SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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54. **TITULO** DERIVADOS DE DIFENILAZETIDINONA QUE POSEEN ACTIVIDAD INHIBIDORA DE LA ABSORCION DE COLESTEROL

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71. **SOLICITANTE** ASTRAZENECA AB

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74. **APODERADO** JUAN PABLO CADENA SAMUDIO

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

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1 **SOLICITUD DE:**

☒ Patente de Invención ☐ Patente de Modelo de Utilidad

☒ Capítulo I. ☐ Capítulo II.

2 **SOLICITANTE (71)**	Nombre: **ASTRAZENECA AB** Dirección. S-1-51 85 Södertalje, Suecia Nacionalidad o Domicilio Suecia Lugar de Constitución Suecia Teléfono: Fax: E-mail	**IDENTIFICACION** C.C ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
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10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $463.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. **Fotocopia Autenticada**
- [x] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [x] Otros Extracto para publicación y Tarjeta de Archivo temático
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11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

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CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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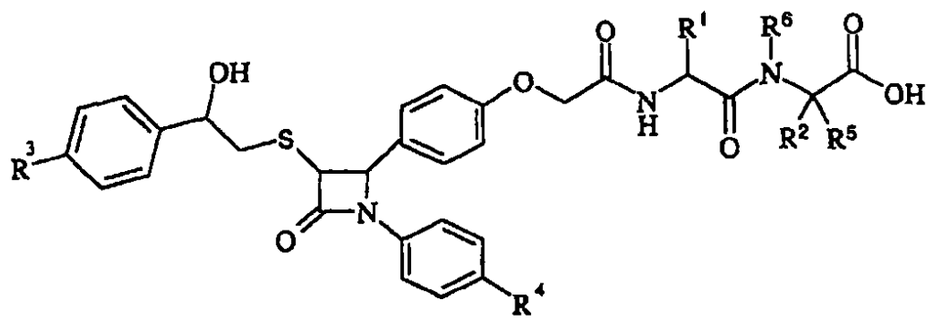
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(54) Title: DIPHENYLAZETIDINONE DERIVATES POSSESSING CHOLESTEROL ABSORPTION INHIBITORY ACTIVITY



(I)

(57) Abstract: Compounds of formula (I) (wherein variable groups are as defined within) pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof and their use as cholesterol absorption inhibitors for the treatment of hyperlipidaemia are described. Processes for their manufacture and pharmaceutical compositions containing them are also described

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Diphenylazetidinone Derivates Possessing Cholesterol Absorption Inhibitory Activity

This invention relates to 2-azetidinone derivatives, or pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof. These 2-azetidinones possess cholesterol absorption inhibitory activity and are accordingly of value in the treatment of disease states associated with hyperlipidaemic conditions. They are therefore useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said 2-azetidinone derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit cholesterol absorption in a warm-blooded animal, such as man. A further aspect of this invention relates to the use of the compounds of the invention in the treatment of dyslipidemic conditions.

Atherosclerotic coronary artery disease is a major cause of death and morbidity in the western world as well as a significant drain on healthcare resources. It is well-known that hyperlipidaemic conditions associated with elevated concentrations of total cholesterol and low density lipoprotein (LDL) cholesterol are major risk factors for cardiovascular atherosclerotic disease (for instance "Coronary Heart Disease: Reducing the Risk; a Worldwide View" Assman G., Carmena R. Cullen P. *et al*; Circulation 1999, 100, 1930-1938 and "Diabetes and Cardiovascular Disease: A Statement for Healthcare Professionals from the American Heart Association" Grundy S, Benjamin L, Burke G., *et al*; Circulation, 1999, 100, 1134-46).

The concentration of plasma cholesterol depends on the integrated balance of endogenous and exogenous pathways of cholesterol metabolism. In the endogenous pathway, cholesterol is synthesized by the liver and extra hepatic tissues and enters the circulation as lipoproteins or is secreted into bile. In the exogenous pathway cholesterol from dietary and biliary sources is absorbed in the intestine and enters the circulation as component of chylomicrons. Alteration of either pathway will affect the plasma concentration of cholesterol.

The precise mechanism by which cholesterol is absorbed from the intestine is however not clear. The original hypothesis has been that cholesterol is crossing the intestine by unspecific diffusion. But more recent studies are suggesting that there are specific transporters involved in the intestinal cholesterol absorption. (See for instance New molecular targets for cholesterol-lowering therapy Izzat, N.N., Deshazer, M.E. and Loose-Mitchell D.S. JPET 293:315-320, 2000.)

A clear association between reduction of total cholesterol and (LDL) cholesterol and decreased instance of coronary artery disease has been established, and several classes of pharmaceutical agents are used to control serum cholesterol. There major options to regulate plasma cholesterol include (i) blocking the synthesis of cholesterol by agents such as HMG-CoA reductase inhibitors, for example statins such as simvastatin and fluvastatin; which also by up-regulation of LDL-receptors will promote the cholesterol removal from the plasma; (ii) blocking the bile acid reabsorption by specific agents resulting in increased bile acid excretion and synthesis of bile acids from cholesterol with agents such as bile acid binders, such as resins e.g. cholestyramine and cholestipol; and (iii) by blocking the intestinal uptake of cholesterol by selective cholesterol absorption inhibitors. High density lipoprotein (HDL) elevating agents such as fibrates and nicotinic acid analogues have also been employed.

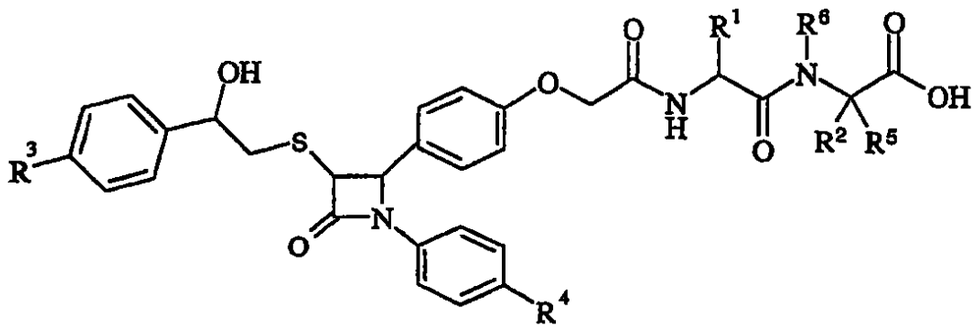
Even with the current diverse range of therapeutic agents, a significant proportion of the hypercholesterolaemic population is unable to reach target cholesterol levels, or drug interactions or drug safety preclude the long term use needed to reach the target levels. Therefore there is still a need to develop additional agents that are more efficacious and are better tolerated.

Compounds possessing such cholesterol absorption inhibitory activity have been described, see for instance the compounds described in WO 93/02048, WO 94/17038, WO 95/08532, WO 95/26334, WO 95/35277, WO 96/16037, WO 96/19450, WO 97/16455, WO 02/50027, WO 02/50060, WO 02/50068, WO 02/50090, WO 02/66464, WO 04/000803, WO 04/000804, WO04/000805, WO 04/043457, WO 04/081002, US 5756470, US 5767115, US 20040180860, US20040180861 and US RE37721.

