLOMBIA

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
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www.olarteraisbeck.com

Power of Attorney

The undersigned,

SmithKline Beecham Corporation

domiciled in

One Franklin Plaza, P O Box 7929, Philadelphia, PA 19101, United States of America

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

SmithKline Beecham Corporation

domiciliado en

One Franklin Plaza, P O Box 7929, Philadelphia, PA 19101, United States of America

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____

Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City,Country/Ciudad,País: Brentford, Middlesex, England

NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL DOCUMENTO QUE TENGO A LA VISTA.

28-AGO 2003

BOGOTA, D.C. - COLOMBIA
NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

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(71) Applicant *(for all designated States except US)*: SMITH KLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: XIANG, JIA-NING [US/US]; 707 DeSoto Drive, Palo Alto, CA 94303 (US). CHRISTENSEN, Siegfried, B. [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). LEE, Jinhwa [KR/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). MERCER, Daniel, J. [US/US]; 1250 South Collegeville Road, Collegeville, PA 19526 (US).

(74) Agents: SIMON, Soma, G. et al.; SMITHKLINE BEECHAM CORPORATION, Coporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (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, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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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.

WO 02/070541 A2

(54) Title: PEPTIDE DEFORMYLASE INHIBITORS

(57) Abstract: Nobel PDF inhibitors and novel methods for their use are provided.

PEPTIDE DEFORMYLASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to the use of novel antibacterial compounds, and pharmaceutical compositions containing these compounds as peptide deformylase inhibitors.

BACKGROUND OF THE INVENTION

Bacterial initiator methionyl tRNA is modified by methionyl tRNA formyltransferase (FMT) to produce formyl-methionyl tRNA. The formyl methionine (f-met) is then incorporated at the N-termini of newly synthesized polypeptides. Polypeptide deformylase (PDF or Def) then deformylates primary translation products to produce N-methionyl polypeptides. Most intracellular proteins are further processed by methionine amino peptidase (MAP) to yield the mature peptide and free methionine, which is recycled. PDF and MAP are both essential for bacterial growth, and PDF is required for MAP activity. This series of reactions is referred to as the methionine cycle (Figure 1).

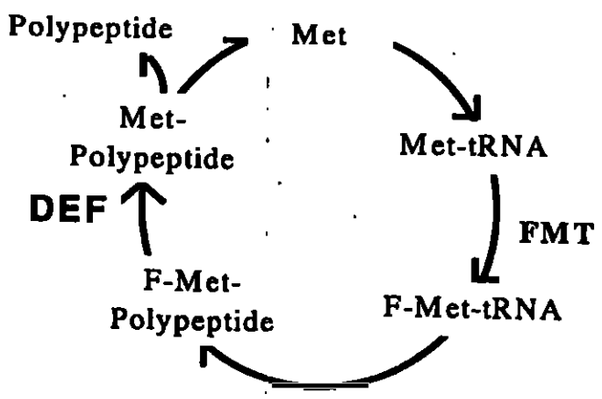


Figure 1. The methionine cycle.

To date, polypeptide deformylase homologous genes have been found in bacteria, in chloroplast-containing plants, in mice and in human. The plant proteins are nuclear encoded but appear to carry a chloroplast localisation signal. This is consistent with the observation that chloroplast RNA and protein synthesis processes are highly similar to those of eubacteria. While there is limited information on protein expression of mammalian PDF gene homologs (Bayer Aktiengesellschaft, Pat. WO2001/42431), no functional role for such proteins has been demonstrated to date (Meinnel, T., Parasitology Today 16(4), 165-168, 2000).

Polypeptide deformylase is found in all eubacteria for which high coverage genomic sequence information is available. Sequence diversity among PDF homologs is high, with as little as 20% identity between distantly related sequences. However, conservation around the active site is very high, with several completely conserved residues, including one cysteine and two histidines which are required to coordinate the active site metal (Meinnel, T. et al., J. Mol. Biol. 267, 749-761, 1997).

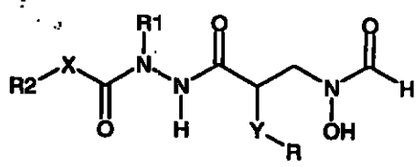
PDF is recognized to be an attractive antibacterial target, as this enzyme has been demonstrated to be essential for bacterial growth in vitro (Mazel, D. et al., EMBO J. 13 (4), 914-923, 1994), is not believed to be involved in eukaryotic protein synthesis (Rajagopalan et al., J. Am. Chem. Soc. 119, 12418-12419, 1997), and is universally conserved in prokaryotes (Kozak, M., Microbiol. Rev. 47, 1-45, 1983). Therefore PDF inhibitors can potentially serve as broad spectrum antibacterial agents.

SUMMARY OF THE INVENTION

The present invention involves novel anti-bacterial compounds represented by Formula (1) hereinbelow and their use as PDF inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect of the present invention, there is provided a compound of formula (1):



(1) X =.O, NR_3 or a bond;

Y = O, CH_2 or a bond

wherein:

R represents:

C_{2-6} alkyl (optionally substituted by alkoxy, halogen, or C_{1-3} alkylsulfanyl), C_{2-6} alkenyl (optionally substituted by alkoxy, halogen, or C_{1-3} alkylsulfanyl), C_{2-6} alkynyl (optionally substituted by alkoxy, halogen, or C_{1-3} alkylsulfanyl), $(CH_2)_n$—C_{3-6} carbocycle (optionally substituted by alkoxy, halogen, or C_{1-3} alkylsulfanyl), $(CH_2)_n$—R4 {where R4 is phenyl, furan, benzofuran, thiophene, benzothiophene, tetrahydrofuran, tetrahydropyran, dioxane, 1,4-benzodioxane or benzo[1,3]dioxole; R4 is optionally substituted by one or more Cl, Br, I, C_{1-3} alkyl (optionally substituted by one to three F) or C_{1-2} alkoxy (optionally substituted by one to three F)};

R1 represents:

hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy, halogen, amino, guanidino, phenyl, pyridyl, pyrrolyl, indolyl, imidazolyl, furanyl, benzofuranyl, piperidinyl, morpholinyl, quinolinyl, piperazinyl or dimethylaminophenyl) or $(CH_2)_n$—C_{3-7} carbocycle;

R2 represents:

hydrogen (provided that X is not O), C_{1-3} substituted alkyl, C_{2-3} substituted alkenyl, C_{2-3} substituted alkynyl, $(CH_2)_n$—C_{3-6} substituted carbocycle, aryl, heteroaryl, heterocyclic, carboxy (provided that X is not NR3 or O) or aminocarbonyl (provided that X is not NR3 or O);

R3 represents:

hydrogen, C_{1-3} substituted alkyl, phenyl, or may be taken together with R2 and the nitrogen atom to which they are attached to form an optionally

substituted heterocyclic ring which is optionally fused to an aryl, a heteroaryl, or a second heterocyclic ring;

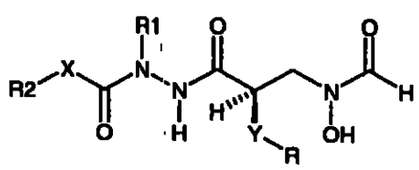
X represents O, NR3 or a covalent bond;

Y represents O, CH_2 or a covalent bond;

n = 0-2;

or a salt, solvate, or physiologically functional derivative thereof.

In this invention the most preferred R1 group is hydrogen. Furthermore, in this invention the most preferred absolute configuration of compounds of the formula (1) is indicated below:



X = O, NR_3 or a bond;

Y = O, CH_2 or a bond

In a second aspect of the present invention, there is provided a compound of Formula (1) wherein X = O, and R, R1, R2, R3, R4, Y and n are as defined above; or a salt, solvate, or physiologically functional derivative thereof.

In a third aspect of the present invention, there is provided a compound of Formula (1) wherein X = NR3, and R, R1, R2, R3, R4, Y and n are as defined above; or a salt, solvate, or physiologically functional derivative thereof.

In a fourth aspect of the present invention, there is provided a compound of Formula (1) wherein X is a covalent bond, and R, R1, R2, R3, R4, Y and n are as defined above; or a salt, solvate, or physiologically functional derivative thereof.

As used herein, the term "alkyl" refers to a straight or branched chain saturated hydrocarbon radical. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like.

As used herein, the term "substituted alkyl" refers to a straight or branched chain saturated hydrocarbon radical, optionally substituted with substituents selected from the group that includes C_{1-3} alkyl (optionally substituted by one to three fluorines), C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-2} alkoxy (optionally substituted by one to three fluorines), sulfanyl, sulfinyl, sulfonyl, oxo, hydroxy, mercapto, amino, guanidino, carboxy, aminocarbonyl, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, aminosulfonyl, sulfonylamino, carboxyamide, ureido, nitro, cyano and halogen, multiple degrees of substitution being allowed.

As used herein, the term "alkenyl" refers to a straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond. Examples of "alkenyl" as used herein include, but are not limited to, ethenyl and propenyl.

As used herein, the term "substituted alkenyl" refers to a straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond, optionally substituted with substituents selected from the group which includes C_{1-3} alkyl (optionally substituted by one to three F), amino, aryl, cyano and halogen, multiple degrees of substitution being allowed.

As used herein, the term "alkynyl" refers to a straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond. Examples of "alkynyl" as used herein include, but are not limited to, acetylenyl and 1-propynyl.

As used herein, the term "substituted alkynyl" refers to a straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond, optionally substituted with substituents selected from the group which includes C_{1-3} alkyl (optionally substituted by one to three F), amino, aryl and halogen, multiple degrees of substitution being allowed.

As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I), and "halo" refers to the halogen radicals fluoro, chloro, bromo and iodo.

As used herein, the term "carbocycle" refers to a non-aromatic cyclic hydrocarbon radical having from three to seven carbon atoms. For carbocycles with five- to seven-membered rings, a ring double bond is allowed. Exemplary

"carbocycle" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, and cycloheptyl.

As used herein, the term "substituted carbocycle" refers to a non-aromatic cyclic hydrocarbon radical having from three to seven carbon atoms, and which is optionally substituted with substituents selected from the group which includes C_{1-3} alkyl (optionally substituted by one to three F), C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-2} alkoxy (optionally substituted by one to three F), sulfanyl, sulfinyl, sulfonyl, oxo, hydroxy, mercapto, amino, guanidino, carboxy, aminocarbonyl, aryl, aryloxy, heteroaryl, heterocyclic, aminosulfonyl, sulfonylamino, carboxyamide, nitro, ureido, cyano and halogen, multiple degrees of substitution being allowed. For carbocycles with five- to seven-membered rings, a ring double bond is allowed.

As used herein, the term "aryl" refers to an optionally substituted benzene ring or to an optionally substituted benzene ring fused to one or more optionally substituted benzene rings to form a ring system. Exemplary optional substituents include C_{1-3} substituted alkyl, C_{2-3} substituted alkenyl, C_{2-3} substituted alkynyl, heteroaryl, heterocyclic, aryl, C_{1-3} alkoxy (optionally substituted by one to three F), aryloxy, aralkoxy, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, sulfanyl, sulfinyl, sulfonyl, aminosulfonyl, sulfonylamino, carboxyamide, aminocarbonyl, carboxy, oxo, hydroxy, mercapto, amino, nitro, cyano, halogen, or ureido, multiple degrees of substitution being allowed. Such a ring or ring system may be optionally fused to one or more optionally substituted aryl rings (including benzene rings), carbocycle rings or heterocyclic rings. Examples of "aryl" groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, biphenyl, indanyl, anthracyl or phenanthryl, as well as substituted derivatives thereof.

As used herein, the term "heteroaryl" refers to an optionally substituted monocyclic five to six membered aromatic ring containing one or more heteroatomic substitutions selected from S, SO, SO_2, O, N, or N-oxide, or to such an aromatic ring fused to one or more optionally substituted rings, such as heteroaryl rings, aryl rings, heterocyclic rings, or carbocycle rings (e.g., a bicyclic or tricyclic ring system). Examples of optional substituents are selected from the group which includes C_{1-3} substituted alkyl, C_{2-3} substituted alkenyl, C_{2-3} substituted alkynyl, heteroaryl,

heterocyclic, aryl, C_{1-3} alkoxy (optionally substituted by one to three F), aryloxy, aralkoxy, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, sulfanyl, sulfinyl, sulfonyl, aminosulfonyl, sulfonylamino, carboxyamide, aminocarbonyl, carboxy, oxo, hydroxy, mercapto, amino, nitro, cyano, halogen or ureido, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include, but are not limited to, benzoimidazolyl, benzothiazolyl, benzoisothiazolyl, benzothiophenyl, benzopyrazinyl, benzotriazolyl, benzo[1,4]dioxanyl, benzofuranyl, 9*H*-*a*-carbolinyl, cinnolinyl, furanyl, furo[2,3-b]pyridinyl, imidazolyl, imidazolidinyl, imidazopyridinyl, isoxazolyl, isothiazolyl, isoquinolinyl, indolyl, indazolyl, indolizinyl, naphthyridinyl, oxazolyl, oxothiadiazolyl, oxadiazolyl, phthalazinyl, pyridyl, pyrrolyl, purinyl, pteridinyl, phenazinyl, pyrazolyl, pyridyl, pyrazolopyrimidinyl, pyrrolizinyl, pyridazyl, pyrazinyl, pyrimidyl, 4-oxo-1,2-dihydro-4H-pyrrolo[3,2,1-ij]-quinolin-4-yl, quinoxalinyl, quinazolinyl, quinolinyl, quinolizinyl, thiophenyl, triazolyl, triazinyl, tetrazolopyrimidinyl, triazolopyrimidinyl, tetrazolyl, thiazolyl, thiazolidinyl, and substituted versions thereof.

As used herein, the term "heterocyclic" refers to a three to seven-membered ring containing one or more heteroatomic moieties selected from S, SO, SO_2, O, N, or N-oxide, optionally substituted with substituents selected from the group which includes C_{1-3} substituted alkyl, C_{2-3} substituted alkenyl, C_{2-3} substituted alkynyl, heteroaryl, heterocyclic, aryl, C_{1-3} alkoxy (optionally substituted by one to three F), aryloxy, aralkoxy, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, sulfanyl, sulfinyl, sulfonyl, aminosulfonyl, sulfonylamino, carboxyamide, aminocarbonyl, carboxy, oxo, hydroxy, mercapto, amino, nitro, cyano, halogen, or ureido, multiple degrees of substitution being allowed. Such a ring can be saturated or have one or more degrees of unsaturation. Such a ring may be optionally fused to one or more other optionally substituted "heterocyclic" ring(s), aryl ring(s), heteroaryl ring(s), or carbocycle ring(s). Examples of "heterocyclic" moieties include, but are not limited to, 1,4-dioxanyl, 1,3-dioxanyl, pyrrolidinyl, pyrrolidin-2-onyl, piperidinyl, imidazolidine-2,4-dionepiperidinyl, piperazinyl, piperazine-2,5-dionyl, morpholinyl, dihydropyranyl, dihydrocinnolinyl, 2,3-dihydrobenzo[1,4]dioxinyl, 3,4-dihydro-2H-

benzo[b][1,4]-dioxepinyl, tetrahydropyranyl, 2,3-dihydrofuranyl, 2,3-dihydrobenzofuranyl, dihydroisoxazolyl, tetrahydrobenzodiazepinyl, tetrahydroquinolinyl, tetrahydrofuranyl, tetrahydronaphthyridinyl, tetrahydropurinyl, tetrahydrothiopyranyl, tetrahydrothiophenyl, tetrahydroquinoxalinyl, tetrahydropyridinyl, tetrahydrocarbolinyl, 4H-benzo[1,3]-dioxinyl, benzo[1,3]dioxonyl, 2,2-difluorobenzo-[1,3]-dioxonyl, 2,3-dihydro-phthalazine-1,4-dionyl, isoindole-1,3-dionyl, and the like.

As used herein, the term "alkoxy" refers to the group $-OR_a$, where R_a is alkyl as defined above. Exemplary alkoxy groups useful in the present invention include, but are not limited to, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and t-butoxy.

As used herein the term "aralkoxy" refers to the group $-OR_aR_b$, where R_a is alkyl and R_b is aryl as defined above.

As used herein the term "aryloxy" refers to the group $-OR_b$, where R_b is aryl as defined above.

As used herein, the term "mercapto" refers to the group -SH.

As used herein, the term "sulfanyl" refers to the group $-SR_a$, where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term "sulfinyl" refers to the group $-S(O)R_a$, where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term "sulfonyl" refers to the group $-S(O)_2R_a$, where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term "oxo" refers to the group =O.

As used herein, the term "hydroxy" refers to the group -OH.

As used herein, the term "amino" refers to the group $-NH_2$. The amino group is optionally substituted by substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term "cyano" refers to the group -CN.

As used herein, the term "aminosulfonyl" refers to the group $-S(O)_2NH_2$. The aminosulfonyl group is optionally substituted by substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term "sulfonylamino" refers to the group $-NHS(O)_2R_a$ where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term "carboxyamide" refers to the group $-NHC(O)R_a$ where R_a is substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term "carboxy" refers to the group -C(O)OH. The carboxy group is optionally substituted by substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term "aminocarbonyl" refers to the group $-C(O)NH_2$. The aminocarbonyl group is optionally substituted by substituted alkyl, substituted carbocycle, aryl, heteroaryl or heterocyclic, as defined above.

As used herein, the term "ureido" refers to the group $-NHC(O)NHR_a$ wherein R_a is hydrogen, alkyl, carbocycle or aryl as defined above.

As used herein, the term "guanidino" refers to the group $-NHC(=NH)NH_2$.

As used herein, the term "acyl" refers to the group $-C(O)R_a$, where R_a is alkyl, carbocycle, or heterocyclic as defined herein.

As used herein, the term "aroyl" refers to the group $-C(O)R_a$, where R_a is aryl as defined herein.

As used herein, the term "heteroaroyl" refers to the group $-C(O)R_a$, where R_a is heteroaryl as defined herein.

As used herein, the term "acyloxy" refers to the group $-OC(O)R_a$, where R_a is alkyl, carbocycle, or heterocyclic as defined herein.

As used herein, the term "aroyloxy" refers to the group $-OC(O)R_a$, where R_a is aryl as defined herein.

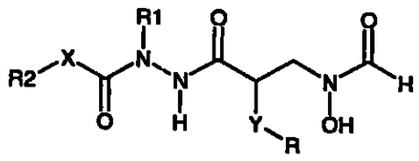
As used herein, the term "heteroaroyloxy" refers to the group $-OC(O)R_a$, where R_a is heteroaryl as defined herein.

Also included in the present invention are pharmaceutically acceptable salts and complexes, such as the hydrochloride, hydrobromide and trifluoroacetate salts and the sodium, potassium and magnesium salts. The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

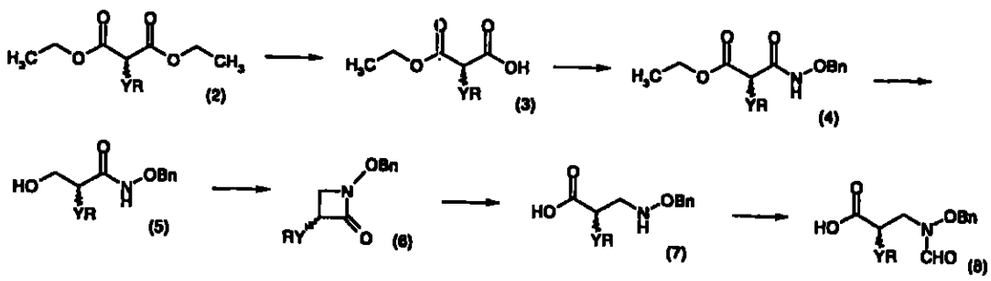
GENERAL SYNTHETIC SEQUENCE

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes, which are merely illustrative of the methods by which the compounds of the invention may be prepared and are not intended to limit the scope of the invention as defined in the appended claims.

The present invention provides compounds of Formula (1) that can be prepared from the common racemic intermediate (8), or common chiral intermediates (17) and (25).



(1) X = O, NR_3 or a bond;
Y = O, CH_2 or a bond

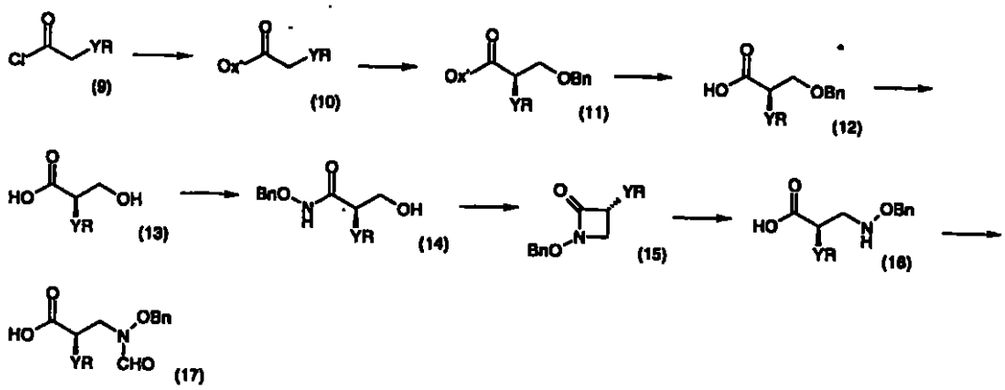


Scheme 1.

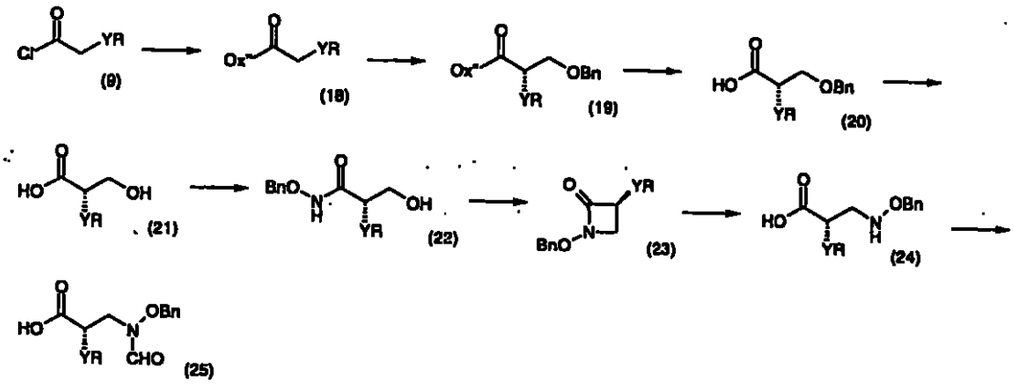
As shown in Scheme 1, intermediate (8) can be prepared by reacting the mono-substituted dialkyl malonate (2) with a base, such as potassium hydroxide, in an appropriate solvent, such as ethanol/water, to afford the mono-acid (3). Coupling of (3) with O-benzylhydroxylamine in the presence of a coupling reagent, such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), and a base, such as 4-dimethylaminopyridine, (DMAP) in an appropriate solvent, such as dichloromethane, gives the amide (4). Reduction of the ester functionality of compound (4) with a reducing agent, such as lithium borohydride, in an appropriate solvent, such as tetrahydrofuran, at room temperature provides the alcohol (5). Treatment of the alcohol (5) under Mitsunobu conditions affords the lactam (6). The same transformation may be achieved by treating (5) with triphenylphosphine, carbon tetrachloride and a base, such as triethylamine, to obtain (6). Hydrolysis of the lactam (6) using, for example, lithium hydroxide in an appropriate solvent mixture, such as THF-H_2O-MeOH, gives acid (7). Formylation of the amine group of (7) is achieved using formic acid and acetic anhydride in a solvent, such as dichloromethane, to provide the formylated compound (8).

Any racemates can be resolved at the level of any intermediate during the synthesis or at the level of the final product using, for example, a chiral chromatography method, to provide compound (8) in each of two enantiomeric forms.

Alternatively, an enantiomer of intermediate (8), such as (17) in Scheme 2 or (25) in Scheme 3, can be prepared by reacting an appropriate acid chloride (9) with a chiral agent, such as Evans' chiral oxazolidinone, in the presence of a base, such as n-butyl lithium, to afford the chiral intermediate (10) in Scheme 2 or (18) in Scheme 3. Treatment of the compound (10) or (18) with a base, such as diisopropylethylamine, in the presence of a chelating agent, such as titanium tetrachloride, in a solvent, such as tetrahydrofuran, followed by addition of an electrophile, such as benzyloxymethylchloride, provides either of two chiral compounds (11) and (19), depending on the selection of chiral auxiliary.



Scheme 2.



Scheme 3.

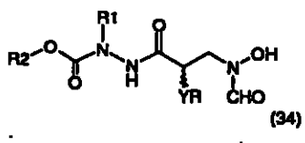
Conversion of compound (11) or (19) to the corresponding hydroxyacid (13) or (21) can be achieved by a sequence comprising oxidative cleavage of the chiral oxazolidinone, using, for example, H_2O_2 and lithium hydroxide to the respective intermediates (12) and (20), followed by hydrogenolysis. Coupling of the acid (13) or (21) with benzyloxyamine in the presence of coupling agents, such as EDCI/DMAP, yields the amides (14) and (22). These can be cyclized to the azetidin-2-ones (15) or (23) using either Mitsunobu conditions or a combination of triphenylphosphine/carbon tetrachloride/triethylamine. Hydrolysis of the azetidin-2-one (15) or (23), using for example lithium hydroxide, in an appropriate solvent,

gives the corresponding acid (16) or (24). Conversion of compound (16) or (24) to the formate (17) or (25) can be achieved using an appropriate formylating agent, such as formic acid/acetic anhydride or methyl formate, in an appropriate solvent, such as dichloromethane.

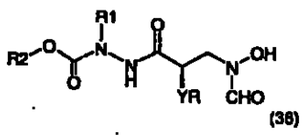
SPECIFIC EMBODIMENTS

Second Embodiment

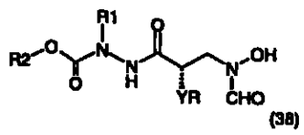
As the second embodiment of the present invention, the compounds of Formula (1) with X = O are disclosed, as in the racemic compound (34) and the chiral compounds (36) and (38). These compounds have preferentially R1 = H.



(34)



(36)



(38)

Preferred compounds useful in the present invention are selected from the group consisting of:

N-Butyl-N-(t-butoxycarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-phenoxycarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Isobutyl-N-(t-butoxycarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Isobutyl-N-phenoxycarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenethyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Cyclohexylmethyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Benzyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-pyridin-3-yl-propyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2-Morpholin-4-yl-ethyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Hydroxy-butyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Amino-butyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Tetrahydro-pyran-4-yl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Methyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-Aminopropyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(t-Butoxycarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-Hydroxypropyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-(t-butoxycarbonyl)-N'-{(2S)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-(phenoxycarbonyl)-N'-{(2S)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[2-(4-Dimethylaminophenyl)ethyl]-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxy amino)methyl]-heptanoyl}-hydrazine.

N-(t-Butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Pentyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[2-(1H-Indol-3-yl)-ethyl]-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Isopentyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Cyclohexyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(1-Ethyl-propyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Isopropyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Propyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Ethyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

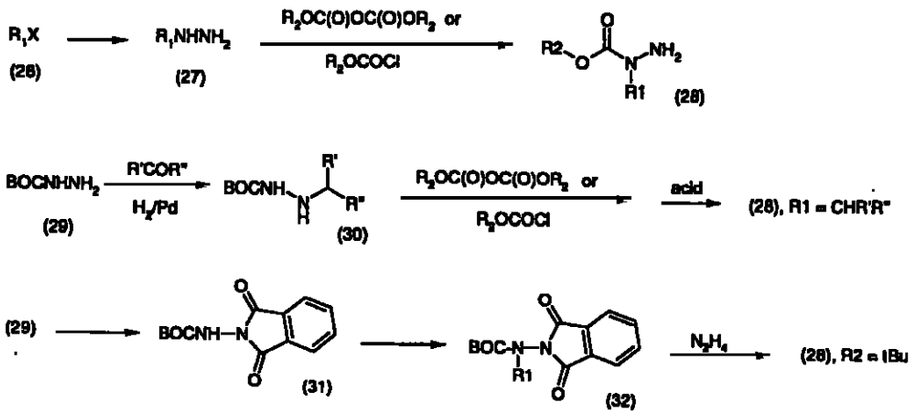
N-Methoxycarbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-(3,5-Dimethoxyphenyl)-1-methyl-ethoxy]carbonyl}-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

The following synthetic schemes are merely illustrative of the methods by which the compounds of the invention may be prepared and are not intended to limit the scope of the invention as defined in the appended claims.

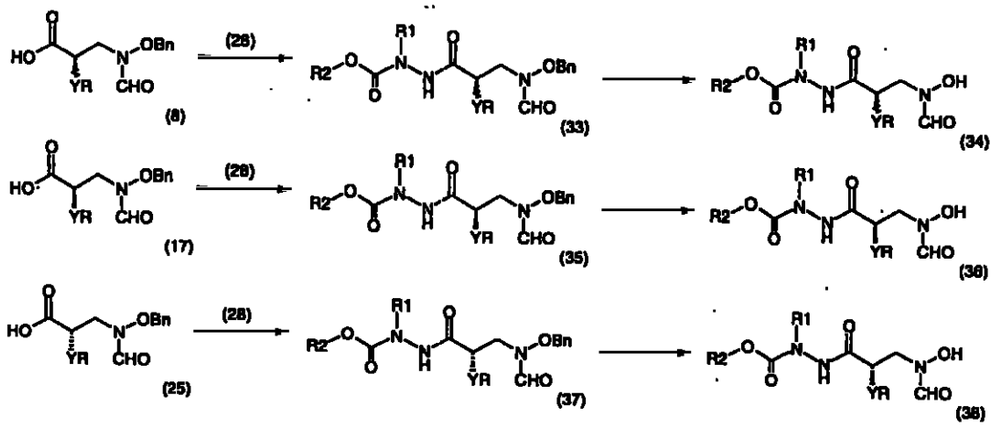
As shown in Scheme 4, treatment of the alkyl halide R1X (26) with hydrazine in a solvent such as ethanol, at an elevated temperature, gives hydrazine derivative (27). Reacting (27) with the carbonate R2OC(O)OC(O)OR2 or the chloroformate R2OCOCl affords the intermediate (28). Alternatively, (28) can be prepared from the Boc-protected hydrazine (29) by reaction with the aldehyde or ketone R'COR", followed by reduction with hydrogen gas in the presence of palladium, to afford hydrazine derivative (30). Reacting hydrazine (30) with a carbonate R2OC(O)OC(O)OR2 or a chloroformate R2OCOCl, followed by removal of the Boc protecting group with an appropriate acid, such as trifluoroacetic acid, gives the hydrazine derivative (28) wherein R1 = CHR'R". Alternatively, the primary amino

group of (29) can be protected as the phthalimide (31). Reacting the compound (31) with an alcohol under Mitsunobu conditions gives compound (32), which, upon hydrazinolysis, is readily converted to a hydrazine of Formula (10) where R2 = t-butyl.



Scheme 4.

As shown in Scheme 5, coupling of the acid (8) with the hydrazine derivative (28) using conditions such as DMAP/EDCI or EDCI/HOAt/NMM provides the hydrazide (33). Hydrogenolysis to remove the benzyl group using a catalyst, such as 10% Pd/C, in an appropriate solvent, such as ethanol, gives desired compound (34). Similarly, coupling of the chiral acid (17) or (25) with the hydrazine derivative (28) provides the corresponding hydrazide (35) or (37). Hydrogenolysis of the benzyl group gives the final desired compound (36) or (38).



Scheme 5.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

Hz (Hertz); TLC (thin layer chromatography);

T_r (retention time); RP (reverse phase);

MeOH (methanol); *i*-PrOH (isopropanol);

EtOH (ethanol); TEA (triethylamine);

TFA (trifluoroacetic acid); THF (tetrahydrofuran);

DMSO (dimethylsulfoxide); AcOEt or EtOAc (ethyl acetate);

DCM (dichloromethane); DMF (*N,N*-dimethylformamide);

CDI (1,1-carbonyldiimidazole); HOAc (acetic acid);

HOSu (*N*-hydroxysuccinimide); Ac (acetyl);

HOBT (1-hydroxybenzotriazole); BOC (*tert*-butyloxycarbonyl);

mCPBA (meta-chloroperbenzoic acid); FMOC (9-fluorenylmethoxycarbonyl);

DCC (dicyclohexylcarbodiimide); CBZ (benzyloxycarbonyl);

NMM (N-methyl morpholine); HOAt (1-hydroxy-7-azabenzotriazole);

DMAP (4-dimethylaminopyridine); Bn (benzyl);

TBAF (tetra-*n*-butylammonium fluoride);

HPLC (high pressure liquid chromatography);

BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);

EDCI (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride);

HBTU (O-Benzotriazole-1-yl-N,N,N',N'- tetramethyluronium hexafluorophosphate).

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted, and all solvents are highest available purity unless otherwise indicated.

^{1}H NMR (hereinafter also "NMR") spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, a Brucker AVANCE-400, a General Electric QE-300 or a Bruker AM 400 spectrometer. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

Mass spectra were run on an open access LC-MS system using electrospray ionization. LC conditions: 4.5% to 90% CH_3CN (0.02% TFA) in 3.2 min with a 0.4 min hold and 1.4 min re-equilibration; detection by MS, UV at 214 nm, and a light scattering detector (ELS). Column: 1 X 40 mm Aquasil (C18).

For preparative (prep) hplc; *ca* 50 mg of the final products were injected in 500 uL of DMSO onto a 50 X 20 mm I. D. YMC CombiPrep ODS-A column at 20 mL/min with a 10 min gradient from 10% CH_3CN (0.1% TFA) to 90% CH_3CN (0.1% TFA) in H_2O (0.1% TFA) and a 2 min hold. Flash chromatography was run over Merck Silica gel 60 (230 - 400 mesh).

Infrared (IR) spectra were obtained on a Nicolet 510 FT-IR spectrometer using a 1-mm NaCl cell. Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid or p-anisaldehyde solution.

The compounds disclosed in Examples 2 to 30 were prepared following the general procedures described in Example 1.

Preparation 1

(4S)-Benzyl-3-heptanoyl-oxazolidin-2-one.

To a solution of (S)-(-)-4-benzyl-2-oxazolidinone (3.3 g, 18.6 mmol) in THF (50 mL) at -78 °C was added dropwise n-BuLi (7.4 mL, 2.5M solution in hexane, 18.6 mmol). After stirring for 30 min at the same temperature, the reaction mixture was then treated with heptanoyl chloride (2.76 g, 18.6 mmol). The reaction mixture was stirred and allowed to warm to 10 °C over 5 h, and then quenched with saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure yielded 4.63 g (86%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 5H), 4.69 (m, 1H), 4.19 (m, 2H), 3.31 (dd, J = 13.4, 3.3 Hz, 1H), 2.95 (m, 2H), 2.79 (dd, J = 13.4, 9.7 Hz, 1H), 1.71 (m, 2H), 1.42-1.32 (m, 6H), 0.92 (t, J = 6.8 Hz, 3H). MH+ 290.

Preparation 2

(4S)-Benzyl-3-[(2R)-benzyloxymethylheptanoyl]oxazolidin-2-one.

To a solution of (S)-4-benzyl-3-heptanoyloxazolidin-2-one (4.63 g, 16.02 mmol) and titanium (IV) chloride (1.9 mL, 16.82 mmol) in dichloromethane (55 mL) at 0 °C was added dropwise diisopropylethylamine (3.1 mL, 17.62 mmol). After stirring at 0 °C for 1 hour, the resulting titanium enolate was then reacted with benzylchloromethyl ether (TCI-America, 4.9 mL, 32.04 mmol) at 0 °C for 6 h. The reaction mixture was then quenched with water (100 mL). The aqueous layer was extracted with dichloromethane (100 mL x 2). The organic extracts were washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, purification by flash column chromatography using an eluting system of hexane/EtOAc (5:1) yielded 4.39 g (67%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 10H), 4.74 (m, 1H), 4.57 (m, 2H), 4.28-4.13 (m, 3H), 3.82 (t, J = 8.7 Hz, 1H), 3.68 (dd, J = 9.0, 4.9 Hz, 1H), 3.25 (dd, J = 13.5, 3.1 Hz, 1H), 2.71 (dd, J = 13.5, 9.3 Hz, 1H), 1.74 (m, 1H), 1.54 (m, 1H), 1.31-1.28 (m, 6H), 0.89 (t, J = 6.7 Hz, 3H). MH+ 410.

Preparation 3

(3R)-Benzyloxy-2-pentylpropionic acid.

A 0.05 M solution of (S)-4-benzyl-3-[(R)-2-benzyloxymethylheptanoyl]oxazolidin-2-one (2.0 g, 4.89 mmol) in a 3:1 mixture of THF and H_2O was treated with 30% H_2O_2 (4.5 mL, 39.12 mmol), followed by LiOH (0.48 g, 9.78 mmol) at 0 °C. The resulting mixture was stirred and allowed to warm to room temperature overnight. THF was then removed under vacuum. The residue was washed with dichloromethane (50 mL x 2) to remove (S)-4-benzyloxazolidin-2-one. The desired product was isolated by EtOAc extraction of the acidified (pH 1~2) aqueous phase. No further purification was required. Standing under high vacuum yielded 1.16 g (95%) of the title compound. ^1H NMR (400 MHz, $CHCl_3$) δ 11.1 (br s, 1H), 7.36 (m, 5H), 4.57 (s, 2H), 3.69 (m, 1H), 3.58 (dd, J = 9.2, 5.2 Hz, 1H), 2.74 (m, 1H), 1.66 (m, 1H), 1.54 (m, 1H), 1.34-1.30 (m, 6H), 0.90 (t, J = 6.7 Hz, 3H). MH+ 251.

Preparation 4

3-Hydroxy-(2R)-pentylpropionic acid.