The present invention is based on the discovery that certain 2-azetidinone derivatives surprisingly inhibit cholesterol absorption. Such properties are expected to be of value in the treatment of disease states associated with hyperlipidaemic conditions. The compounds of the present invention are not disclosed in any of the above applications and we have surprisingly found that the compounds of the present invention possess beneficial efficacious, metabolic and toxicological profiles that make them particularly suitable for *in vivo* administration to a warm blooded animal, such as man. In particular certain compounds of the present invention have a low degree of absorption compared to compounds of the prior art whilst retaining their ability to inhibit cholesterol absorption.

Accordingly there is provided a compound of formula (I):

(I)



(I)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, guanidino, carbamoyl, carboxy, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_1-C_6 alkylcarbonylamino C_{1-6}alkylS(O)$_a$ wherein a is 0-2, C_{3-6}cycloalkyl or aryl; and wherein any aryl group may be optionally substituted by one or two substituents selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^2 and R^5 are independently hydrogen, a branched or unbranched C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, guanidino, cyano, carbamoyl, carboxy, C_{1-6}alkoxy, aryl C_{1-6}alkoxy,$(C_1$-$C_4)_3$Si, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$, C_{3-6}cycloalkyl, aryl or aryl C_{1-6} alkylS(O)$_a$ wherein a is 0-2; and wherein any aryl group may be optionally substituted by one or two substituents selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^3 is hydrogen, alkyl, halo, C_{1-6}alkoxy or C_{1-6} alkylS-;

R^4 is hydrogen, C_{1-6} alkyl, halo or C_{1-6}alkoxy;

R^6 is hydrogen, C_{1-6} alkyl, or arylC_{1-6} alkyl;

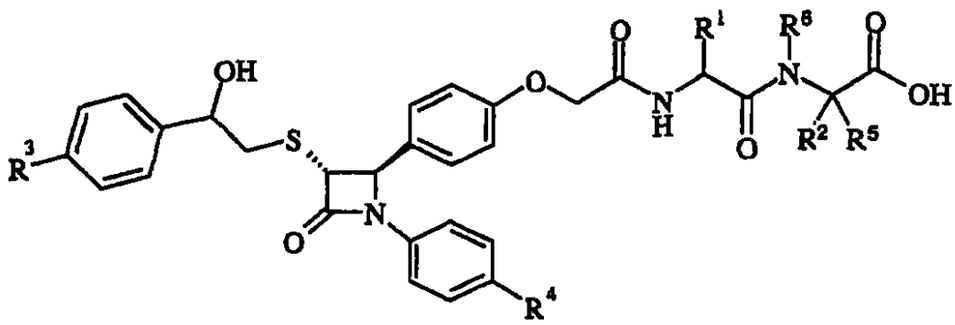
wherein R^5 and R^2 may form a ring with 2-7 carbon atoms and wherein R^6 and R^2 may form a ring with 3-6 carbon atoms;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof;

with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-[4-(*N*-{*N*-[(R)-1-(carboxy)-2-(hydroxy)ethyl]carbamoylmethyl} carbamoylmethoxy)phenyl]azetidin-2-one; or 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-

2-hydroxyethylsulphanyl]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy) ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one.

In one aspect of the invention it is provided for a compound of formula I2:



I2

wherein variable groups are defined above as for formula (I). What is said further for formula (I) will, apart from the process schemes below, apply also to formula (I2).

In one aspect of the invention R^1 is hydrogen. According to another aspect of the invention, R^2 is hydrogen, a branched or unbranched C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, C_{1-6}alkyl$S(O)_a$ wherein a is 0-2, C_{3-6}cycloalkyl or aryl; and wherein any aryl group may be optionally substituted by hydroxy. According to a further aspect of the invention, R^3 is hydrogen, methoxy, or alkyl, for instance a C_1-C_2alkyl, i.e. methyl or ethyl, for instance methyl, or a halogen, for instance chlorine or fluorine.

According to yet another aspect of the invention R^4 is hydrogen or halo, for instance chlorine or fluorine. According to a further aspect of the invention, R^6 is hydrogen, arylC_{1-6} or R^6 and R^2 form a ring with 3-6 carbon atoms.

According to one aspect of the invention R^1 is hydrogen, R^2 is a branched or unbranched C_{1-4}alkyl, optionally substituted by a C_{3-6}cycloalkyl, R^3 and R^4 are halo, R^5 is hydrogen or C_{1-6} alkyl, and R^6 is hydrogen.

The invention further provides for one or more compounds chosen from:

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-N^6-acetyl-D-lysine;

1-(4-Fluorophenyl)-3-(R)-[2-(4-fluorophenyl)-2-hydroxyethylthio]-4-(R)-{4-[*N*-{*N*-[2-(phenyl)-1-(R)-(carboxy)ethyl]carbamoylmethyl}carbamoylmethoxy]phenyl}azetidin-2-one;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-tyrosine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-proline;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-lysine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-hydroxy-2-(4-methoxyphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-2-butylnorleucine;

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-methyl-L-cysteine;

N-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-cyclohexyl-D-alanine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-cyclohexyl-D-alanine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-4-methylleucine;

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-alanyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-hydroxy-2-(4-methylphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-methyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-(2-naphthyl)-D-alanine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-methyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-(3*R*,4*S*,5*R*)-3,4,5,6-tetrahydroxy-D-norleucine;

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*N*,2-dimethylalanine;

N-({4-[(2*R*,3*R*)-1-(4-Fluorophenyl)-3-({2-hydroxy-2-[4-(methylthio)phenyl]ethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetyl)glycyl-3-methyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-(4-methylbenzyl)-D-cysteine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-(*tert*-butyl)-D-cysteine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-b,b-dimethyl-D-phenylalanine.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" and "C_{1-4}alkyl" include propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "phenylC_{1-6}alkyl" would include benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

The term "aryl" refers to a 4-10 membered aromatic mono or bicyclic ring containing 0 to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur. Examples of aryls include phenyl, pyrrolyl, furanyl, imidazolyl, triazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl, 1,2,4-triazolyl, thienyl, naphthyl, benzofuranyl, benzimidazolyl, benzthienyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, 1,3-benzodioxolyl, indolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, phthalazinyl, cinnolinyl and naphthyridinyl. Particularly "aryl" refers to phenyl, thienyl, pyridyl, imidazolyl or indolyl. The term"aryl" includes both unsubstituted and substituted aromatic rings.

Examples of "C_{1-6}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl,

ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "*N*-(C_{1-6}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. "C_{3-6}cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

A suitable pharmaceutically acceptable salt of a compound of the invention, or other compounds disclosed herein, is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric, acetate or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula (I), or other compounds disclosed herein, may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include *in vivo* hydrolysable esters and *in vivo* hydrolysable amides of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I), or other compounds disclosed herein, containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I), or other compounds disclosed herein, containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A

selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

A suitable value for an *in vivo* hydrolysable amide of a compound of the formula (I), or other compounds disclosed herein, containing a carboxy group is, for example, a *N*-C_{1-6}alkyl or *N,N*-di-C_{1-6}alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess cholesterol absorption inhibitory activity.

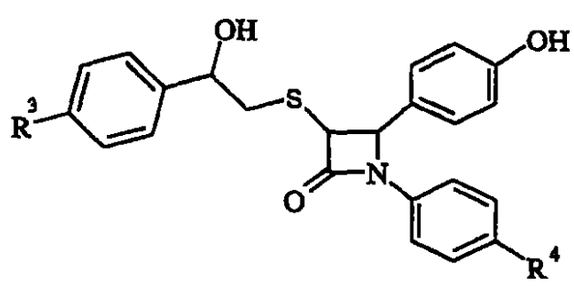
The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess cholesterol absorption inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess cholesterol absorption inhibitory activity.

Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

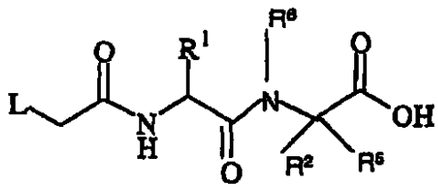
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

Process 1) reacting a compound of formula (II):



(II)

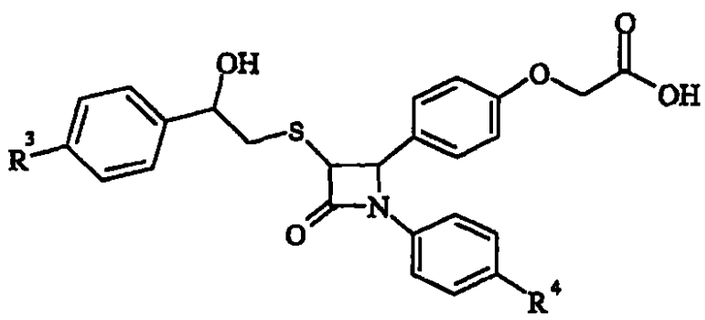
with a compound of formula (III):



(III)

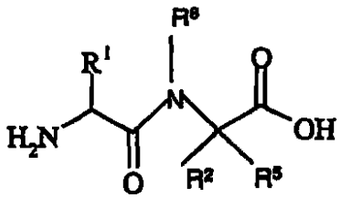
wherein L is a displaceable group;

Process 2) reacting an acid of formula (IV):



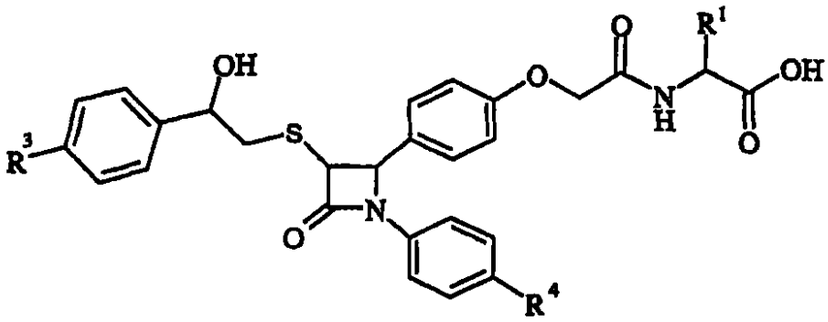
(IV)

or an activated derivative thereof; with an amine of formula (V):



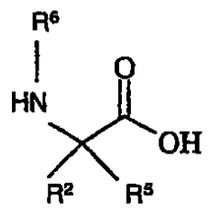
(V)

Process 3): reacting an acid of formula (VI):



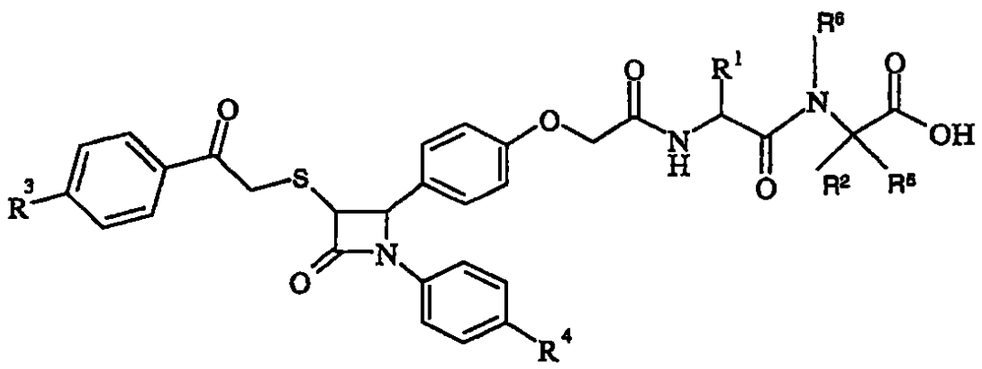
(VI)

or an activated derivative thereof, with an amine of formula (VII):



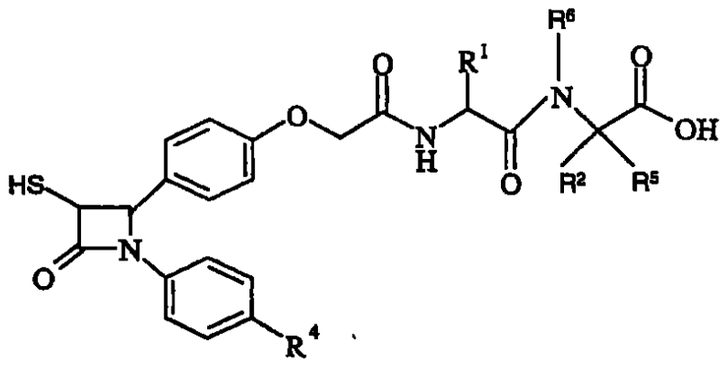
(VII)

Process 4): reducing a compound of formula (VIII):



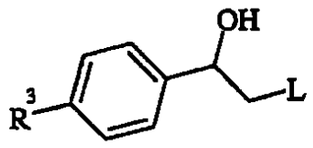
(VIII)

Process 5): reacting a compound of formula (IX):



(IX)

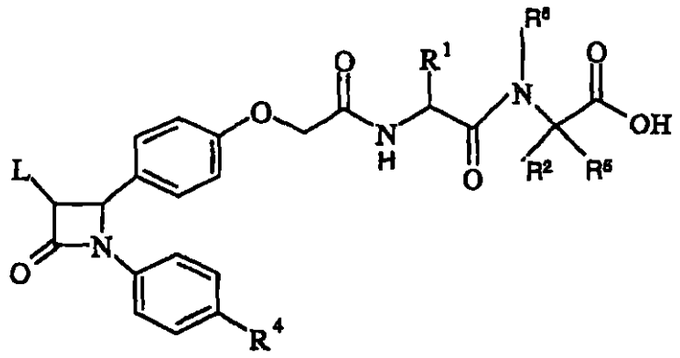
with a compound of formula (X):



(X)

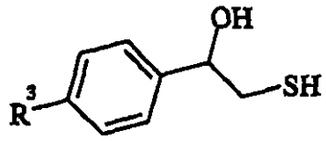
wherein L is a displaceable group;

Process 6): reacting a compound of formula (XI):