To a solution of (R)-3-benzyloxy-2-pentyl-propionic acid (1.54 g, 6.16 mmol) in EtOH (100 mL) was added 10% Pd/C (310 mg). The reaction mixture was subjected to hydrogenation overnight at room temperature. After the reaction was completed, the reaction mixture was filtered through a pad of Celite, and washed with EtOH (50 mL x 3). Removal of the solvent provided the title compound (0.92 g, 93%). No further purification was required. ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.30 (br s, 1H), 3.81 (d, J = 5.4 Hz, 2H), 2.64 (m, 1H), 1.69 (m, 1H), 1.56 (m, 1H), 1.41-1.27 (m, 6H), 0.91 (t, J = 7.7 Hz, 3H). MH+ 161.

Preparation 5

N-Benzyloxy-3-hydroxy-(2R)-pentylpropionamide.

To a mixture of (R)-3-hydroxy-2-pentylpropionic acid (0.92 g, 5.75 mmol), O-benzyl hydroxylamine hydrochloride (0.92 g, 5.75 mmol) and 4-(dimethylamino)pyridine (1.41 g, 11.50 mmol) in dichloromethane (25 mL) at 0 °C was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.11 g, 5.75 mmol). After stirring at room temperature overnight, the reaction was then quenched with 1N aqueous HCl solution (25 mL) and extracted using dichloromethane (25 mL x 2). The organic extracts were washed with water, brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure yielded the title compound (1.43 g, 94%). ^{1}H NMR (400 MHz, $CHCl_3$) δ 9.22 (br s, 1H), 7.41-7.28 (m, 5H), 4.89 (q, J = 10.6 Hz, 2H), 3.70-3.37 (m, 3H), 2.17 (m, 1H), 1.54 (br s, 1H), 1.27 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H). MH+ 266.

Preparation 6

1-benzyloxy-(3R)-pentylazetidin-2-one.

To a mixture of (R)-N-benzyloxy-3-hydroxy-2-pentylpropionamide (1.41 g, 5.32 mmol) and triphenylphosphine (1.68 g, 6.39 mmol) in THF (53 mL) was added dropwise diethyl azodicarboxylate (1.1 mL, 6.39 mmol) at 0 °C. The reaction mixture was stirred and allowed to warm to room temperature overnight. The reaction was then quenched with water (50 mL). The aqueous layer was extracted with EtOAc (50

mL x 2). The combined organic layers were washed with brine, and dried over $MgSO_4$. After removing the solvent under vacuum, the residue was purified by flash column chromatography (hex:EtOAc 5/1) to provide the title compound (1.17 g, 89%). ^1H NMR (400 MHz, $CHCl_3$) δ 7.35-7.25 (m, 5H), 4.87 (s, 2H), 3.28 (t, J = 4.85 Hx, 1H), 2.84 (q, J 2.35 Hz, 1H), 2.77 (m, 1H), 1.62 (m, 1H), 1.36 (m, 1H), 1.25-1.16 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H). MH+ 248.

Preparation 7

3-benzyloxyamino-(2R)-pentylpropionic acid.

To a mixture of (R)-1-benzyloxy-3-pentylazetidin-2-one (0.96 g, 3.89 mmol) in a mixture of THF-H_2O-MeOH (50 mL, 3:1:1 v/v) was added lithium hydroxide monohydrate (1.91 g, 38.9 mmol). After stirring at room temperature overnight, water (25 mL) was added to the mixture. The solution was acidified to pH 5~6 with 3N aqueous HCl solution. It was extracted with EtOAc (50 mL x 2). The combined organic layers were dried over $MgSO_4$. Removal of the solvent under vacuum provided the title compound (0.98 g, 95%). ^1H NMR (400 MHz, $CHCl_3$) δ 9.80 (br s, 1H), 7.37 (m, 5H), 4.75 (m, 2H), 3.14 (m, 2H), 2.74 (m, 1H), 1.70 (m, 1H), 1.53 (m, 1H), 1.38-1.25 (m, 6H), 0.91 (t, J = 6.8 Hz, 3H). MH+ 266.

Preparation 8

(2R)-[(benzyloxyformylamino)methyl]heptanoic acid.

To a cold solution of (R)-3-Benzyloxyamino-2-pentylpropionic acid (1.03 g, 3.89 mmol) in HCO_2H (19 mL) and dichloromethane (19 mL) at 0 °C was added acetic anhydride (3.9 mL, 41.2 mmol). The mixture was stirred at 0 °C for 3 hours. The volatiles were removed by evaporation under vacuum. Dichloromethane (50 mL) was added to it. It was washed with brine (50 mL x 2), and dried over $MgSO_4$. Filtration and evaporation under vacuum provided the title compound (1.08 g, 95%). ^1H NMR (400 MHz, $CHCl_3$) δ 8.07 (br s, 1H), 7.29 (m, 5H), 4.91-4.71 (m, 2H), 3.76 (m, 2H), 2.67 (m, 1H), 1.54 (m, 1H), 1.41(m, 1H), 1.20 (m, 6H), 0.80 (t, J = 7.0 Hz, 3H). MH+ 294.

30 82

31

Preparation 9

Butylhydrazine.

1-Iodobutane (5.1 mL, 45.1 mmol) was added through a condenser for 30 min to a refluxing solution of hydrazine monohydrate (11.3 g, 225.5 mmol) in EtOH (100 mL). After stirring and refluxing for 18 hours, ethanol was removed by evaporation under vacuum. The residue was extracted with ether (50 mL x 2). The combined organic layers were dried (K_2CO_3), filtered and evaporated to yield 2.6 g (66%) of the title compound. ^1H NMR (400 MHz, $CHCl_3$) δ 3.15 (br s, 2H), 2.73 (t, J = 7.2 Hz, 2H), 1.44 (m, 2H), 1.33 (m, 2H), 0.89 (t, J 7.2 Hz, 3H). MH+ 89.

Preparation 10

N-Butylhydrazinecarboxylic acid tert-buyl ester.

To a solution of butylhydrazine (510 mg, 5.80 mmol) and triethylamine (1.2 mL, 8.69 mmol) in dichloromethane (20 mL) at 0 °C was added di-t-butyl dicarbonate (1.26 g, 5.80 mmol). The reaction mixture was stirred and allowed to warm up to room temperature overnight. Water (20 mL) was then added to the reaction mixture. The aqueous layer was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried ($MgSO_4$). Filtration and evaporation under vacuum provided the title compound (820 mg, 75%). ^1H NMR (400 MHz, $CHCl_3$) δ 3.89 (br s, 2H), 3.29 (t, J = 7.1 Hz, 2H), 1.46 (m, 2H), 1.40 (s, 9H), 1.24 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H). MH+ 189.

Preparation 11

N-Butyl-N-(t-butoxycarbonyl)-N'-{(2R)-[(benzyloxyformylamino)methyl]heptanoyl}-hydrazine.

To a solution of (R)-2-[(benzyloxyformyl-amino)methyl]heptanoic acid (180 mg, 0.614 mmol), N-butyl-hydrazinecarboxylic acid tert-buyl ester (140 mg, 0.737 mmol) and 4-dimethylaminopyridine (90 mg, 0.737 mmol) in dichloromethane (6.5 mL) at 0 °C was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (142 mg, 0.737 mmol). After stirring at room temperature overnight, the reaction was then quenched with aqueous 1N HCl and extracted with dichloromethane (15 mL x 2).

The organic extracts were washed with brine (30 mL), and dried over $MgSO_4$. Evaporation of the solvent under vacuum, followed by purification by flash column chromatography yielded 195 mg (69%) of the title compound. ^1H NMR (400 MHz, $CHCl_3$) δ 8.09 (br s, 1H), 7.25 (s, 5H), 4.80 (m, 2H), 4.10 (dd, J = 14.1, 4.0 Hz, 1H), 3.62 (m, 1H), 3.35 (m, 2H), 2.55 (m, 1H), 1.72 (m, 1H), 1.56 (m, 1H), 1.50 (s, 9H), 1.30 (m, 10H), 0.90 (m, 6H). MH+ 464.

Example 1

N-Butyl-N-(t-butoxycarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

To a solution of N'-{(R)-2-[(benzyloxy-formylamino)methyl]heptanoyl}-N-butylhydrazine carboxylic acid tert-buyl ester (195 mg, 0.421 mmol) in EtOH (15 mL) was added 10% Pd/C (60 mg). The reaction mixture was subjected to hydrogenation overnight at room temperature. After the reaction was completed, the reaction mixture was filtered through a pad of Celite, and washed with EtOH (10 mL x 2). Removal of the solvent provided the crude product, which was further purified by HPLC to yield the title compound (52 mg, 33%). ^1H NMR (400 MHz, $CHCl_3$) δ 9.94 (s, 1H), 9.39 (s, 1H), 8.32 (s, 1H), 4.10 (dd, J = 14.1, 4.0 Hz, 1H), 3.62 (m, 1H), 3.35 (m, 2H), 2.55 (m, 1H), 1.72 (m, 1H), 1.56 (m, 1H), 1.50 (s, 9H), 1.30 (m, 10H), 0.90 (m, 6H). MH+ 374.

Preparation 12

N-Butylhydrazinecarboxylic acid phenyl ester.

To a solution of butylhydrazine (370 mg, 4.20 mmol) and triethylamine (0.88 mL, 6.30 mmol) in dichloromethane (15 mL) at 0 °C was added phenyl chloroformate (0.53 mL, 4.20 mmol). The reaction mixture was stirred and allowed to warm up to room temperature overnight. Water (20 mL) was then added to the reaction mixture. The aqueous layer was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried ($MgSO_4$). Filtration and evaporation under vacuum, followed by purification by flash column chromatography provided the title compound (250 mg, 29%). ^1H NMR (400 MHz, $CHCl_3$) δ 7.40-7.10 (m, 5H), 4.20 (t,

J = 7.1 Hz, 2H), 3.60 (br s, 2H), 1.71 (m, 2H), 1.41 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H). MH+ 209.

Example 2

N-Butyl-N-phenoxycarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

Purification by preparative HPLC yielded 49 mg (41%) of the title compound. ^{1}H NMR (400 MHz, $CHCl_3$) δ 9.78 (s, 1H), 9.39 (s, 1H), 8.27 (s, 1H), 7.40-7.10 (m, 5H), 4.20-3.30 (m, 4H), 2.70 (m, 1H), 1.80-1.20 (m, 10H), 0.90 (m, 6H). MH+ 394.

Example 3

N-Isobutyl-N-(t-butoxycarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

Purification by preparative HPLC yielded 44 mg (22%, 2 steps) of the title compound. ^{1}H NMR (400 MHz, $CHCl_3$) δ 9.94 (s, 1H), 9.54 (s, 1H), 8.32 (s, 1H), 4.11 (dd, J = 3.9, 14.1 Hz, 1H), 3.46 (m, 1H), 3.35 (m, 1H), 3.12 (dd, J = 6.3, 14.1 Hz, 1H), 2.54 (m, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.50 (s, 9H), 1.49-1.25 (m, 7H), 0.95-0.88 (m, 9H). MH+ 374.

Example 4

N-Isobutyl-N-phenoxycarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

Purification by preparative HPLC yielded 44 mg (22%, 2 steps) of the title compound. ^{1}H NMR (400 MHz, $CHCl_3$) δ 9.97 (s, 1H), 9.38 (s, 1H), 8.27 (s, 1H), 7.41-7.13 (m, 5H), 4.08 (dd, J = 3.9, 14.1 Hz, 1H), 3.37 (m, 2H), 2.65 (m, 1H), 2.02 (m, 1H), 1.74 (m, 1H), 1.32-1.02 (m, 7H), 0.92-0.82 (m, 9H). MH+ 394.

Example 5

N-Phenethyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 9.03 (s, 1H), 8.35 (s, 1H), 7.22 (s, 5H), 4.11-3.36 (m, 4H), 2.86 (t, 3H), 2.52 (m, 1H), 2.07 (m, 1H), 1.72 (m, 1H), 1.41-1.34 (m, 15H), 0.92 (t, 3H). MH+ 422.

Example 6

N-Cyclohexylmethyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.70 (br s, 1H), 4.20-3.05 (m, 4H), 2.50 (m, 1H), 1.74-0.90 (m, 31H). MH+ 414.

Example 7

N-Benzyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (br s, 1H), 8.77 (br s, 1H), 8.25 (s, 1H), 7.64-7.28 (m, 5H), 5.00 (d, J = 14.7 Hz, 1H), 2.40 (m, 1H), 1.66 (m, 1H), 1.56 (m, 1H), 1.52 (s, 9H), 1.48-1.10 (m, 6H), 0.87 (t, J = 7.1 Hz, 3H). MH+ 408.

Example 8

N-(3-pyridin-3-yl-propyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79-7.25 (m, 5H), 4.15-3.03 (m, 4H), 2.75 (m, 1H), 2.56 (m, 2H), 2.07-1.72 (m, 4H), 1.49 (s, 9H), 1.46-1.28 (m, 6H), 0.85 (t, J = 6.9 Hz, 3H). MH+ 437.

Example 9

N-(2-Morpholin-4-yl-ethyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.88 (br s, 1H), 4.20-3.30 (m, 8H), 2.70 (m, 1H), 2.60-2.45 (m, 6H), 1.72 (m, 1H), 1.50 (s, 9H), 1.39 (m, 1H), 1.29 (m, 6H), 0.89 (t, J = 7.1 Hz, 3H). MH+ 431.

Example 10

N-(4-Hydroxy-butyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (br s, 1H), 8.37 (br s, 1H), 4.07-3.46 (m, 6H), 2.54 (m, 1H), 1.64-1.30 (m, 12H), 1.47 (s, 9H), 0.89 (t, J = 6.9 Hz, 3H). MH+ 390.

Example 11

N-(4-Amino-butyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (s, 1H), 7.70 (s, 1H), 4.00 (m, 2H), 3.70-3.40 (m, 4H), 3.0 (m, 2H), 2.50 (m, 1H), 1.70 (m, 1H), 1.50 (m, 1H), 1.49 (s, 9H), 1.48-1.20 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H). MH+ 389.

Example 12

N-(Tetrahydro-pyran-4-yl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (br s, 1H), 8.31 (s, 1H), 4.16-4.00 (m, 4H), 3.44-3.39 (m, 3H), 2.60 (m, 1H), 1.97-1.26 (m, 12H), 0.90 (t, J = 6.9 Hz, 3H). MH+ 402.

Example 13

N-Methyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (br s, 1H), 8.90 (br s, 1H), 8.29 (br s, 1H), 4.06 (m, 1H), 3.24 (m, 1H), 3.10 (s, 3H), 2.43 (m, 1H), 1.64 (m, 1H), 1.42 (s, 9H), 1.31 (m, 1H), 1.19 (m, 6H), 0.79 (t, J = 6.9 Hz, 3H). MH+ 332.

Example 14

N-(3-Amino-propyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.78 (s, 1H), 3.76-3.32 (m, 4H), 2.84 (m, 2H), 2.68 (m, 1H), 1.80 (m, 1H), 1.74 (m, 1H), 1.48 (s, 9H), 1.35 (m, 8H), 0.93 (t, J = 6.8 Hz, 3H). MH+ 375.

Example 15

N-(t-Butoxycarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.17 (s, 1H), 6.68 (s, 1H), 4.11 (m, 1H), 3.38 (m, 1H), 2.63 (m, 1H), 1.70 (m, 1H), 1.49 (s, 9H), 1.42 (m, 1H), 1.29 (m, 6H), 0.87 (t, J = 6.8 Hz, 3H). MH+ 318.

Example 16

N-(3-Hydroxy-propyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.33 (s, 1H), 7.83 (s, 1H), 3.83-3.43 (m, 6H), 2.81 (m, 1H), 1.78-1.65 (m, 2H), 1.52-1.29 (m, 8H), 1.45 (s, 9H), 0.87 (s, 9H). MH+ 376.

Example 17

N-Butyl-N-(t-butoxycarbonyl)-N'-[(2S)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 374.

Example 18

N-Butyl-N-(phenoxycarbonyl)-N'-{(2S)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.20 (s, 1H), 7.32-7.04 (m, 5H), 3.80-3.31 (m, 4H), 2.55 (s, 1H), 1.66 (s, 1H), 1.59-1.24 (m, 11H), 0.90-0.82 (m, 6H). MH+ 394.

Example 19

N-[2-(4-Dimethylaminophenyl)ethyl]-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxy amino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.89 (s, 1H), 8.33 (s, 1H), 7.06 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 4.17-3.33 (m, 4H), 2.93 (s, 6H), 2.80 (m, 2H), 2.48 (m, 1H), 1.71 (m, 1H), 1.41 (s, 9H), 1.32 (m, 7H), 0.91 (t, 3H). MH+ 465.

Example 20

N-(t-Butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 9.54 (s, 1H), 8.46 (s, 1H), 6.78 (s, 1H), 3.85-3.37 (m, 2H), 2..80-2.62 (m, 1H), 1.71 (m, 1H), 1.49 (s, 9H), 1.30-1.25 (m, 7H), 0.89 (t, 3H). MH+ 318.

Example 21

N-Pentyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.43 (s, 1H), 4.14-3.05 (m, 4H), 2.86-2.48 (m, 1H), 1.61 (m, 1H), 1.41 (m,.9H), 1.25-1.16 (m, 13H), 0.84 (m, 6H). MH+ 388.

Example 22

N-[2-(1H-Indol-3-yl)-ethyl]-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.55 (s, 1H), 8.33 (s, 1H), 8.15 (s, 1H), 7.55-7.05 (m, 5H), 4.10-3.92 (m, 2H), 3.71-3.30 (m, 2H), 3.02 (m, 2H), 2.40 (m, 1H), 1.67 (m, 1H), 1.50-1.20 (m, 16H), 0.89 (m, 6H). MH+ 461.

Example 23

N-Isopentyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.39 (s, 1H), 4.05-3.63 (m, 2H), 3.31 (t, 2H), 2.54 (m, 1H), 1.70 (m, 1H), 1.55 (m, 1H), 1.50-1.18 (m, 18H), 0.88 (m, 9H). MH+ 388.

Example 24

N-Cyclohexyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.30 (s, 1H), 4.11 (m, 1H), 3.85 (m, 1H), 3.35 (m, 1H), 2.55 (m, 1H), 1.94 (m, 1H), 1.81-1.57 (m, 5H), 1.51-1.18 (m, 18H), 0.89 (m, 3H). MH+ 400.

Example 25

N-(1-Ethyl-propyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.41 (s, 1H), 4.11-3.32 (m, 3H), 2.55 (m, 1H), 1.80 (m, 1H), 1.58-1.15 (m, 20H), 1.05 (m, 3H), 0.89 (m, 6H). MH+ 388.

Example 26

N-Isopropyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.31 (s, 1H), 4.34-4.08 (m, 2H), 3.37 (m, 1H), 2.76 (m, 1H), 1.73 (m, 1H), 1.51 (s, 9H), 1.31 (m, 7H), 1.11 (m, 6H), 0.88 (m, 3H). MH+ 360.

Example 27

N-Propyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.24 (s, 1H), 4.03-3.17 (m, 4H), 2.42 (m, 1H), 1.61 (m, 1H), 1.52-1.31 (m, 11H), 1.20 (m, 7H), 0.82 (m, 6H). MH+ 360.

Example 28

N-Ethyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.05 (s, 1H), 4.21-3.25 (m, 4H), 2.48 (m, 1H), 1.51-1.02 (m, 20H), 0.88 (m, 3H). MH+ 346.

Example 29

N-Methoxycarbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.05 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 3.68 (m, 3H), 3.37 (d, J = 5.5 Hz, 2H), 2.72 (m, 1H), 1.61 (m, 1H), 1.41-1.12 (m, 7H), 0.85 (m, 3H). MH+ 276.

Example 30

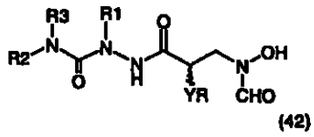
N-{[1-(3,5-Dimethoxyphenyl)-1-methyl-ethoxy]carbonyl}-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.21 (s, 1H), 7.76 (s, 1H), 6.62 (s, 1H), 6.36 (d, J = 4.7 Hz, 1H), 3.83-3.69 (m, 7H), 3.38 (m, 1H), 2.70(m, 1H), 1.82-1.55 (m, 7H), 1.43-1.21 (m, 7H), 0.84 (m, 3H). MH+ 440.

39 A1

Third Embodiment

As the third embodiment of the present invention, the compounds of Formula (I) with X = NR3 are disclosed, as in the racemic compound (42) and the chiral compounds (44) and (46). These compounds have preferentially R1 = H.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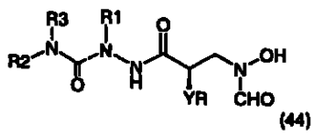
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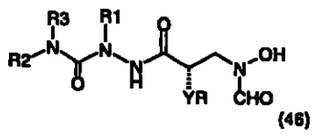

(46)

Preferred compounds useful in the present invention are selected from the group consisting of:

N-Butyl-N-[(4-methylpiperazin-1-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-diphenylaminocarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-(t-butylamino)carbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-[(3,5-dimethyl-4,5-dihydro-isoxazol-4-yl)aminocarbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-[(1-morpholin-4-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-4-phenyl-butanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-hexanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-3-phenyl-propanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-3-(3,4-dichlorophenyl)-propanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3,4-Dichlorophenylaminocarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3,4-Dichlorophenylaminocarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Morpholin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Methoxyphenyl)aminocarbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,4-Dichlorophenyl)aminocarbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,6-Dichlorophenyl)aminocarbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(4-Methyl-piperazin-1-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

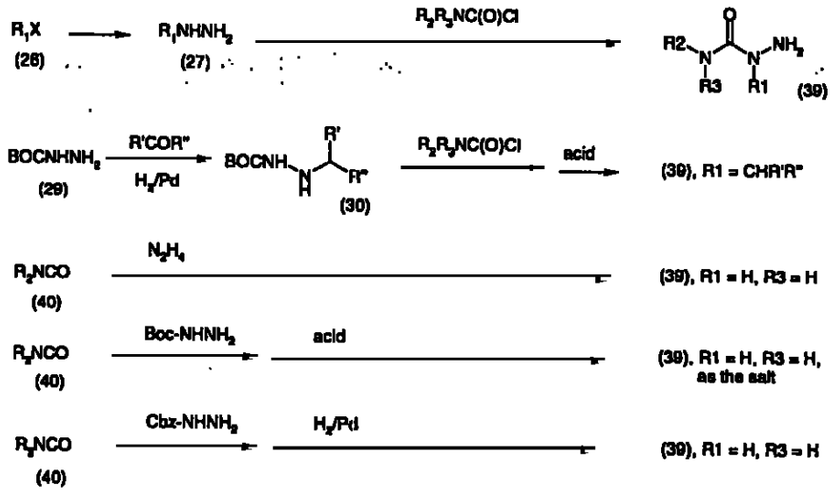
N-[(4-Chloro-3-trifluoromethylphenyl)aminocarbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Methyl-phenyl-amino)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

The following synthetic schemes are merely illustrative of the methods by which the compounds of the invention may be prepared and are not intended to limit the scope of the invention as defined in the appended claims.

As shown in Scheme 6, treatment of an alkyl halide R1X (26) with hydrazine in a solvent such as ethanol, at an elevated temperature, gives the hydrazine derivative (27). Reacting compound (27) with the carbamyl chloride R2R3NC(O)Cl affords

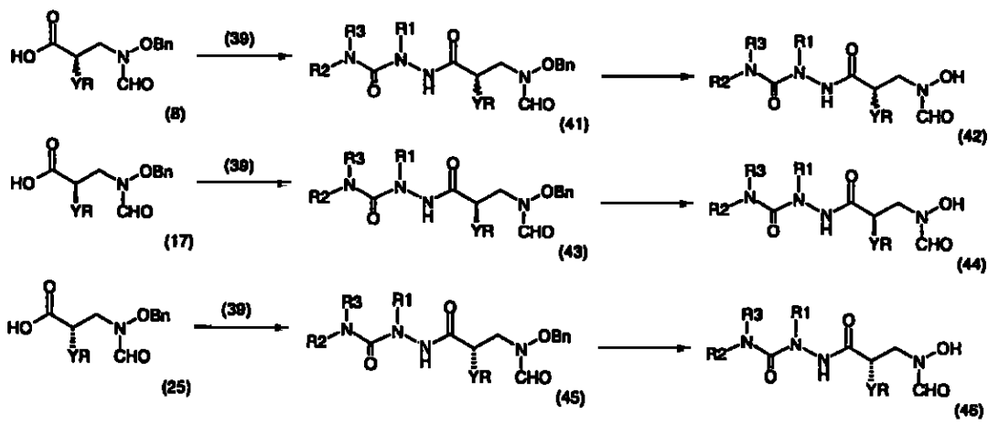
intermediate (39). Alternatively, compound (39) can be prepared from the Boc-protected hydrazine (29) by reaction with the aldehyde or ketone R'COR", followed by reduction with hydrogen gas in the presence of palladium, to afford hydrazine derivative (30). Reacting hydrazine (30) with the carbamyl chloride R2R3NC(O)Cl, followed by removing the Boc protecting group with an appropriate acid, such as trifluoroacetic acid, gives the hydrazine derivative (39) wherein R1 = CHR'R". Alternatively, reacting the isocyanate R2NCO (40) with hydrazine affords compound (39) wherein R1 = H and R3 = H. Alternatively, reacting the isocyanate R2NCO (40) with Boc-protected hydrazine, followed by acid treatment, affords the salt form of compound (39) wherein R1 = H and R3 = H. Alternatively, reacting the isocyanate R2NCO (40) with Cbz-protected hydrazine, followed by hydrogenation, affords compound (39) wherein R1 = H and R3 = H.



Scheme 6.

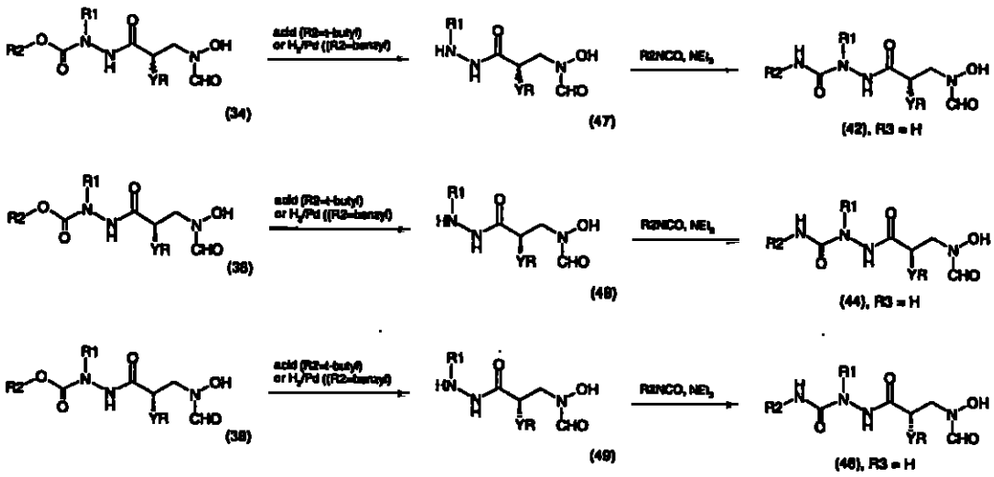
As shown in Scheme 7, coupling of the carboxylic acid (8) with the hydrazine derivative (39) provides hydrazide (41). Hydrogenolysis to remove the benzyl group using a catalyst, such as 10% Pd/C, in an appropriate solvent, such as ethanol, gives compound (42). Similarly, coupling of the chiral acid (17) or (25) with hydrazine

derivative (39) provides the corresponding hydrazide (43) or (45). Hydrogenolysis of the benzyl group gives the final compounds (44) or (46).



Scheme 7.

Alternatively, as shown in Scheme 8, the carbamate (34) wherein R2 = t-butyl or benzyl can be converted to the hydrazide (47) by acid treatment or hydrogenolysis, respectively. Reaction of (47) with an isocyanate in an appropriate solvent, such as methylene chloride, and in the optional presence of an appropriate base, such as triethylamine, gives compound (42) wherein R3 = H. Similarly, appropriate deprotection of the chiral carbamates (36) and (38), followed by reaction with an isocyanate, gives the chiral hydrazide (44) and (46), wherein R3 = H.



Scheme 8.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. The same experimental general conditions and conventions described in the Experimental Section of the Second Embodiment are applicable here.

The compounds disclosed in Examples 31 to 51 were prepared following the general procedures described in Example 1.

Preparation 13.

N-[(4-Methylpiperazine)carbonyl]-N-butylhydrazine.

To a solution of butyl-hydrazine (200 mg, 2.27 mmol) and triethylamine (0.95 mL, 6.81 mmol) in dichloromethane (10 mL) at -78 °C was added 4-methyl-1-piperazine carbonyl chloride hydrochloride (0.45 g, 2.27 mmol). The reaction mixture was stirred and allowed to warm up to room temperature overnight. Saturated aqueous $NaHCO_3$ (20 mL) was then added to the reaction mixture. The aqueous layer was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried ($MgSO_4$). Filtration and evaporation under vacuum, followed by purification by flash column chromatography (CH_2Cl_2:MeOH:Et_3N = 9:1:0.05) provided the title

compound (350 mg, 72%). ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.89 (br s, 2H), 3.41 (t, J = 4.9 Hz, 2H), 3.31 (t, J = 4.9 Hz, 2 H), 3.14 (t, J = 7.6 Hz, 2H), 2.44-2.41 (m, 4H), 2.33 (s, 3H), 1.64 (m, 2H), 1.32 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). MH+ 215.

Example 31

N-Butyl-N-[(4-methylpiperazin-1-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

Purification by preparative HPLC yielded 44 mg (22%, 2 steps) of the title compound. MH+ 400.

Example 32

N-Butyl-N-diphenylaminocarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

Purification by preparative HPLC yielded 85 mg (16%, 2 steps) of the title compound. ^{1}H NMR (400 MHz, $CHCl_3$) δ 9.52 (s, 1H), 8.89 (s, 1H), 8.35 (s, 1H), 7.39-7.07 (m, 10H), 4.03 (m, 1H), 3.51-3.26 (m, 3H), 2.54 (m, 1H), 1.74 (m, 1H), 1.41 (m, 1H), 1.30-1.07 (m, 10H), 0.90 (t, J = 7.3 Hz, 3H), 0.76 (t, J = 7.3Hz, 3H). MH+ 469.

Example 33

N-Butyl-N-(t-butylamino)carbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.81 (s, 1H), 4.10-3.20 (m, 6H), 3.01 (br s, 1H), 2.42 (m, 1H), 1.55-1.20 (m, 12H), 1.27 (s, 9H), 0.88-0.85 (m, 6H). MH+ 373.

Example 34

N-Butyl-N-phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.81 (s, 1H), 7.25 (br s, 1H), 4.10-3.20 (m, 6H), 3.00 (br s, 1H), 2.42 (m, 1H), 1.60-1.15 (m, 12H), 0.88-0.83 (m, 6H). MH+ 393.

Example 35

N-Butyl-N-[(3,5-dimethyl-4,5-dihydro-isoxazol-4-yl)aminocarbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.10 (s, 1H), 7.75 (s, 1H), 3.90-3.20 (m, 6H), 2.75 (m, 1H), 2.20-1.90 (m, 6H), 1.80-1.32 (m, 12H), 0.97-0.91 (m, 6H). MH+ 414.

Example 36

N-Butyl-N-[(1-morpholin-4-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.80 (s, 1H), 3.80-3.20 (m, 12H), 2.75 (m, 1H), 1.80-1.30 (m, 14H), 0.96-0.90 (m, 6H). MH+ 387.

Example 37

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-4-phenyl-butanoyl}-hydrazine.

MH+ 371.

Example 38

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-hexanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 7.84 (s, 1H), 7.29 (m, 5H), 3.90-3.40 (m, 2H), 2.86 (m, 1H), 1.70 (m, 1H), 1.50-1.15 (m, 5H), 0.89 (m, 3H). MH+ 323.

Example 39

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-3-phenyl-propanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.40 (s, 1H), 7.70 (s, 1H), 7.30-7.00 (m, 10H), 4.15-3.55 (m, 4H), 3.10 (m, 1H), 2.85 (m, 1H), 2.70 (m, 1H). MH+ 357.

Example 40

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-3-(3,4-dichlorophenyl)-propanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.50 (s, 1H), 7.70 (s, 1H), 7.28-7.05 (m, 8H), 4.10-3.45 (m, 2H), 3.10 (m, 1H), 2.95 (m, 1H), 2.70 (m, 1H). MH+ 425.

Example 41

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.40 (s, 1H), 7.95 (s, 1H), 7.81 (s, 1H), 7.41-6.95 (m, 5H), 3.90-3.40 (m, 2H), 2.83 (m, 1H), 1.61 (m, 1H), 1.42-1.12 (m, 7H), 0.87 (m, 3H). MH+ 337.

Example 42

N-(3,4-Dichlorophenylaminocarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.75 (s, 1H), 7.52 (s, 1H), 7.22-7.15 (m, 4H), 3.98-3.29 (m, 2H), 2.85-2.43 (m, 1H), 1.59 (m, 1H), 1.41-1.15 (m, 7H), 0.80 (m, 3H). MH+ 406.

Example 43

N-Phenylaminocarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.71 (s, 1H), 7.27-6.81 (m, 5H), 3.81-3.25 (m, 2H) 2.75-2.41 (m, 1H), 1.45 (m, 1H), 1.31-1.01 (m, 7H), 0.72 (m, 3H). MH+ 337.

Example 44

N-(3,4-Dichlorophenylaminocarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.41 (s, 1H), 8.28 (s, 1H), 8.16 (d, J = 7 Hz, 1H), 7.74 (s, 1H), 7.38-6.81 (m, 3H), 3.81-3.38 (m, 2H), 2.81-2.52 (m, 1H), 1.68-1.07 (m, 8H), 0.78 (m, 3H). MH+ 405.

Example 45

N-[(1-Morpholin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.25 (s, 1H), 8.15 (s, 1H), 4.08-3.49 (m, 6H), 3.35 (m, 4H), 2.78-2.55 (m, 1H), 1.52 (m, 1H), 1.41-1.08 (m, 7H), 0.79 (m, 3H). MH+ 331.

Example 46

N-[(2-Methoxyphenyl)aminocarbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.99 (s, 1H), 7.05-6.70 (m, 4H) 4.14-3.32 (m, 5H), 2.85-2.59 (m, 1H), 1.60 (m, 1H), 1.42-1.18 (m, 7H), 0.87 (m, 3H). MH+ 367.

Example 47

N-[(2,4-Dichlorophenyl)aminocarbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 405.

Example 48

N-[(2,6-Dichlorophenyl)aminocarbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 405.

Example 49

N-[(4-Methyl-piperazin-1-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 344.

Example 50

N-[(4-Chloro-3-trifluoromethylphenyl)aminocarbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 439.

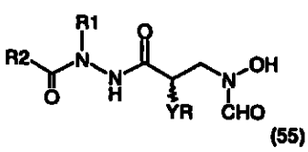
Example 51

N-[(Methyl-phenyl-amino)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 351.

Fourth Embodiment

As the fourth embodiment of the present invention, the compounds of Formula (1) where X is a covalent bond are disclosed, as in the racemic compound (55) and the chiral compounds (57) and (59). These compounds have preferentially R1 = H.



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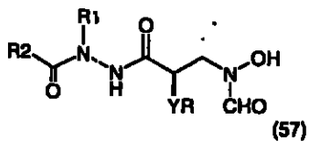

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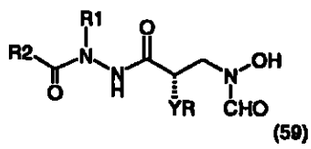


(59)

Preferred compounds useful in the present invention are selected from the group consisting of:

N-[(Phenylaminocarbonyl)-carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-{[1-(t-butoxycarbonyl)-piperidin-4-yl]-carbonyl}-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-{[(1-t-butoxycarbonyl)-pyrrolidin-(2S)-yl]carbonyl}-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-{[(1-t-butylaminocarbonyl)piperidin-4-yl]carbonyl}]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-{[(1-t-butylcarbonyl)piperidin-4-yl]carbonyl}]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-[(1,2,3,4-tetrahydro-quinoxalin-2-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(p-Methoxyphenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenoxyacetyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(p-Methoxy-phenoxy)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2,6-Dichlorophenyl-acetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3,4-Dichlorophenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Ethoxycarbonyl)carbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2,4-Dichlorophenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2,3-Dichlorophenoxyacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3,4-Dimethoxyphenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1H-Indol-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Methyl-pyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Methoxy-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,3-Dihydro-benzo[1,4]dioxin-(2S)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2,3,4-Tetrahydro-quinolin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Tetrahydro-furan-(2S)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Tetrahydro-furan-(2R)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Methyl-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Pyridin-2-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{3-[3-(4-Methoxybenzyl)-1H-benzoimidazol-2-yl]-propanoyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Pyrimidin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Isoquinolin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Methyl-2,5-dioxo-imidazolidin-4-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-3-phenyl-propanoyl}-hydrazine.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-3-(3,4-dichloro)phenyl-propanoyl}-hydrazine.

N-[(4-Imidazol-1-yl)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-Methyl-5-oxo-2-S-(pyridin-3-yl)-pyrrolidin-(3S)-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2-Dihydro-cinnolin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[4-(4-Acetylpiperazin-1-yl)phenoxyacetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenylacetyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-Benzyl-5-oxo-pyrrolidin-(2S)-yl]-carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-Benzyl-5-oxo-pyrrolidin-(2R)-yl]-carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5S)-Benzyl-3,6-dioxo-piperazin-(2S)-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-8-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2,3,4-Tetrahydroquinolin-8-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(N"-Acetyl-L-tyrosyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Acetyl-1,2,3,4-tetrahydro-quinolin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxy amino) methyl]-heptanoyl}-hydrazine.

N-[(1H-Benzoimidazol-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-(2-Hydroxyacetyl)-1,2,3,4-tetrahydro-quinolin-6-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1H-Indol-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{4-[Methyl-(4,6-dimethylpyrimidin-2-yl)-amino]benzoyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine).

N-[(1-Benzo[1,3]dioxol-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[4-(3,5-Dimethyl-pyrazol-1-yl)methyl]benzoyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[4-(Morpholin-4-yl)-benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[4-Hydroxy-3-(morpholin-4-yl)methyl-benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-Hydroxy-3-methyl-butanoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Methylamino-benzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Isopropyl-1H-benzotriazol-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2,3,4-Tetrahydro-isoquinolin-(3S)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Chloro-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-(Dimethylaminocarbonylmethyl)-3,4-dihydro-2H-quinolin-6-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,2-Difluoro-benzo[1,3]dioxol-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Amino-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(4-Oxo-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(7-Hydroxy-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(6-Methoxy-benzofuran-2-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Acetamidobenzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,3-Dihydro-benzo[1,4]dioxin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Amino-4,6-dimethyl-furo[2,3-b]pyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Methyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(6-Fluoro-4H-benzo[1,3]dioxin-8-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(7-Amino-1H-indol-2-yl)carbonyl)]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Methyl-1,2,3,4-tetrahydro-quinolin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxy amino) methyl]-heptanoyl}-hydrazine.

N'-[(6,7,9,10,12,13,15,16-Octahydro-5,8,11,14,17-pentaoxa-benzocyclopentadecen-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Benzo[1,3]dioxol-5-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Pentanoyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Benzoyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Trifluoroacetamido-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Hydroxy-naphthalen-2-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenylacetyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Furan-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Methoxybenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1H-Indol-3-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Dimethylaminobenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2-Hydroxybenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Piperidin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2,5,6-Tetrahydro-pyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(7-Methoxy-benzofuran-2-yl)carbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Chloro-4-methoxy-phenyl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1H-Pyrrol-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-7-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Pyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Chloro-3-methoxy-benzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-Methoxybenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Methyl-2-phenyl-oxazol-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinoxalin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-4-phenylbutanoyl}-hydrazine.

N-[(3-Methoxy-quinoxalin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,6-Dimethoxypyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(N"-Methylsulfonyl)-L-tyrosyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[5-Oxo-pyrrolidin-(2S)-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(4-(Pyrrol-1-yl)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Acetamidobenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Cyclopentyloxy-4-methoxy)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 7.80 (s, 1H), 7.30 (m, 4H), 4.55-3.20 (m, 5H), 2.85 (m, 1H), 1.85 (m, 1H), 1.65-1.24 (m, 7H), 0.93 (t, J = 6.2 Hz, 3 H). MH+ 380.

Example 72

N-[(Quinolin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.51-7.72 (m, 6H), 3.88 (m, 1H), 3.61 (m, 1H), 2.99 (m, 1H), 1.69 (m, 1H), 1.58-1.26 (m, 7H), 0.97 (t, J = 6.7 Hz, 3H). MH+ 373.

Example 73

N-[(1,2,3,4-Tetrahydro-quinolin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.36 (s, 1H), 7.48 (br s, 2H), 6.45 (d, J = 9.04 Hz, 1H), 3.96-3.32 (m, 4H), 2.91 (m, 1H), 2.77 (t, J = 6.12 Hz, 2H), 1.98 (m, 2H), 1.65 (m, 1H), 1.49 (m, 1H), 1.36 (m, 6H), 0.94 (br s, 3H). MH+ 377.

Example 74

N-[(Tetrahydro-furan-(2S)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.32 (s, 1H), 4.44 (m, 1H), 4.03 (m, 1H), 3.88 (m, 3H), 3.50 (m, 1H), 2.85 (m, 1H), 2.35-1.93 (m, 4H), 1.49 (m, 1H), 1.40 (m, 1H), 1.35 (m, 6H), 0.92 (t, J = 6.9 Hz, 3H). MH+ 316.

Example 75

N-[(Tetrahydro-furan-(2R)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.32 (s, 1H), 4.43 (m, 1H), 4.03 (m, 1H), 3.87 (m, 3H), 3.55 (m, 1H), 2.86 (m, 1H), 2.28-1.93 (m, 4H), 1.63 (m, 1H), 1.50 (m, 1H), 1.34 (m, 6H), 0.93 (br s, 3H). MH+ 316.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-3-cyclopentyl-propanoyl}-hydrazine.

N-[(7-Methoxy-benzofuran-2-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-3-cyclopentyl-propanoyl}-hydrazine.

N-[3-(Morpholin-4-yl)propanoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,3-Dihydro-benzofuran-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

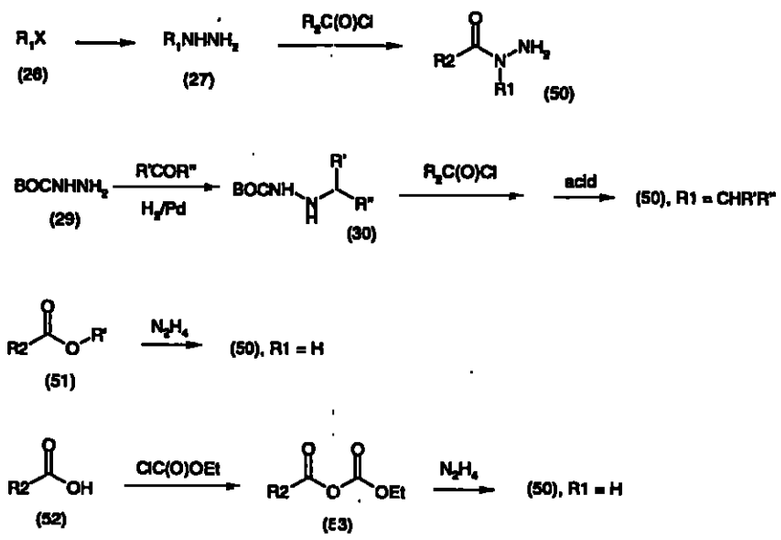
N-[(4,6-Dimethoxy-pyrimidin-2-yl)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Trifluoromethyl-5,6,7,8-tetrahydro-naphthyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(9H-beta-Carbolin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

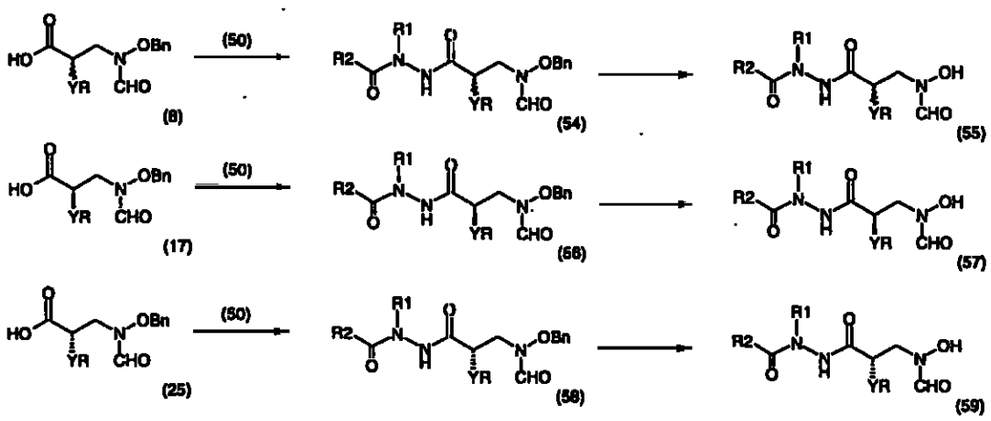
The following synthetic schemes are merely illustrative of the methods by which the compounds of the invention may be prepared and are not intended to limit the scope of the invention as defined in the appended claims.

As shown in Scheme 9, treatment of an alkyl halide R1X (26) with hydrazine in a solvent such as ethanol, at an elevated temperature, gives the hydrazine derivative (27). Reacting compound (27) with the acid chloride R2C(O)Cl affords intermediate (50). Alternatively, compound (50) can be prepared from the Boc-protected hydrazine (29) by reaction with the aldehyde or ketone R'COR", followed by reduction with hydrogen gas in the presence of palladium, to afford hydrazine derivative (30). Reacting hydrazine (30) with the acid chloride R2C(O)Cl, followed by removal of the Boc protecting group with an appropriate acid, such as trifluoroacetic acid, gives the hydrazine (50) wherein R1 = CHR'R". Alternatively, ester (51) can be submitted to hydrazinolysis to afford (50) wherein R1 = H. Alternatively, acid (52) can be reacted with ethyl chloroformate to form the intermediate mixed anhydride (53), which upon hydrazinolysis yields (50) wherein R1 = H.



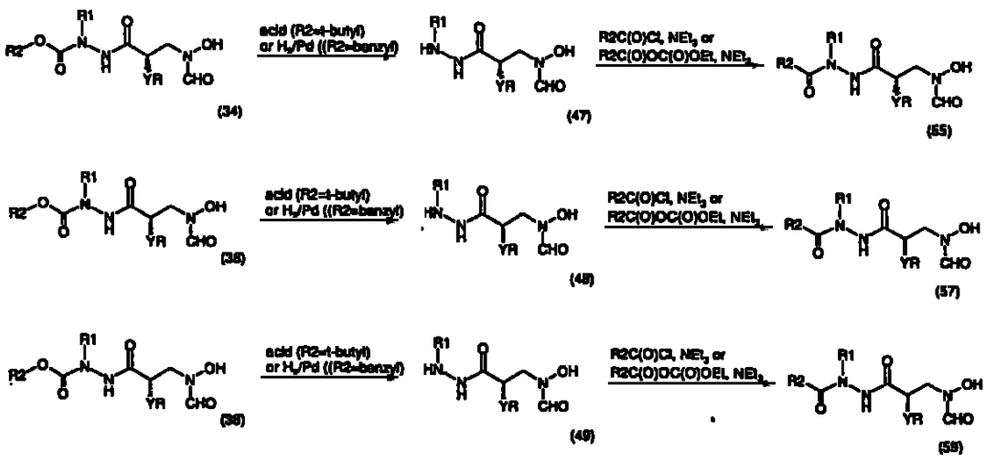
Scheme 9.

As shown in Scheme 10, coupling of the carboxylic acid (8) with the hydrazine derivative (50) provides acylated hydrazide (54). Hydrogenolysis to remove the benzyl group using a catalyst, such as 10% Pd/C, in an appropriate solvent, such as ethanol, gives compound (55). Similarly, coupling of the chiral acid (17) or (25) with hydrazine derivative (50) provides the corresponding hydrazide (56) or (58). Hydrogenolysis of the benzyl group gives the final compounds (57) or (59).



Scheme 10.

Alternatively, as shown in Scheme 11, the carbamate (34) wherein R2 = t-butyl or benzyl can be converted to the hydrazide (47) by acid treatment or hydrogenolysis, respectively. Reaction of (47) with the acyl chloride R2C(O)Cl or the mixed anhydride R2C(O)OC(O)OEt in an appropriate solvent, such as methylene chloride, and in the presence of an optional appropriate base, such as triethylamine, gives compound (55). Similarly, appropriate deprotection of the chiral carbamates (36) and (38), followed by reaction with an acyl chloride or a mixed anhydride, gives the chiral acylated hydrazide (57) or (59).



Scheme 11.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. The same experimental general conditions and conventions described in the Experimental Section of the Second Embodiment are applicable here.

The compounds disclosed in Examples 52 to 165 were prepared following the general procedures described in Example 1.

Example 52

N-[(Phenylaminocarbonyl)-carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 9.20 (s, 1H), 7.85 (s, 1H), 7.70-7.00 (m, 5H), 3.75 (m, 1H), 3.40 (m, 1H), 2.88 (m, 1H), 1.63 (m, 1H), 1.39-1.15 (m, 7H), 0.79 (t, J = 6.8 Hz, 3H). MH+ 365.

Example 53

N-Butyl-N-{[1-(t-butoxycarbonyl)-piperidin-4-yl]-carbonyl}-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (br s, 1H), 8.33 (br s, 1H), 7.81 (br s, 1H), 4.30-3.20 (m, 8H), 2.80-2.50 (m, 2H), 1.92-1.22 (m, 14H), 1.47 (s, 9H), 0.97-0.90 (m, 6H). MH+ 485.

Example 54

N-Butyl-N-{[(1-t-butoxycarbonyl)-pyrrolidin-(2S)-yl]carbonyl}-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (br s, 1H), 8.21 (s, 1H), 7.80 (s, 1H), 4.51-3.20 (m, 6H), 2.86 (m, 1H), 2.18-1.41 (m, 6H), 1.38 (s, 9H), 1.38-1.17 (m, 10H), 0.88 (m, 6H). MH+ 471.

Example 55

N-Butyl-N-{[(1-t-butylaminocarbonyl)piperidin-4-yl]carbonyl}]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (br s, 1H), 8.38 (s, 1H), 4.15-3.47 (m, 8H), 2.89 (m, 1H), 2.67 (m, 1H), 1.75-1.26 (m, 16H), 1.37 (s, 9H), 0.99-0.90 (m, 6H). MH+ 484.

Example 56

N-Butyl-N-{[(1-t-butylcarbonyl)piperidin-4-yl]carbonyl}]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.25 (s, 1H), 7.80 (s, 1H), 4.39-3.34 (m, 8H), 2.95 (m, 1H), 2.79 (m, 1H), 1.89-1.25 (m, 16H), 1.29 (s, 9H), 0.99-0.90 (m, 6H). MH+ 469.

Example 57

N-Butyl-N-[(1,2,3,4-tetrahydro-quinoxalin-2-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (s, 1H), 8.20 (s, 1H), 7.80 (s, 1H), 6.70-6.51 (m, 4H), 4.16-3.22 (m, 6H), 2.87 (m, 1H), 2.75 (m, 1H), 1.64-1.26 (m, 12H), 0.97-0.87 (m, 6H). MH+ 434.

Example 58

N-(p-Methoxyphenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H), 8.30 (s, 1H), 7.50 (s, 1H), 7.24 (d, J = 16.3 Hz, 2H), 6.90 (d, J = 16.3 Hz, 2H), 3.95-3.38 (m, 4H), 3.77 (s, 3H), 2.83 (m, 1H), 1.64 (m, 1H), 1.34 (m, 1H), 1.29 (m, 6H), 0.86 (t, J = 6.3 Hz, 3H). MH+ 366.

Example 59

N-Phenoxyacetyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 352.

Example 60

N-[(p-Methoxy-phenoxy)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.53 (s, 1H), 7.48 (s, 1H), 6.79-6.73 (m, 4H), 4.49 (m, 2H), 3.73 (s, 3H), 3.44 (m, 2H), 2.82 (m, 1H), 1.64 (m, 1H), 1.25 (m, 1H), 1.24-1.19 (m, 6H), 0.80 (t, J = 6.7 Hz, 3H). MH+ 382.

Example 61

N-(2,6-Dichlorophenyl-acetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.80 (s, 1H), 7.30-7.10 (m, 3H), 4.09 (s, 2H), 3.85-3.50 (m, 2H), 2.90 (m, 1H), 1.80-1.28 (m, 6H), 0.89 (br s, 3H). MH+ 405.

Example 62

N-(3,4-Dichlorophenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.91 (s, 1H), 7.20-7.10 (m, 3H), 3.45-3.10 (m, 2H), 3.25 (br s, 2H), 1.85 (m, 1H), 1.62 (m, 1H), 1.45 (m, 1H), 1.32 (m, 6H), 0.91 (br s, 3H). MH+ 405.

Example 63

N-(Ethoxycarbonyl)carbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 9.27 (s, 1H), 7.77 (s, 1H), 4.37 (m, 2H), 3.90 (m, 1H), 3.51 (m, 1H), 2.96 (m, 1H), 1.71 (m, 1H), 1.41 (m, 1H), 1.40-1.32 (m, 9H), 0.91 (br s, 3H). MH+ 318.

Example 64

N-(2,4-Dichlorophenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.80 (s, 1H), 7.50-7.20 (m, 3H), 3.82 (m, 2H), 3.55 (m, 2H), 2.85 (m, 1H), 1.85 (m, 1H), 1.61 (m, 1H), 1.45-1.22 (m, 6H), 0.85 (br s, 3H). MH+ 405.

Example 65

N-[(Benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.68 (s, 1H), 7.78 (s, 1H), 7.54-7.06 (m, 5H), 4.15-3.30 (m, 2H), 2.95 (m, 1H), 1.85 (m, 1H), 1.62 (m, 1H), 1.27-1.18 (m, 6H), 0.84 (br s, 3H). MH+ 362.

Example 66

N-(2,3-Dichlorophenoxyacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 7.88 (br s, 1H), 7.28-7.14 (m, 3H), 4.73 (m, 2H), 3.76 (m, 1H), 3.49 (m, 1H), 2.90 (m, 1H), 1.74 (m, 1H), 1.41-1.28 (m, 7H), 0.90 (br s, 3H). MH+ 421.

Example 67

N-(3,4-Dimethoxyphenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 7.58 (s, 1H), 6.83 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.74-3.44 (m, 4H), 1.65 (m, 1H), 1.36 (m, 1H), 1.29-1.23 (m, 6H), 0.88 (t, J = 6.5 Hz, 3H). MH+ 396.

Example 68

N-[(1H-Indol-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (s, 1H), 8.50 (s, 1H), 7.81 (s, 1H), 7.50-6.80 (m, 5H), 4.20-3.45 (m, 2H), 2.95 (m, 1H), 1.82 (m, 1H), 1.75-1.20 (m, 7H), 1.00 (br s, 3H). MH+ 396.

Example 69

N-[(2-Methyl-pyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.80 (s, 1H), 7.70-7.00 (m, 3H), 3.84 (m, 1H), 3.50 (m, 1H), 2.58 (s, 1H), 1.73 (m, 1H), 1.44 (m, 1H), 1.43-1.27 (m, 6H), 0.89 (br s, 3H). MH+ 337.

Example 70

N-[(5-Methoxy-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (s, 1H), 8.50 (s, 1H), 7.85 (s, 1H), 7.50-6.80 (m, 4H), 3.90 (m, 1H), 3.80 (s, 3H), 3.55 (m, 1H), 3.00 (m, 1H), 1.85 (m, 1H), 1.60-1.25 (m, 7H), 0.95 (br s, 3H). MH+ 392.

Example 71

N-[(2,3-Dihydro-benzo[1,4]dioxin-(2S)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

67
65

Example 76

N-[(3-Methyl-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.54-7.20 (m, 4H), 4.04 (m, 1H), 3.48 (m, 1H), 2.97 (s, 3H), 2.59 (m, 1H), 1.66 (m, 1H), 1.28 (m, 1H), 1.27 (m, 6H), 0.83 (t, J = 6.7 Hz, 3H). MH+ 376.

Example 77

N-[(Pyridin-2-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.48 (s, 1H), 7.90-7.33 (m, 4H), 4.00-3.50 (m, 4H), 2.87 (m, 1H), 1.62 (m, 1H), 1.46 (m, 1H), 1.33 (m, 6H), 0.90 (br s, 3H). MH+ 337.

Example 78

N-{3-[3-(4-Methoxybenzyl)-1H-benzoimidazol-2-yl]-propanoyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.31 (s, 1H), 7.61 (m, 1H), 7.42 (m, 1H), 7.25 (m, 2H), 7.10 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.46 (s, 2H), 3.77 (s, 3H), 3.90-3.50 (m, 2H), 3.23 (m, 2H), 2.85 (m, 2H), 2.69 (m, 1H), 1.65 (m, 1H), 1.61 (m, 1H), 1.33 (m, 6H), 0.92 (m, 3H). MH+ 510.

Example 79

N-[(Pyrimidin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 9.26 (s, 1H), 8.84 (s, 1H), 8.72 (s, 1H), 7.95 (s, 1H), 3.85-3.40 (m, 2H), 2.86 (m, 1H), 1.67 (m, 1H), 1.47 (m, 1H), 1.37 (m, 6H), 0.94 (t, J = 6.8 Hz, 3H). MH+ 324.

68
66

Example 80

N-[(2-Methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.92 (s, 1H), 7.44 (s, 1H), 3.90-3.60 (m, 2H), 3.43 (m, 2H), 2.94 (m, 1H), 2.75 (m, 2H), 2.47 (s, 3H), 1.98 (m, 2H), 1.66 (m, 1H), 1.45 (m, 1H), 1.37 (m, 6H), 0.94 (br s, 3H). MH+ 392.

Example 81

N-[(Isoquinolin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 9.17 (s, 1H), 8.48 (s, 1H), 8.03-7.73 (m, 5H), 4.03-3.99 (m, 1H), 3.59 (m, 1H), 2.70 (m, 1H), 1.71 (m, 1H), 1.43 (m, 1H), 1.26 (m, 6H), 0.86 (t, J = 6.7 Hz, 3H). MH+ 373.

Example 82

N-[(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.93 (br s, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.21 (d, J 7.31 Hz, 1H), 3.82 (m, 1H), 3.55 (m, 1H), 3.43 (br s, 2H), 2.94 (m, 1H), 2.80 (br s, 2H), 1.92 (m, 2H), 1.65 (m, 1H), 1.60-1.09 (m, 7H), 0.94 (br s, 3H). MH+ 378.

Example 83

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (s, 1H), 7.60 (s, 1H), 7.33 (m, 5H), 3.90-3.42 (m, 4H), 2.83 (m, 1H), 1.67 (m, 1H), 1.32-1.20 (m, 5H), 0.89 (t, J = 6.7 Hz, 3H). MH+ 322.

Example 84

N-[(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, J = 9.2 Hz, 1H), 7.82 (s, 1H), 7.45-7.28 (m, 2H), 4.30-3.40 (m, 6H), 2.96 (m, 1H), 2.22 (m, 2H), 1.70 (m, 1H), 1.55 (m, 1H), 1.35-1.23 (m, 6H), 0.88 (t, J = 6.7 Hz, 3H). MH+ 394.

Example 85

N-[(1-Methyl-2,5-dioxo-imidazolidin-4-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (s, 1H), 4.39 (m, 1H), 3.84-3.50 (m, 2H), 2.97 (s, 3H), 2.85 (m, 1H), 2.67 (m, 1H), 1.62 (m, 1H), 1.49 (m, 1H), 1.34 (m, 6H), 0.93 (br s, 3H). MH+ 372.

Example 86

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-3-phenyl-propanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (br s, 1H), 8.10 (s, 1H), 7.22 (m, 10H), 3.96-3.43 (m, 4H), 3.15 (m, 1H), 3.02 (m, 1H), 2.70 (m, 1H). MH+ 356.

Example 87

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-3-(3,4-dichloro)phenyl-propanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (br s, 1H), 7.60 (s, 1H), 7.37-7.00 (m, 8H), 4.17-3.51 (m, 4H), 3.05 (m, 1H), 2.95 (m, 1H), 2.65 (m, 1H). MH+ 424.

Example 88

N-[(4-Imidazol-1-yl)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.37-7.71 (m, 7H), 7.21 (s, 1H), 3.87 (m, 1H), 3.71-3.57 (m, 1H), 2.95 (m, 1H), 1.67 (m, 1H), 1.54 (m, 1H), 1.37 (m, 6H), 0.95 (t, J = 6.7 Hz, 3H). MH+ 388.

Example 89

N-{[1-Methyl-5-oxo-2-S-(pyridin-3-yl)-pyrrolidin-(3S)-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.57 (m, 1H), 7.90 (s, 1H), 7.84 (m, 1H), 7.55 (m, 1H), 3.79 (m, 1H), 3.53 (m, 1H), 3.08 (m, 1H), 2.92-2.69 (m, 3H), 2.68 (s, 3H), 1.62 (m, 1H), 1.47 (m, 1H), 1.35 (m, 6H), 0.93 (br s, 3H). MH+ 420.

Example 90

N-[(1,2-Dihydro-cinnolin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.91 (s, 1H), 7.22 (m, 2H), 6.98 (m, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.64 (m, 1H), 4.36 (br s, 1H), 3.79 (m, 1H), 3.53 (m, 1H), 2.87 (m, 1H), 1.63 (m, 1H), 1.48 (m, 1H), 1.34 (m, 6H), 0.92 (br s, 3H). MH+ 376.

Example 91

N-[4-(4-Acetylpiperazin-1-yl)phenoxyacetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.92 (s, 1H), 4.60 (br s, 2H), 3.90-3.50 (m, 6H), 3.07 (m, 4H), 3.04 (m, 1H), 2.16 (s, 3H), 1.62 (m, 1H), 1.51 (m, 1H), 1.35 (m, 6H), 0.93 (br s, 3H). MH+ 478.

Example 92

N-Phenylacetyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.30 (s, 1H), 7.90 (s, 1H), 7.32 (br s, 5H), 3.84-3.47 (m, 4H), 2.84 (m, 1H), 1.62 (m, 1H), 1.44 (m, 1H), 1.32 (m, 6H), 0.90 (br s, 3H). MH+ 336.

Example 93

N-{[1-Benzyl-5-oxo-pyrrolidin-(2S)-yl]-carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 9.20 (s, 1H), 7.63 (s, br s, 1H), 7.13 (m, 5H), 4.92 (m, 1H), 3.94-3.31 (m, 4H), 2.82 (m, 1H), 2.60-1.90 (m, 4H), 1.49 (m, 1H), 1.23 (m, 1H), 1.11 (m, 6H), 0.85 (t, J = 6.7 Hz, 3H). MH+ 419.

Example 94

N-{[1-Benzyl-5-oxo-pyrrolidin-(2R)-yl]-carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 9.45 (br s, 1H), 7.82 (s, 1H), 7.30 (m, 5H), 5.06 (m, 1H), 4.10-3.50 (m, 4H), 2.95 (m, 1H), 2.85-2.10 (m, 4H), 1.67 (m, 1H), 1.41-1.26 (m, 7H), 0.87 (t, J = 6.7 Hz, 3H). MH+ 419.

Example 95

N-[(5S)-Benzyl-3,6-dioxo-piperazin-(2S)-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (s, 1H), 7.38-7.23 (m, 5H), 4.34-4.21 (m, 2H), 3.82 (m, 1H), 3.49 (m, 1H), 3.31 (m, 1H), 3.06 (m, 1H), 2.85 (m, 1H), 1.57 (m, 1H), 1.46 (m, 1H), 1.34 (m, 6H), 0.92 (t, J = 6.7 Hz, 3H). MH+ 462.

Example 96

N-[(Quinolin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (br s, 1H), 8.30-7.40 (m, 6H), 3.90 (m, 1H), 3.51 (m, 1H), 3.12 (m, 1H), 1.69 (m, 1H), 1.41 (m, 1H), 1.30 (m, 6H), 0.86 (t, J = 6.7 Hz, 3H). MH+ 373.

Example 97

N-[(Quinolin-8-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 9.03 (m, 1H), 8.66 (t, J = 6.3 Hz, 1H), 8.46 (m, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.84 (s, 1H), 7.67 (m, 2H), 3.84-3.30 (m, 2H), 1.66 (m, 1H), 1.43-1.18 (m, 7H), 0.82 (t, J = 6.7 Hz, 3H). MH+ 373.

Example 98

N-[(1,2,3,4-Tetrahydroquinolin-8-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.83 (s, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.91 (m, 1H), 6.34 (m, 1H), 3.71 (m, 1H), 3.50 (m, 1H), 3.26 (t, J = 5.6 Hz, 2H), 2.81 (m, 1H), 2.66 (t, J = 6.2 Hz, 2H), 1.77 (m, 2H), 1.55 (m, 1H), 1.40 (m, 1H), 1.38 (m, 1H), 1.25 (m, 6H), 0.83 (t, J = 6.7 Hz, 3H). MH+ 377.

Example 99

N-(N''-Acetyl-L-tyrosyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.91 (s, 1H), 7.09 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 4.62 (m, 1H), 3.87 (m, 1H), 3.57 (m, 1H), 3.12 (dd, J = 14.0, 4.6 Hz, 1H), 2.85 (m, 2H), 2.72 (m, 1H), 1.91 (s, 3H), 1.65 (m, 1H), 1.48 (m, 1H), 1.34 (m, 6H), 0.92 (t, J = 6.7 Hz, 3H). MH+ 423.

Example 100

N-[(1-Acetyl-1,2,3,4-tetrahydro-quinolin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxy amino) methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.75 (m, 3H), 3.85 (m, 1H), 3.82 (t, J = 6.4 Hz, 2H), 3.56 (m, 1H), 2.95 (m, 1H), 2.83 (t, J = 6.5 Hz, 2H), 2.05 (s, 3H), 2.00 (m, 2H), 1.65 (m, 1H), 1.52 (m, 1H), 1.37 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 419.

Example 101

N-[(1H-Benzoimidazol-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (br s, 1H), 7.70 (br s, 2H), 7.32 (br s, 2H), 3.98-3.50 (m, 2H), 2.98 (m, 1H), 1.69 (m, 1H), 1.55 (m, 1H), 1.45 (m, 6H), 0.88 (t, J = 6.7 Hz, 3H). MH+ 362.

Example 102

N-{[1-(2-Hydroxyacetyl)-1,2,3,4-tetrahydro-quinolin-6-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.81 (s, 1H), 7.70-7.50 (m, 3H), 4.27 (s, 2H), 3.75 (m, 1H), 3.60 (m, 2H), 3.55 (m, 1H), 2.81 (m, 1H), 2.72 (m, 2H), 2.85 (m, 2H), 3.55 (m, 1H), 2.81 (m, 1H), 2.72 (m, 2H), 2.85 (m, 2H), 1.55 (m, 1H), 1.45 (m, 1H), 1.25 (m, 6H), 0.82 (t, J = 6.7 Hz, 3H). MH+ 435.

Example 103

N-[(1H-Indol-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.25 (br s, 1H), 7.95 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.46 (m, 1H), 7.35 (br s, 1H), 6.59 (br s, 1H), 3.95 (m, 1H), 3.59 (m, 1H), 2.96 (m, 1H), 1.66 (m, 1H), 1.54 (m, 1H), 1.36 (m, 6H), 0.95 (t, J = 6.7 Hz, 3H). MH+ 361.

Example 104

N-{4-[Methyl-(4,6-dimethylpyrimidin-2-yl)-amino]benzoyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine).

^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (s, 1H), 7.88 (m, 2H), 7.46 (m, 2H), 6.57 (s, 1H), 3.91 (m, 1H), 3.62 (m, 1H), 3.57 (s, 3H), 2.96 (m, 1H), 2.29 (s, 6H), 1.68 (m, 1H), 1.52 (m, 1H), 1.37 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 457.

Example 105

N-[(1-Benzo[1,3]dioxol-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (s, 1H), 7.49 (m, 1H), 7.36 (s, 1H), 6.92 (dd, J = 8.2, 2.5 Hz, 1H), 6.06 (s, 2H), 3.92 (m, 1H), 3.58 (m, 1H), 2.93 (m, 1H), 1.63 (m, 1H), 1.49 (m, 1H), 1.38 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 366.

Example 106

N-{[4-(3,5-Dimethyl-pyrazol-1-yl)methyl]benzoyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 5.97 (s, 1H), 5.33 (s, 2H), 3.88 (m, 1H), 3.57 (m, 1H), 2.95 (m, 1H), 2.22 (s, 3H), 2.20 (s, 3H), 1.59 (m, 1H), 1.44 (m, 1H), 1.26 (m, 6H), 0.93 (t, J = 6.7 Hz, 3H). MH+ 430.

Example 107

N-[4-(Morpholin-4-yl)-benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.81 (d, J = 6.6 Hz, 2H), 7.00 (d, J = 6.6 Hz, 2H), 3.96 (m, 1H), 3.84 (m, 4H), 3.60 (m, 1H), 3.28 (m, 4H), 2.94 (m, 1H), 1.67 (m, 1H), 1.53 (m, 1H), 1.37 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 407.

Example 108

N-[4-Hydroxy-3-(morpholin-4-yl)methyl-benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 3.85 (m, 2H), 3.80 (m, 1H), 3.74 (m, 4H), 3.55 (m, 1H), 2.93 (m, 1H), 2.68 (br s, 4H), 1.66 (m, 1H), 1.50 (m, 1H), 1.38 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 444.

Example 109

N-(3-Hydroxy-3-methyl-butanoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 3.82 (m, 1H), 3.55 (m, 1H), 2.86 (m, 1H), 2.42 (d, J = 5.7 Hz, 2H), 1.56 (m, 1H), 1.44 (m, 1H), 1.43-1.29 (m, 15 H), 0.93 (t, J = 6.7 Hz, 3H). MH+ 318.

Example 110

N-(4-Methylamino-benzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.73 (d, J = 7.7 Hz, 2H), 6.60 (d, J = 7.7 Hz, 2H), 3.96 (m, 1H), 3.58 (m, 1H), 2.93 (m, 1H), 2.83 (s, 3H), 1.52 (m, 1H), 1.38 (m, 1H), 1.26 (m, 6H), 0.94 (t, J 6.7 Hz, 3H). MH+ 351.

Example 111

N-[(1-Isopropyl-1H-benzotriazol-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.75 (s, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 5.26 (m, 1H), 3.86 (m, 1H), 3.65 (m, 1H), 2.96 (m, 1H), 1.75 (d, J = 6.8 Hz, 6H), 1.70 (m, 1H), 1.56 (m, 1H), 1.28 (m, 6H), 0.95 (t, J = 6.7 Hz, 3H). MH+ 405.

Example 112

N-[(1,2,3,4-Tetrahydro-isoquinolin-(3S)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (s, 1H), 7.20 (m, 4H), 4.30-3.40 (m, 5H), 3.10 (m, 1H), 2.90 (m, 1H), 2.72 (m, 1H), 1.65 (m, 1H), 1.50 (m, 1H), 1.36 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 377.

Example 113

N-[(5-Chloro-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.79 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 5.1 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 3.86 (m, 1H), 3.55 (m, 1H), 3.95 (m, 1H), 1.65 (m, 1H), 1.55 (m, 1H), 1.36 (m, 6H), 0.95 (t, J = 6.8 Hz, 3H). MH+ 396.

Example 114

N-{[1-(Dimethylaminocarbonylmethyl)-3,4-dihydro-2H-quinolin-6-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (br s, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.51 (s, 1H), 6.38 (d, J = 8.3 Hz, 1H), 4.28 (s, 2H), 3.95 (m, 1H), 3.63 (m, 1H), 3.41 (t, J = 5.4 Hz, 2H), 3.13 (s, 3H), 2.98 (s, 3H), 2.97 (m, 1H), 2.83 (t, J = 5.4 Hz, 2H), 1.99 (m, 4H), 1.65 (m, 1H), 1.50 (m, 1H), 1.36 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 462.

Example 115

N-[(2,2-Difluoro-benzo[1,3]dioxol-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.59 (m, 1H), 7.42 (m, 1H), 7.30 (m, 1H), 3.85 (m, 1H), 3.54 (m, 1H), 2.95 (m, 1H), 1.64 (m, 1H), 1.54 (m, 1H), 1.38 (m, 6H), 0.94 (t, J 6.7 Hz, 3H). MH+ 402.

Example 116

N-[(5-Amino-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.35 (m, 2H), 6.96 (m, 2H), 3.84 (m, 1H), 3.54 (m, 1H), 2.82 (m, 1H), 1.67 (m, 1H), 1.38 (m, 1H), 1.37 (m, 6H), 0.95 (t, J = 6.7 Hz, 3H). MH+ 377.

Example 117

N-[(4-Oxo-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.90 (br s, 1H), 7.95 (s, 1H), 7.66 (m, 1H), 7.58 (m, 1H), 7.34 (m, 1H), 4.52 (br s, 2H), 3.85 (m, 1H), 3.54 (m, 1H), 3.52 (m, 2H), 2.92 (m, 1H), 1.64 (m, 1H), 1.36-1.24 (m, &H), 0.94 (t, J = 6.8 Hz, 3H). MH+ 415.

Example 118

N-[(7-Hydroxy-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.55 (m, 1H), 7.21-7.13 (m, 2H), 6.92 (m, 1H), 3.89 (m, 1H), 3.68 (m, 1H), 2.92 (m, 1H), 1.66 (m, 1H), 1.54 (m, 1H), 1.37 (m, 6H), 0.94 (t, J = 6.8 Hz, 3H). MH+ 378.

Example 119

N-[(6-Methoxy-benzofuran-2-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.91 (s, 1H), 7.63 (s, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.05 (d, J = 1.9 Hz, 1H), 6.88 (dt, J = 8.6, 2.2 Hz, 1H), 3.84 (s, 3H), 3.76 (m, 1H), 3.64 (d, J = 7.2 Hz, 2H), 3.53 (m, 1H), 2.86 (m, 1H), 1.65 (m, 1H), 1.48 (m, 1H), 1.26 (m, 1H), 0.92 (t, J = 6.7 Hz, 3H). MH+ 406.

Example 120

N-[(5-Acetamidobenzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.36 (s, 1H), 8.04 (br s, 1H), 7.54 (m, 3H), 3.85 (m, 1H), 3.54 (m, 1H), 2.94 (m, 1H), 2.17 (s, 3H), 1.54 (m, 1H), 1.52 (m, 1H), 1.37 (m, 6H), 0.95 (t, J = 6.8 Hz, 3H). MH+ 419.

Example 121

N-[(2,3-Dihydro-benzo[1,4]dioxin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (s, 1H), 7.42 (m, 2H), 6.92 (m, 1H), 4.31 (m, 4H), 3.85 (m, 1H), 3.55 (m, 1H), 2.93 (m, 1H), 1.65(m, 1H), 1.51 (m, 1H), 1.37 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 380.

Example 122

N-[(3-Amino-4,6-dimethyl-furo[2,3-b]pyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.02 (s, 1H), 3.97 (m, 1H), 3.60 (m, 1H), 2.93 (m, 1H), 2.70 (s, 3H), 2.57 (s, 3H), 1.66 (m, 1H), 1.52 (m, 1H), 1.38 (m, 6H), 0.95 (t, J = 6.7 Hz, 3H). MH+ 406.

Example 123

N-[(2-Methyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.69 (br s, 1H), 3.71 (m, 1H), 3.45 (m, 1H), 3.05 (m, 2H), 2.90 (m, 2H), 2.68 (m, 2H), 2.50 (s, 3H), 1.65 (m, 1H), 1.48 (m, 1H), 1.36 (m, 6H), 0.95 (t, J = 6.7 Hz, 3H). MH+ 392.

Example 124

N-[(6-Fluoro-4H-benzo[1,3]dioxin-8-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.55 (dd, J = 9.2, 2.8 Hz, 1H), 7.07 (dd, J = 7.8, 3.4 Hz, 1H), 5.40 (s, 2H), 4.97 (s, 2H), 3.86 (m, 1H), 3.65 (m, 1H), 2.95 (m, 1H), 1.67 (m, 1H), 1.51 (m, 1H), 1.26 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 398.