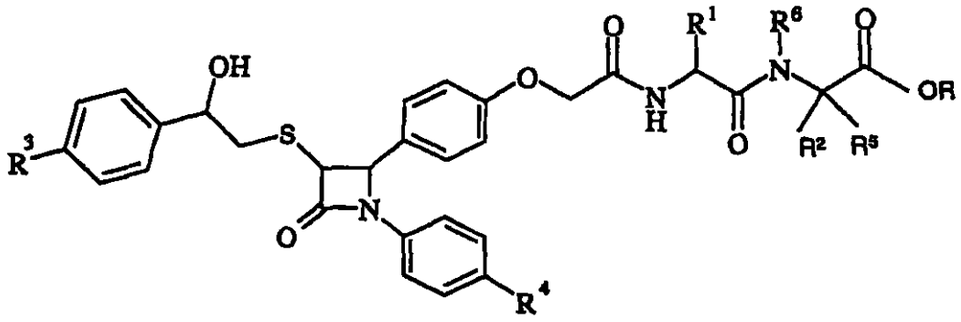
(XI)

wherein L is a displaceable group; with a compound of formula (XII):



(XII)

Process 7): De-esterifying a compound of formula (XIII)



(XIII)

wherein the group C(O)OR is an ester group;

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug; or

iv) separating two or more enantiomers.

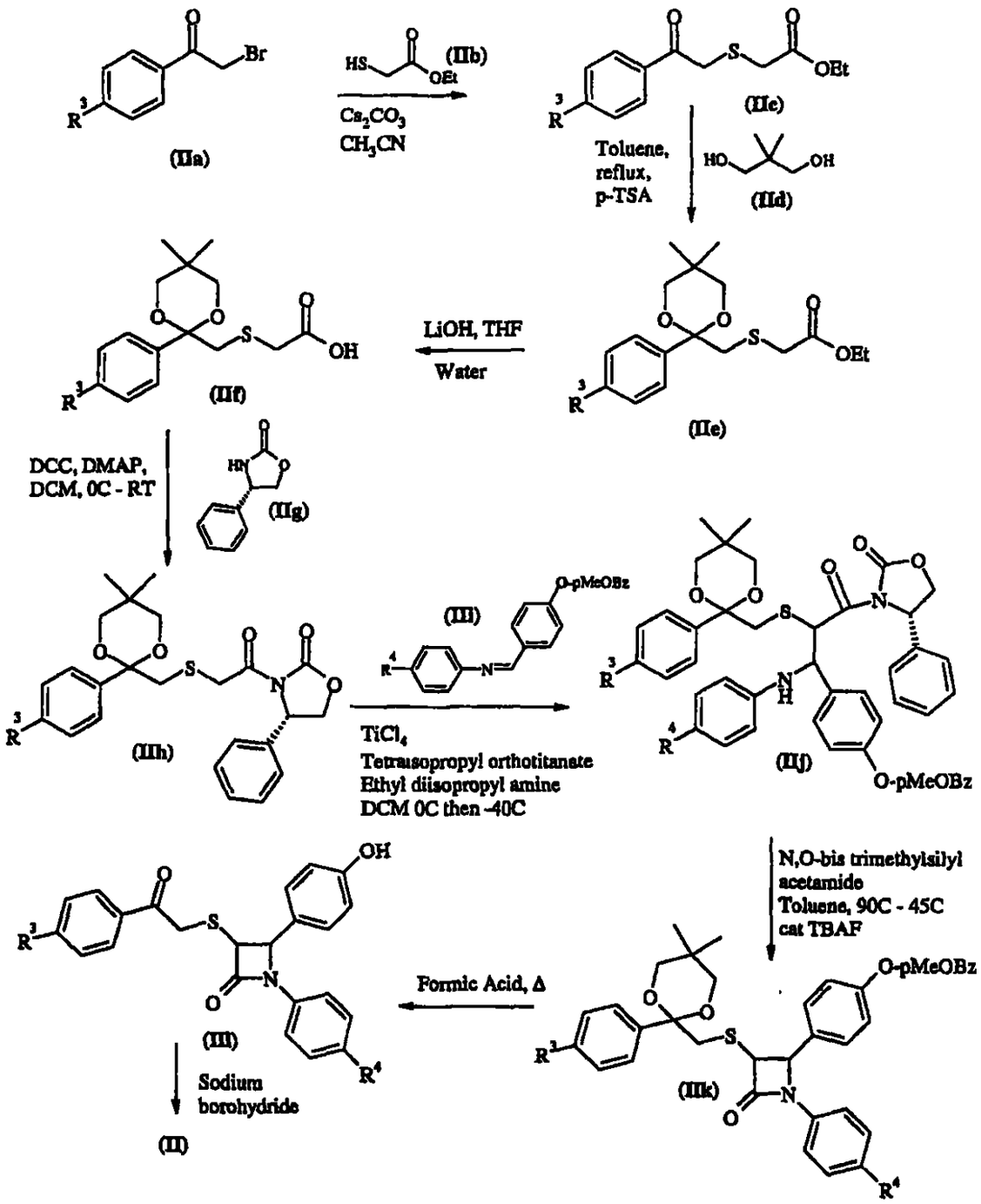
L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

C(O)OR is an ester group, suitable values for C(O)OR are methoxycarbonyl, ethoxycarbonyl, *t*-butoxycarbonyl and benzyloxycarbonyl.

The starting materials used in the present invention can be prepared by modifications of the routes described in EP 0 792 264 B1. Alternatively they can be prepared by the following reactions.

Process 1): Alcohols of formula (II) may be reacted with compounds of formula (III) in the presence of a base for example an inorganic base such as sodium carbonate, or an organic base such as Hunigs base, in the presence of a suitable solvent such as acetonitrile, dichloromethane or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux.

Compounds of formula (II) may be prepared according to the following scheme:



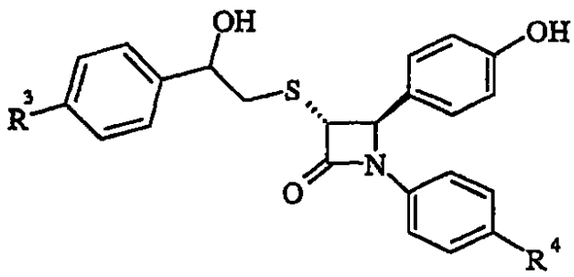
Scheme 1

wherein pMeOBz is para methoxy benzyl.