Example 125

N-[(7-Amino-1H-indol-2-yl)carbonyl)]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (s, 1H), 7.12 (d, J = 6.3 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.89 (m, 1H), 6.60 (m, 1H), 3.90 (m, 1H), 3.55 (m, 1H), 2.95 (m, 1H), 1.67 (m, 1H), 1.51 (m, 1H), 1.26 (m, 6H), 0.94 (t, J = 6.7 Hz, 3H). MH+ 376.

Example 126

N-[(1-Methyl-1,2,3,4-tetrahydro-quinolin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxy amino) methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (s, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.49 (s, 1H), 6.59 (d, J = 8.7 Hz, 1H), 3.85 (m, 1H), 3.55 (m, 1H), 3.36 (m, 2H), 2.97 (s, 3H), 2.80 (t, J = 6.3 Hz, 2H), 1.96 (m, 2H), 1.66 (m, 1H), 1.51 (m, 1H), 1.26 (m, 6H), 0.93 (t, J = 6.7 Hz, 3H). MH+ 391.

Example 127

N'-[(6,7,9,10,12,13,15,16-Octahydro-5,8,11,14,17-pentaoxa-benzocyclopentadecen-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 7.50 (m, 1H), 7.49 (s, 1H), 7.01 (dd, J 8.4, 3.1 Hz, 1H), 4.18 (m, 4H), 3.89 (m, 4H), 3.86 (m, 1H), 3.73 (br s, 8H), 3.56 (m, 1H), 2.96 (m, 1H), 1.67 (m, 1H), 1.51 (m, 1H), 1.26 (m, 6H), 0.93 (t, J = 6.7 Hz, 3H). MH+ 512.

Example 128

N-[(2-Benzo[1,3]dioxol-5-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H), 6.85 (s, 1H), 6.77 (m, 2H), 5.93 (s, 2H), 3.84 (m, 1H), 3.56 (m, 1H), 3.49 (d, J = 6.2 Hz, 2H), 2.86 (m, 1H), 1.60 (m, 1H), 1.48 (m, 1H), 1.34 (m, 6H), 0.92 (t, J = 6.9 Hz, 3H). MH+ 380.

Example 129

N-Pentanoyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (m, 1H), 9.46 (s, 1H), 9.05 (d, J = 3.5 Hz, 2H), 7.75 (s, 1H), 3.98-3.43 (m, 2H), 2.88 (m, 1H), 2.28 (m, 2H), 1.67 (m, 2H), 1.51-1.22 (m, 10H), 0.89 (m, 3H). MH+ 302.

Example 130

N-Benzoyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.75 (m, 2H), 7.51-7.20 (m, 3H), 3.86-3.27 (m, 2H), 3.03 (s, 2H), 2.82-2.65 (m, 1H), 1.62 (m, 1H), 1.41-1.12 (m, 7H), 0.89 (m, 3H). MH+ 322.

Example 131

N-Trifluoroacetamido-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 9.08 (s, 1H), 4.25-3.45 (m, 2H), 2.91 (m, 1H), 1.69 (m, 1H), 1.61-1.21 (m, 7H), 0.88 (m, 3H). MH+ 314.

Example 132

N-[(3-Hydroxy-naphthalen-2-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.97 (s, 1H), 7.81 (m, 1H), 7.68 (m, 1H), 7.52 (m, 1H), 7.35-7.21 (m, 1H), 3.90-3.51 (m, 2H) 3.02 (m, 1H), 1.67 (m, 1H), 1.59-1.21 (m, 7H), 0.88 (m, 3H). MH+ 388.

Example 133

N-Phenylacetyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 9.33 (s, 1H), 8.93 (s, 1H), 8.21 (s, 1H), 7.15 (m, 5H), 3.72-3.25 (m, 6H) 2.75-2.50 (m, 1H), 1.52 (m, 1H), 1.32-1.09 (m, 7H), 0.78 (m, 3H). MH+ 336.

Example 134

N-[(Furan-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.78 (s, 1H), 7.31 (s, 1H), 7.21-7.11 (m, 3H), 6.35 (m, 1H), 5.31 (s, 1H), 4.15-3.43 (m, 2H) 3.00-2.65 (m, 1H), 1.75 (m, 1H), 1.62-1.20 (m, 7H), 0.90 (m, 3H). MH+ 312.

Example 135

N-(4-Methoxybenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (m, 1H), 6.89 (d, 1H), 6.72 (d, 1H), 4.05-3.40 (m, 5H) 3.00-2.58 (m, 1H), 1.82-1.11 (m, 8H), 0.88 (m, 3H). MH+ 352.

Example 136

N-[(1H-Indol-3-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.48 (m, 1H), 7.36-6.94 (m, 4H), 3.89-3.19 (m, 4H) 2.71-2.42 (m, 1H), 2.02-1.04 (m, 8H), 0.76 (m, 3H). MH+ 375.

Example 137

N-(4-Dimethylaminobenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40(s, 1H), 7.71 (m, 2H), 6.61 (m, 2H), 4.05-3.38 (m, 2H) 3.02 (d, J = 8 Hz, 6H), 2.93-2.55 (m, 1H), 1.68 (m, 1H), 1.52-1.21 (m, 7H), 0.89 (m, 3H). MH+ 365.

Example 138

N-(2-Hydroxybenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.82-7.57 (m, 2H), 7.41-6.81 (m, 2H), 6.65 (m, 1H), 3.95-3.35 (m, 2H) 3.00-2.57 (m, 1H), 1.75-1.05 (m, 8H), 0.89 (m, 3H). MH+ 338.

Example 139

N-[(Piperidin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.81 (s, 1H), 4.04-3.32 (m, 5H), 3.12-2.72 (m, 2H), 2.62-2.28 (m, 2H), 2.05-1.85 (m, 5H), 1.60 (m, 1H) 1.50-1.18 (m, 7H), 0.85 (m, 3H). MH+ 329.

Example 140

N-[(1,2,5,6-Tetrahydro-pyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.50 (s, 1H), 8.42 (s, 1H), 7.85 (m, 1H), 7.60-7.12 (m, 2H), 4.75 (m, 1H), 4.11 (m, 1H), 3.81-3.20 (m, 2H) 2.85-2.50 (m, 1H), 2.35-2.20 (m, 2H), 1.90 (m, 1H), 1.81-1.15 (m, 8H), 0.81 (m, 3H). MH+ 327.

Example 141

N-[(7-Methoxy-benzofuran-2-yl)carbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (s, 1H), 7.55 (m, 1H), 7.30 (m, 1H), 7.05 (m, 1H), 4.01 (s, 3H), 3.52-3.89 (m, 2H), 2.99 (M, 1H), 1.65 (m, 1H), 1.53 (m, 1H), 1.40 (m, 6H), 0.95 (m, 3H). MH+ 392.

Example 142

N-[(3-Chloro-4-methoxy-phenyl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 400.

Example 143

N-[(1H-Pyrrol-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 311.

Example 144

N-[(Quinolin-7-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 373.

Example 145

N-[(Pyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 323.

Example 146

N-(4-Chloro-3-methoxy-benzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 386.

Example 147

N-(3-Methoxybenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 352.

Example 148

N-[(Quinolin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 373.

Example 149

N-[(5-Methyl-2-phenyl-oxazol-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
MH+ 403.

Example 150

N-[(Quinoxalin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
MH+ 374.

Example 151

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-4-phenylbutanoyl}-hydrazine.
MH+ 370.

Example 152

N-[(3-Methoxy-quinoxalin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
MH+ 404.

Example 153

N-[(2,6-Dimethoxypyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
MH+ 383.

Example 154

N-[(N''-Methylsulfonyl)-L-tyrosyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
MH+ 459.

Example 155

N-{[5-Oxo-pyrrolidin-(2S)-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
MH+ 329.

Example 156

N-[(4-(Pyrrol-1-yl)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
MH+ 387.

Example 157

N-(4-Acetamidobenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
MH+ 379.

Example 158

N-[(3-Cyclopentyloxy-4-methoxy)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
MH+ 436.

Example 159

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-3-cyclopentyl-propanoyl}-hydrazine.
MH+ 348.

Example 160

N-[(7-Methoxy-benzofuran-2-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-3-cyclopentyl-propanoyl}-hydrazine.
MH+ 404.

Example 161

N-[3-(Morpholin-4-yl)propanoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 359.

Example 162

N-[(2,3-Dihydro-benzofuran-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 364.

Example 163

N-[(4,6-Dimethoxy-pyrimidin-2-yl)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 460.

Example 164

N-[(2-Trifluoromethyl-5,6,7,8-tetrahydro-naphthyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

MH+ 446.

Example 165

N-[(9H-beta-Carbolin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

^{1}H NMR (400 MHz, CD_3OD): δ 8.20 (m, 1H), 8.59 (m, 1H), 8.05 (m, 1H), 7.80 (s, 1H), 7.46 (m, 2H), 7.16 (m, 1H), 7.75 (m, 1H), 3.43 (m, 1H), 2.89 (m, 1H), 1.56 (m, 1H), 1.43 (m, 1H), 1.30 (m, 6H), 0.83 (t, J = 6.7 Hz, 3H). MH+ 412.

COMPOSITIONS, ADMINISTRATION AND BIOLOGICAL ASSAYS

Compounds of Formula (1) and their pharmaceutically acceptable salts may be administered in a standard manner for antibiotics, for example orally, parenterally, sub-lingually, dermally, transdermally, rectally, via inhalation or via buccal administration.

Compositions of Formula (1) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules, creams and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example, using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example, aqueous gums, celluloses, silicates or oils, and incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example, polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example, polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example, a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg/Kg, of a compound of Formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (1).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg of a compound of Formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg of a compound of Formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (1) are demonstrated by the following test:

Biological Assay

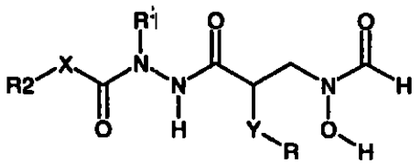
S. aureus or E. coli PDF activity is measured at 25°C, using a continuous enzyme-linked assay developed by Lazennec & Meinnel ("Formate dehydrogenase-coupled spectrophotometric assay of peptide deformylase", Anal. Biochem. 1997, 244, pp.180-182), with minor modifications. The reaction mixture is contained in 50 uL with 50 mM potassium phosphate buffer (pH 7.6), 15 mM NAD, 0.25 U formate dehydrogenase. The substrate peptide, f-Met-Ala-Ser, is included at the K_M concentration. The reaction is triggered with the addition of 10 nM Def1 enzyme, and absorbance is monitored for 20 min at 340 nm.

Antimicrobial Activity Assay

Whole-cell antimicrobial activity was determined by broth microdilution using the National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A4, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically" (incorporated by reference herein). The compound was tested in serial two-fold dilutions ranging from 0.06 to 64 mcg/ml. A panel of 12 strains were evaluated in the assay. This panel consisted of the following laboratory strains: Staphylococcus aureus Oxford, Staphylococcus aureus WCUH29, Enterococcus faecalis I, Enterococcus faecalis 7, Haemophilus influenzae Q1, Haemophilus influenzae NEMC1, Moraxella catarrhalis 1502, Streptococcus pneumoniae 1629, Streptococcus pneumoniae N1387, Streptococcus pneumoniae N1387, E. coli 7623 (AcrABEFD+) and E. coli 120 (AcrAB-). The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound that inhibited visible growth.. A mirror reader was used to assist in determining the MIC endpoint.

What is claimed is:

1. A compound according to Formula (1):



(1) X = O, NR_3 or a bond;

Y = C, CH_2 or a bond

wherein:

R represents:

C_{2-6} alkyl (optionally substituted by alkoxy, halogen, or C_{1-3} alkylsulfanyl), C_{2-6} alkenyl (optionally substituted by alkoxy, halogen, or C_{1-3} alkylsulfanyl), C_{2-6} alkynyl (optionally substituted by alkoxy, halogen, or C_{1-3} alkylsulfanyl), $(CH_2)_n$—C_{3-6} carbocycle (optionally substituted by alkoxy, halogen, or C_{1-3} alkylsulfanyl), $(CH_2)_n$—R4 {where R4 is phenyl, furan, benzofuran, thiophene, benzothiophene, tetrahydrofuran, tetrahydropyran, dioxane, 1,4-benzodioxane or benzo[1,3]dioxole; R4 is optionally substituted by one or more Cl, Br, I, C_{1-3} alkyl (optionally substituted by one to three F) or C_{1-2} alkoxy (optionally substituted by one to three F)};

R1 represents:

hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy, halogen, amino, guanidino, phenyl, pyridyl, pyrrolyl, indolyl, imidazolyl, furanyl, benzofuranyl, piperidinyl, morpholinyl, quinolinyl, piperazinyl or dimethylaminophenyl) or $(CH_2)_n$—C_{3-7} carbocycle;

R2 represents:

hydrogen (provided that X is not O), C_{1-3} substituted alkyl, C_{2-3} substituted alkenyl, C_{2-3} substituted alkynyl, $(CH_2)_n$—C_{3-6} substituted carbocycle, aryl, heteroaryl, heterocyclic, carboxy (provided that X is not NR3 or O) or aminocarbonyl (provided that X is not NR3 or O);

R3 represents:

hydrogen, C_{1-3} substituted alkyl, phenyl, or may be taken together with R2 and the nitrogen atom to which they are attached to form an optionally substituted heterocyclic ring which is optionally fused to an aryl, a heteroaryl, or a second heterocyclic ring;

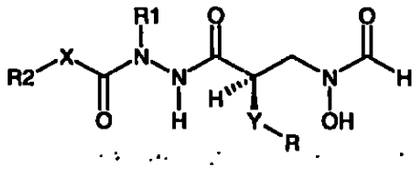
X represents O, NR3 or a covalent bond;

Y represents O, CH_2 or a covalent bond;

n = 0-2;

or a salt, solvate, or physiologically functional derivative thereof.

2. A compound as claimed in claim 1, with the following absolute configuration:



X = O, NR_3 or a bond;

Y = O, CH_2 or a bond

or a salt, solvate or physiologically functional derivative thereof.

3. A compound as claimed in claim 2, wherein R1 = H; or a salt, solvate or physiologically functional derivative thereof.

4. A compound as claimed in claim 1, wherein X = O; or a salt, solvate, or physiologically functional derivative thereof.

5. A compound according to claim 4 selected from the group consisting of:

N-Butyl-N-(t-butoxycarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-phenoxycarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Isobutyl-N-(t-butoxycarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Isobutyl-N-phenoxycarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenethyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Cyclohexylmethyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Benzyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-pyridin-3-yl-propyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2-Morpholin-4-yl-ethyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Hydroxy-butyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Amino-butyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Tetrahydro-pyran-4-yl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Methyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-Aminopropyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(t-Butoxycarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-Hydroxypropyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-(t-butoxycarbonyl)-N'-{(2S)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-(phenoxycarbonyl)-N'-{(2S)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[2-(4-Dimethylaminophenyl)ethyl]-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxy amino)methyl]-heptanoyl}-hydrazine.

N-(t-Butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Pentyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[2-(1H-Indol-3-yl)-ethyl]-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Isopentyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Cyclohexyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(1-Ethyl-propyl)-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Isopropyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Propyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Ethyl-N-(t-butoxycarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Methoxycarbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-(3,5-Dimethoxyphenyl)-1-methyl-ethoxy]carbonyl}-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

6. A compound as claimed in claim 1, wherein X = NR3; or a salt, solvate, or physiologically functional derivative thereof.

7. A compound according to claim 6 selected from the group consisting of:

N-Butyl-N-[(4-methylpiperazin-1-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-diphenylaminocarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-(t-butylamino)carbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-[(3,5-dimethyl-4,5-dihydro-isoxazol-4-yl)aminocarbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Butyl-N-[(1-morpholin-4-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-4-phenyl-butanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-hexanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-3-phenyl-propanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-3-(3,4-dichlorophenyl)-propanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3,4-Dichlorophenylaminocarbonyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenylaminocarbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3,4-Dichlorophenylaminocarbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Morpholin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Methoxyphenyl)aminocarbonyl]-N'-{(2R)-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-[(2,4-Dichlorophenyl)aminocarbonyl]-N'-{(2R)-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-[(2,6-Dichlorophenyl)aminocarbonyl]-N'-{(2R)-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-[(4-Methyl-piperazin-1-yl)carbonyl]-N'-{(2R)-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-[(4-Chloro-3-trifluoromethylphenyl)aminocarbonyl]-N'-{(2R)-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-[(Methyl-phenyl-amino)carbonyl]-N'-{(2R)-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

8. A compound as claimed in claim 1, wherein X is a covalent bond; or a salt, solvate, or physiologically functional derivative thereof.

9. A compound according to claim 8 selected from the group consisting of:

N-[(Phenylaminocarbonyl)-carbonyl]-N'-{(2R)-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-Butyl-N-{[1-(t-butoxycarbonyl)-piperidin-4-yl]-carbonyl}-N'-{2-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-Butyl-N-{[(1-t-butoxycarbonyl)-pyrrolidin-(2S)-yl]carbonyl}-N'-{2-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-Butyl-N-{[(1-t-butylaminocarbonyl)piperidin-4-yl]carbonyl}]-N'-{2-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-Butyl-N-{[(1-t-butylcarbonyl)piperidin-4-yl]carbonyl}]-N'-{2-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.
N-Butyl-N-[(1,2,3,4-tetrahydro-quinoxalin-2-yl)carbonyl]-N'-{2-
[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(p-Methoxyphenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenoxyacetyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(p-Methoxy-phenoxy)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2,6-Dichlorophenyl-acetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3,4-Dichlorophenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Ethoxycarbonyl)carbonyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2,4-Dichlorophenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2,3-Dichlorophenoxyacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3,4-Dimethoxyphenylacetyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1H-Indol-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Methyl-pyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Methoxy-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,3-Dihydro-benzo[1,4]dioxin-(2S)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2,3,4-Tetrahydro-quinolin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Tetrahydro-furan-(2S)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Tetrahydro-furan-(2R)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Methyl-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Pyridin-2-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{3-[3-(4-Methoxybenzyl)-1H-benzoimidazol-2-yl]-propanoyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Pyrimidin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Isoquinolin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Methyl-2,5-dioxo-imidazolidin-4-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-3-phenyl-propanoyl}-hydrazine.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-3-(3,4-dichloro)phenyl-propanoyl}-hydrazine.

N-[(4-Imidazol-1-yl)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-Methyl-5-oxo-2-S-(pyridin-3-yl)-pyrrolidin-(3S)-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2-Dihydro-cinnolin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[4-(4-Acetylpiperazin-1-yl)phenoxyacetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenylacetyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-Benzyl-5-oxo-pyrrolidin-(2S)-yl]-carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-Benzyl-5-oxo-pyrrolidin-(2R)-yl]-carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5S)-Benzyl-3,6-dioxo-piperazin-(2S)-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-8-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2,3,4-Tetrahydroquinolin-8-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(N"-Acetyl-L-tyrosyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Acetyl-1,2,3,4-tetrahydro-quinolin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxy amino) methyl]-heptanoyl}-hydrazine.

N-[(1H-Benzoimidazol-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-(2-Hydroxyacetyl)-1,2,3,4-tetrahydro-quinolin-6-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1H-Indol-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{4-[Methyl-(4,6-dimethylpyrimidin-2-yl)-amino]benzoyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine).

N-[(1-Benzo[1,3]dioxol-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[4-(3,5-Dimethyl-pyrazol-1-yl)methyl]benzoyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[4-(Morpholin-4-yl)-benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[4-Hydroxy-3-(morpholin-4-yl)methyl-benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-Hydroxy-3-methyl-butanoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Methylamino-benzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Isopropyl-1H-benzotriazol-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2,3,4-Tetrahydro-isoquinolin-(3S)-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Chloro-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[1-(Dimethylaminocarbonylmethyl)-3,4-dihydro-2H-quinolin-6-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,2-Difluoro-benzo[1,3]dioxol-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Amino-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(4-Oxo-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(7-Hydroxy-benzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(6-Methoxy-benzofuran-2-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Acetamidobenzofuran-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,3-Dihydro-benzo[1,4]dioxin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Amino-4,6-dimethyl-furo[2,3-b]pyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Methyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(6-Fluoro-4H-benzo[1,3]dioxin-8-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(7-Amino-1H-indol-2-yl)carbonyl)]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1-Methyl-1,2,3,4-tetrahydro-quinolin-6-yl)carbonyl]-N'-{(2R)-[(formylhydroxy amino) methyl]-heptanoyl}-hydrazine.

N'-[(6,7,9,10,12,13,15,16-Octahydro-5,8,11,14,17-pentaoxa-benzocyclopentadecen-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Benzo[1,3]dioxol-5-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Pentanoyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Benzoyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Trifluoroacetamido-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Hydroxy-naphthalen-2-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-Phenylacetyl-N'-{2-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Furan-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Methoxybenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1H-Indol-3-yl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Dimethylaminobenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(2-Hydroxybenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Piperidin-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1,2,5,6-Tetrahydro-pyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(7-Methoxy-benzofuran-2-yl)carbonyl-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Chloro-4-methoxy-phenyl)acetyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(1H-Pyrrol-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-7-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Pyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Chloro-3-methoxy-benzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(3-Methoxybenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinolin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(5-Methyl-2-phenyl-oxazol-4-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(Quinoxalin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-4-phenylbutanoyl}-hydrazine.

N-[(3-Methoxy-quinoxalin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,6-Dimethoxypyridin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(N"-Methylsulfonyl)-L-tyrosyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-{[5-Oxo-pyrrolidin-(2S)-yl]carbonyl}-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(4-(Pyrrol-1-yl)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(4-Acetamidobenzoyl)-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(3-Cyclopentyloxy-4-methoxy)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-(Phenylacetyl)-N'-{2-[(formylhydroxyamino)methyl]-3-cyclopentyl-propanoyl}-hydrazine.

N-[(7-Methoxy-benzofuran-2-yl)carbonyl]-N'-{2-[(formylhydroxyamino)methyl]-3-cyclopentyl-propanoyl}-hydrazine.

N-[3-(Morpholin-4-yl)propanoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2,3-Dihydro-benzofuran-5-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(4,6-Dimethoxy-pyrimidin-2-yl)benzoyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(2-Trifluoromethyl-5,6,7,8-tetrahydro-naphthyridin-2-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

N-[(9H-beta-Carbolin-3-yl)carbonyl]-N'-{(2R)-[(formylhydroxyamino)methyl]-heptanoyl}-hydrazine.

10. A method of treating a bacterial infection by administering to a subject in need of treatment a compound according to claim 1.

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INHIBIDORES DE PÉPTIDO-DEFORMILASA

CAMPO DE LA INVENCIÓN

La presente invención se refiere al uso de nuevos compuestos antibacterianos y a composiciones farmacéuticas que contienen estos compuestos como inhibidores de péptido-deformilasa.

ANTECEDENTES DE LA INVENCIÓN

El iniciador bacteriano metionil-tRNA es modificado por metionil-tRNA-formiltransferasa (FMT) para producir formil-metionil-tRNA. La formil-metionina (f-met) es seguidamente incorporada en el N terminal de los polipéptidos recientemente sintetizados. La polipéptido-deformilasa (PDF o Def) deformila seguidamente los productos de traducción primarios para producir N-metionil-polipéptidos. La mayoría de las proteínas intracelulares son adicionalmente tratadas por metionina-amino-peptidasa (MAP) para producir el péptido maduro y metionina libre, que es reciclada. La PDF y la MAP son ambas esenciales para el crecimiento bacteriano, y la PDF es requerida para la actividad de la MAP. Esta serie de reacciones se denomina el ciclo de metionina (Figura 1).

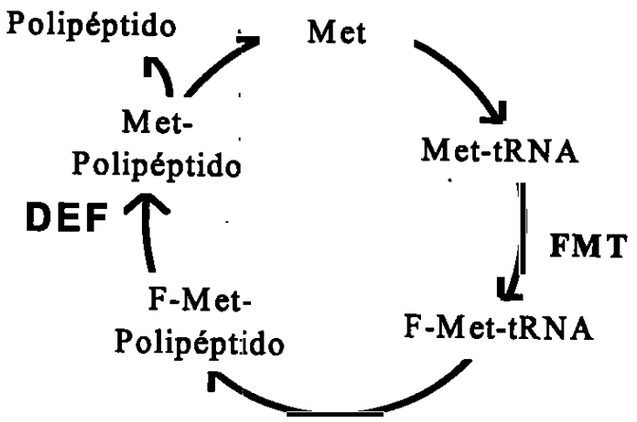


Figura 1. El ciclo de la metionina.

Hasta la fecha, los genes homólogos de polipéptido-deformilasa se han encontrado en bacterias, en plantas que contienen cloroplastos, en ratones y en seres humanos. Las proteínas de las plantas tienen una codificación nuclear pero parece que portan una señal de localización de cloroplastos. Esto es congruente con la observación de que el RNA de cloroplastos y los procedimientos de síntesis de proteínas son altamente similares a los de las eubacterias. Aunque hay una información limitada sobre la expresión de proteínas de homólogos de genes de PDF de mamíferos (Bayer Aktiengesellschaft. patente WO 2001/42431) no se ha demostrado hasta la fecha ningún papel funcional para tales proteínas (Meinnel. T., Paarasitology Today 16(4), 165-168, 2000).

La polipéptido-deformilasa se encuentra en todas las eubacterias para las que está diponible la información de secuencias genómicas de cobertura. La diversidad de secuencias entre los homólogos de PDF es elevada, con una identidad muy pequeña de 20% entre secuencias distantemente relacionadas. Sin embargo, la conservación alrededor del sitio activo es muy elevada, con varios residuos completamente conservados, incluida una cisteína y dos histidinas que se requieren para coordinar el metal del sitio activo (Meinnel, T. et al., J. Mol. Biol. 267, 749-761, 1997).

La PDF se reconoce que es una diana antibacteriana atractiva, ya que esta enzima se ha demostrado que es esencial para el crecimiento bacteriano in vitro (Mazel, D. et al., EMBO J. 13 (4), 914-923, 1994), no se cree que esté involucrada en la síntesis de proteínas eucarióticas (Rajagopalan et al., J. Am. Chem. Soc. 119, 12418-12419, 1997), y está universalmente conservada en procariotas (Kozak, M., Microbiol. Rev. 47, 1-45, 1983). Por lo tanto, los inhibidores de

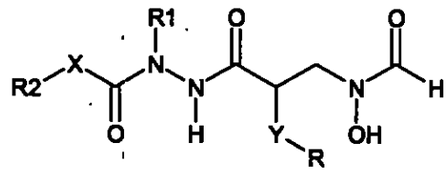
PDF pueden servir potencialmente como agentes antibacterianos de amplio espectro.

SUMARIO DE LA INVENCIÓN

La presente invención incluye nuevos compuestos antibacterianos representados por la fórmula (1) posterior y su uso como inhibidores de PDF.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

En un aspecto de la presente invención, se proporcina un compuesto de fórmula (1):



(1) X = O, NR_3 o un enlace

Y= O, CH_2 o un enlace

en la cual:

R representa:

alquilo C_{2-6} (opcionalmente sustituido con alcoxi, halógeno o alquilsulfanilo C_{1-3}), alquenilo C_{2-6} (opcionalmente sustituido con alcoxi, halógeno o alquilsulfanilo C_{1-3}), alquinilo C_{2-6} (opcionalmente sustituido con alcoxi, halógeno o alquilsulfanilo C_{1-3}), $(CH_2)_n$-carbociclo C_{3-6} (opcionalmente sustituido con alcoxi, halógeno o alquilsulfanilo C_{1-3}, $(CH_2)_n$-R4 (en donde R4 es fenilo, furano, benzofurano, tiofeno, benzotiofeno, tetrahidrofurano, tetrahidropirano, dioxano, 1,4-benzodioxano o benzo[1,3]dioxol; R4 está opcionalmente sustituido con uno o más Cl, Br, I, alquilo C_{1-3} (opcionalmente sustituido con uno a tres F) o alcoxi C_{1-2} (opcionalmente sustituido con uno a tres F));

R1 representa:

hidrógeno, alquilo C_{1-6} (opcionalmente sustituido con

hidroxi, halógeno, amino, guanidino, fenilo, piridilo, pirrolilo, indolilo, imidazolilo, furanilo, benzofuranilo, piperidinilo, morfolinilo, quinolinilo, piperazinilo o dimetilaminofenilo) o $(CH_2)_n$-carbociclo C_{3-7};

R2 representa:

hidrógeno (con la condición de que X no es O), alquilo C_{1-3} sustituido, alquenilo C_{2-3} sustituido, alquinilo C_{2-3} sustituido, $(CH_2)_n$-carbociclo C_{3-6} sustituido, arilo, heteroarilo, heterocíclico, carboxi (con la condición de que X no es NR3 ni O) o aminocarbonilo (con la condición de que X no es NR3 ni O);

R3 representa:

hidrógeno, alquilo C_{1-3} sustituido, fenilo o se puede tomar conjuntamente con R2 y el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico opcionalmente sustituido que está opcionalmente condensado a un anillo de arilo, heteroarilo o un segundo heterocíclico;

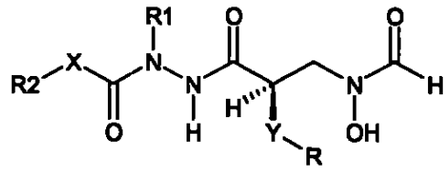
X representa O, NR3 o un enlace covalente;

Y representa O, CH_2 o un enlace covalente;

n = 0-2;

o una sal, solvato o derivado fisiológicamente funcional del mismo.

En esta invención, el grupo R1 más preferido es hidrógeno. Además de ello, en esta invención la configuración absoluta más preferida de los compuestos de fórmula (1) se indica a continuación:



X = O; NR_3 o un enlace;

Y = O, CH_2o un enlace

En un segundo aspecto de la presente invención, se proporciona un compuesto de fórmula (1) en el que X = O, y R, R1, R2, R3, R4, Y y n son como se definieron anteriormente; o una sal, solvato o derivado fisiológicamente funcional del mismo.

En un tercer aspecto de la presente invención, se proporciona un compuesto de fórmula (1) en la que X = NR3 y R, R1, R2, R3, R4, Y y n son como se definieron anteriormente; o una sal, solvato o derivado fisiológicamente funcional del mismo.

En un cuarto aspecto de la presente invención, se proporciona un compuesto de fórmula (1) en la que X es un enlace covalente y R, R1, R2, R3, R4, Y y n son como se definieron anteriormente; o una sal, solvato o derivado fisiológicamente funcional del mismo.

Tal como se usa en la presente memoria descriptiva, el término "alquilo" se refiere a un radical hidrocarbonado saturado de cadena lineal o ramificada. Ejemplos de "alquilo" como se usa en la presente memoria descriptiva incluyen, pero sin limitación, metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, t-butilo, n-pentilo, isopentilo, hexilo y similares.

Tal como se usa en la presente memoria descriptiva, la expresión "alquilo sustituido" se refiere a un radical hidrocarbonado saturado de cadena lineal o ramificada, opcionalmente sustituido con sustituyentes seleccionados entre el grupo que incluye alquilo C_{1-3} (opcionamlente sustituido con uno a tres átomos de flúros), alquenilo C_{2-3}, alquinilo C_{2-3}, alcoxi C_{1-2} (opcionalmente sustituido con uno a tres átomos de flúor), sulfanilo, sulfinilo, sulfonilo, oxo, hidroxi, mercapto, amino, guanidino, carboxi, aminocarbonilo, arilo, ari-

loxi, heteroarilo, heteroariloxi, heterocíclico, aminosulfonilo, sulfonilamino, carboxiamido, ureido, nitro, ciano y halógeno, estando permitidos múltiples grasos de sustitución.

Tal como se usa en la presente memoria descriptiva, el término "alquenilo" se refiere a un radical hidrocarbonado de cadena lineal o ramificada que tiene al menos un enlace doble carbono-carbono. Ejemplos de "alquenilo", tal como se usa en la presente memoria descriptiva, incluyen, pero sin limitación, etenilo y propenilo.

Tal como se usa en la presente memoria descriptiva, "alquenilo sustituido" se refiere a un radical hidrocarbonado de cadena lineal o ramificada que tiene al menos un enlace doble carbono-carbono, opcionalmente sustituido con sustituyentes seleccionados entre el grupo que incluye alquilo C_{1-3} (opcionalmente sustituido con uno a tres F), amino, arilo, ciano y halógeno, estando permitidos múltiples grados de sustitución.

Tal como se usa en la presente memoria descriptiva, el término "alquinilo" se refiere a un radical hidrocarbonad de cadena lineal o ramificada que tiene al menos un enlace triple carbono-carbono. Ejemplos de "alquinilo", tal como se usa en la presente memoria descriptiva, incluyen, pero sin limitación, acetilenilo y 1-propinilo.

Tal como se usa en la presente memoria descriptiva, la expresión "alquinilo sustituido" se refiere a un radical hidrocarbonado de cadena lineal o ramificada que tiene al menos un enlace triple carbono-carbono, opcionalmente sustituido con sustituyentes seleccionados entre el grupo que incluye alquilo C_{1-3} (opcionalmente sustituido con uno a tres F), amino, arilo y halógeno, estando permitidos múltiples grados de sustitución.

Tal como se usa en la presente memoria descriptiva, el término "halógeno" se refiere a flúor (F), cloro (Cl), bromo

(Br) o Yodo (I) y "halo" se refiere a los radicales de halógenos flúor, cloro, bromo y yodo.

Tal como se usa en la presente memoria descriptiva, el término "carbociclo" se refiere a un radical hidrocarbonado cíclico no aromático que tiene de tres a siete átomos de carbono. Para los carbociclos con anillos de cinco a siete miembros, se permite un enlace doble en el anillo. Ejemplos de grupos de "carbociclo" incluyen, pero sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexilo y cicloheptilo.

Tal como se usa en la presente memoria descriptiva, la expresión "carbociclo sustituido" se refiere a un radical hidrocarbonado cíclico no aromático que tiene de tres a siete átomos de carbono, y que está opcionalmente sustituido con sustituyentes seleccionados entre el grupo que incluye alquilo C_{1-3} (opcionalmente sustituido con uno a tres F), alquenilo C_{2-3}, alquinilo C_{2-3}, alcoxi C_{1-2} (opcionalmente sustituido con uno a tres F), sulfanilo, sulfinilo, sulfonilo, oxo, hidroxi, mercapto, amino, guanidino, carboxi, aminocarbonilo, arilo, ariloxi, heteroarilo, heterocíclico, aminosulfonilo, sulfonilamino, carboxiamido, nitro, ureido, ciano y halógeno, estando permitidos múltiples grados de sustitución. Para carbociclos con anillos de cinco a siete miembros, estando permitido un enlace doble en el anillo.

Tal como se usa en la presente memoria descriptiva, el término "arilo" se refiere a un anillo de benceno opcionalmente sustituido o a un anillo de benceno opcionalmente sustituido condensado con uno o más anillos de benceno opcionalmente sustituidos para formar un sistema de anillos. Ejemplos de sustituyentes opcionales incluyen alquilo C_{1-3} sustituido, alquenilo C_{2-3} sustituido, alquinilo C_{2-3} sustituido, heteroarilo, heterocíclico, arilo, alcoxi C_{1-3} (opcionalmente susti-

tuido con uno a tres F), ariloxi, aralcoxi, acilo, aroilo, heteroaroilo, aciloxi, aroiloxi, heteroaroiloxi, sulfanilo, sulfinilo, sulfonilo, aminosulfonilo, sulfonilamino, carboxiamido, aminocarbonilo, carboxi, oxo, hidroxi, mercapto, amino, nitro, ciano, halógeno o ureido, estando permitidos múltiples grados de sustitución. Tal anillo o sistema de anillos puede estar opcionalmente condensado a uno o más anillos de arilo opcionalmente sustituidos (incluidos anillos de benceno), anillos carbocíclicos o anillos heterocíclicos. Ejemplos de grupos "arilo" incluyen, pero sin limitación, fenilo, naftilo, tetrahidronaftilo, bifenilo, indanilo, antracilo o fenantrilo, así como sus derivados sustituidos.

Tal como se usa en la presente memoria descriptiva, el término "heteroarilo" se refiere a un anillo aromático de cinco a seis miembros monocíclico opcionalmente sustituido que contiene uno o más sustituciones heteroaromáticas seleccionadas entre S, SO, SO_2, O, N o N-óxido, o a uno de tales anillos aromáticos condensado con uno o más anillos opcionalmente sustituidos, como anillos de heteroarilo, anillos de arilo, anillos heterocíclicos o anillos carbocíclicos (por ejemplo, un sistema de anillos bicíclico o tricíclico). Ejemplos de sustituyentes opcionales se seleccionan entre el grupo que incluye alquilo C_{1-3} sustituido, alquenilo C_{2-3} sustituido, alquinilo C_{2-3} sustituido, heteroarilo,, heterocíclico, arilo, alcoxi C_{1-3} (opcionalmente sustituido con uno a tres F), ariloxi, aralcoxi, acilo, aroilo, heteroaroilo, aciloxi, aroiloxi, heteroaroiloxi, sulfanilo, sulfinilo, sulfonilo, aminosulfonilo, sulfonilamino, carboxiamido, aminocarbonilo, carboxi, oxo, hidroxi, mercapto, amino, nitro, ciano, halógeno o ureido, estando permitidos múltiples grados de sustitución. Ejemplos de grupos "heteroarilo" usados en la presente invención incluyen, pero sin limitación, benzoimidazolilo,

benzotiazolilo, benzoisotiazolilo, benzotiofenilo, benzopirazinilo, benzotrizolilo, benzo[1,4]dioxanilo, benzofuranilo, 9H-α-carbolinilo, cinolinilo, furanilo, furo[2,3-b]piridinilo, imidazolilo, imidazolidinilo, imidazopiridinilo, isoxazolilo, isotiazolilo, isoquinolinilo, indolilo, indazolilo, indolizinilo, naftiridinilo, oxazolilo, oxotiadiazolilo, oxadiazolilo, ftalazinilo, piridilo, pirrolilo, pirinilo, pteridinilo, fenazinilo, pirazolilo, piridilo, pirazolopirimidinilo, pirrolizinilo, piridazilo, pirazinilo, pirimidilo, 4-oxo-1,2-dihidro-4H-pirrolo[3,2,1-ij]-quinolín-4-ilo, quinoxalinilo, quinazolinilo, quinolinilo, quinolizinilo, tiofenilo, triazolilo, triazinilo, tetrazolopirimidinilo, triazolopirimidinilo, tetrazolilo, tiazolilo, tiazolidinilo y sus versiones sustituidas.

Tal como se usa en la presente memoria descriptiva, el término "heterocíclico" se refiere a un anillo de tres a siete miembros que contiene uno o más restos heteroatómicos seleccionados entre S, SO, SO_2, O, N o N-óxido, opcionalmente sustituido con sustituyentes seleccionados entre el grupo que incluye alquilo C_{1-3} sustituido, alquenilo C_{2-3} sustituido, alquinilo C_{2-3} sustituido, heteroarilo, heterocíclico, arilo, alcoxi C_{1-3} (opcionalmente sustituido con uno a tres F), ariloxi, aralcoxi, acilo, aroilo, heteroaroilo, aciloxi, aroiloxi, heteroaroiloxi, sulfanilo, sulfinilo, sulfonilo, aminosulfonilo, sulfonilamino, carboxiamido, aminocarbonilo, carboxi, oxo, hidroxi, mercapto, amino, nitro, ciano, halógeno o ureido, estando permitidos múltiples grados de sustitución. Tal anillo puede ser saturado o tener uno o más grados de insaturación. Tal anillo puede estar opcionalmente condensado a uno o más de otro(s) anillo(s) "heterocíclico(s)" opcionalmente sustituido(s), anillos(s) de arilo, anillo(s) de heteroarilo o anillo(s) carbocíclico(s). Ejemplos de restos

"heterocíclicos" incluyen, pero sin limitación, 1,4-dioxanilo, 1,3-dioxanilo, pirrolidinilo, pirrolidin-2-onilo, piperidinilo, imidazolidin-2,4-dionapiperidinilo, piperazinilo, piperazino-2,5-dionilo, morfilinilo, dihidropiranilo, dihidrocinolinilo, 2,3-dihidrobenzo[1,4]dioxinilo, 3,4-dihidro-2H-benzo[b][1,4]-dioxepinilo, tetrahidropiranilo, 2,3-dihidrofuranilo, 2,3-dihidrobenzofuranilo, dihidroisoxazolilo, tetrahidrobenzodiazepinilo, tetrahidroquinolinilo, tetrahidrofuranilo, tetrahidronaftiridinilo, tetrahidropurinilo, tetrahidrotiopiranilo, tetrahidrotiofenilo, tetrahidroquinoxalinilo, tetrahidropiridinilo, tetrahidrocarbolinilo, 4H-benzo[1,3]-dioxinilo, benzo[1,3]dioxonilo, 2,2-difluorobenzo-[1,3]-dioxonilo, 2,3-dihidro-ftalazino-1,4-dionilo, isoindol-1,3-dionilo o similares.

Tal como se usa en la presente memoria descriptiva, el término "alcoxi" se refiere al grupo $-OR_a$, en el que R_a es alquilo como se definió con anterioridad. Ejemplos de grupos alcoxi útiles en la presente invención incluye, pero sin limitación, metoxi, difluorometoxi, trifluorometoxi, etoxi, n-propoxi, isopropoxi, n-butoxi y t-butoxi.

Tal como se usa en la presente memoria descriptiva, el término "aralcoxi" se refiere al grupo $-OR_aR_b$, en el que R_a es alquilo y R_b es arilo como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "ariloxi" se refiere al grupo $-OR_a$, en el que R_a es arilo como se definió con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "mercapto" se refiere al grupo -SH.

Tal como se usa en la presente memoria descriptiva, el término "sulfanilo" se refiere al grupo $-SR_a$, en el que R_a es alguilo sustituido, carbociclo sustituido, arilo, heteroarilo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "sulfinilo" se refiere al grupo $-S(O)R_a$, en el que R_a es alquilo sustituido, carbociclo sustituido, arilo, heteroarilo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "sulfonilo" se refiere al grupo $-S(O)_2R_a$, en el que R_a es alquilo sustituido, carbociclo sustituido, arilo, heteroarilo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "oxo" se refiere al grupo =O.

Tal como se usa en la presente memoria descriptiva, el término "hidroxi" se refiere al grupo -OH.

Tal como se usa en la presente memoria descriptiva, el término "amino" se refiere al grupo $-NH_2$. El grupo amino está opcionalmente sustituido con alquilo sustituido, carbociclo sustituido, arilo, heteroarilo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "ciano" se refiere al grupo -CN.

Tal como se usa en la presente memoria descriptiva, el término "aminosulfonilo" se refiere al grupo $-S(O)_2NH_2$. El grupo aminosulfonilo está opcionalmente sustituido con alquilo sustituido, carbociclo sustituido, arilo, heteroarilo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "sulfonilamino" se refiere al grupo $-NHS(O)_2R_a$ en el que R_a es alquilo sustituido, carbociclo sustituido, arilo, heteroarilo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "carboxiamido" se refiere al grupo $-NHC(O)R_a$ en el que R_a es alquilo sustituido, carbociclo sustituido, arilo,

heteroarilo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "carboxi" se refiere al grupo -C(O)OH. El grupo carboxi está opcionalmente sustituido con alquilo sustituido, carbociclo sustituido, arilo, heteroarilo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "aminocarbonilo" se refiere al grupo $-C(O)NH_2$. El grupo aminocarbonilo está opcionalmente sustituido con alquilo sustituido, carbociclo sustituido, arilo, heteroarilo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "ureido" se refiere al grupo $-NHC(O)NHR_a$ en el que R_a es hidrógeno, alquilo, carbociclo o arilo, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "guanidino" se refiere al grupo $-NHC(=NH)NH_2$.

Tal como se usa en la presente memoria descriptiva, el término "acilo" se refiere al grupo $-C(O)R_a$, en el que R_a es alquilo, carbociclo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "aroilo" se refiere al grupo $-C(O)R_a$, en el que R_a es arilo como se definió con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "heteroaroilo" se refiere al grupo $-C(O)R_a$, en el que R_a es heteroarilo, como se definió con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "aciloxi" se refiere al grupo $-OC(O)R_a$, en el que R_a es alquilo, carbociclo o heterocíclico, como se definieron con anterioridad.

Tal como se usa en la presente memoria descriptiva, el término "aroiloxi" se refiere al grupo $-OC(O)R_a$, en el que R_a es arilo, como se definió con anterioridad.

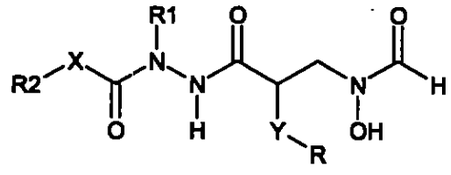
Tal como se usa en la presente memoria descriptiva, el término "heteroariloxi" se refiere al grupo $-OC(O)R_a$, en el que R_a es heteroarilo, como se definió con anterioridad.

También están incluidas en la presente invención las sales y complejos farmacéuticamente aceptables, como las sales de hidrocloruro, hidrobromuro y trifluoroacetato y las sales de sodio, potasio y magnesio. Los compuestos de la presente invención pueden contener uno o más átomos de carbono asimétricos, y pueden existir en formas racémicas y ópticamente activas. Todos estos compuestos y diastereómeros se consideran que están dentro del alcance de la presente invención.

SECUENCIA SINTÉTICA GENERAL

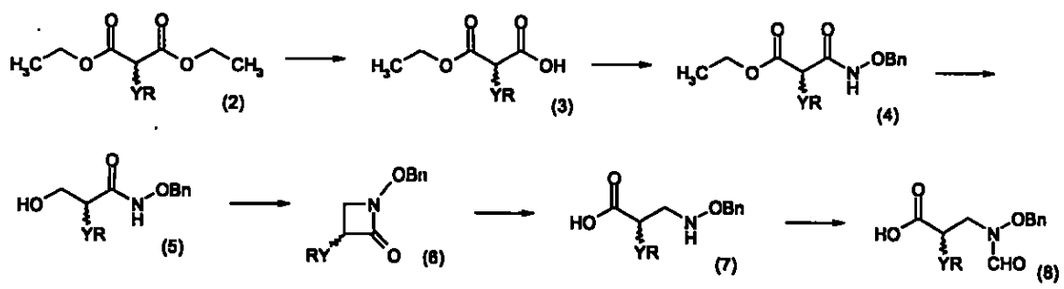
Los compuestos y procedimientos de la presente invención se comprenderán mejor en relación con los siguientes esquemas sintéticos, que son meramente ilustrativos de los métodos mediante los cuales se pueden preparar los compuestos de la invención, y no está previsto que limiten el alcance de la invención tal como se define en las reivindicaciones anejas.

La presente invención proporciona compuestos de fórmula (1) que se pueden preparar a partir del intermedio racémico común (8), o los intermedios quirales comunes (17) y (25).



(1) X = O, NR_3 o un enlace;

Y = O, CH_2 o un enlace



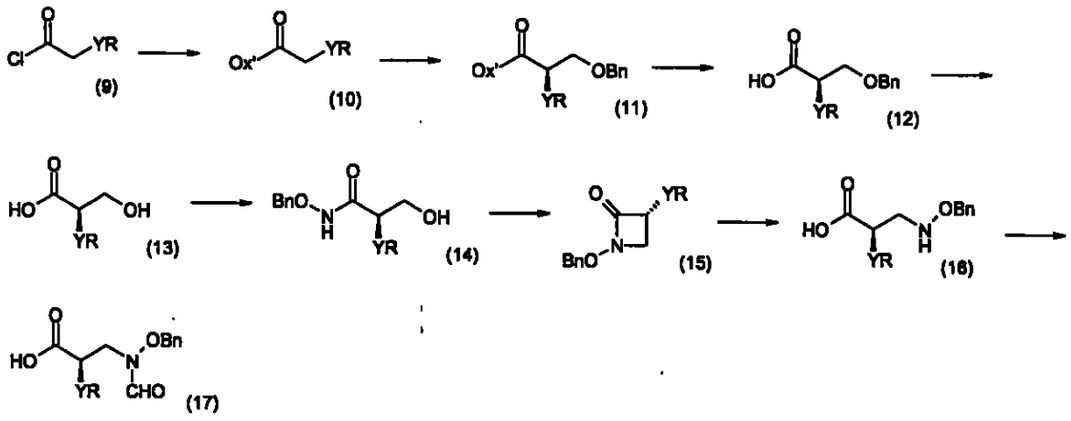
Esquema 1

Tal como se muestra en el Esquema 1, el intermedio (8) se puede preparar haciendo reaccionar el malonato de dialquilo mono-sustituido (2) con una base, como hidróxido de potasio, en un disolvente apropiado, como etanol/agua, para suministrar el mono-ácido (3). El acoplamiento de (3) con O-bencilhidroxilamina en presencia de un agente de acoplamiento como hidrocloruro de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (EDCI), y una base, como 4-dimetilaminopiridina (DMAP) en un disolvente apropiado, como diclorometano, proporciona la amida (4). La reducción de la funcionalidad éster del compuesto (4) con un agente reductor, como borohidruro de litio, en un disolvente apropiado, como tetrahidrofurano, a temperatura ambiente, proporciona el alcohol (5). El tratamiento del alcohol (5) bajo condiciones de Mitsunobu proporciona la lactama (6). La misma transformación se puede conseguir tratando (5) con trifenilfosfina, tetracloruro de carbono y una base, como trietilamina, para obtener (6). La hidrólisis de la lactama (6) usando, por ejemplo, hidróxido de litio en una mezcla disolvente apropiada, como THF-H_2O-MeOH, proporciona el ácido (7). La formulación del grupo amino de (7) se consigue usando ácido fórmico y anhídrido acético en un disolvente, como diclorometano, para proporcionar el compuesto formilado (8).

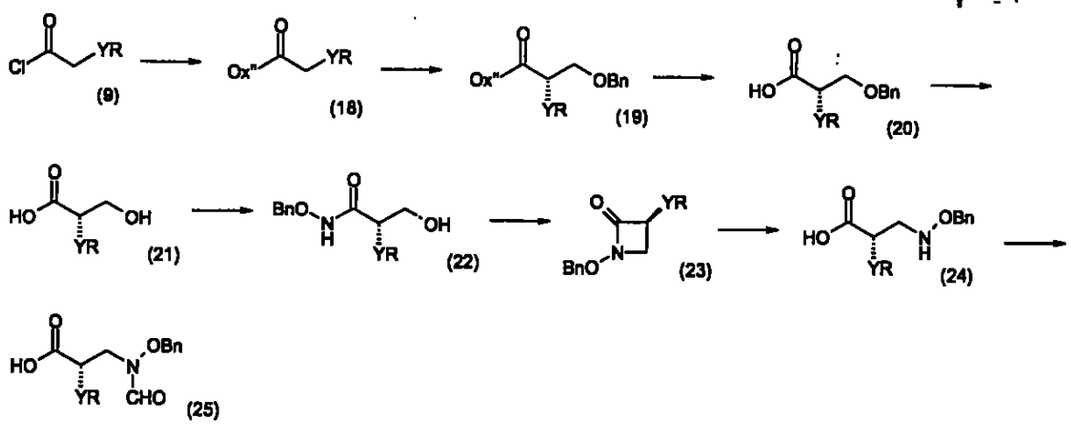
Cualesquiera racematos se pueden resolver al nivel de

cualquier intermedio durante la síntesis o al nivel del producto final usando, por ejemplo, un método de cromatografía quiral, para proporcionar el compuesto (8) en cada una de las dos formas enantiómeras.

Alternativamente, un enantiómero del intermedio (8), como (17) en el Esquema 2 o (25) en el Esquema 3, puede ser preparado haciendo reaccionar un cloruro de ácido (9) apropiado con un agente quiral, como una oxazolidinona quiral de Evans, en presencia de una base, como n-butil-litio, para proporcionar el intermedio quiral (10) en el Esquema 2 o (18) en el Esquema 3. El tratamiento del compuesto (10) o (18) con una base, como diisopropiletilamina, en presencia de un agente quelante, como tetracloruro de titanio, en un disolvente, como tetrahidrofurano, seguido de la adición de un electrófilo, como cloruro de benciloximetilo, proporciona cualquiera de los dos compuestos quirales (11) y (19), dependiendo de la selección de la auxiliaridad quiral.



Esquema 2



Esquema 3

La conversión del compuesto (11) o (19) en el correspondiente hidroxiácido (13) o (21) se puede conseguir mediante una secuencia que comprende la escisión oxidativa de la oxazolidinona quiral usando, por ejemplo, H_2O_2 e hidróxido de litio para los respectivos intermedios (12) y (20) seguida de hidrogenolisis. El acopiamiento del ácido (13) o (21) con benciloxiamina en presencia de agentes de acoplamiento como EDCI/DMAP, produce las amidas (14) y (22). Estas pueden ser cicladas a las azetidin-2-onas (15) o (23) usando condiciones de Mitsunobu o una combinación de trifenilfosfina/tetracloruro de carbono/trietilamina. La hidrólisis de la azetidin-2-ona (15) o (23) usando, por ejemplo, hidróxido de litio, en un disolvente apropiado, proporciona el correspondiente ácido (16) o (24). La conversión del compuesto (16) o (24) en el formiato (17) o (25) se puede conseguir usando un agente de formilación apropiado, como ácido fórmico/anhídrido acético o formiato de metilo, en un disolvente apropiado, como diclorometano.

REALIZACIONES ESPECÍFICAS

Segunda realización

Como la segunda realización de la presente invención, se

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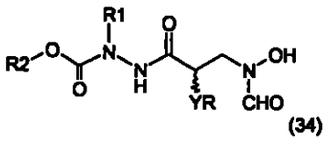
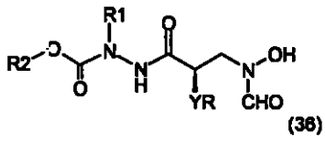
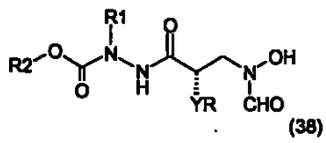
describen los compuestos de Fórmula (1) en la que X=O, en la forma del compuesto racémico (34) y los compuestos quirales (36) y (38). Estos compuestos tienen preferentemente R1=H.


(34)


(36)


(38)

Los compuestos preferidos útiles en la presente invención se seleccionan entre el grupo que consiste en:

N-Butil-N-(t-butoxicarbonil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-butil-N-fenoxicarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-isobutil-N-(t-butoxicarbonil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-isobutil-N-fenoxicarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-fenetil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-ciclohexilmetil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-bencil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3-piridin-3-il-propil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(2-morfolin-4-il-etil)-N-(t-butoxicarbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-hidroxi-butil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-amino-butil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(tetrahidro-piran-4-il)-N-(t-butoxicarbonil)-N'-{2-

[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-metil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3-aminopropil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(t-butoxicarbonil-N'-{(2R)-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

N-(3-hidroxipropil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-butil-N-(t-butoxicarbonil)-N'-[(2S)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-butil-N-(fenoxicarbonil)-N'-[(2S)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[2-(4-dimetilaminofenil)etil]-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

N-pentil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[2-(1H-indol-3-il)-etil]-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-isopentil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-ciclohexil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(1-etil-propil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-isopropil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-propil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-etil-N-(t-butoxicarbonil)-N'-{2-

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[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-metoxicarbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[1-(3,5-dimetoxifenil)-1-metil-etoxi]carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

Los siguientes esquemas sintéticos son meramente ilustrativos de los métodos mediante los cuales se pueden preparar los compuestos de la invención, y no están previsto que limiten el alcance de la invención según se define en las reivindicaciones anejas.

Como se muestra en el Esquema 4, el tratamiento del haluro de alquilo R1X (26) con hidrazina en un disolvente como etanol, a una temperatura elevada, proporciona el derivado de hidrazina (27). Haciendo reaccionar (27) con el carbonato R2OC(O)OC(O)OR2 o el cloroformiato R2OCOCl proporciona el intermedio (28). Alternativamente, (28) se puede preparar a partir de la hidrazina (29) protegida con Boc mediante reacción con el aldehído o cetona R'COR'', seguida de reducción con gas hidrógeno en presencia de paladio, para proporcionar un derivado de hidrazina (30). Haciendo reaccionar la hidrazina (30) con un carbonato R2OC(O)OC(O)OR2 o un cloroformiato R2OCOCl y seguidamente separando el grupo protector Boc con un ácido apropiado, como ácido trifluoroacético, se proporciona el derivado de hidrazina (28) en el que R1 = CHR'R''. Alternativamente, el grupo amino primario de (29) puede ser protegido en forma de la ftalimida (31). Haciendo reaccionar el compuesto (31) con un alcohol bajo condiciones de Mitsunobu se proporciona el compuesto (32) que, tras una hidrazinolisis, es fácilmente convertido en una hidrazina de fórmula (10) en la que R2 = t-butilo.

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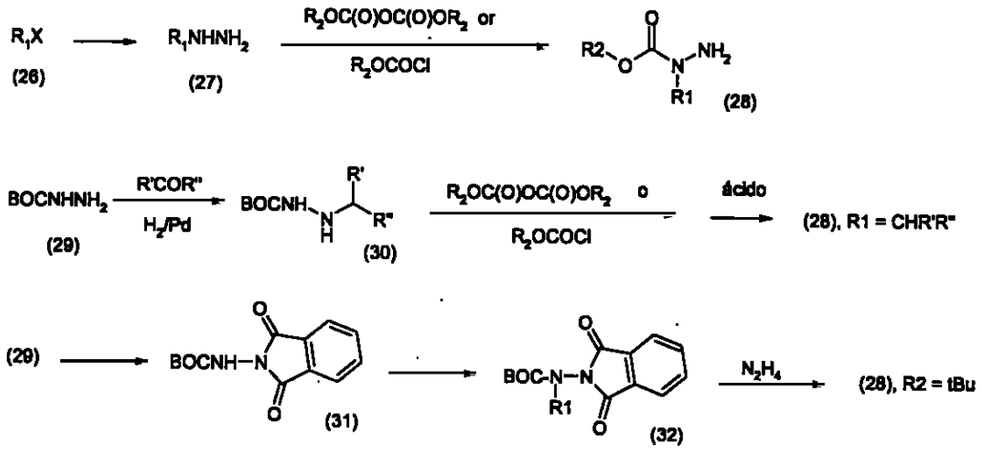
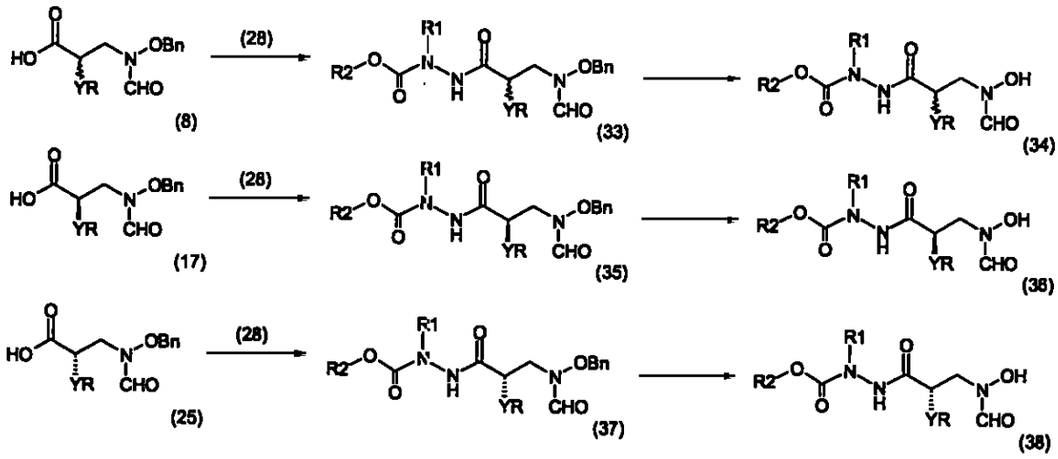


Esquema 4

Como se muestra en el Esquema 5, el acoplamiento del ácido (8) con el derivado de hidrazina (28) usando condiciones como DMAP/EDCI o EDCI/HOAt/NMM se proporciona la hidrazida (33). La hidrogenolisis para separar el grupo bencilo usando un catalizador, como 10% de Pd/C, en un disolvente apropiado como etanol, proporciona el compuesto deseado (34). Análogamente, el acoplamiento del ácido quiral (17) o (25) con el derivado de hidrazina (28) proporciona la correspondiente hidrazida (35) o (37). La hidrogenolisis del grupo bencilo proporciona el compuesto deseado final (36) o (38).



Esquema 5

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EJEMPLOS SINTÉTICOS

La invención se describirá seguidamente haciendo referencia a los siguientes ejemplos, que son meramente ilustrativos y no se conciben como una limitación del alcance de la presente invención.

Tal como se usan en la presente memoria descriptiva, los símbolos y convenciones usados en estos procedimientos, esquemas y ejemplos son congruentes con los usados en la bibliografía científica contemporánea, por ejemplo el *Journal of the American Chemical Society* o el *Journal of Biological Chemistry*. Las abreviaturas estándar de una letra o tres letras se usan generalmente para designar residuos de aminoácidos, que se supone que están en la configuración L salvo que se indique otra cosa.

Salvo que se indique otra cosa, todos los materiales de partida se obtuvieron a partir de proveedores comerciales y se usan sin purificación adicional.

Hz (Hertzios); TLC (cromatografía de capa fina);

T_r (tiempo de retención); RP (fase inversa);

MeOH (metanol); *i*-PrOH (isopropanol);

EtOH (etanol); TEA (trietilamina);

TFA (ácido trifluoroacético); THF (tetrahidrofurano);

DMSO (dimetilsulfóxido); AcOEt o EtOAc (acetato de etilo);

DCM (diclorometano); DMF (N,N-dimetilformamida);

CDI (1,1-carbonildiimidazol); HOAc (ácido acético);

HOSu (N-hidroxisuccinimida); Ac (acetilo);

HOBT (1-hidroxibenzotriazol); BOC (terc-butiloxicarbonilo);

mCPBA (ácido meta-cloroperbenzoico); FMOC (9-

fluorenilmetoxicarbonilo);

DCC (diciclohexilcarbodiimida); CBZ (benciloxicarbonilo);

NMM (N-metil-morfolina); HOAt (1-hidroxi-7-azabenzotriazol);

DMAP (4-dimetilaminopiridina); Bn (bencilo);

TBAF (fluoruro de tetra-n-butilamonio);

HPLC (cromatografía líquida a presión elevada);

BOP (cloruro de bis(2-oxo-3-oxazolidinil)fosfínico);

EDCI (hidrocloruro de 1-etil-3-[3-dimetilaminopropil]carbodiimida);

HBTU (hexafluorofosfato de O-benzotriazol-1-il-N,N-N',N'-tetrametiluronio).

Todas las referencias a éter son a dietil-éter; salmuera se refiere a una solución acuosa saturada de NaCl. Salvo que se indique otra cosa, todas las temperaturas están expresadas en °C (grados centígrados).

Todas las reacciones se realizan bajo una atmósfera inerte a temperatura ambiente salvo que se indique otra cosa, y todos los disolventes son de la mayor pureza disponible salvo que se indique otra cosa.

Los espectros de H^1 RMN (en lo sucesivo también "RMN") se registraron en un instrumento Varian VXR-300, un Varian Unity-300 o un Varian Unity-400, un Brucker AVANCE-400, un espectrómetro General Electric QE-300 o Brucker AM 400. Los desplazamientos químicos se expresan en partes por millón (ppm, unidades δ). Las constantes de acoplamiento están en unidades de Hertzios (Hz). Los modelos de división describen las multiplicidades aparentes y se indican como s (singlete), d (doblete), t (triplete), q (cuartete), quint (quintete), m (multiplete), br (ancho).

Los espectros de masas se realizaron en un sistema LC-MS de acceso abierto usando ionización por electropulverización.

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Condiciones LC: 4,5% a 90% de CH_3CN (0,02% de TFA) en 3,2 minutos con un mantenimiento de 0,4 minutos y un re-equilibrio de 1,4 minutos; detección por MS, UV a 214 nm y un detector de dispersión de la luz (ELS). Columna: Aquasil 1 X 40 mm (C18).

Paa la HPLC preparativa (prep); aproximadamente 50 mg de los productos finales fueron inyectados en 500 µl de DMSO en una columna YMC CombiPrep ODS-A de 5 X 20 mm a 20 ml/minuto con un gradiente de 10 minutos desde 10% de CH_3CN (0,1% de TFA) hasta 90% de CH_3CN (0,1% de TFA) en H_2O (0,1% de TFA) y mantenimiento de 2 minutos. La cromatografía rápida se realizó sobre gel de sílice (Merck 60 (malla 230-400).

Los espectros infrarrojos (IR) se obtuvieron en un espectrómetro Nicolet 510 FT-IR usando una celda de NaCl de 1 mm. La mayor parte de las reacciones se verificaron por cromatografía de capa fina en placas de gel de sílice E. Merck de 0,25 mm (60F-254), disualizadas con luz UV, solución etanólica al 5% de ácido fosfomolíbdico o p-anisaldehído.

Los compuestos descritos en los Ejemplos 2 a 30 se prepararon siguiendo los procedimientos generales descritos en el Ejemplo 1.

Preparación 1

(4S)-Bencil-3-heptanoil-oxazolidin-2-ona.

A una solución de (S)-(-)-4-bencil-2-oxazolidinona (3,3 g, 18,6 mmol) en THF (50 ml) a -78°C se añadió gota a gota n-BuLi (7,4 ml, solución 2,5 M en hexano, 18,6 mmol). Después de agitar durante 30 minutos a la misma temperatura, la mezcla de reacción se trató seguidamente con cloruro de heptanoilo (2,76 g, 18,6 mmol). La mezcla de reacción se agitó y se dejó calentar a 10°C durante 5 h y seguidamente se inactivó con solución acuosa saturada de NH_4Cl (100 ml). La capa acuosa se extrajo con EtOAc (100 ml x 2). Las capas orgánicas

combinadas se lavaron con salmuera y se secaron sobre $MgSO_4$. La separación del disolvente bajo presión reducida produjo 4,63 g (86%) del compuesto del título. H^1 RMN (400 MHz, $CDCl_3$) δ 7,37-7,22 (m, 5H), 4,69 (m, 1H), 4,19 (m, 2H), 3,31 (dd, J = 13,4, 3,3 Hz, 1H), 2,95 (m, 2H), 2,79 (dd, J = 13,4, 9,7 Hz, 1H), 1,71 (m, 2H), 1,42-1,32 (m, 6H), 0,92 (t, J = 6,8 Hz, 3H), MH+ 290.

Preparación 2

(4S)-Bencil-3-[(2R)-benciloximetilheptanoil]-oxazolidin-2-ona.

A una solución de (S)-4-bencil-3-heptanoiloxazolidin-2-ona (4,63 g, 16,02 mmol) y cloruro de titanio (IV) (1,9 ml, 16,82 mmol) en diclorometano (55 ml) a 0°C se añadió gota a gota diisopropiletilamina (3,1 ml, 17,62 mmol). Después de agitar a 0°C durante 1 hora, el enolato de titanio resultante se hizo reaccionar seguidamente con bencil-clorometil-éter (TCI-America, 4,9 ml, 32,04 mmol) a 0°C durante 6 h. La mezcla de reacción se inactivó seguidamente con agua (100 ml). La capa acuosa se extrajo con diclorometano (100 ml x 2). Los extractos orgánicos se lavaron con salmuera y se secaron sobre $MgSO_4$. Después de separar el disolvente bajo presión reducida, purificación por cromatografía de columna rápida usando un sistema de elución de hexano/EtOAc (5:1) se produjeron 4,39 g (67%) del compuesto del título. H^1 RMN (400 MHz, $CDCl_3$) δ 7,38-7,21 (m, 10H), 4,74 (m, 1H), 4,57 (m, 2H), 4,28-4,13 (m, 3H), 3,82 (t, J = 8,7 Hz, 1H), 3,68 (dd, J = 9,0, 4,9 Hz, 1H), 3,25 (dd, J = 13,5, 3,1 Hz, 1H), 2,71 (dd, J = 13,5, 9,3 Hz, 1H), 1,74 (m, 1H), 1,54 (m, 1H), 1,31-1,28 (m, 6H), 0,89 (t, J = 6,7 Hz, 3H), MH+ 410.

Preparación 3

Ácido (3R)-benciloxi-2-pentilpropiónico.

Una solución 0,05 M de (S)-4-bencil-3-[(R)-2-

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benciloximetilheptanoil)oxazolidin-2-ona (2,0 g, 4,89 mmol) en una mezcla 3:1 de THF y H_2O fue tratada con H_2O_2 a 30% (4,5 ml, 39,12 mmol) y seguidamente con LiOH (0,48 g, 9,78 mmol) a 0°C. La mezcla resultante se agitó y se dejó calentar a temperatura ambiente durante una noche. Seguidamente se separó THF bajo vacío. El residuo se lavó con diclorometano (50 ml x 2) para separar (S)-4-benciloxazolidin-2-ona. El producto deseado se aisló por extracción con EtOAc de la fase acuosa acidificada (pH 1~2). No se requirió ninguna purificación adicional. Un reposo bajo alto vacío produjo 1,16 g (95%) del compuesto del título. H^1 RMN (400 MHz, $CHCl_3$) δ 11,1 (br s, 1H), 7,36 (m, 5H), 4,57 (s, 2H), 3,69 (m, 1H), 3,58 (dd, J = 9,2, 5,2 Hz, 1H), 2,74 (m, 1H), 1,66 (m, 1H), 1,54 (m, 1H), 1,34-1,30 (m, 6H), 0,90 (t, J = 6,7 Hz, 3H), MH+ 251.

Preparación 4

Ácido 3-hidroxi-(2R)-pentilpropiónico.

A una solución de ácido (R)-3-benciloxi-2-pentilpropiónico (1,54 g, 6,16 mmol) en EtOH (100 ml) se añadió 10% de Pd/C (310 mg). La mezcla de reacción se sometió a una hidrogenación durante una noche a temperatura ambiente. Después de que la reacción se completó, la mezcla de reacción se filtró a través de una almohadilla de celite y se lavó con EtOH (50 ml x 3). La separación del disolvente proporcionó el compuesto del título (0,92 g, 93%). No se requirió ninguna purificación adicional. H^1 RMN (400 MHz, $CHCl_3$) δ 6,30 (br s, 1H), 3,81 (d, J = 5,4 Hz, 2H), 2,64 (m, 1H), 1,69 (m, 1H), 1,56 (m, 1H), 1,41-1,27 (m, 6H), 0,91 (t, J = 7,7 Hz, 3H), MH+ 161.

Preparación 5

N-Benciloxi-3-hidroxi-(2R)-pentilpropionamida.

A una mezcla de ácido (R)-3-hidroxi-2-pentilpropiónico (0,92 g, 5,75 mmol), hidrocloruro de O-bencil-hidroxilamina

(0,92 g, 5,75 mmol) y 4-(dimetilamino)piridina (1,41 g, 11,50 mmol) en diclorometano (25 ml) a 0°C se añadió hidrocloruro de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (1,11 g, 5,75 mmol). Después de agitar a temperatura ambiente durante una noche, la reacción fue seguidamente inactivada con solución acuosa 1 N de HCl (25 ml) y se extrajo usando diclorometano (25 ml x 2). Los extractos orgánicos se lavaron con agua, salmuera y se secaron sobre $MgSO_4$. La separación del disolvente bajo presión reducida produjo el compuesto del título (1,43 g, 94%). H^1 RMN (400 MHz, $CHCl_3$) δ 9,22 (br s, 1H), 7,41-7,28 (m, 5H), 4,89 (q, J = 10,6 Hz, 2H), 3,70-3,37 (m, 3H), 2,17 (m, 1H), 1,54 (br s, 1H), 1,27 (m, 6H), 0,88 (t, J = 6,9 Hz, 3H), MH+ 266.

Preparación 6

1-Benciloxi-(3R)-pentilazetidin-2-ona.

A una mezcla de (R)-N-benciloxi-3-hidroxi-2-pentilpropionamida (1,41 g, 5,32 mmol) y trifenilfosfina (1,68 g, 6,39 mmol) en THF (53 ml) se añadió gota a gota azodicarboxilato de dietilo (1,1 ml, 6,39 mmol) a 0°C. La mezcla de reacción se agitó y se dejó calentar a temperatura ambiente durante una noche. La reacción fue seguidamente inactivada con agua (50 ml). La capa acuosa se extrajo con EtOAc (50 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera y se secaron sobre $MgSO_4$. Después de separar el disolvente bajo vacío, el residuo se purificó por cromatografía de columna rápida (hex:EtOAc 5/1) para proporcionar el compuesto del título (1,17 g, 89%). H^1 RMN (400 MHz, $CHCl_3$) δ 7,35-7,25 (m, 5H), 4,87 (s, 2H), 3,28 (t, J = 4,85 Hx, 1H), 2,84 (q, J 2,35 Hz, 1H), 2,77 (m, 1H), 1,62 (m, 1H), 1,36 (m, 1H), 1,25-1,16 (m, 6H), 0,88 (t, J = 6,9 Hz, 3H), MH+ 248.

Preparación 7

Ácido 3-benciloxiamino-(2R)-pentilpropiónico.

A una mezcla de (R)-1-benciloxi-3-pentilacetidin-2-ona (0,96 g, 3,89 mmol) en una mezcla de THF-H_2O-MeOH (500 ml, 3:1 v/v) se añadió monohidrato de hidróxido de litio (1,91 g, 38,9 mmol). Después de agitar a temperatura ambiente durante una noche, se añadió agua (25 ml) a la mezcla. La solución se acidificó a pH 5~6 con solución acuosa 3 N de HCl. Se extrajo con EtOAc (50 ml x 2). Las capas orgánicas combinadas se secaron sobre $MgSO_4$. La separación del disolvente bajo vacío proporcionó el compuesto del título (0,98 g, 95%). H^1 RMN (400 MHz, $CHCl_3$) δ 9,80 (br s, 1H), 7,37 (m, 5H), 4,75 (m, 2H), 3,14 (m, 2H), 2,74 (m, 1H), 1,70 (m, 1H), 1,53 (m, 1H), 1,38-1,25 (m, 6H), 0,91 (t, J = 6,8 Hz, 3H), MH+ 266.

Preparación 8

Ácido (2R)-[(benciloxiformilamino)metil]heptanoico.

A una solución fría de ácido (R)-3-benciloxiamino-2-pentilpropiónico (1,03 g, 3,89 mmol) en HCO_2H (19 ml) y diclorometano (19 ml) a 0°C se añadió anhídrido acético (3,9 ml, 41,2 mmol). La mezcla se agitó a 0°C durante 3 horas. Los elementos volátiles se separaron por evaporación bajo vacío. Se le añadió diclorometano (50 ml). Se lavó con salmuera (50 ml x 2) y se secó sobre $MgSO_4$. Una filtración y evaporación bajo vacío proporcionaron el compuesto del título (1,08 g, 95%). H^1 RMN (400 MHz, $CHCl_3$) δ 8,07 (br s, 1H), 7,29 (m, 5H), 4,91-4,71 (m, 2H), 3,76 (m, 2H), 2,67 (m, 1H), 1,54 (m, 1H), 1,41(m, 1H), 1,20 (m, 6H), 0,80 (t, J = 7,0 Hz, 3H), MH+ 294.

Preparación 9

Butilhidrazina.

Se añadió 1-yodobutano (5,1 ml, 45,1 mmol) a través de un condensador durante 30 minutos a una solución a reflujo de monohidrato de hidrazina (11,3 g, 225,5 mmol) en EtOH (100 ml). Después de agitar y llevar a reflujo durante 18 horas,

se separó etanol por evaporación bajo vacío. El residuo se extrajo con éter (50 ml x 2). Las capas orgánicas combinadas se secaron (K_2CO_3), se filtraron y se evaporaron para producir 2,6 g (66%) del compuesto del título. H^1 RMN (400 MHz, $CHCl_3$) δ 3,15 (br s, 2H), 2,73 (t, J = 7,2 Hz, 2H), 1,44 (m, 2H), 1,33 (m, 2H), 0,89 (t, J 7,2 Hz, 3H), MH+ 89.