Compounds of formula (IIb), (IId), (IIg) and (III) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

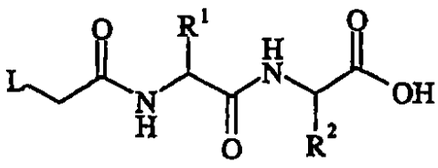
Another aspect of the present invention provides a process for preparing a compound of formula (I2) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

Process 1) reacting a compound of formula (II2):



(II2)

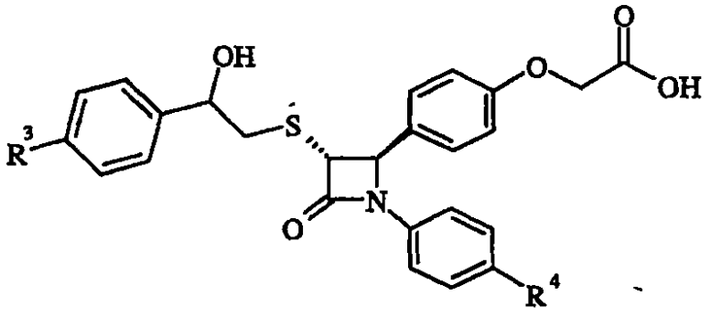
with a compound of formula (III):



(III)

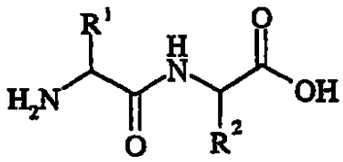
wherein L is a displaceable group;

Process 2) reacting an acid of formula (IV2):



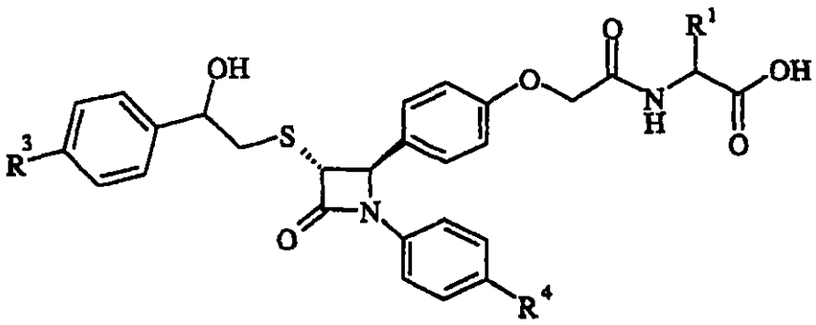
(IV)

or an activated derivative thereof; with an amine of formula (V):



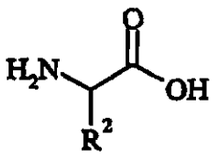
(V)

Process 3): reacting an acid of formula (VI2):



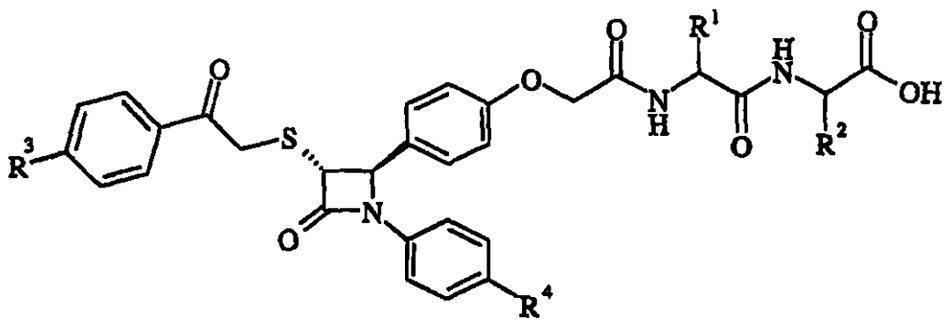
(VI2)

or an activated derivative thereof, with an amine of formula (VII):



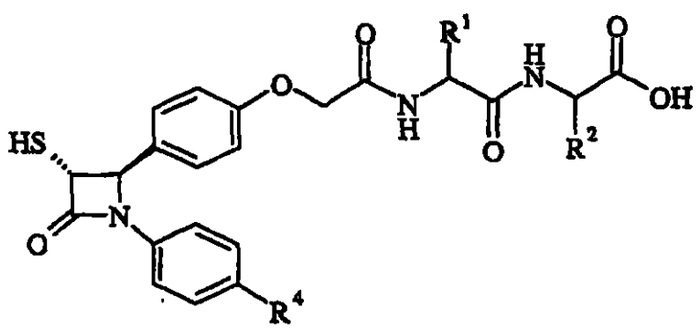
(VII)

Process 4): reducing a compound of formula (VIII2):



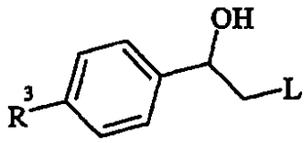
(VIII2)

Process 5): reacting a compound of formula (IX2):



(IX2)

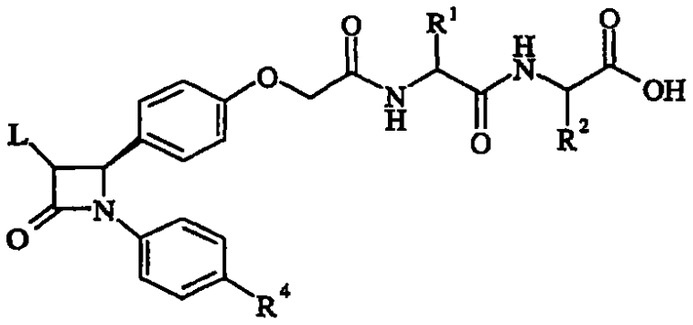
with a compound of formula (X):



(X)

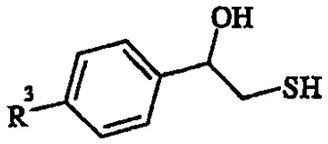
wherein L is a displaceable group;

Process 6): reacting a compound of formula (XI2):



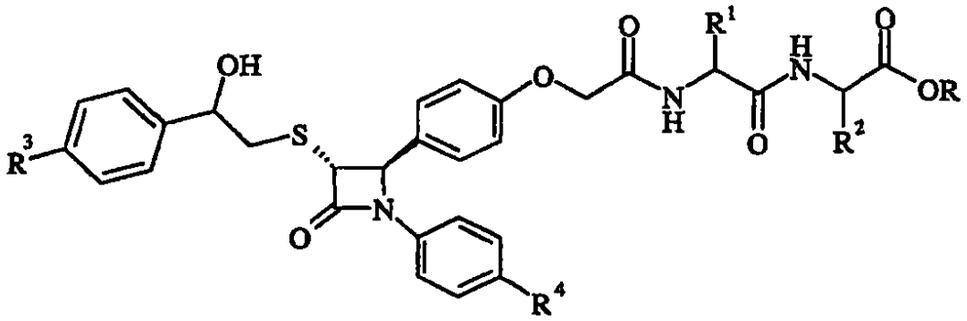
(XI2)

wherein L is a displaceable group; with a compound of formula (XII):



(XII)

Process 7): De-esterifying a compound of formula (XIII2)



(XIII2)

wherein the group C(O)OR is an ester group;

and thereafter if necessary or desirable:

i) converting a compound of the formula (I2) into another compound of the formula (I2);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug; or iv) separating two or more enantiomers.