Preparación 10

Éster terc-butílico de ácido N-butilhidrazinocarboxílico.

A una solución de butilhidrazina (510 mg, 5,80 mmol) y trietilamina (1,2 ml, 8,69 mmol) en diclorometano (20 ml) a 0°C se añadió dicarbonato de di-t-butilo (1,26 g, 5,80 mmol). La mezcla de reacción se agitó y se dejó calentar a temperatura ambiente durante una noche. Seguidamente se añadió agua (20 ml) a la mezcla de reacción. La capa acuosa se extrajo con diclorometano (20 ml x 2). Las capas orgánicas combinadas se secaron ($MgSO_4$). Una filtración y evaporación bajo vacío proporcionó el compuesto del título (820 mg, 75%). H^1 RMN (400 MHz, $CHCl_3$) δ 3,89 (br s, 2H), 3,29 (t, J = 7,1 Hz, 2H), 1,46 (m, 2H), 1,40 (s, 9H), 1,24 (m, 2H), 0,86 (t, J = 7,3 Hz, 3H), MH+ 189.

Preparación 11

N-Butil-N-(t-butoxicarbonil)-N-{(2R)-[(benciloxiformilamino)metil]heptanoil}-hidrazina.

A una solución de ácido (R)-2-[(benciloxiformilamino)metil]heptanoico (180 mg, 0,614 mmol), éster terc-butílico de ácido N-butil-hidrazinocarboxílico (140 mg, 0,737 mmol) y 4-dimetilaminopiridina (90 mg, 0,737 mmol) en diclorometano (6,5 ml) a 0°C se añadió hidrocloruro de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (142 mg, 0,737 mmol). Después de agitar a temperatura ambiente durante una noche, la reacción fue seguidamente inactivada con HCl 1 N

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acuoso y se extrajo con diclorometano (15 ml x 2).

Los extractos orgánicos se lavaron con salmuera (30 ml) y se secaron sobre $MgSO_4$. La evaporación del disolvente bajo vacío, seguida de purificación por cromatografía de columna rápida, produjo 195 mg (69%) del compuesto del título. H^1 RMN (400 MHz, $CHCl_3$) δ 8,09 (br s, 1H), 7,25 (s, 5H), 4,80 (m, 2H), 4,10 (dd, J = 14,1, 4,0 Hz, 1H), 3,62 (m, 1H), 3,35 (m, 2H), 2,55 (m, 1H), 1,72 (m, 1H), 1,56 (m, 1H), 1,50 (s, 9H), 1,30 (m, 10H), 0,90 (m, 6H), MH+ 464.

Ejemplo 1

N-Butil-N-(t-butoxicarbonil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

A una solución de éster terc-butílico de ácido N'-{(R)-2-[(benciloxi-formilamino)metil]heptanoil}-N-butilhidrazinocarboxílico (195 mg, 0,421 mmol) en EtOH (15 ml) se añadió 10% de Pd/C (60 mg). La mezcla de reacción se sometió seguidamente a hidrogenación durante una noche a temperatura ambiente. Después de que la reacción se completó, la mezcla de reacción se filtró a través de una almohadilla de Celite y se lavó con EtOH (10 ml x 2). La separación del disolvente proporcionó el producto en bruto, que se purificó adicionalmente por HPLC para producir el compuesto del título (52 mg, 33%). H^1 RMN (400 MHz, $CHCl_3$) δ 9,94 (s, 1H), 9,39 (s, 1H), 8,32 (s, 1H), 4,10 (dd, J = 14,1, 4,0 Hz, 1H), 3,62 (m, 1H), 3,35 (m, 2H), 2,55 (m, 1H), 1,72 (m, 1H), 1,56 (m, 1H), 1,50 (s, 9H), 1,30 (m, 10H), 0,90 (m, 6H), MH+ 374.

Preparación 12

Éster fenílico de ácido N-butilhidrazinocarboxílico.

A una solución de butilhidrazina (370 mg, 4,20 mmol) y trietilamina (0,88 ml, 6,30 mmol) en diclorometano (15 ml) a 0°C se añadió cloroformiato de fenilo (0,53 ml, 4,20 mmol). La mezcla de reacción se agitó y se dejó calentar a tempera-

tura ambiente durante una noche. Seguidamente se añadió agua (20 ml) a la mezcla de reacción. La capa acuosa se extrajo con diclorometano (20 ml x 2). Las capas orgánicas combinadas se secaron ($MgSO_4$). Una filtración y evaporación bajo vacío, seguida de purificación por cromatografía de columna rápida, proporcionó el compuesto del título (250 mg, 29%). H^1 RMN (400 MHz, $CHCl_3$) δ 7,40-7,10 (m, 5H), 4,20 (t, J = 7,1 Hz, 2H), 3,60 (br s, 2H), 1,71 (m, 2H), 1,41 (m, 2H), 0,98 (t, J = 7,3 Hz, 3H), MH+ 209.

Ejemplo 2

N-Butil-N-fenoxicarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

Una purificación por HPLC preparativa produjo 49 mg (41%) del compuesto del título. H^1 RMN (400 MHz, $CHCl_3$) δ 9,78 (s, 1H), 9,39 (s, 1H), 8,27 (s, 1H), 7,40-7,10 (m, 5H), 4,20-3,30 (m, 4H), 2,70 (m, 1H), 1,80-1,20 (m, 10H), 0,90 (m, 6H), MH+ 394.

Ejemplo 3

N-Isobutil-N-(t-butoxicarbonil)N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

Una purificación por HPLC preparativa produjo 44 mg (22%, 2 etapas) del compuesto del título. H^1 RMN (400 MHz, $CHCl_3$) δ 9,94 (s, 1H), 9,54 (s, 1H), 8,32 (s, 1H), 4,11 (dd, J = 3,9, 14,1 Hz, 1H), 3,46 (m, 1H), 3,35 (m, 1H), 3,12 (dd, J = 6,3, 14,1 Hz, 1H), 2,54 (m, 1H), 1,88 (m, 1H), 1,72 (m, 1H), 1,50 (s, 9H), 1,49-1,25 (m, 7H), 0,95-0,88 (m, 9H), MH+ 374.

Ejemplo 4

N-Isobutil-N-fenoxicarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

Una purificación por HPLC preparativa produjo 44 mg (22%, 2 etapas) del compuesto del título. H^1 RMN (400 MHz,

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$CHCl_3$) δ 9,97 (s, 1H), 9,38 (s, 1H), 8,27 (s, 1H), 7,41-7,13 (m, 5H), 4,08 (dd, J = 3,9, 14,1 Hz, 1H), 3,37 (m, 2H), 2,65 (m, 1H), 2,02 (m, 1H), 1,74 (m, 1H), 1,32-1,02 (m, 7H), 0,92-0,82 (m, 9H), MH+ 394.

Ejemplo 5

N-Fenetil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CHCl_3$) δ 9,80 (s, 1H), 9,03 (s, 1H), 8,35 (s, 1H), 7,22 (s, 5H), 4,11-3,36 (m, 4H), 2,86 (t, 3H), 2,52 (m, 1H), 2,07 (m, 1H), 1,72 (m, 1H), 1,41-1,34 (m, 15H), 0,92 (t, 3H), MH+ 422.

Ejemplo 6

N-Ciclohexilmetil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,44 (s, 1H), 7,70 (br s, 1H), 4,20-3,05 (m, 4H), 2,50 (m, 1H), 1,74-0,90 (m, 31H), MH+ 414.

Ejemplo 7

N-Bencil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,70 (br s, 1H), 8,77 (br s, 1H), 8,25 (s, 1H), 7,64-7,28 (m, 5H), 5,00 (d, J = 14,7 Hz, 1H), 2,40 (m, 1H), 1,66 (m, 1H), 1,56 (m, 1H), 1,52 (s, 9H), 1,48-1,10 (m, 6H), 0,87 (t, J = 7,1 Hz, 3H), MH+ 408.

Ejemplo 8

N-(3-Piridin-3-il-propil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,79-7,25 (m, 5H), 4,15-3,03 (m, 4H), 2,75 (m, 1H), 2,56 (m, 2H), 2,07-1,72 (m, 4H), 1,49 (s, 9H), 1,46-1,28 (m, 6H), 0,85 (t, J = 6,9 Hz, 3H), MH+ 437.

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Ejemplo 9

N-(2-Morfolin-4-il-etil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,45 (br s, 1H), 7,88 (br s, 1H), 4,20-3,30 (m, 8H), 2,70 (m, 1H), 2,60-2,45 (m, 6H), 1,72 (m, 1H), 1,50 (s, 9H), 1,39 (m, 1H), 1,29 (m, 6H), 0,89 (t, J = 7,1 Hz, 3H), MH+ 431.

Ejemplo 10

N-(4-HIdroxi-butil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,04 (br s, 1H), 8,37 (br s, 1H), 4,07-3,46 (m, 6H), 2,54 (m, 1H), 1,64-1,30 (m, 12H), 1,47 (s, 9H), 0,89 (t, J = 6,9 Hz, 3H), MH+ 390.

Ejemplo 11

N-(4-Amino-butil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 7,90 (s, 1H), 7,70 (s, 1H), 4,00 (m, 2H), 3,70-3,40 (m, 4H), 3,0 (m, 2H), 2,50 (m, 1H), 1,70 (m, 1H), 1,50 (m, 1H), 1,49 (s, 9H), 1,48-1,20 (m, 10H), 0,89 (t, J = 6,9 Hz, 3H), MH+ 389.

Ejemplo 12

N-(Tetrahidro-piran-4-il)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,88 (br s, 1H), 8,31 (s, 1H), 4,16-4,00 (m, 4H), 3,44-3,39 (m, 3H), 2,60 (m, 1H), 1,97-1,26 (m, 12H), 0,90 (t, J = 6,9 Hz, 3H), MH+ 402.

Ejemplo 13

N-Metil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,74 (br s, 1H), 8,90 (br s, 1H), 8,29 (br s, 1H), 4,06 (m, 1H), 3,24 (m, 1H), 3,10 (s,

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3H), 2,43 (m, 1H), 1,64 (m, 1H), 1,42 (s, 9H), 1,31 (m, 1H), 1,19 (m, 6H), 0,79 (t, J = 6,9 Hz, 3H), MH+ 332.

Ejemplo 14

N-(3-Amino-propil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,27 (s, 1H), 7,78 (s, 1H), 3,76-3,32 (m, 4H), 2,84 (m, 2H), 2,68 (m, 1H), 1,80 (m, 1H), 1,74 (m, 1H), 1,48 (s, 9H), 1,35 (m, 8H), 0,93 (t, J = 6,8 Hz, 3H), MH+ 375.

Ejemplo 15

N-(t-butoxicarbonil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,53 (s, 1H), 8,17 (s, 1H), 6,68 (s, 1H), 4,11 (m, 1H), 3,38 (m, 1H), 2,63 (m, 1H), 1,70 (m, 1H), 1,49 (s, 9H), 1,42 (m, 1H), 1,29 (m, 6H), 0,87 (t, J = 6,8 Hz, 3H), MH+ 318.

Ejemplo 16

N-(3-Hidroxi-propil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,34 (s, 1H), 8,33 (s, 1H), 7,83 (s, 1H), 3,83-3,43 (m, 6H), 2,81 (m, 1H), 1,78-1,65 (m, 2H), 1,52-1,29 (m, 8H), 1,45 (s, 9H), 0,87 (s, 9H), MH+ 376.

Ejemplo 17

N-Butil-N-(t-butoxicarbonil)-N'-[(2S)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 374.

Ejemplo 18

N-Butil-N-(fenoxicarbonil)-N'-[(2S)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,27 (s, 1H), 8,20 (s, 1H), 7,32-7,04 (m, 5H), 3,80-3,31 (m, 4H), 2,55 (s, 1H), 1,66 (s, 1H), 1,59-1,24 (m, 11H), 0,90-0,82 (m, 6H), MH+ 394.

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Ejemplo 19

N-[2-(4-Dimetilaminofenil)etil]-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,81 (s, 1H), 8,89 (s, 1H), 8,33 (s, 1H), 7,06 (d, J = 8,5 Hz, 2H), 6,71 (d, J = 8,5 Hz, 2H), 4,17-3,33 (m, 4H), 2,93 (s, 6H), 2,80 (m, 2H), 2,48 (m, 1H), 1,71 (m, 1H), 1,41 (s, 9H), 1,32 (m, 7H), 0,91 (t, 3H), MH+ 465.

Ejemplo 20

N-(t-Butoxicarbonil)-N'-{2-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,81 (s, 1H), 9,54 (s, 1H), 8,46 (s, 1H), 6,78 (s, 1H), 3,85-3,37 (m, 2H), 2,,80-2,62 (m, 1H), 1,71 (m, 1H), 1,49 (s, 9H), 1,30-1,25 (m, 7H), 0,89 (t, 3H), MH+ 318.

Ejemplo 21

N-Pentil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,10 (s, 1H), 8,43 (s, 1H), 4,14-3,05 (m, 4H), 2,86-2,48 (m, 1H), 1,61 (m, 1H), 1,41 (m, 9H), 1,25-1,16 (m, 13H), 0,84 (m, 6H), MH+ 388.

Ejemplo 22

N-[2-(1H-Indol-3-il)-etil]-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,78 (s, 1H), 8,55 (s, 1H), 8,33 (s, 1H), 8,15 (s, 1H), 7,55-7,05 (m, 5H), 4,10-3,92 (m, 2H), 3,71-3,30 (m, 2H), 3,02 (m, 2H), 2,40 (m, 1H), 1,67 (m, 1H), 1,50-1,20 (m, 16H), 0,89 (m, 6H), MH+ 461.

Ejemplo 23

N-Isopentil-N-(tbutoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

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H^1 RMN (400 MHz, $CDCl_3$) δ 9,92 (s, 1H), 8,39 (s, 1H), 4,05-3,63 (m, 2H), 3,31 (t, 2H), 2,54 (m, 1H), 1,70 (m, 1H), 1,55 (m, 1H), 1,50-1,18 (m, 18H), 0,88 (m, 9H), MH+ 388.

Ejemplo 24

N-Ciclohexil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,79 (s, 1H), 8,30 (s, 1H), 4,11 (m, 1H), 3,85 (m, 1H), 3,35 (m, 1H), 2,55 (m, 1H), 1,94 (m, 1H), 1,81-1,57 (m, 5H), 1,51-1,18 (m, 18H), 0,89 (m, 3H), MH+ 400.

Ejemplo 25

N-(1-Etil-propil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,81 (s, 1H), 8,41 (s, 1H), 4,11-3,32 (m, 3H), 2,55 (m, 1H), 1,80 (m, 1H), 1,58-1,15 (m, 20H), 1,05 (m, 3H), 0,89 (m, 6H), MH+ 388.

Ejemplo 26

N-Isopropil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,92 (s, 1H), 8,31 (s, 1H), 4,34-4,08 (m, 2H), 3,37 (m, 1H), 2,76 (m, 1H), 1,73 (m, 1H), 1,51 (s, 9H), 1,31 (m, 7H), 1,11 (m, 6H), 0,88 (m, 3H), MH+ 360.

Ejemplo 27

N-Propil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,37 (s, 1H), 8,24 (s, 1H), 4,03-3,17 (m, 4H), 2,42 (m, 1H), 1,61 (m, 1H), 1,52-1,31 (m, 11H), 1,20 (m, 7H), 0,82 (m, 6H), MH+ 360.

Ejemplo 28

N-Etil-N-(t-butoxicarbonil)-N'-{2-

[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,79 (s, 1H), 8,05 (s, 1H), 4,21-3,25 (m, 4H), 2,48 (m, 1H), 1,51-1,02 (m, 20H), 0,88 (m, 3H), MH+ 346.

Ejemplo 29

N-Metoxicarbonil-N'-{2-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,35 (s, 1H), 8,05 (s, 1H), 7,64 (s, 1H), 7,50 (s, 1H), 3,68 (m, 3H), 3,37 (d, J = 5,5 Hz, 2H), 2,72 (m, 1H), 1,61 (m, 1H), 1,41-1,12 (m, 7H), 0,85 (m, 3H), MH+ 276.

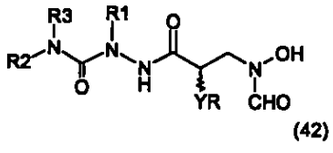
Ejemplo 30

N-{[1-(3,5-Dimetoxifenil)-1-metil-etoxi]carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

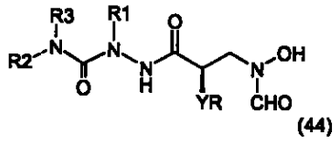
H^1 RMN (400 MHz, $CDCl_3$) δ 8,71 (s, 1H), 8,21 (s, 1H), 7,76 (s, 1H), 6,62 (s, 1H), 6,36 (d, J = 4,7 Hz, 1H), 3,83-3,69 (m, 7H), 3,38 (m, 1H), 2,70(m, 1H), 1,82-1,55 (m, 7H), 1,43-1,21 (m, 7H), 0,84 (m, 3H), MH+ 440.

Tercera realización

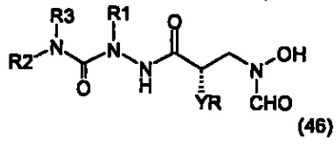
Como la tercera realización de la presente invención, se describen los compuestos de Fórmula (1) en la que X=NR3, en la forma del compuesto racémico (42) y los compuestos quirales (44) y (46). Estos compuestos tienen preferentemente R1=H.



(42)



(44)



(46)

Los compuestos preferidos útiles en la presente invención se seleccionan entre el grupo que consiste en:

N-Butil-N-[(4-metilpiperazin-1-il)carbonil]-N'-{(2R)-

[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-difenilaminocarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-(t-butilamino)carbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-fenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-[(3,5-dimetil-4,5-dihidro-isoxazol-4-il)aminocarbonil]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-[(1-morfolin-4-il)carbonil]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]-4-fenil-butanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]hexanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]-3-fenil-propanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]-3-(3,4-diclorofenil)-propanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-(3,4-Diclorofenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3,4-Diclorofenilaminocarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Morfolin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2-Metoxifenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,4-Diclorofenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,6-Diclorofenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(4-Metil-piperazin-1-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

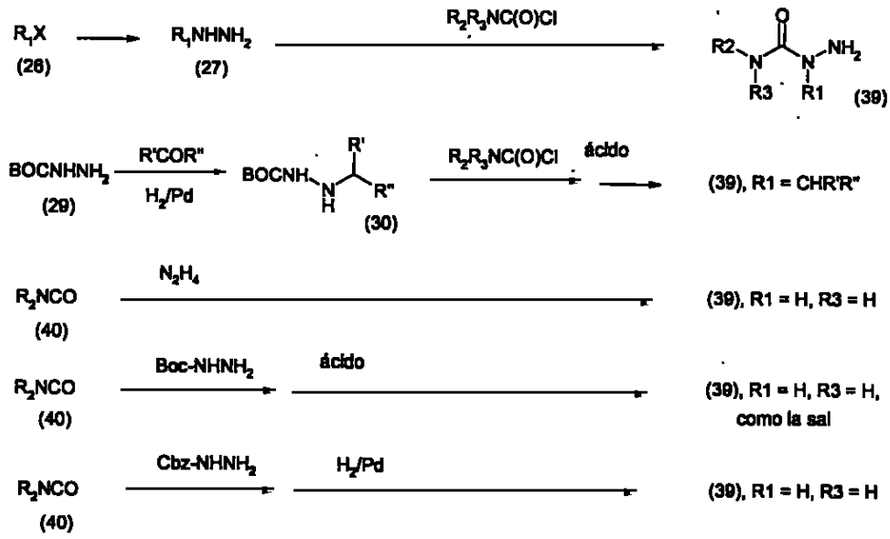
N-[(4-Cloro-3-trifluorometilfenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Metil-fenil-amino)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

Los siguientes esquemas sintéticos son meramente ilustrativos de los métodos mediante los cuales se pueden preparar los compuestos de la invención, y no está previsto que limiten el alcance de la invención tal como se define en las reivindicaciones anejas.

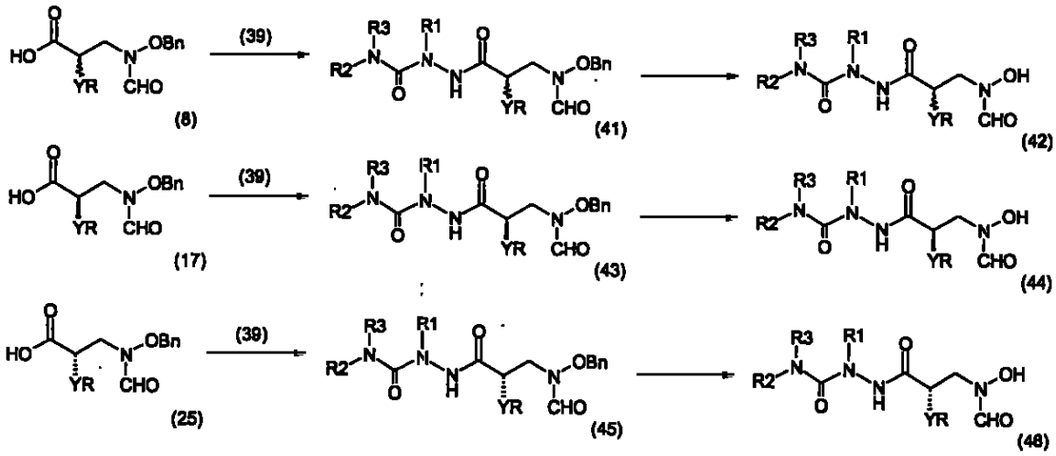
Como se muestra en el Esquema 6, el tratamiento de un haluro de alquilo R1X (26) con hidrazina en un disolvente como etanol, a una temperatura elevada, proporciona el derivado de hidrazina (27). Haciendo reaccionar el compuesto (27) con el cloruro de carbamilo R2R3NC(O)Cl se proporciona el intermedio (39). Alternativamente, el compuesto (39) se puede preparar a partir de la hidrazina (29) protegida con Boc mediante reacción con el aldehído o cetona R'COR'', seguida de reducción con gas hidrógeno en presencia de paladio, para proporcionar el derivado de hidracina (30). Haciendo reacciones la hidrazina (30) con cloruro de carbamilo R2R3NC(O)Cl, seguida de la separación del grupo protector Boc con un ácido apropiado, como ácido trifluoroacético, se proporciona el derivado de hidrazina (39) en el que R1=CHR'R''. Alternativamente, haciendo reaccionar el isocianato R2NCO (40) con hidrazina se proporciona el compuesto (39) en el que R1=H y R3=H. Alternativamente, haciendo reaccionar el isocianato

R2NCO (40) con hidrazina protegida con Boc, seguida de tratamiento con un ácido, se proporciona la forma de sal del compuesto (39) en la que R1=H y R3=H. Alternativamente, haciendo reaccionar el isocianato R2NCO (40) con una hidrazina protegida con Cbz, seguida de hidrogenación, se proporciona el compuesto (39) en el que R1=H y R3=H.



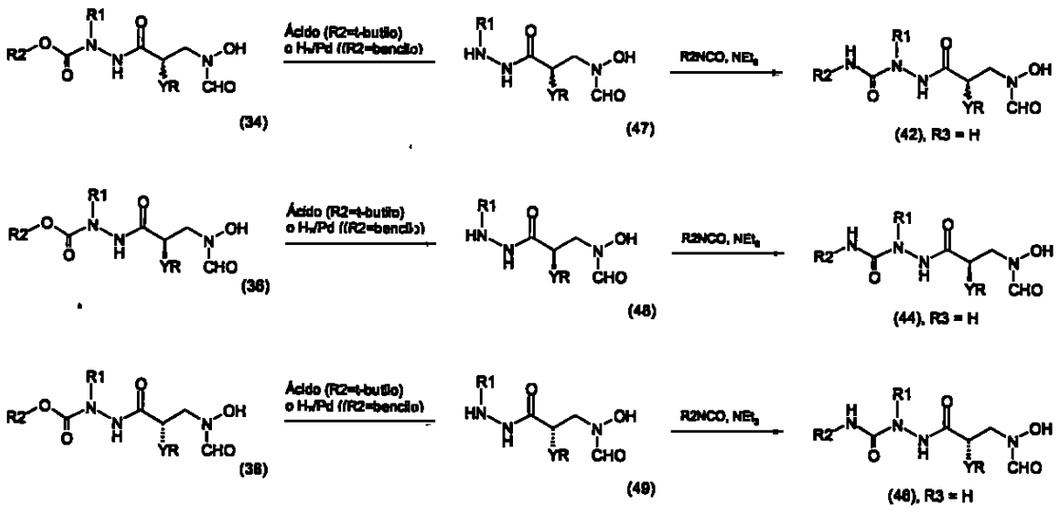
Esquema 6

Como se muestra en el Esquema 7, el acoplamiento del ácido carboxílico (8) con el derivado de hidrazina (39) proporciona la hidrazida (41). La hidrogenolisis para separar el grupo bencilo usando un catalizador, como 10% de Pd/C, en un disolvente apropiado como etanol, proporciona el compuesto (42). Análogamente, el acoplamiento del ácido quiral (17) o (25) con un derivado de hidrazina (39) proporciona la correspondiente hidrazida (43) o (45). La hidrogenolisis del grupo bencilo proporciona los compuestos finales (44) o (46).



Esquema 7

Alternativamente, como se muestra en el Esquema 8, el carbamato (34) en el que R2=t-butilo o bencilo se puede convertir en la hidrazida (47) mediante tratamiento con ácido o hidrogenolisis, respectivamente. La reacción de (47) con un isocianato en un disolvente apropiado, como cloruro de metileno, y en la presencia opcional de una base apropiada, como trietilamina, proporciona el compuesto (42) en el que R3=H. Análogamente, la desprctección apropiada de los carbamatos quirales (36) y (38), seguida de una reacción con un isocianato, proporciona la hidrazida quiral (44) y (46) en las que R3=H.



Esquema 8

EJEMPLOS SINTÉTICOS

La invención se describe seguidamente mediante referencia a los siguientes ejemplos, que son meramente ilustrativos y no están concebidos como una limitación del alcance de la presente invención. Son aplicables en los mismos las mismas condiciones y convenciones generales experimentales descritas en la Sección Experimental y en la Segunda Realización.

Los compuestos descritos en los Ejemplos 31 a 51 se prepararon siguiendo los procedimientos generales descritos en el Ejemplo 1.

Preparación 13

N-[(4-Metilpiperazino)carbonil]-N-butilhidrazina.

A una solución de butil-hidrazina (200 mg, 2,27 mmol) y trietilamina (0,95 ml, 6,81 mmol) en diclorometano (10 ml) a -78°C se añadió hidrocloruro de cloruro de 4-metil-1-piperazino-carbonilo (0,45 g, 2,27 mmol). La mezcla de reacción se agitó y se dejó calentar a temperatura ambiente durante una noche. Seguidamente se añadió $NaHCO_3$ acuoso saturado (20 ml) a la mezcla de reacción. La capa acuosa se extrajo con diclorometano (20 ml x 2). Las capas orgánicas combinadas se secaron ($MgSO_4$). Una filtración y evaporación bajo vacío, seguida de purificación por cromatografía de columna rápida (CH_2Cl_2:MeOH:Et_3N=9:1:0,05) proporcionó el compuesto del título (350 mg, 72%). H^1 RMN (400 MHz, $CHCl_3$) 3,89 (br s, 2H), 3,41 (t, J = 4,9 Hz, 2H), 3,31 (t, J = 4,9 Hz, 2 H), 3,14 (t, J = 7,6 Hz, 2H), 2,44-2,41 (m, 4H), 2,33 (s, 3H), 1,64 (m, 2H), 1,32 (m, 2H), 0,95 (t, J = 7,3 Hz, 3H), MH+ 215.

Ejemplo 31

N-Butil-N-[(4-metilpiperazin-1-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

Una purificación por HPLC preparativa produjo 44 mg (22%, 2 etapas) del compuesto del título. MH+ 400.

Ejemplo 32

N-Butil-N-difenilaminocarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

Una purificación por HPLC preparativa produjo 85 mg (16%, 2 etapas) del compuesto del título. H^1 RMN (400 MHz, $CHCl_3$) δ 9,52 (s, 1H), 8,89 (s, 1H), 8,35 (s, 1H), 7,39-7,07 (m, 10H), 4,03 (m, 1H), 3,51-3,26 (m, 3H), 2,54 (m, 1H), 1,74

(m, 1H), 1,41 (m, 1H), 1,30-1,07 (m, 10H), 0,90 (t, J = 7,3 Hz, 3H), 0,76 (t, J = 7,3Hz, 3H), MH+ 469.

Ejemplo 33

N-Butil-N-(t-butilamino)carbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,25 (s, 1H), 7,81 (s, 1H), 4,10-3,20 (m, 6H), 3,01 (br s, 1H), 2,42 (m, 1H), 1,55-1,20 (m, 12H), 1,27 (s, 9H), 0,88-0,85 (m, 6H), MH+ 373.

Ejemplo 34

N-Butil-N-fenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,26 (s, 1H), 7,81 (s, 1H), 7,25 (br s, 1H), 4,10-3,20 (m, 6H), 3,00 (br s, 1H), 2,42 (m, 1H), 1,60-1,15 (m, 12H), 0,88-0,83 (m, 6H), MH+ 393.

Ejemplo 35

N-Butil-N-[(3,5-dimetil-4,5-dihidro-isoxazol-4-il)aminocarbonil]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,30 (s, 1H), 8,10 (s, 1H), 7,75 (s, 1H), 3,90-3,20 (m, 6H), 2,75 (m, 1H), 2,20-1,90 (m, 6H), 1,80-1,32 (m, 12H), 0,97-0,91 (m, 6H), MH+ 414.

Ejemplo 36

N-Butil-N-[(1-morfolin-4-il)carbonil]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,80 (s, 1H), 7,80 (s, 1H), 3,80-3,20 (m, 12H), 2,75 (m, 1H), 1,80-1,30 (m, 14H), 0,96-0,90 (m, 6H), MH+ 387.

Ejemplo 37

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-etil]heptanoil}-hidrazina.

MH+ 371.

Ejemplo 38

145

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-metil]-hexanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,80 (br s, 1H), 7,84 (s, 1H), 7,29 (m, 5H), 3,90-3,40 (m, 2H), 2,86 (m, 1H), 1,70 (m, 1H), 1,50-1,15 (m, 5H), 0,89 (m, 3H), MH+ 323.

Ejemplo 39

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-metil]-3-fenil-propanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,90 (br s, 1H), 8,40 (s, 1H), 7,70 (s, 1H), 7,30-7,00 (m, 10H), 4,15-3,55 (m, 4H), 3,10 (m, 1H), 2,85 (m, 1H), 2,70 (m, 1H), MH+ 357.

Ejemplo 40

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-metil]-3-(3,4-diclorofenil)-propanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,90 (br s, 1H), 8,50 (s, 1H), 7,70 (s, 1H), 7,28-7,05 (m, 8H), 4,10-3,45 (m, 2H), 3,10 (m, 1H), 2,95 (m, 1H), 2,70 (m, 1H), MH+ 425.

Ejemplo 41

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,90 (s, 1H), 8,40 (s, 1H), 7,95 (s, 1H), 7,81 (s, 1H), 7,41-6,95 (m, 5H), 3,90-3,40 (m, 2H), 2,83 (m, 1H), 1,61 (m, 1H), 1,42-1,12 (m, 7H), 0,87 (m, 3H), MH+ 337.

Ejemplo 42

N-(3,4-Diclorofenilaminocarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,29 (s, 1H), 7,75 (s, 1H), 7,52 (s, 1H), 7,22-7,15 (m, 4H), 3,98-3,29 (m, 2H), 2,85-2,43 (m, 1H), 1,59 (m, 1H), 1,41-1,15 (m, 7H), 0,80 (m, 3H), MH+ 406.

146 149

Ejemplo 43

N-Fenilaminocarbonil-N'-{(2R)-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,28 (s, 1H), 7,71 (s, 1H), 7,27-6,81 (m, 5H), 3,81-3,25 (m, 2H) 2,75-2,41 (m, 1H), 1,45 (m, 1H), 1,31-1,01 (m, 7H), 0,72 (m, 3H), MH+ 337.

Ejemplo 44

N-(3,4-Diclorofenilaminocarbonil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 10,00 (s, 1H), 8,41 (s, 1H), 8,28 (s, 1H), 8,16 (d, J = 7 Hz, 1H), 7,74 (s, 1H), 7,38-6,81 (m, 3H), 3,81-3,38 (m, 2H), 2,81-2,52 (m, 1H), 1,68-1,07 (m, 8H), 0,78 (m, 3H), MH+ 405.

Ejemplo 45

N-[(1-Morfolin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,29 (s, 1H), 8,25 (s, 1H), 8,15 (s, 1H), 4,08-3,49 (m, 6H), 3,35 (m, 4H), 2,78-2,55 (m, 1H), 1,52 (m, 1H), 1,41-1,08 (m, 7H), 0,79 (m, 3H), MH+ 331.

Ejemplo 46

N-[(2-Metoxifenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,33 (s, 1H), 7,99 (s, 1H), 7,05-6,70 (m, 4H) 4,14-3,32 (m, 5H), 2,85-2,59 (m, 1H), 1,60 (m, 1H), 1,42-1,18 (m, 7H), 0,87 (m, 3H), MH+ 367.

Ejuemplo 47

N-[(2,4-Diclorofenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 405.

Ejemplo 48

N-[(2,6-Diclorofenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

147

150

MH+ 405.

Ejemplo 49

N-[(4-Metil-piperazin-1-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 344.

Ejemplo 50

N-[(4-Cloro-3-trifluorometilfenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 439.

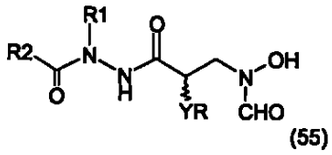
Ejemplo 51

N-[(Metil-fenil-amino)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

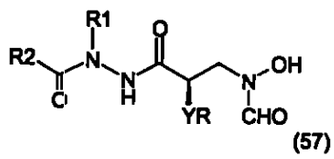
MH+ 351.

Cuarta realización

Como la cuarta realización de la presente invención, se describen los compuestos de Fórmula (1) en la que X es un enlace covalente, en forma del compuesto racémico (55) y los compuestos quirales (57) y (59). Estos compuestos tienen preferentemente R1=H.



(55)



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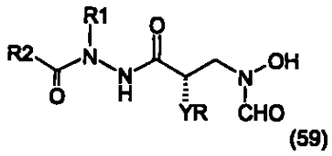

(59)

Los compuestos preferidos útiles en la presente invención se seleccionan entre el grupo que consiste en:

N-[(Fenilaminocarbonil)-carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-{[1-(t-butoxicarbonil)-piperidin-4-il]-carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-{[(1-t-butoxicarbonil)-pirrolidin-(2S)-il]carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-

148

151

hidrazina.

N-Butil-N-{[(1-t-butilaminocarbonil)piperidin-4-il]carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-{[(1-t-butilcarbonil)piperidin-4-il]carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-[(1,2,3,4-tetrahidro-quinoxalin-2-il)carbonil]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(p-metoxifenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Fenoxiacetil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(p-Metoxi-fenoxi)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(2,6-Diclorofenil-acetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3,4-Diclorofenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Etoxicarbonil)carbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(2,4-Diclorofenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(2,3-Diclorfenoxiacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3,4-Dimetoxifenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1H-Indol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2-Metil-piridin-3-il)carbonil]-N'-{(2R)-

[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Metoxi-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,3-Dihidro-benzo[1,4]dioxin-(2S)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinolin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1,2,3,4-Tetrahidro-quinolin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Tetrahidro-furan-(2S)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Tetrahidro-furan-(2R)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(3-Metil-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Piridin-2-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{3-[3-(4-Metoxibencil)-1H-benzoimidazol-2-il]-propanoil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Pirimidin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2-Metil-5,6,7,8-tetrahidro-[1,8]naftiridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Isoquinolin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5,6,7,8-Tetrahidro-[1,8]naftiridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(3,4-Dihidro-2H-benzo[b][1,4]dioxepin-7-il)carbonil]-

N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Metil-2,5-dioxo-imidazolidin-4-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-3-fenil-propanoil}-hidrazina.

N-(Fenilacetil)-N'-{2-[(formilhidroxiamina)metil]-3-(3,4-dicloro)fenil-propanoil}-hidrazina.