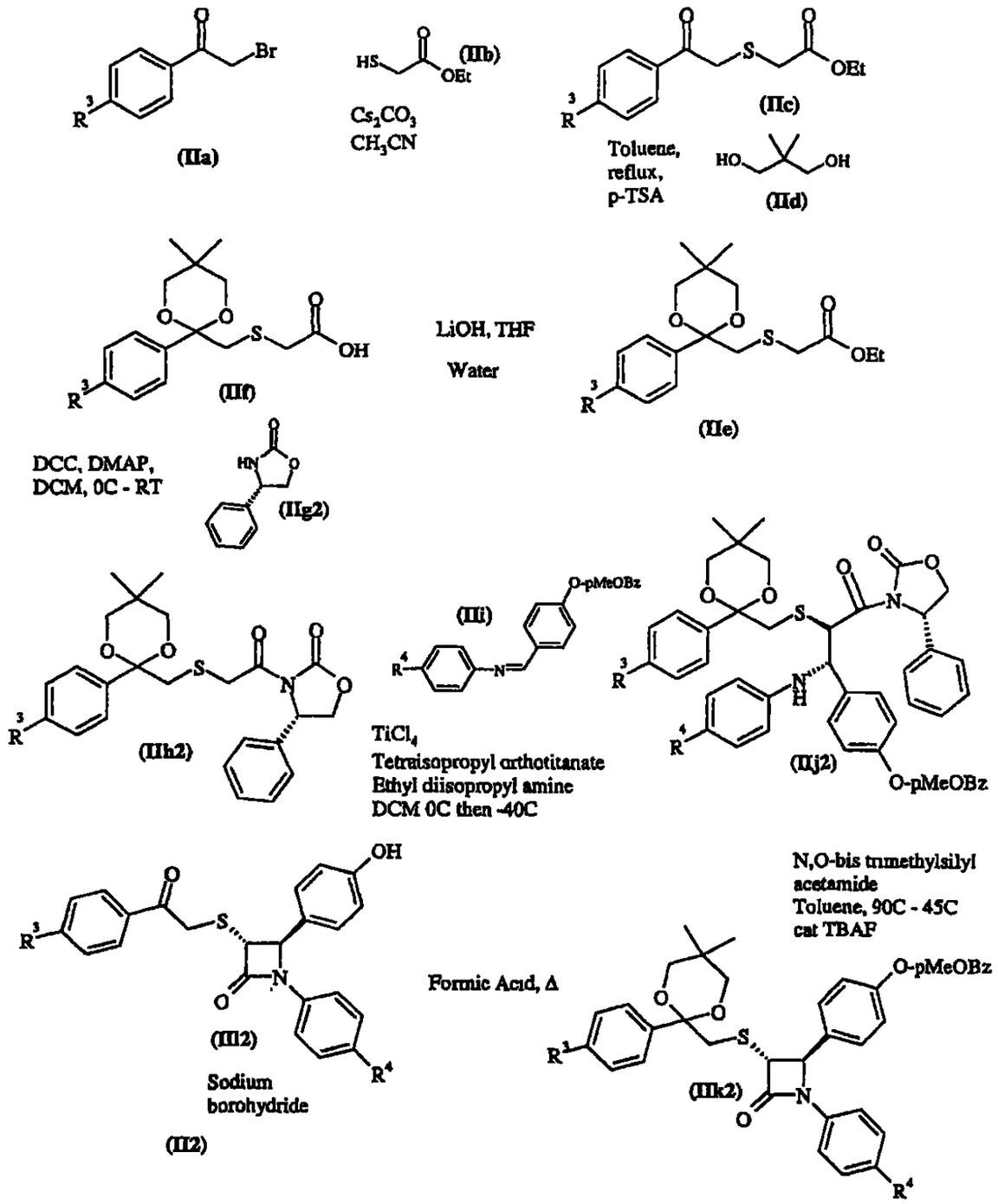
L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

C(O)OR is an ester group, suitable values for C(O)OR are methoxycarbonyl, ethoxycarbonyl, *t*-butoxycarbonyl and benzyloxycarbonyl.

The starting materials used in the present invention can be prepared by modifications of the routes described in EP 0 792 264 B1. Alternatively they can be prepared by the following reactions.

Process 1): Alcohols of formula (II2) may be reacted with compounds of formula (III) in the presence of a base for example an inorganic base such as sodium carbonate, or an organic base such as Hunigs base, in the presence of a suitable solvent such as acetonitrile, dichloromethane or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux.

Compounds of formula (II2) may be prepared according to the following scheme:



Scheme 1

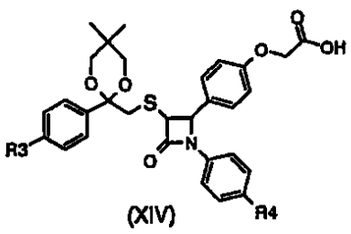
wherein pMeOBz is para methoxy benzyl.

Compounds of formula (IIb), (IId), (Iig2) and (III2) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

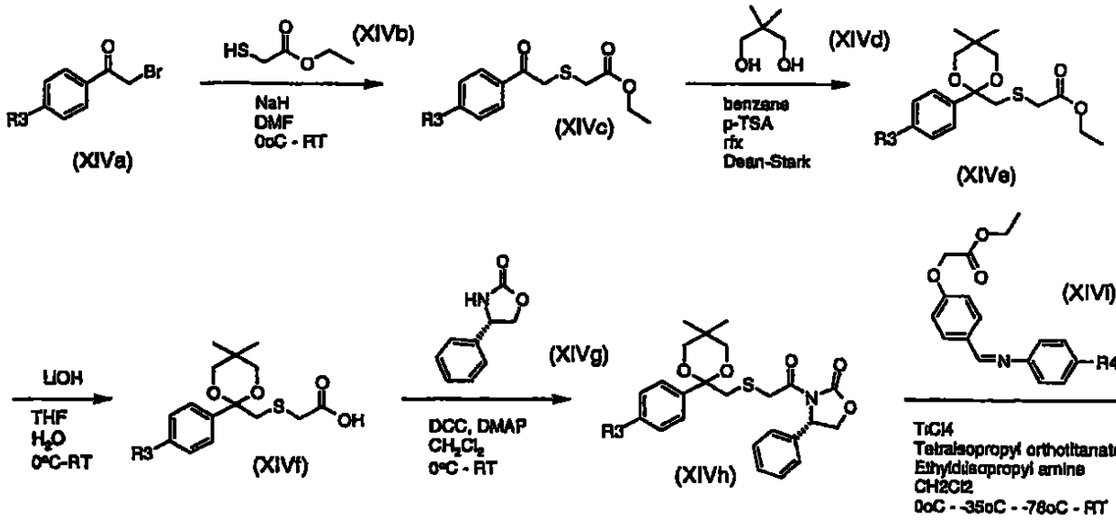
A compound of formula (III) may also be reacted with a compound of formula (XIV).

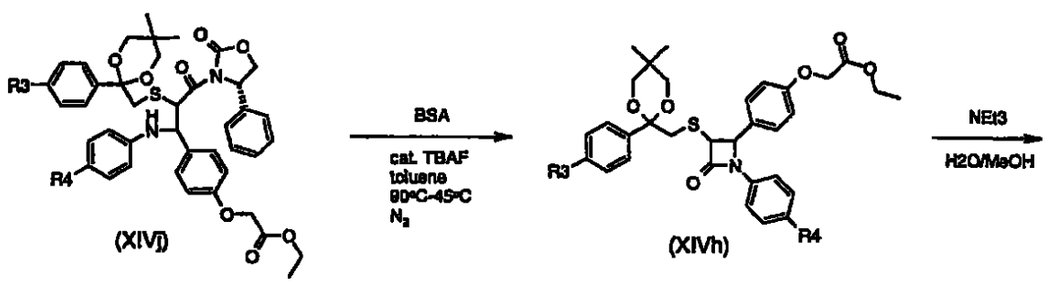
Compounds of formula(XIV) may be prepared according to the following route:

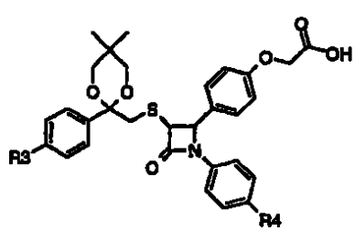
5



(XIV)

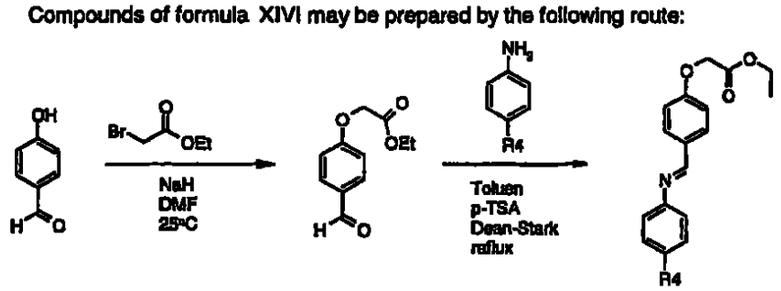






(XIV)

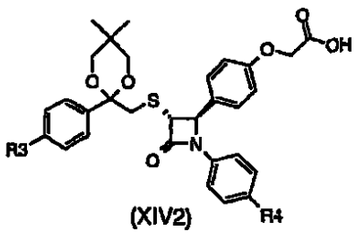
Compounds of formula XIVi may be prepared by the following route:



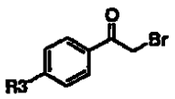
(XIVi)

A compound of formula (III2) may also be reacted with a compound of formula (XIV2).

Compounds of formula(XIV2) may be prepared according to the following route:

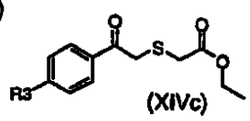


(XIV2)



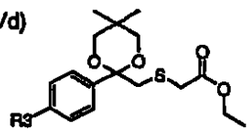
(XIVa)

(XIVb)



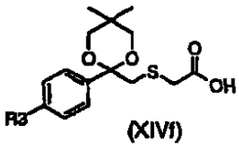
(XIVc)

(XIVd)

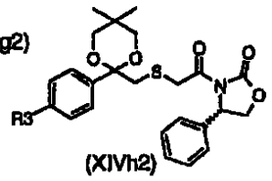


(XIVe)

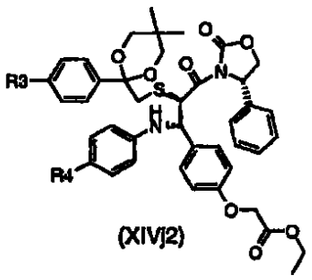
(XIVf)



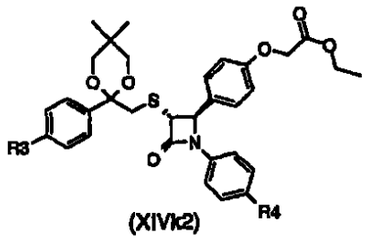
(XIVg2)



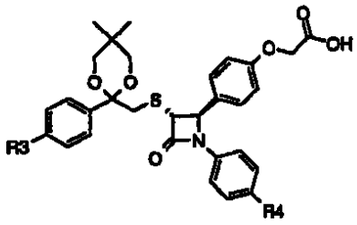
(XIVh2)



(XIVj2)

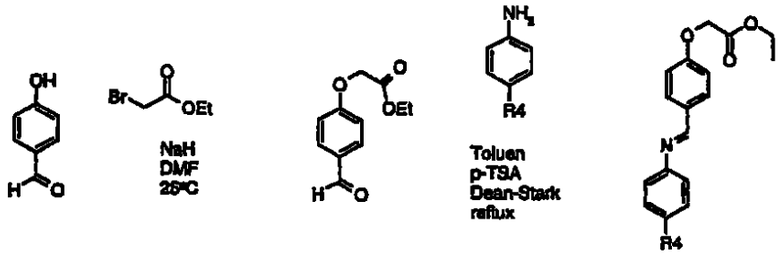


(XIVk2)



(XIV2)

Compounds of formula XIVi may be prepared by the following route:



(XIVi)

For XIV and XIV2 both, the following applies:

Process 2) and *Process 3)*: Acids and amines may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Acids of formula (IV) and (VI) may be prepared from compounds of formula (II) by reacting them with the appropriate, optionally protected, side chain using the conditions of *Process 1)*. Alternatively, acids of formula (IV) and (VI) may be prepared by a modification of *Scheme I*.

Amines of formula (V) and (VII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 4): Reduction of compounds of formula (VIII) could be performed with a hydride reagent such as sodium borohydride in a solvent such as methanol at temperatures suitable between -20-40°C.

Compounds of formula (VIII) can be prepared from compounds of formula (III), by deprotecting the benzyl group and performing *Process 1*. Alternatively compound (IIk) could be debenzylated, *Process 1* could be performed and the resulting compound deprotected to reveal the ketone.

Process 5) and *Process 6)*: these compounds may be reacted together in the presence of a base for example an inorganic base such as sodium carbonate, or an organic base such as

Hunigs base, in the presence of a suitable solvent such as acetonitrile, dichloromethane or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux.

Compounds of formula (IX) and (XI) may be prepared by an appropriate modification of *Scheme 1*.

Compounds of formula (X) and (XII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 7): Esters of formula (XIII) may be deprotected under standard conditions such as those described below, for example a methyl or ethyl ester may be deprotected with sodium hydroxide in methanol at room temperature.

Compounds of formula (XIII) may be prepared by a modification of any of the processes described herein for the preparation of compounds of formula (I).

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley

and Sons, 1999). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

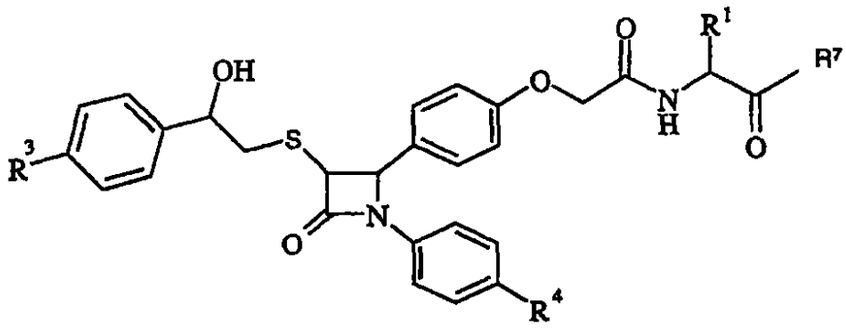
A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

The invention further provides for a compound of the formula (XV) or hydrolysable esters or amides thereof:



(XV)

wherein R^7 is an hydroxy group or a C_{1-3} alkoxy group. R^1, R^3 and R^4 are as defined above regarding formula (I). A compound of formula (XV) may be an intermediate to formula (I).