N-[(4-Imidazol-1-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[1-Metil-5-oxo-2-S-(piridin-3-il)pirrolidin(3S)-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1,2-Dihidro-cinolin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[4-(4-Acetilpiperazin-1-il)fenoxiacetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Fenilacetil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[1-Bencil-5-oxo-pirrolidin-(2S)-il]-carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Bencil-5-oxo-pirrolidin-(2R)-il]-carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5S)-Bencil-3,6-dioxo-piperazin-(2S)-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinolin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinolin-8-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1,2,3,4-Tetrahidroquinolin-8-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(N''-Acetil-L-tirosil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Acetil-1,2,3,4-tetrahidro-quinolin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1H-Benzoimidazol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[1-(2-Hidroxiacetil)-1,2,3,4-tetrahidro-quinolin-6-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1H-Indol-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-{4-[Metil-(4,6-dimetilpirimidin-2-il)amino]benzoil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Benzo[1,3]dioxol-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(4-(3,5-Dimetil-pirazol-1-il)metil]benzoil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[4-(Morfolin-4-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[4-Hidroxi-3-(morfolin-4-il)metil-benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3-Hidroxi-3-metil-butanoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-Metilamino-benzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Isopropil-1H-benzotriazol-5-il)carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1,2,3,4-Tetrahidro-isoquinolin-(3S)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Cloro-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[1-(Dimetilaminocarbonilmetil)-3,4-dihidro-2H-quinolin-6-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

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N-[(2,2-Difluoro-benzo[1,3]dioxol-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Amino-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(4-Oxo-1,2-dihidro-4H-pirrolo[3,2,1-ij]quinolin-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(7-Hidroxi-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(6-Metoxi-benzofuran-2-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Acetamidobenzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,3-Dihidro-benzo[1,4]dioxin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(3-Amino-4,6-dimetil-furo[2,3-b]piridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2-Metil-5,6,7,8-tetrahidro-[1,6]naftiridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(6-Fluoro-4H-benzo[1,3]dioxin-8-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(7-Amino-1H-indol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-metil-1,2,3,4-tetrahidro-quinolin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N'-[(6,7,9,10,12,13,15,16-Octahidro-5,8,11,14,17-pentaoxa-benzociclopentadecen-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2-Benzo[1,3]dioxol-5-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

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N-Pentanoil-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-Benzoil-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-Trifluoroacetamido-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-[(3-Hidroxi-naftalen-2-il)carbonil]-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-Fenilacetil-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-[(Furan-2-il)carbonil]-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-(4-Metoxibenzoil)-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-[(1H-Indol-3-il)acetil]-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-(4-Dimetilaminobenzoil)-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-(2-Hidroxibenzoil)-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-[(Piperidin-4-il)carbonil]-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-[(1,2,5,6-Tetrahidro-piridin-3-il)carbonil]-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-[(7-Metoxi-benzofuran-2-il)carbonil]-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-[(3-Cloro-4-metoxi-fenil)acetil]-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-[(1H-Pirrolo-2-il)carbonil]-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.
N-[(Quinolin-7-il)carbonil]-N'-{(2R)-
[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Piridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-Cloro-3-metoxi-benzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3-Metoxibenzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinolin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Metil-2-fenil-oxazol-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinoxalin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Fenilacetil)-N'-{2-[(formilhidroxiamina)metil]-4-fenilbutanoil}-hidrazina.

N-[(3-Metoxi-quinoxalin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,6-Dimetoxipiridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(N''-Metilsulfonil)-L-tirosil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[5-Oxo-pirrolidin-(2S)-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[4-(Pirrol-1-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-Acetamidobenzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(3-Ciclopentiloxi-4-metoxi)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-3-ciclopentil-propanoil}-hidrazina.

N-[(7-Metoxi-benzofuran-2-il)carbonil]-N'-{2-[(formilhidroxiamino)metil]-3-ciclopentil-propanoil}-

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hidrazina.

N-[3-(Morfolin-4-il)propanoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,3-Dihidro-benzofuran-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(4,6-Dimetoxi-pirimidin-2-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

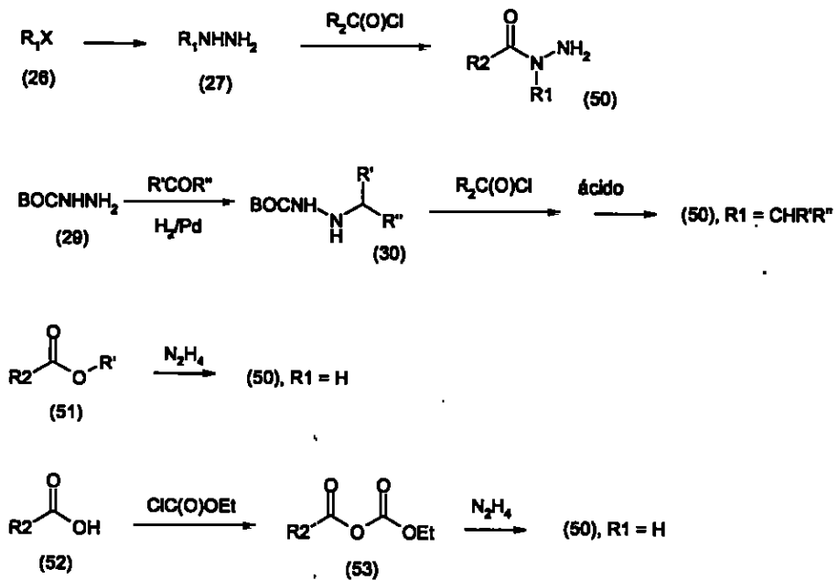
N-[(2-Trifluorometil-5,6,7,8-tetrahidro-naftiridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(9H-beta-carbolin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

Los siguientes esquemas sintéticos son meramente ilustrativos de los métodos mediante los cuales se pueden preparar los compuestos de la invención, y no está previsto que limiten el alcance de la invención según se define en las reivindicaciones anejas.

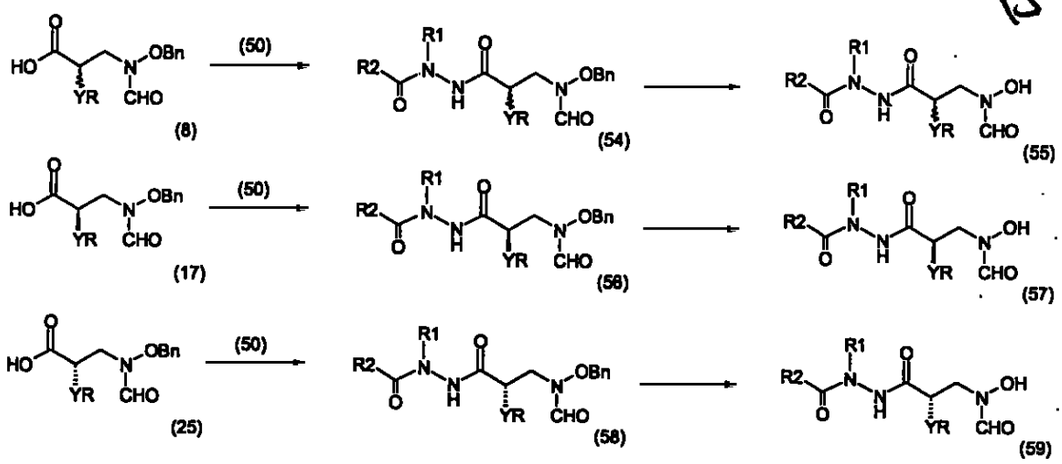
Como se muestra en el Esquema 9, el tratamiento de un haluro de alquilo R1X (26) con hidrazina en un disolvente como etanol, a una temperatura elevada, proporciona el derivado de hidrazina (27). La reacción del compuesto (27) con el cloruro de ácido R2C(O)Cl proporciona el intermedio (50). Alternativamente, el compuesto (50) se puede preparar a partir de la hidrazina (29) protegida con Boc mediante reacción con el aldehído o cetona R'COR'', seguida de reducción con gas hidrógeno en presencia de paladio, para proporcionar el derivado de hidrazina (30). La reacción de la hidrazina (30) con el cloruro de ácido R2C(O)Cl, seguida de la separación del grupo protector Boc con un ácido apropiado como ácido trifluoroacético, proporciona la hidrazina (50) en la que R1=CHR'R''. Alternativamente, el éster (51) puede ser sometido a hidrazinolisis para proporcionar (50) en el que R1=H.

Alternativamente, el ácido (52) se puede hacer reaccionar con cloroformiato de etilo para formar el anhídrido mixto intermedio (53), que tras una hidrazinolisis proporciona (50) en donde R1=H.



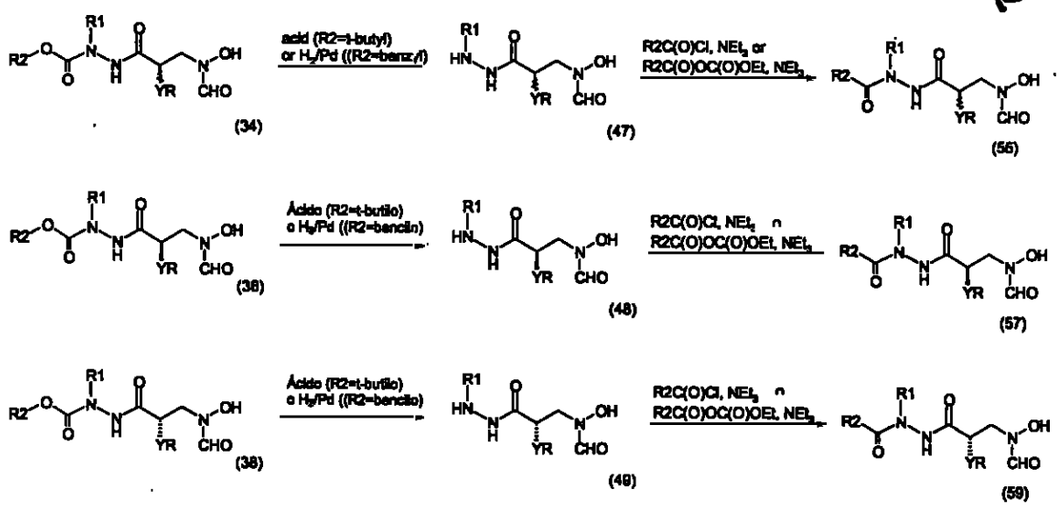
Esquema 9

Como se muestra en el Esquema 10, el acoplamiento del ácido carboxílico (8) con el derivado de hidrazina (50) proporciona la hidrazina acilada (54). La hidrogenolisis para separar el grupo bencilo usando un catalizador, como 10% de Pd/C, en un disolvente apropiado, como etanol, proporciona el compuesto (55). Análogamente, el acoplamiento del ácido quiral (17) o (25) con el derivado de hidrazina (50) proporciona la correspondiente hidrazida (56) o (59). La hidrogenolisis del grupo bencilo proporciona los compuestos finales (57) o (59).



Esquema 10

Alternativamente, como se muestra en el Esquema 11, el carbamato (34) en el que R2=t-butilo o bencilo puede ser convertido en la hidrazida (47) mediante tratamiento ácido o hidrogenolisis, respectivamente. La reacción de (47) con el cloruro de acilo R2C(O)Cl o el anhídrido mixto R2C(O)OC(O)OEt en un disolvente apropiado como cloruro de metileno, y en presencia de una base apropiada opcional como trietilamina, proporciona el compuesto (55). Análogamente, la desprotección apropiada de los carbamatos quirales (36) y (38), seguida de reacción con un cloruro de acilo o un anhidrido mixto, proporciona la hidrazida acilada quiral (57) o (59).



Esquema 11

EJEMPLOS SINTÉTICOS

La invención se describe seguidamente mediante la referencia a los siguientes ejemplos, que son meramente ilustrativos y no están concebidos como una limitación del alcance de la presente invención. Son aplicable en los mismos las mismas condiciones generales experimentales y convenciones descritas en la Sección Experimental de la segunda realización.

Los compuestos descritos en los Ejemplos 52 a 165 se prepararon siguiendo los procedimientos generales descritos en el Ejemplo 1.

Ejemplo 52

N-[(Fenilaminocarbonil)-carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,50 (s, 1H), 9,20 (s, 1H), 7,85 (s, 1H), 7,70-7,00 (m, 5H), 3,75 (m, 1H), 3,40 (m, 1H), 2,88 (m, 1H), 1,63 (m, 1H), 1,39-1,15 (m, 7H), 0,79 (t, J = 6,8 Hz, 3H), MH+ 365.

Ejemplo 53

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N-Butil-N-{[1-(t-butoxicarbonil)piperidin-4-il]-carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,14 (br s, 1H), 8,33 (br s, 1H), 7,81 (br s, 1H), 4,30-3,20 (m, 8H), 2,80-2,50 (m, 2H), 1,92-1,22 (m, 14H), 1,47 (s, 9H), 0,97-0,90 (m, 6H), MH+ 485.

Ejemplo 54

N-Butil-N-{[(1-t-butoxicarbonil)-pirrolidin-(2S)-il]carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,70 (br s, 1H), 8,21 (s, 1H), 7,80 (s, 1H), 4,51-3,20 (m, 6H), 2,86 (m, 1H), 2,18-1,41 (m, 6H), 1,38 (s, 9H), 1,38-1,17 (m, 10H), 0,88 (m, 6H), MH+ 471.

Ejemplo 55

N-Butil-N-{[(1-t-butilaminocarbonil)piperidin-4-il]carbonil}]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,67 (br s, 1H), 8,38 (s, 1H), 4,15-3,47 (m, 8H), 2,89 (m, 1H), 2,67 (m, 1H), 1,75-1,26 (m, 16H), 1,37 (s, 9H), 0,99-0,90 (m, 6H), MH+ 484.

Ejemplo 56

N-Butil-N-{[(1-t-butilcarbonil)piperidin-4-il]carbonil}]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,30 (s, 1H), 8,25 (s, 1H), 7,80 (s, 1H), 4,39-3,34 (m, 8H), 2,95 (m, 1H), 2,79 (m, 1H), 1,89-1,25 (m, 16H), 1,29 (s, 9H), 0,99-0,90 (m, 6H), MH+ 469.

Ejemplo 57

N-Butil-N-[(1,2,3,4-tetrahidro-quinoxalin-2-

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il)carbonil]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,28 (s, 1H), 8,20 (s, 1H), 7,80 (s, 1H), 6,70-6,51 (m, 4H), 4,16-3,22 (m, 6H), 2,87 (m, 1H), 2,75 (m, 1H), 1,64-1,26 (m, 12H), 0,97-0,87 (m, 6H), MH+ 434.

Ejemplo 58

N-(p-Metoxifenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,20 (s, 1H), 8,30 (s, 1H), 7,50 (s, 1H), 7,24 (d, J = 16,3 Hz, 2H), 6,90 (d, J = 16,3 Hz, 2H), 3,95-3,38 (m, 4H), 3,77 (s, 3H), 2,83 (m, 1H), 1,64 (m, 1H), 1,34 (m, 1H), 1,29 (m, 6H), 0,86 (t, J = 6,3 Hz, 3H), MH+ 366.

Ejemplo 59

N-Fenoxiacetil-N'-{2-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

MH+ 352.

Ejemplo 60

N-[(p-Metoxi-fenoxi)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,39 (s, 1H), 8,53 (s, 1H), 7,48 (s, 1H), 6,79-6,73 (m, 4H), 4,49 (m, 2H), 3,73 (s, 3H), 3,44 (m, 2H), 2,82 (m, 1H), 1,64 (m, 1H), 1,25 (m, 1H), 1,24-1,19 (m, 6H), 0,80 (t, J = 6,7 Hz, 3H), MH+ 382.

Ejemplo 61

N-(2,6-Diclorofenil-acetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,35 (s, 1H), 7,80 (s, 1H), 7,30-7,10 (m, 3H), 4,09 (s, 2H), 3,85-3,50 (m, 2H), 2,90 (m, 1H), 1,80-1,28 (m, 6H), 0,89 (br s, 3H), MH+ 405.

Ejemplo 62

N-(3,4-Diclorofenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,30 (s, 1H), 7,91 (s, 1H), 7,20-7,10 (m, 3H), 3,45-3,10 (m, 2H), 3,25 (br s, 2H), 1,85 (m, 1H), 1,62 (m, 1H), 1,45 (m, 1H), 1,32 (m, 6H), 0,91 (br s, 3H), MH+ 405.

Ejemplo 63

N-(Etoxicarbonil)carbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,96 (s, 1H), 9,27 (s, 1H), 7,77 (s, 1H), 4,37 (m, 2H), 3,90 (m, 1H), 3,51 (m, 1H), 2,96 (m, 1H), 1,71 (m, 1H), 1,41 (m, 1H), 1,40-1,32 (m, 9H), 0,91 (br s, 3H), MH+ 318.

Ejemplo 64

N-(2,4-Diclorofenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,70 (s, 1H), 7,80 (s, 1H), 7,50-7,20 (m, 3H), 3,82 (m, 2H), 3,55 (m, 2H), 2,85 (m, 1H), 1,85 (m, 1H), 1,61 (m, 1H), 1,45-1,22 (m, 6H), 0,85 (br s, 3H), MH+ 405.

Ejemplo 65

N-[(Benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ δ 9,87 (s, 1H), 8,68 (s, 1H), 7,78 (s, 1H), 7,54-7,06 (m, 5H), 4,15-3,30 (m, 2H), 2,95 (m, 1H), 1,85 (m, 1H), 1,62 (m, 1H), 1,27-1,18 (m, 6H), 0,84 (br s, 3H), MH+ 362.

Ejemplo 66

N-(2,3-Diclorofenoxiacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,17 (s, 1H), 7,88 (br s, 1H),

7,28-7,14 (m, 3H), 4,73 (m, 2H), 3,76 (m, 1H), 3,49 (m, 1H), 2,90 (m, 1H), 1,74 (m, 1H), 1,41-1,28 (m, 7H), 0,90 (br s, 3H), MH+ 421.

Ejemplo 67

N-(3,4-Dimetoxifenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,92 (s, 1H), 7,58 (s, 1H), 6,83 (m, 3H), 3,87 (s, 3H), 3,85 (s, 3H), 3,74-3,44 (m, 4H), 1,65 (m, 1H), 1,36 (m, 1H), 1,29-1,23 (m, 6H), 0,88 (t, J = 6,5 Hz, 3H), MH+ 396.

Ejemplo 68

N-[(1H-Indol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,51 (s, 1H), 8,50 (s, 1H), 7,81 (s, 1H), 7,50-6,80 (m, 5H), 4,20-3,45 (m, 2H), 2,95 (m, 1H), 1,82 (m, 1H), 1,75-1,20 (m, 7H), 1,00 (br s, 3H), MH+ 396.

Ejemplo 69

N-[(2-Metil-piridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,50 (s, 1H), 7,80 (s, 1H), 7,70-7,00 (m, 3H), 3,84 (m, 1H), 3,50 (m, 1H), 2,58 (s, 1H), 1,73 (m, 1H), 1,44 (m, 1H), 1,43-1,27 (m, 6H), 0,89 (br s, 3H), MH+ 337.

Ejemplo 70

N-[(5-Metoxi-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,50 (s, 1H), 8,50 (s, 1H), 7,85 (s, 1H), 7,50-6,80 (m, 4H), 3,90 (m, 1H), 3,80 (s, 3H), 3,55 (m, 1H), 3,00 (m, 1H), 1,85 (m, 1H), 1,60-1,25 (m, 7H), 0,95 (br s, 3H), MH+ 392.

Ejemplo 71

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N-[(2,3-Dihidro-benzo[1,4]dioxin-(2S)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,50 (s, 1H), 7,80 (s, 1H), 7,30 (m, 4H), 4,55-3,20 (m, 5H), 2,85 (m, 1H), 1,85 (m, 1H), 1,65-1,24 (m, 7H), 0,93 (t, J = 6,2 Hz, 3 H), MH+ 380.

Ejemplo 72

N-[(Quinolin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,51-7,72 (m, 6H), 3,88 (m, 1H), 3,61 (m, 1H), 2,99 (m, 1H), 1,69 (m, 1H), 1,58-1,26 (m, 7H), 0,97 (t, J = 6,7 Hz, 3H), MH+ 373.

Ejemplo 73

N-[(1,2,3,4-Tetrahidro-quinolin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,36 (s, 1H), 7,48 (br s, 2H), 6,45 (d, J = 9,04 Hz, 1H), 3,96-3,32 (m, 4H), 2,91 (m, 1H), 2,77 (t, J = 6,12 Hz, 2H), 1,98 (m, 2H), 1,65 (m, 1H), 1,49 (m, 1H), 1,36 (m, 6H), 0,94 (br s, 3H), MH+ 377.

Ejemplo 74

N-[(Tetrahidro-furan-(2S)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,32 (s, 1H), 4,44 (m, 1H), 4,03 (m, 1H), 3,88 (m, 3H), 3,50 (m, 1H), 2,85 (m, 1H), 2,35-1,93 (m, 4H), 1,49 (m, 1H), 1,40 (m, 1H), 1,35 (m, 6H), 0,92 (t, J = 6,9 Hz, 3H), MH+ 316.

Ejemplo 75

N-[(Tetrahidro-furan-(2R)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,32 (s, 1H), 4,43 (m, 1H), 4,03 (m, 1H), 3,87 (m, 3H), 3,55 (m, 1H), 2,86 (m, 1H), 2,28-1,93 (m, 4H), 1,63 (m, 1H), 1,50 (m, 1H), 1,34 (m, 6H), 0,93

(br s, 3H), MH+ 316.

Ejemplo 76

N-[(3-Metil-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,36 (s, 1H), 7,54-7,20 (m, 4H), 4,04 (m, 1H), 3,48 (m, 1H), 2,97 (s, 3H), 2,59 (m, 1H), 1,66 (m, 1H), 1,28 (m, 1H), 1,27 (m, 6H), 0,83 (t, J = 6,7 Hz, 3H), MH+ 376.

Ejemplo 77

N-[(Piridin-2-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,48 (s, 1H), 7,90-7,33 (m, 4H), 4,00-3,50 (m, 4H), 2,87 (m, 1H), 1,62 (m, 1H), 1,46 (m, 1H), 1,33 (m, 6H), 0,90 (br s, 3H), MH+ 337.

Ejemplo 78

N-{3-[3-(4-Metoxibencil)-1H-benzoimidazol-2-il]-propanoil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,31 (s, 1H), 7,61 (m, 1H), 7,42 (m, 1H), 7,25 (m, 2H), 7,10 (d, J = 8,6 Hz, 2H), 6,88 (d, J = 8,6 Hz, 2H), 5,46 (s, 2H), 3,77 (s, 3H), 3,90-3,50 (m, 2H), 3,23 (m, 2H), 2,85 (m, 2H), 2,69 (m, 1H), 1,65 (m, 1H), 1,61 (m, 1H), 1,33 (m, 6H), 0,92 (m, 3H), MH+ 510.

Ejemplo 79

N-[(Pirimidin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 9,26 (s, 1H), 8,84 (s, 1H), 8,72 (s, 1H), 7,95 (s, 1H), 3,85-3,40 (m, 2H), 2,86 (m, 1H), 1,67 (m, 1H), 1,47 (m, 1H), 1,37 (m, 6H), 0,94 (t, J = 6,8 Hz, 3H), MH+ 324.

Ejemplo 80

N-[(2-Metil-5,6,7,8-tetrahidro-[1,8]naftiridin-3-

il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,92 (s, 1H), 7,44 (s, 1H), 3,90-3,60 (m, 2H), 3,43 (m, 2H), 2,94 (m, 1H), 2,75 (m, 2H), 2,47 (s, 3H), 1,98 (m, 2H), 1,66 (m, 1H), 1,45 (m, 1H), 1,37 (m, 6H), 0,94 (br s, 3H), MH+ 392.

Ejemplo 81

N-[(Isoquinolin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 9,17 (s, 1H), 8,48 (s, 1H), 8,03-7,73 (m, 5H), 4,03-3,99 (m, 1H), 3,59 (m, 1H), 2,70 (m, 1H), 1,71 (m, 1H), 1,43 (m, 1H), 1,26 (m, 6H), 0,86 (t, J = 6,7 Hz, 3H), MH+ 373.

Ejemplo 82

N-[(5,6,7,8-Tetrahidro-[1,8]naftiridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,93 (br s, 1H), 7,31 (d, J = 7,2 Hz, 1H), 7,21 (d, J 7,31 Hz, 1H), 3,82 (m, 1H), 3,55 (m, 1H), 3,43 (br s, 2H), 2,94 (m, 1H), 2,80 (br s, 2H), 1,92 (m, 2H), 1,65 (m, 1H), 1,60-1,09 (m, 7H), 0,94 (br s, 3H), MH+ 378.

Ejemplo 83

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,86 (s, 1H), 7,60 (s, 1H), 7,33 (m, 5H), 3,90-3,42 (m, 4H), 2,83 (m, 1H), 1,67 (m, 1H), 1,32-1,20 (m, 5H), 0,89 (t, J = 6,7 Hz, 3H), MH+ 322.

Ejemplo 84

N-[(3,4-Dihidro-2H-benzo[b][1,4]dioxepin-7-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,45 (d, J = 9,2 Hz, 1H), 7,82

(s, 1H), 7,45-7,28 (m, 2H), 4,30-3,40 (m, 6H), 2,96 (m, 1H), 2,22 (m, 2H), 1,70 (m, 1H), 1,55 (m, 1H), 1,35-1,23 (m, 6H), 0,88 (t, J = 6,7 Hz, 3H), MH+ 394.

Ejemplo 85

N-[(1-Metil-2,5-dioxo-imidazolidin-4-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,90 (s, 1H), 4,39 (m, 1H), 3,84-3,50 (m, 2H), 2,97 (s, 3H), 2,85 (m, 1H), 2,67 (m, 1H), 1,62 (m, 1H), 1,49 (m, 1H), 1,34 (m, 6H), 0,93 (br s, 3H), MH+ 372.

Ejemplo 86

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-3-fenil-propanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,80 (br s, 1H), 8,10 (s, 1H), 7,22 (m, 10H), 3,96-3,43 (m, 4H), 3,15 (m, 1H), 3,02 (m, 1H), 2,70 (m, 1H), MH+ 356.

Ejemplo 87

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-3-(3,4-dicloro)fenil-propanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,36 (br s, 1H), 7,60 (s, 1H), 7,37-7,00 (m, 8H), 4,17-3,51 (m, 4H), 3,05 (m, 1H), 2,95 (m, 1H), 2,65 (m, 1H), MH+ 424.

Ejemplo 88

N-[(4-Imidazol-1-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,37-7,71 (m, 7H), 7,21 (s, 1H), 3,87 (m, 1H), 3,71-3,57 (m, 1H), 2,95 (m, 1H), 1,67 (m, 1H), 1,54 (m, 1H), 1,37 (m, 6H), 0,95 (t, J = 6,7 Hz, 3H), MH+ 388.

Ejemplo 89

N-{[1-Metil-5-oxo-2-S-(piridin-3-il)-pirrolidin-(3S)-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-

hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,57 (m, 1H), 7,90 (s, 1H), 7,84 (m, 1H), 7,55 (m, 1H), 3,79 (m, 1H), 3,53 (m, 1H), 3,08 (m, 1H), 2,92-2,69 (m, 3H), 2,68 (s, 3H), 1,62 (m, 1H), 1,47 (m, 1H), 1,35 (m, 6H), 0,93 (br s, 3H), MH+ 420.

Ejemplo 90

N-[(1,2-Dihidro-cinolin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 7,91 (s, 1H), 7,22 (m, 2H), 6,98 (m, 1H), 6,81 (d, J = 7,8 Hz, 1H), 6,64 (m, 1H), 4,36 (br s, 1H), 3,79 (m, 1H), 3,53 (m, 1H), 2,87 (m, 1H), 1,63 (m, 1H), 1,48 (m, 1H), 1,34 (m, 6H), 0,92 (br s, 3H), MH+ 376.

Ejemplo 91

N-[4-(4-Acetilpiperazin-1-il)fenoxiacetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 7,92 (s, 1H), 4,60 (br s, 2H), 3,90-3,50 (m, 6H), 3,07 (m, 4H), 3,04 (m, 1H), 2,16 (s, 3H), 1,62 (m, 1H), 1,51 (m, 1H), 1,35 (m, 6H), 0,93 (br s, 3H), MH+ 478.

Ejemplo 92

N-Fenilacetil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,30 (s, 1H), 7,90 (s, 1H), 7,32 (br s, 5H), 3,84-3,47 (m, 4H), 2,84 (m, 1H), 1,62 (m, 1H), 1,44 (m, 1H), 1,32 (m, 6H), 0,90 (br s, 3H), MH+ 336.

Ejemplo 93

N-{[1-Bencil-5-oxo-pirrolidin-(2S)-il]-carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,20 (s, 1H), 7,63 (s, br s, 1H), 7,13 (m, 5H), 4,92 (m, 1H), 3,94-3,31 (m, 4H), 2,82 (m,

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1H), 2,60-1,90 (m, 4H), 1,49 (m, 1H), 1,23 (m, 1H), 1,11 (m, 6H), 0,85 (t, J = 6,7 Hz, 3H), MH+ 419.

Ejemplo 94

N-{[1-Bencil-5-oxo-pirrolidin-(2R)-il]-carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,45 (br s, 1H), 7,82 (s, 1H), 7,30 (m, 5H), 5,06 (m, 1H), 4,10-3,50 (m, 4H), 2,95 (m, 1H), 2,85-2,10 (m, 4H), 1,67 (m, 1H), 1,41-1,26 (m, 7H), 0,87 (t, J = 6,7 Hz, 3H), MH+ 419.

Ejemplo 95

N-[(5S)-Bencil-3,6-dioxo-piperazin-(2S)-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,90 (s, 1H), 7,38-7,23 (m, 5H), 4,34-4,21 (m, 2H), 3,82 (m, 1H), 3,49 (m, 1H), 3,31 (m, 1H), 3,06 (m, 1H), 2,85 (m, 1H), 1,57 (m, 1H), 1,46 (m, 1H), 1,34 (m, 6H), 0,92 (t, J = 6,7 Hz, 3H), MH+ 462.

Ejemplo 96

N-[(Quinolin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,11 (br s, 1H), 8,30-7,40 (m, 6H), 3,90 (m, 1H), 3,51 (m, 1H), 3,12 (m, 1H), 1,69 (m, 1H), 1,41 (m, 1H), 1,30 (m, 6H), 0,86 (t, J = 6,7 Hz, 3H), MH+ 373.

Ejemplo 97

N-[(Quinolin-8-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 9,03 (m, 1H), 8,66 (t, J = 6,3 Hz, 1H), 8,46 (m, 1H), 8,05 (d, J = 8,1 Hz, 1H), 7,84 (s, 1H), 7,67 (m, 2H), 3,84-3,30 (m, 2H), 1,66 (m, 1H), 1,43-1,18 (m, 7H), 0,82 (t, J = 6,7 Hz, 3H), MH+ 373.

Ejemplo 98

N-[(1,2,3,4-Tetrahidroquinolin-8-il)carbonil]-N'-{(2R)-

169

[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,83 (s, 1H), 7,26 (d, J = 8,0 Hz, 1H), 6,91 (m, 1H), 6,34 (m, 1H), 3,71 (m, 1H), 3,50 (m, 1H), 3,26 (t, J = 5,6 Hz, 2H), 2,81 (m, 1H), 2,66 (t, J = 6,2 Hz, 2H), 1,77 (m, 2H), 1,55 (m, 1H), 1,40 (m, 1H), 1,38 (m, 1H), 1,25 (m, 6H), 0,83 (t, J = 6,7 Hz, 3H), MH+ 377.

Ejemplo 99

N-(N''-Acetil-L-tirosil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,91 (s, 1H), 7,09 (d, J = 8,4 Hz, 2H), 6,71 (d, J = 8,4 Hz, 2H), 4,62 (m, 1H), 3,87 (m, 1H), 3,57 (m, 1H), 3,12 (dd, J = 14,0, 4,6 Hz, 1H), 2,85 (m, 2H), 2,72 (m, 1H), 1,91 (s, 3H), 1,65 (m, 1H), 1,48 (m, 1H), 1,34 (m, 6H), 0,92 (t, J = 6,7 Hz, 3H), MH+ 423.

Ejemplo 100

N-[(1-Acetil-1,2,3,4-tetrahidro-quinolin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,75 (m, 3H), 3,85 (m, 1H), 3,82 (t, J = 6,4 Hz, 2H), 3,56 (m, 1H), 2,95 (m, 1H), 2,83 (t, J = 6,5 Hz, 2H), 2,05 (s, 3H), 2,00 (m, 2H), 1,65 (m, 1H), 1,52 (m, 1H), 1,37 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 419.

Ejemplo 101

N-[(1H-Benzoimidazol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (br s, 1H), 7,70 (br s, 2H), 7,32 (br s, 2H), 3,98-3,50 (m, 2H), 2,98 (m, 1H), 1,69 (m, 1H), 1,55 (m, 1H), 1,45 (m, 6H), 0,88 (t, J = 6,7 Hz, 3H), MH+ 362.

Ejemplo 102

N-{[1-(2-Hidroxiacetil)-1,2,3,4-tetrahidro-quinolin-6-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-

hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,81 (s, 1H), 7,70-7,50 (m, 3H), 4,27 (s, 2H), 3,75 (m, 1H), 3,60 (m, 2H), 3,55 (m, 1H), 2,81 (m, 1H), 2,72 (m, 2H), 2,85 (m, 2H), 3,55 (m, 1H), 2,81 (m, 1H), 2,72 (m, 2H), 2,85 (m, 2H), 1,55 (m, 1H), 1,45 (m, 1H), 1,25 (m, 6H), 0,82 (t, J = 6,7 Hz, 3H), MH+ 435.

Ejemplo 103

N-[(1H-Indol-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,25 (br s, 1H), 7,95 (s, 1H), 7,68 (d, J = 8,5 Hz, 1H), 7,46 (m, 1H), 7,35 (br s, 1H), 6,59 (br s, 1H), 3,95 (m, 1H), 3,59 (m, 1H), 2,96 (m, 1H), 1,66 (m, 1H), 1,54 (m, 1H), 1,36 (m, 6H), 0,95 (t, J = 6,7 Hz, 3H), MH+ 361.

Ejemplo 104

N-{4-[Metil-(4,6-dimetilpirimidin-2-il)-amino]benzoil}-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,96 (s, 1H), 7,88 (m, 2H), 7,46 (m, 2H), 6,57 (s, 1H), 3,91 (m, 1H), 3,62 (m, 1H), 3,57 (s, 3H), 2,96 (m, 1H), 2,29 (s, 6H), 1,68 (m, 1H), 1,52 (m, 1H), 1,37 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 457.

Ejemplo 105

N-[(1-Benzo[1,3]dioxol-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,94 (s, 1H), 7,49 (m, 1H), 7,36 (s, 1H), 6,92 (dd, J = 8,2, 2,5 Hz, 1H), 6,06 (s, 2H), 3,92 (m, 1H), 3,58 (m, 1H), 2,93 (m, 1H), 1,63 (m, 1H), 1,49 (m, 1H), 1,38 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 366.

Ejemplo 106

N-{[4-(3,5-Dimetil-pirazol-1-il)metil]benzoil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,85 (d, J = 8,2 Hz, 2H), 7,16 (d, J = 8,2 Hz, 2H), 5,97 (s, 1H), 5,33 (s, 2H), 3,88 (m, 1H), 3,57 (m, 1H), 2,95 (m, 1H), 2,22 (s, 3H), 2,20 (s, 3H), 1,59 (m, 1H), 1,44 (m, 1H), 1,26 (m, 6H), 0,93 (t, J = 6,7 Hz, 3H), MH+ 430.

Ejemplo 107

N-[4-(Morfolin-4-il)-benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,81 (d, J = 6,6 Hz, 2H), 7,00 (d, J = 6,6 Hz, 2H), 3,96 (m, 1H), 3,84 (m, 4H), 3,60 (m, 1H), 3,28 (m, 4H), 2,94 (m, 1H), 1,67 (m, 1H), 1,53 (m, 1H), 1,37 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 407.

Ejemplo 108

N-[4-Hidroxi-3-(morfolin-4-il)metil-benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,85 (d, J = 8,4 Hz, 2H), 6,85 (d, J = 8,4 Hz, 2H), 3,85 (m, 2H), 3,80 (m, 1H), 3,74 (m, 4H), 3,55 (m, 1H), 2,93 (m, 1H), 2,68 (br s, 4H), 1,66 (m, 1H), 1,50 (m, 1H), 1,38 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 444.

Ejemplo 109

N-(3-Hidroxi-3-metil-butanoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 3,82 (m, 1H), 3,55 (m, 1H), 2,86 (m, 1H), 2,42 (d, J = 5,7 Hz, 2H), 1,56 (m, 1H), 1,44 (m, 1H), 1,43-1,29 (m, 15 H), 0,93 (t, J = 6,7 Hz, 3H), MH+ 318.

Ejemplo 110

N-(4-Metilamino-benzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

172

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,73 (d, J = 7,7 Hz, 2H), 6,60 (d, J = 7,7 Hz, 2H), 3,96 (m, 1H), 3,58 (m, 1H), 2,93 (m, 1H), 2,83 (s, 3H), 1,52 (m, 1H), 1,38 (m, 1H), 1,26 (m, 6H), 0,94 (t, J 6,7 Hz, 3H), MH+ 351.

Ejemplo 111

N-[(1-Isopropil-1H-benzotriazol-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,75 (s, 1H), 8,09 (d, J = 8,7 Hz, 1H), 7,96 (s, 1H), 7,93 (s, 1H), 5,26 (m, 1H), 3,86 (m, 1H), 3,65 (m, 1H), 2,96 (m, 1H), 1,75 (d, J = 6,8 Hz, 6H), 1,70 (m, 1H), 1,56 (m, 1H), 1,28 (m, 6H), 0,95 (t, J = 6,7 Hz, 3H), MH+ 405.

Ejemplo 112

N-[(1,2,3,4-Tetrahidro-isoquinolin-(3S)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,90 (s, 1H), 7,20 (m, 4H), 4,30-3,40 (m, 5H), 3,10 (m, 1H), 2,90 (m, 1H), 2,72 (m, 1H), 1,65 (m, 1H), 1,50 (m, 1H), 1,36 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 377.

Ejemplo 113

N-[(5-Cloro-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,79 (s, 1H), 7,62 (d, J = 8,8 Hz, 1H), 7,57 (d, J = 5,1 Hz, 1H), 7,49 (d, J = 8,8 Hz, 1H), 3,86 (m, 1H), 3,55 (m, 1H), 3,95 (m, 1H), 1,65 (m, 1H), 1,55 (m, 1H), 1,36 (m, 6H), 0,95 (t, J = 6,8 Hz, 3H), MH+ 396.

Ejemplo 114

N-{[1-(Dimetilaminocarbonilmetil)-3,4-dihidro-2H-quinolin-6-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,94 (br s, 1H), 7,55 (d, J = 8,3 Hz, 1H), 7,51 (s, 1H), 6,38 (d, J = 8,3 Hz, 1H), 4,28 (s, 2H), 3,95 (m, 1H), 3,63 (m, 1H), 3,41 (t, J = 5,4 Hz, 2H), 3,13 (s, 3H), 2,98 (s, 3H), 2,97 (m, 1H), 2,83 (t, J = 5,4 Hz, 2H), 1,99 (m, 4H), 1,65 (m, 1H), 1,50 (m, 1H), 1,36 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 462.

Ejemplo 115

N-[(2,2-Difluoro-benzo[1,3]-dioxol-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,59 (m, 1H), 7,42 (m, 1H), 7,30 (m, 1H), 3,85 (m, 1H), 3,54 (m, 1H), 2,95 (m, 1H), 1,64 (m, 1H), 1,54 (m, 1H), 1,38 (m, 6H), 0,94 (t, J 6,7 Hz, 3H), MH+ 402.

Ejemplo 116

N-[(5-Amino-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,35 (m, 2H), 6,96 (m, 2H), 3,84 (m, 1H), 3,54 (m, 1H), 2,82 (m, 1H), 1,67 (m, 1H), 1,38 (m, 1H), 1,37 (m, 6H), 0,95 (t, J = 6,7 Hz, 3H), MH+ 377.

Ejemplo 117

N-[(4-Oxo-1,2-dihidro-4H-pirrolo[3,2,1-ij]quinolin-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,90 (br s, 1H), 7,95 (s, 1H), 7,66 (m, 1H), 7,58 (m, 1H), 7,34 (m, 1H), 4,52 (br s, 2H), 3,85 (m, 1H), 3,54 (m, 1H), 3,52 (m, 2H), 2,92 (m, 1H), 1,64 (m, 1H), 1,36-1,24 (m, 8H), 0,94 (t, J = 6,8 Hz, 3H), MH+ 415.

Ejemplo 118

N-[(7-Hidroxi-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,55 (m, 1H), 7,21-7,13 (m, 2H), 6,92 (m, 1H), 3,89 (m, 1H), 3,68 (m, 1H), 2,92 (m, 1H), 1,66 (m, 1H), 1,54 (m, 1H), 1,37 (m, 6H), 0,94 (t, J = 6,8 Hz, 3H), MH+ 378.

Ejemplo 119

N-[(6-Metoxi-benzofuran-2-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,91 (s, 1H), 7,63 (s, 1H), 7,53 (d, J = 8,6 Hz, 1H), 7,05 (d, J = 1,9 Hz, 1H), 6,88 (dt, J = 8,6, 2,2 Hz, 1H), 3,84 (s, 3H), 3,76 (m, 1H), 3,64 (d, J = 7,2 Hz, 2H), 3,53 (m, 1H), 2,86 (m, 1H), 1,65 (m, 1H), 1,48 (m, 1H), 1,26 (m, 1H), 0,92 (t, J = 6,7 Hz, 3H), MH+ 406.

Ejemplo 120

N-[(5-Acetamidobenzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,36 (s, 1H), 8,04 (br s, 1H), 7,54 (m, 3H), 3,85 (m, 1H), 3,54 (m, 1H), 2,94 (m, 1H), 2,17 (s, 3H), 1,54 (m, 1H), 1,52 (m, 1H), 1,37 (m, 6H), 0,95 (t, J = 6,8 Hz, 3H), MH+ 419.

Ejemplo 121

N-[(2,3-Dihidro-benzo[1,4]dioxin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,94 (s, 1H), 7,42 (m, 2H), 6,92 (m, 1H), 4,31 (m, 4H), 3,85 (m, 1H), 3,55 (m, 1H), 2,93 (m, 1H), 1,65(m, 1H), 1,51 (m, 1H), 1,37 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 380.

Ejemplo 122

N-[(3-Amino-4,6-dimetil-furo[2,3-b]piridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,02 (s, 1H),

175

3,97 (m, 1H), 3,60 (m, 1H), 2,93 (m, 1H), 2,70 (s, 3H), 2,57 (s, 3H), 1,66 (m, 1H), 1,52 (m, 1H), 1,38 (m, 6H), 0,95 (t, J = 6,7 Hz, 3H), MH+ 406.

Ejemplo 123

N-[(2-Metil-5,6,7,8-tetrahidro-[1,6]naftiridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,69 (br s, 1H), 3,71 (m, 1H), 3,45 (m, 1H), 3,05 (m, 2H), 2,90 (m, 2H), 2,68 (m, 2H), 2,50 (s, 3H), 1,65 (m, 1H), 1,48 (m, 1H), 1,36 (m, 6H), 0,95 (t, J = 6,7 Hz, 3H), MH+ 392.

Ejemplo 124

N-[(6-Fluoro-4H-benzo[1,3]dioxin-8-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,55 (dd, J = 9,2, 2,8 Hz, 1H), 7,07 (dd, J = 7,8, 3,4 Hz, 1H), 5,40 (s, 2H), 4,97 (s, 2H), 3,86 (m, 1H), 3,65 (m, 1H), 2,95 (m, 1H), 1,67 (m, 1H), 1,51 (m, 1H), 1,26 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 398.

Ejemplo 125

N-[(7-Amino-1H-indol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,96 (s, 1H), 7,12 (d, J = 6,3 Hz, 1H), 7,03 (d, J = 8,1 Hz, 1H), 6,89 (m, 1H), 6,60 (m, 1H), 3,90 (m, 1H), 3,55 (m, 1H), 2,95 (m, 1H), 1,67 (m, 1H), 1,51 (m, 1H), 1,26 (m, 6H), 0,94 (t, J = 6,7 Hz, 3H), MH+ 376.

Ejemplo 126

N-[(1-Metil-1,2,3,4-tetrahidro-quinolin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,94 (s, 1H), 7,61 (d, J = 8,7 Hz, 1H), 7,49 (s, 1H), 6,59 (d, J = 8,7 Hz, 1H), 3,85 (m,

1H), 3,55 (m, 1H), 3,36 (m, 2H), 2,97 (s, 3H), 2,80 (t, J = 6,3 Hz, 2H), 1,96 (m, 2H), 1,66 (m, 1H), 1,51 (m, 1H), 1,26 (m, 6H), 0,93 (t, J = 6,7 Hz, 3H), MH+ 391.

Ejemplo 127

N'-[(6,7,9,10,12,13,15,16-Octahidro-5,8,11,14,17-pentaoxa-benzociclopentadecen-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 7,50 (m, 1H), 7,49 (s, 1H), 7,01 (dd, J 8,4, 3,1 Hz, 1H), 4,18 (m, 4H), 3,89 (m, 4H), 3,86 (m, 1H), 3,73 (br s, 8H), 3,56 (m, 1H), 2,96 (m, 1H), 1,67 (m, 1H), 1,51 (m, 1H), 1,26 (m, 6H), 0,93 (t, J = 6,7 Hz, 3H), MH+ 512.

Ejemplo 128

N-[(2-Benzo[1,3]dioxol-5-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,95 (s, 1H), 6,85 (s, 1H), 6,77 (m, 2H), 5,93 (s, 2H), 3,84 (m, 1H), 3,56 (m, 1H), 3,49 (d, J = 6,2 Hz, 2H), 2,86 (m, 1H), 1,60 (m, 1H), 1,48 (m, 1H), 1,34 (m, 6H), 0,92 (t, J = 6,9 Hz, 3H), MH+ 380.

Ejemplo 129

N-Pentanoil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,88 (m, 1H), 9,46 (s, 1H), 9,05 (d, J = 3,5 Hz, 2H), 7,75 (s, 1H), 3,98-3,43 (m, 2H), 2,88 (m, 1H), 2,28 (m, 2H), 1,67 (m, 2H), 1,51-1,22 (m, 10H), 0,89 (m, 3H), MH+ 302.

Ejemplo 130

N-Benzoil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,31 (s, 1H), 7,75 (m, 2H), 7,51-7,20 (m, 3H), 3,86-3,27 (m, 2H), 3,03 (s, 2H), 2,82-2,65 (m, 1H), 1,62 (m, 1H), 1,41-1,12 (m, 7H), 0,89 (m, 3H), MH+

322.

Ejemplo 131

N-Trifluoroacetamido-N'-{2-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,98 (s, 1H), 9,08 (s, 1H), 4,25-3,45 (m, 2H), 2,91 (m, 1H), 1,69 (m, 1H), 1,61-1,21 (m, 7H), 0,88 (m, 3H), MH+ 314.

Ejemplo 132

N-[(3-Hidroxi-naftalen-2-il)carbonil]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,48 (s, 1H), 7,97 (s, 1H), 7,81 (m, 1H), 7,68 (m, 1H), 7,52 (m, 1H), 7,35-7,21 (m, 1H), 3,90-3,51 (m, 2H) 3,02 (m, 1H), 1,67 (m, 1H), 1,59-1,21 (m, 7H), 0,88 (m, 3H), MH+ 388.

Ejemplo 133

N-Fenilacetil-N'-{2-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 9,67 (s, 1H), 9,33 (s, 1H), 8,93 (s, 1H), 8,21 (s, 1H), 7,15 (m, 5H), 3,72-3,25 (m, 6H) 2,75-2,50 (m, 1H), 1,52 (m, 1H), 1,32-1,09 (m, 7H), 0,78 (m, 3H), MH+ 336.

Ejemplo 134

N-[(Furan-2-il)carbonil]-N'-{2-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,40 (s, 1H), 7,78 (s, 1H), 7,31 (s, 1H), 7,21-7,11 (m, 3H), 6,35 (m, 1H), 5,31 (s, 1H), 4,15-3,43 (m, 2H) 3,00-2,65 (m, 1H), 1,75 (m, 1H), 1,62-1,20 (m, 7H), 0,90 (m, 3H), MH+ 312.

Ejemplo 135

N-(4-Metoxibenzoil)-N'-{(2R)-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

178

H^1 RMN (400 MHz, $CDCl_3$) δ 7,75 (m, 1H), 6,89 (d, 1H), 6,72 (d, 1H), 4,05-3,40 (m, 5H) 3,00-2,58 (m, 1H), 1,82-1,11 (m, 8H), 0,88 (m, 3H), MH+ 352.

Ejemplo 136

N-[(1H-Indol-3-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,28 (s, 1H), 7,48 (m, 1H), 7,36-6,94 (m, 4H), 3,89-3,19 (m, 4H) 2,71-2,42 (m, 1H), 2,02-1,04 (m, 8H), 0,76 (m, 3H), MH+ 375.

Ejemplo 137

N-(4-Dimetilaminobenzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,40(s, 1H), 7,71 (m, 2H), 6,61 (m, 2H), 4,05-3,38 (m, 2H) 3,02 (d, J = 8 Hz, 6H), 2,93-2,55 (m, 1H), 1,68 (m, 1H), 1,52-1,21 (m, 7H), 0,89 (m, 3H), MH+ 365.

Ejemplo 138

N-(2-Hidroxibenzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,37 (s, 1H), 7,82-7,57 (m, 2H), 7,41-6,81 (m, 2H), 6,65 (m, 1H), 3,95-3,35 (m, 2H) 3,00-2,57 (m, 1H), 1,75-1,05 (m, 8H), 0,89 (m, 3H), MH+ 338.

Ejemplo 139

N-[(Piperidin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 8,38 (s, 1H), 7,81 (s, 1H), 4,04-3,32 (m, 5H), 3,12-2,72 (m, 2H), 2,62-2,28 (m, 2H), 2,05-1,85 (m, 5H), 1,60 (m, 1H) 1,50-1,18 (m, 7H), 0,85 (m, 3H), MH+ 329.

Ejemplo 140

N-[(1,2,5,6-Tetrahidro-piridin-3-il)carbonil]-N'-{(2R)-

179

[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, $CDCl_3$) δ 10,50 (s, 1H), 8,42 (s, 1H), 7,85 (m, 1H), 7,60-7,12 (m, 2H), 4,75 (m, 1H), 4,11 (m, 1H), 3,81-3,20 (m, 2H) 2,85-2,50 (m, 1H), 2,35-2,20 (m, 2H), 1,90 (m, 1H), 1,81-1,15 (m, 8H), 0,81 (m, 3H), MH+ 327.

Ejemplo 141

N-[(7-Metoxi-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 7,94 (s, 1H), 7,55 (m, 1H), 7,30 (m, 1H), 7,05 (m, 1H), 4,01 (s, 3H), 3,52-3,89 (m, 2H), 2,99 (M, 1H), 1,65 (m, 1H), 1,53 (m, 1H), 1,40 (m, 6H), 0,95 (m, 3H), MH+ 392.

Ejemplo 142

N-[(3-Cloro-4-meoxi-fenil)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 400.

Ejemplo 143

N-[(1H-pirrol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 311.

Ejemplo 144

N-[(Quinolin-7-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 373.

Ejemplo 145

N-[(Piridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 323.

Ejemplo 146

N-(4-Cloro-3-metoxi-benzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 386.

180

Ejemplo 147

N-(3-Metoxibenzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 352.

Ejemplo 148

N-[(Quinolin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 373.

Ejemplo 149

N-[(5-Metil-2-fenil-oxazol-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 403.

Ejemplo 150

N-[(Quinoxalin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 374.

Ejemplo 151

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-4-fenilbutanoil}-hidrazina.

MH+ 370.

Ejemplo 152

N-[(3-Meoxi-quinoxalin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 404.

Ejemplo 153

N-[(2,6-Dimetoxipiridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 383.

Ejemplo 154

N-[(N''-Metilsulfonil)-L-tirosil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 459.

Ejemplo 155

N-{[5-Oxo-pirrolidin-(2S)-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 329.

Ejemplo 156

N-[(4-(Pirrol-1-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 387.

Ejemplo 157

N-(4-Acetamidobenzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 379.

Ejemplo 158

N-[(3-Ciclopentiloxi-4-meoxi)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 436.

Ejemplo 159

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-3-ciclopentil-propanoil}-hidrazina.

MH+ 348.

Ejemplo 160

N-[(7-Meoxi-benzofuran-2-il)carbonil]-N'-{2-[(formilhidroxiamino)metil]-3-ciclopentil-propanoil{-hidrazina.

MH+ 404.

Ejemplo 161

N-[3-(Morfolin-4-il)propanoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 359.

Ejemplo 162

N-[(2,3-Dihidro-benzofuran-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

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MH+ 364.

Ejemplo 163

N-[(4,6-Dimetoxi-pirimidin-2-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 460.

Ejemplo 164

N-[(2-Trifluorometil-5,6,7,8-tetrahidro-naftiridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

MH+ 446.

Ejemplo 165

N-[(9H-beta-carbolin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

H^1 RMN (400 MHz, CD_3OD) δ 8,20 (m, 1H), 8,59 (m, 1H), 8,05 (m, 1H), 7,80 (s, 1H), 7,46 (m, 2H), 7,16 (m, 1H), 7,75 (m, 1H), 3,43 (m, 1H), 2,89 (m, 1H), 1,56 (m, 1H), 1,43 (m, 1H), 1,30 (m, 6H), 0,83 (t, J = 6,7 Hz, 3H), MH+ 412.

COMPOSICIONES, ADMINISTRACIÓN Y ENSAYOS BIOLÓGICOS

Los compuestos de Fórmula (1) y sus sales farmacéuticamente aceptables se pueden adminsitrar de una manera estándar para antibióticos, por ejemplo, por vía oral, parenteral, sub-lingual, dermal, transdermal, rectal, por medio de inhalación o por administración por vía bucal.

Las composiciones de Fórmula (1) y sus sales farmacéuticamente aceptables, que son activas cuando se proporcionan por vía oral, se pueden formular como jarabes, comprimidos, cápsulas, cremas y pastillas. Una formulación de jarabe consistirá generalmente en una suspensión o solución del compuesto o sal en un vehículo líquido, por ejemplo, etanol, aceite de cacahuete, aceite de oliva, glicerina o agua con un agente aromático o colorante. Cuando la composición está en la forma de un comprimido, se puede usar cualquier vehículo

farmacéutico rutinariamente usado para preparar formulaciones sólidas. Ejemplos de tales vehículos incluyen estearato de magnesio, alabastro, talco, gelatina, goma arábiga, ácido esteárico, almidón, lactosa y sacarosa. Cuando la composición está en la forma de una cápsula, es adecuada cualquier encapsulación rutinaria, por ejemplo, usando los vehículos anteriormente mencionados en una envoltura para cápsulas de gelatina dura. Cuando la composición está en la forma de una cápsula de envoltura de gelatina blanda, se puede considerar cualquier vehículo farmacéutico rutinariamente usado para preparar dispesiones o suspensiones, por ejemplo, gomas acuosas, celulosas, silicatos o aceites, e incorporarlos en una envoltura de cápsula de gelatina blanda.

Las composiciones parenteales normales consisten en una solución o suspensión de un compuesto o sal en un vehículo estéril acuoso o no acuoso que contiene opcionamlente un aceite aceptable por vía parenteral, por ejemplo, polietilenlgicol, polivinilpirrolidona, lecitina, aceite de cacahuete o aceite de sésamo.

Las composiciones normales para inhalación están en la forma de una solución, suspensión o emulsión que se puede adminsitrar como un polvo seco o en la forma de un aerosol, usando un propelente convencional como diclorodifluoromeano o triclorofluorometano.

Una formulación para supositorios normal comprende un compuesto de Fórmula (1) o una sal farmacéuticamente aceptable del mismo que sea activo cuando se adminsitra de esta forma, con un agente aglutinante y/o lubricante, por ejemplo, glicoles polímeros, gelatinas, manteca de cacao u otras ceras o grasas vegetales de bajo punto de fusión o sus análogos sintéticos.

Las formulaciones dermales ys transdermales normales

comprenden un vehículo convencional acuoso o no acuoso, por ejemplo, una crema, ungüento, loción o pasta o están en la forma de un vendaje, parche o membrana.

Preferentemente, la composición está en una forma de dosificación unitaria, por ejemplo, un comprimido, cápsula o dosis medida para aerosol, de forma que el paciente pueda administrar una única dosis.

Cada unidad de dosificación para administración oral contiene adecuadamente de 0,1 mg a 500 mg/kg y, preferentemente, de 1 mg a 100 mg/kg, y cada unidad de dosificación para administración parenteral contiene adecuadamente de 0,1 mg a 100 mg/kg de un compuesto de Fórmula (1) o una sal farmacéuticamente aceptable del mismo, calculado como el ácido libre. Cada unidad de dosificación para administración intranasal contiene adecuadamente 1-400 mg y, preferentemente, 10 a 200 mg por persona. Una formulación tópica contiene adecuadamente 0,01 a 5,0% de un compuesto de Fórmula (1).

El régimen de dosificación diaria para una administración oral es adecuadamente de aproximadamente 0,01 mg/kg a 40 mg/kg de un compuesto de Fórmula (1) o una sal farmacéuticamente aceptable del mismo, calculado como el ácido libre. El régimen de dosificación diaria para una administración parenteral es adecuadamente de aproximadamente 0,001 mg/kg a 40 mg/kg de un compuesto de Fórmula (1) o una sal farmacéuticamente aceptable del mismo, calculado como el ácido libre. El régimen de dosificación diaria para una administración intranasal y una inhalación oral es adecuadamente de aproximadamente 10 a aproximadamente 500 mg/persona. El ingrediente activo puede ser administrado de 1 a 6 veces al día, suficiente para exhibir la actividad deseada.

No son de esperar efectos toxicológicos inaceptables cuando los compuestos de la presente invención se adminsitran

de acuerdo con la presente invención.

La actividad biológica de los compuetos de Fórmula (1) se demuestra mediante el siguiente ensayo:

Ensayo biológico

La actividad de PDF de S. aureus o E. coli se mide a 25°C, usando un ensayo de unión enzimática continua de Lazennec & Meinnel ("Formate dehydrogenase-coupled spectrophotometris assays of peptide deformylase", Anal. Biochem. 1997, 244, pag. 180-182), con modificaciones menores. La mezcla de reacción está contenida en 50 µl con tampón de fosfato de potasio 50 mM (pH 7,6), NAD 15 mM y 0,25 U de formiatodeshidrogenasa. El péptido del sustrato, f-Met-Ala-Ser, se incluye a la concentración de K_M. La reacción se provoca mediante la adición de enzima Defl 10 nM, y la absorbancia se verifica durante 20 minutos a 340 nm.

Ensayo de actividad antimicrobiana

La actividad antimicrobiana de células completas se determinó por microdilución de caldos de cultivo usando el procedimiento recomendado por la entidad National Committee for Clinical Laboratory Standards (NCCLS), documento M7-A4, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically" (incorporado como referencia a la presente memoria descriptiva). El compuesto se ensayó en diluciones en serie de dos veces que variaban en el intervalo de 0,06 a 64 mcg/ml. Se evaluó un conjunto de 12 cepas en el ensayo. Este conjunto consistía en las siguientes cepas de laboratorio: Staphylococcus aureus Oxford, Staphylococcus aureus WCUH29, Enterococcus faecalis I, Enterococcus faecalis 7, Haemophilus influenzae Q1, Haemophilus influenzae NEMC1, Moraxella catarrhalis 1502, Streptococcus pneumoniae 1629, Streptococcus pneumoniae N1387, Streptococcus pneumoniae N1387, E. coli 7623, (AcrABEFD+) y E. coli 120 (AcrAB-). La concentración

inhibidora mínima (MIC) se determinó como la concentración más baja de compuesto que inhibía el crecimiento visible. Se usó un lector especular para ayudar a la determinación del punto final de la MIC.

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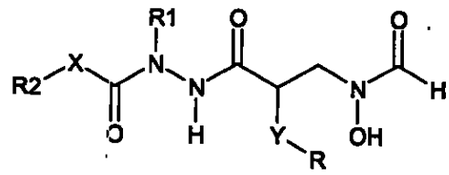
REIVINDICACIONES

1. Un compuesto según la Fórmula (1):



Hidrazida

WO0035440

(1) X = O, NR_3 o un enlace

Y= O, CH_2 o un enlace

en la cual:

R representa:

alquilo C_{2-6} (opcionalmente sustituido con alcoxi, halógeno o alquilsulfanilo C_{1-3}), alquenilo C_{2-6} (opcionalmente sustituido con alcoxi, halógeno o alquilsulfanilo C_{1-3}), alquinilo C_{2-6} (opcionalmente sustituido con alcoxi, halógeno o alquilsulfanilo C_{1-3}), $(CH_2)_n$-carbociclo C_{3-6} (opcionalmente sustituido con alcoxi, halógeno o alquilsulfanilo C_{1-3}, $(CH_2)_n$-R4 {en donde R4 es fenilo, furano, benzofurano, tiofeno, benzotiofeno, tetrahidrofurano, tetrahidropirano, dioxano, 1,4-benzodioxano o benzo[1,3]dioxol; R4 está opcionalmente sustituido con uno o más Cl, Br, I, alquilo C_{1-3} (opcionalmente sustituido con uno a tres F) o alcoxi C_{1-2} (opcionalmente sustituido con uno a tres F)};

R1 representa:

hidrógeno, alquilo C_{1-6} (opcionalmente sustituido con hidroxi, halógeno, amino, guanidino, fenilo, piridilo, pirrolilo, indolilo, imidazolilo, furanilo, benzofuranilo, piperidinilo, morfolinilo, quinolinilo, piperazinilo o dimetilaminofenilo) o $(CH_2)_n$-carbociclo C_{3-7};

R2 representa:

hidrógeno (con la condición de que X no es O), alquilo C_{1-3} sustituido, alquenilo C_{2-3} sustituido, alquinilo C_{2-3}

sustituido, $(CH_2)_n$-carbociclo C_{3-6} sustituido, arilo, heteroarilo, heterocíclico, carboxi (con la condición de que X no es NR3 ni O) o aminocarbonilo (con la condición de que X no es NR3 ni O);

R3 representa:

hidrógeno, alquilo C_{1-3} sustituido, fenilo o se puede tomar conjuntamente con R2 y el átomo de nitrógeno al que están unidos para formar un anillo heterocíclico opcionalmente sustituido que está opcionalmente condensado a un anillo de arilo, heteroarilo o un segundo heterocíclico;

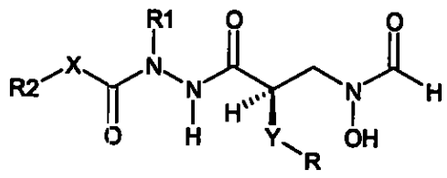
X representa O, NR3 o un enlace covalente;

Y representa O, CH_2 o un enlace covalente;

n = 0-2;

o una sal, solvato o derivado fisiológicamente funcional del mismo.

2. Un compuesto según la reivindicación 1, con la siguiente configuración absoluta:



X = O, NR_3 o un enlace;

Y = O, CH_2o un enlace

o una sal, solvato o derivado fisiológicamente funcional del mismo.

3. Un compuesto según la reivindicación 2, en el que R1=H; o una sal, solvato o derivado fisiológicamente funcional del mismo.

4. Un compuesto según la reivindicación 1, en el que X=O; o una sal, solvato o derivado fisiológicamente funcional

del mismo.

5. Un compuesto según la reivindicación 4, seleccionado entre el grupo que consiste en:

N-Butil-N-(t-butoxicarbonil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-butil-N-fenoxicarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-isobutil-N-(t-butoxicarbonil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-isobutil-N-fenoxicarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-fenetil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-ciclohexilmetil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-bencil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3-piridin-3-il-propil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(2-morfolin-4-il-etil)-N-(t-butoxicarbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-hidroxi-butil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-amino-butil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(tetrahidro-piran-4-il)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-metil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3-aminopropil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(t-butoxicarbonil-N'-{(2R)-[(formilhidroxiamino)-

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metil]heptanoil}-hidrazina.

N-(3-hidroxipropil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-butil-N-(t-butoxicarbonil)-N'-[(2S)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-butil-N-(fenoxicarbonil)-N'-[(2S)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[2-(4-dimetilaminofenil)etil]-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

N-pentil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[2-(1H-indol-3-il)-etil]-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-isopentil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-ciclohexil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(1-etil-propil)-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-isopropil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-propil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-etil-N-(t-butoxicarbonil)-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-metoxicarbonil-N'-{2-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-{[1-(3,5-dimetoxifenil)-1-metil-etoxi]carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

6. Un compuesto según la reivindicación 1, en el que

X=NR3; o una sal, solvato o derivado fisiológicamente funcional del mismo.

7. Un compuesto según la reivindicación 6, seleccionado entre el grupo que consiste en:

N-Butil-N-[(4-metilpiperazin-1-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-difenilaminocarbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-(t-butilamino)carbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-fenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-[(3,5-dimetil-4,5-dihidro-isoxazol-4-il)aminocarbonil]-N'-{2-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-Butil-N-[(1-morfolin-4-il)carbonil]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-metil]-4-fenil-butanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-metil]hexanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-metil]-3-fenil-propanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-metil]-3-(3,4-diclorofenil)-propanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{2-[(formilhidroxiamino)-metil]-heptanoil}-hidrazina.

N-(3,4-Diclorofenilaminocarbonil-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Fenilaminocarbonil-N'-{(2R)-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

N-(3,4-Diclorofenilaminocarbonil-N'-{(2R)-

[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Morfolin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2-Metoxifenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,4-Diclorofenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,6-Diclorofenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

- N-[(4-Metil-piperazin-1-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(4-Cloro-3-trifluorometilfenil)aminocarbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Metil-fenil-amino)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

8. Un compuesto según la reivindicasción 1, en el que X es un enlace covalente; o una sal, solvato o derivado fisiológicamente funcional del mismo.

9. Un compuesto según la reivindicación 8, seleccionado entre el grupo que consiste en:

N-[(Fenilaminocarbonil)-carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-{[1-(t-butoxicarbonil)-piperidin-4-il]-carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

- N-Butil-N-{[(1-t-butoxicarbonil)-pirrolidin-(2S)-il]carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-{[(1-t-butilaminocarbonil)piperidin-4-il]carbonil}-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-{[(1-t-butilcarbonil)piperidin-4-il]carbonil}-

N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Butil-N-[(1,2,3,4-tetrahidro-quinoxalin-2-il)carbonil]-N'-{2-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(p-metoxifenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Fenoxiacetil-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(p-Metoxi-fenoxi)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(2,6-Diclorofenil-acetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3,4-Diclorofenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Etoxicarbonil)carbonil-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(2,4-Diclorofenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(2,3-Diclorfenoxiacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3,4-Dimetoxifenilacetil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1H-Indol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2-Metil-piridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Metoxi-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,3-Dihidro-benzo[1,4]dioxin-(2S)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinolin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1,2,3,4-Tetrahidro-quinolin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Tetrahidro-furan-(2S)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Tetrahidro-furan-(2R)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(3-Metil-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Piridin-2-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{3-[3-(4-Metoxibencil)-1H-benzoimidazol-2-il]-propanoil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Pirimidin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2-Metil-5,6,7,8-tetrahidro-[1,8]naftiridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(Isoquinolin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5,6,7,8-Tetrahidro-[1,8]naftiridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(3,4-Dihidro-2H-benzo[b][1,4]dioxepin-7-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(1-Metil-2,5-dioxo-imidazolidin-4-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-3-fenil-propanoil}-hidrazina.

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N-(Fenilacetil)-N'-{2-[(formilhidroxiamina)metil]-3-(3,4-dicloro)fenil-propanoil}-hidrazina.

N-[(4-Imidazol-1-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[1-Metil-5-oxo-2-S-(piridin-3-il)pirrolidin(3S)-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(1,2-Dihidro-cinolin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[4-(4-Acetilpiperazin-1-il)fenoxiacetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Fenilacetil-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-{[1-Bencil-5-oxo-pirrolidin-(2S)-il]-carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Bencil-5-oxo-pirrolidin-(2R)-il]-carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5S)-Bencil-3,6-dioxo-piperazin-(2S)-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinolin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinolin-8-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1,2,3,4-Tetrahidroquinolin-8-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(N''-Acetil-L-tirosil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Acetil-1,2,3,4-tetrahidro-quinolin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(1H-Benzoimidazol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[1-(2-Hidroxiacetil)-1,2,3,4-tetrahidro-quinolin-6-

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il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(1H-Indol-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-{4-[Metil-(4,6-dimetilpirimidin-2-il)amino]benzoil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Benzo[1,3]dioxol-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(4-(3,5-Dimetil-pirazol-1-il)metil]benzoil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[4-(Morfolin-4-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[4-Hidroxi-3-(morfolin-4-il)metil-benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3-Hidroxi-3-metil-butanoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-Metilamino-benzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1-Isopropil-1H-benzotriazol-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1,2,3,4-Tetrahidro-isoquinolin-(3S)-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Cloro-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[1-(Dimetilaminocarbonilmetil)-3,4-dihidro-2H-quinolin-6-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

N-[(2,2-Difluoro-benzo[1,3]dioxol-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Amino-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(4-Oxo-1,2-dihidro-4H-pirrolo[3,2,1-ij]quinolin-5-

il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(7-Hidroxi-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(6-Metoxi-benzofuran-2-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Acetamidobenzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,3-Dihidro-benzo[1,4]dioxin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(3-Amino-4,6-dimetil-furo[2,3-b]piridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(2-Metil-5,6,7,8-tetrahidro-[1,6]naftiridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(6-Fluoro-4H-benzo[1,3]dioxin-8-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(7-Amino-1H-indol-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

- N-[(1-metil-1,2,3,4-tetrahidro-quinolin-6-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N'-[(6,7,9,10,12,13,15,16-Octahidro-5,8,11,14,17-pentaoxa-benzociclopentadecen-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

- N-[(2-Benzo[1,3]dicxol-5-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Pentanoil-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-Benzoil-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-Trifluoroacetamido-N'-{(2R)-[(formilhidroxiamino)-

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metil]heptanoil}-hidrazina.

N-[(3-Hidroxi-naftalen-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-Fenilacetil-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(Furan-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-Metoxibenzoil)-N'-{(2R)-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

• N-[(1H-Indol-3-il)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-Dimetilaminobenzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(2-Hidroxibenzoil)-N'-{(2R)-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

N-[(Piperidin-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1,2,5,6-Tetrahidro-piridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

• N-[(7-Metoxi-benzofuran-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(3-Cloro-4-metoxi-fenil)acetil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(1H-Pirrolo-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinolin-7-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Piridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-Cloro-3-metoxi-benzoil)-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(3-Metoxibenzoil)-N'-{(2R)-[(formilhidroxiamino)-

metil]heptanoil}-hidrazina.

N-[(Quinolin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(5-Metil-2-fenil-oxazol-4-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(Quinoxalin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-4-fenilbutanoil}-hidrazina.

N-[(3-Metoxi-quinoxalin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,6-Dimetoxipiridin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(N''-Metilsulfonil)-L-tirosil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-{[5-Oxo-pirrolidin-(2S)-il]carbonil}-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[4-(Pirrol-1-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(4-Acetamidobenzoil)-N'-{(2R)-[(formilhidroxiamino)-metil]heptanoil}-hidrazina.

N-[(3-Ciclopentiloxi-4-metoxi)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-(Fenilacetil)-N'-{2-[(formilhidroxiamino)metil]-3-ciclopentil-propanoil}-hidrazina.

N-[(7-Metoxi-benzofuran-2-il)carbonil]-N'-{2-[(formilhidroxiamino)metil]-3-ciclopentil-propanoil}-hidrazina.

N-[3-(Morfolin-4-il)propanoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2,3-Dihidro-benzofuran-5-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(4,6-Dimetoxi-pirimidin-2-il)benzoil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

N-[(2-Trifluorometil-5,6,7,8-tetrahidro-naftiridin-2-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]-heptanoil}-hidrazina.

N-[(9H-beta-carbolin-3-il)carbonil]-N'-{(2R)-[(formilhidroxiamino)metil]heptanoil}-hidrazina.

10. Un medio para tratar una infección bacteriana, admihnistrando a un sujeto que necesita el tratamiento un compuesto según la reivindicación 1.

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RESUMEN DE LA DESCRIPCIÓN

Se proporcionan nuevos inhibidores de PDF y nuevos métodos para su uso.

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2003 JAN 13 A 11:56

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
SOMA G. SIMON
SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY, UW2220
709 SWEDELAND ROAD, P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (*day/month/year*)	08 JAN 2003
Applicant's or agent's file reference P51228	IMPORTANT NOTIFICATION

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US02/06275	01 March 2002 (01.03.2002)	01 March 2001 (01.03.2001)

Applicant

SMITHKLINE BEECHAM CORPORATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Valerie Bell-Harris for Paul A. Zucker Telephone No. 703-308-0196

Form PCT/IPEA/416 (July 1992)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P51228	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/06275	International filing date *(day/month/year)* 01 March 2002 (01.03.2002)	Priority date *(day/month/year)* 01 March 2001 (01.03.2001)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07C 245/00, 51/31; A61k 31/19, 31/181, 31/85 and US Cl.: 562/621, 622, 623 400, 495, 543, 623; 514/575, 613, 614, 825, 925		
Applicant SMITHKLINE BEECHAM CORPORATION		

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 3 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 consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report 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	Date of completion of this report
05 September 2002 (05.09.2002)	04 December 2002 (04.12.2002)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Valerie Bell-Harrison Paul A. Zucker Telephone No. 703-308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/06275

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-80 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 81-94, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the drawings.
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

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

☐ contained in the international application in printed form.

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

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/06275

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-10	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-10	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-10	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

NEW CITATIONS

WO 00/35400 A1 (HUNTER et al) 22 June 2000, see abstract, paragraph bidging pages 5-6, page 7, line 1- page 8, line 14.

Claims 1-10 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the instantly claimed structures containing a hydrazide substructure. The closest prior art of record Hunter (WO 00/35440, see abstract) teaches a genus of N-formyl hydroxyl amine derivatives as antibacterial agents. These compounds bear a close structural relationship to the instant compounds of Formula (I). There is, however, no teaching or suggestion of a hydrazide substructure. The instant compounds are therefore distinct from those taught by Hunter.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2002 (12.09.2002)

PCT

(10) International Publication Number
WO 02/070541 A3

(51) International Patent Classification[7]: C07C 245/00, 51/31, A61K 31/19, 31/181, 31/85

(21) International Application Number: PCT/US02/06275

(22) International Filing Date: 1 March 2002 (01.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/272,570 1 March 2001 (01.03.2001) US

(71) Applicant *(for all designated States except US)*: SMITH KLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: XIANG, JIA-NING [US/US]; 707 DeSoto Drive, Palo Alto, CA 94303 (US). CHRISTENSEN, Siegfried, B. [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). LEE, Jinhwa [KR/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). MERCER, Daniel, J. [US/US]; 1250 South Collegeville Road, Collegeville, PA 19526 (US).

(74) Agents: SIMON, Soma, G._ et al.; SMITHKLINE BEECHAM CORPORATION, Coporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (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, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, 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).

Published:
— *with international search report*

(88) Date of publication of the international search report:
19 December 2002

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.

WO 02/070541 A3

(54) Title: PEPTIDE DEFORMYLASE INHIBITORS

(57) Abstract: Nobel PDF inhibitors and novel methods for their use are provided.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/05275

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 245/00, 51/31; A61K 31/19, 31/181, 31/85
US CL : 562/621, 622, 623, 400, 495, 543, 623; 514/575, 613, 614, 575, 902, 825, 925

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)
U.S. :

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 practicable, search terms used)
WEST, STN (CAOLD, CAPLUS, MARPAT)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,013,792 A(CASTELHANO et al) 11 January 2000.	1-10
A	US 4,996,358 A (HANDA et al) 26 February 1991.	1-10
A	US 5,691,382 A (CRIMMIN et al) 25 November 1997.	1-10
A	US 6,028,110 A (MILLER et al) 22 February 2000.	1-10
A	US 6,037,472 A (CASTELHANO et al) 14 March 2000.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family 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 application or patent published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2002 (15.07.2002)	19 SEP 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Farhad Forohar Telephone No. (703)305-1022

Form PCT/ISA/210 (second sheet) (July 1998)

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 03075595 00000000
Fecha (AMD): 2003-09-01 16:46:14 Folios: 212
Tramite : 011 PCT-PATENT 220 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN X 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 gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable: Edwin Navarro

Fecha: 01-09-2003

209 245

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
CARLOS R. OLARTE
Apoderado
SMITHKLINE BEECHAM CORPORATION

Oficio N° 09536

ASUNTO:

Radicación N°	03-75595
Solicitud internacional	PCT/US02/06275
Fecha inicio fase nacional	01/10/2003
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento el 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 aclara el numero de paginas de los anexos del reporte de examen preliminar internacional
- ☐ La solicitud no contiene la traducción de los anexos (si los tiene) del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT).
- ☐ 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).

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 CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

31 OCT. 2003

El anterior requerimiento fue notificado por fijación en lista de fecha_____.

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