As stated hereinbefore the compounds defined in the present invention possess cholesterol absorption inhibitory activity. These properties may be assessed, using the following biological tests.

In vivo testing of cholesterol absorption inhibitors (A)

C57BL/6 female mice were maintained on regular chow diet and housed in individual cages to collect faeces. Mice were fasted for 3 hours and then gavaged with vehicle or compound. Half an hour later the mice were gavaged with radiolabelled cholesterol. Six hours after the ^{14}C-cholesterol gavage blood samples were taken via the tail and plasma prepared to determine how much cholesterol were absorbed. 24 hours after the gavage of ^{14}C-cholesterol the mice were bled and plasma were prepared for analysis. Faeces were collected for 24 hours to assess absorption efficiency.

In vivo testing of cholesterol absorption inhibitors (B).

C57BL/6 female mice were maintained on regular chow diet and housed in individual cages to collect faeces. Mice were fasted for 3 hours and then gavaged with vehicle or compound. One to ten hours later the mice were gavaged with radiolabelled cholesterol. Six hours after the ^{14}C-cholesterol gavage blood sample was taken via the tail and plasma prepared to determine how much cholesterol was absorbed. 24 hours after the gavage of ^{14}C-

cholesterol the mice were bled and plasma analysed for radioactivity. Faeces were also collected for 24 hours to assess absorption efficiency.

References

1. E. A. Kirk, G. L. Moe, M. T. Caldwell, J. Å. Lemmark, D. L. Wilson, R. C. LeBoeuf. Hyper- and hypo-responsiveness to dietary fat and cholesterol among inbred mice: searching for level and variability genes. J. Lipid Res. 1995 36:1522-1532.

2. C. P. Carter, P. N. Howles, D. Y. Hui. Genetic variation in cholesterol absorption efficiency among inbred strains of mice. J. Nutr. 1997 127:1344-1348.

3. C. D. Jolley, J. M. Dietschy, S. D. Turley. Genetic differences in cholesterol absorption in 129/Sv and C57BL/6 mice: effect on cholesterol responsiveness. Am. J. Physiol. 1999 276:G1117-G1124.

Administration of 5 μmol/kg of Example 96 gave 87% inhibition of ^{14}C-cholesterol absorption (procedure A). Administration of 5 μmol/kg of Example 94 gave 89% inhibition of ^{14}C-cholesterol absorption (procedure A).

Administration of 0.2 μmol/kg of Example 91 gave 58% inhibition of ^{14}C-cholesterol absorption (procedure A). Administration of 0.2 μmol/kg of Example 85 gave 47% inhibition of ^{14}C-cholesterol absorption (procedure A).

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range of approximately 0.02-100 mg/kg, preferably 0.02 –50 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet

or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg, particularly 0.1-10 mg/kg is employed. In another aspect a daily dose in the rage of 0.01-20 mg/kg is employed. In one aspect of the invention the daily dose of a compound of formula (I) is less than or equal to 100mg. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are effective cholesterol absorption inhibitors, and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use as a medicament.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the production of a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man.

Herein, where the production of a cholesterol absorption inhibitory effect or a cholesterol lowering effect is stated, suitably this relates to the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man. Additionally is relates to the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertrigliceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia

and hypoalphalipoproteinemia (low HDL) in a warm-blooded animal, such as man. Furthermore it relates to the treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks in a warm-blooded animal, such as man. It also relates to the treatment of atherosclerosis, coronary heart diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks in a warm-blooded animal, such as man.

The production of a cholesterol absorption inhibitory effect or a cholesterol lowering effect also relates to a method of treating and/or preventing atherosclerotic lesions, a method of preventing plaque rupture and a method of promoting lesion regression. Furthermore it relates to a method of inhibiting monocytes-macrophage accumulation in atherosclerotic lesions, a method of inhibiting expression of matrix metalloproteinases in atherosclerotic lesions, a method of inhibiting the destabilization of atherosclerotic lesions, a method for preventing atherosclerotic plaque rupture and a method of treating unstable angina.

The production of a cholesterol absorption inhibitory effect or a cholesterol lowering effect also relates to a method of treating sitosterolemia.

Compounds of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may also have value in the treatment or prevention of Alzheimer's Disease (see for example WO 02/096415). Therefore in a further aspect of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, for use in the treatment or prevention of Alzheimer's Disease.

Compounds of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may also have value in the treatment or prevention of cholesterol associated tumors. Therefore in a further aspect of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, for use in the treatment or prevention of cholesterol associated tumors.

Compounds of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may also have value in the treatment or prevention of vascular inflammation (see for example WO 03/026644). Therefore in a further aspect of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, for use in the treatment or prevention of vascular inflammation.

According to a further feature of this aspect of the invention there is provided a method for producing a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

The cholesterol absorption inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore and an additional cholesterol absorption inhibitory substance as defined hereinbefore and an additional hypolipidaemic agent for the conjoint treatment of hyperlipidaemia.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with cholesterol biosynthesis inhibitors, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable cholesterol biosynthesis inhibitors include HMG Co-A reductase inhibitors, squalene synthesis inhibitors and squalene epoxidase inhibitors. A suitable squalene synthesis inhibitor is squalestatin 1 and a suitable squalene epoxidase inhibitor is NB-598.

In this aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with an HMG Co-A reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable HMG Co-A reductase inhibitors, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are statins well known in the art. Particular statins are fluvastatin, lovastatin, pravastatin,

simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin and rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A further particular statin is pitavastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A further particular statin is rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A preferable particular statin is rosuvastatin calcium salt.

Therefore in an additional feature of the invention, there is provided a combination of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing a cholesterol lowering effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of a cholesterol lowering effect.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of a matrix metalloproteinase inhibitor.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a

prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of a Apo A-1 Mimetic Peptide.

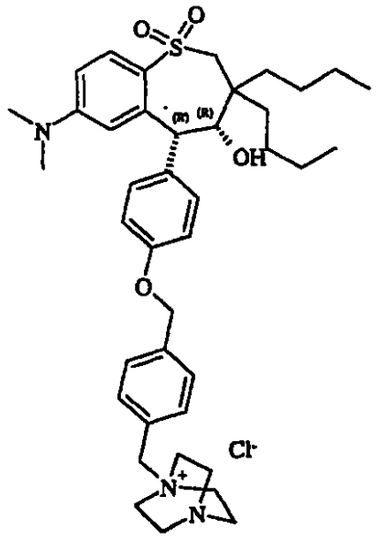
In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with an ileal bile acid (IBAT) inhibitor or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. Suitable compounds possessing IBAT inhibitory activity for use in combination with compounds of the present invention have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 94/24087, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07749,WO 98/38182, WO 98/40375, WO 98/56757, WO 99/32478, WO 99/35135, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 00/35889, WO 01/34570, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 00/47568, WO 00/61568, WO 01/66533, WO 01/68096, WO 01/68637, WO 02/08211, DE 19825804, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 489 423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595, EP 864 582, EP 869 121 and EP 1 070 703 and the contents of these patent applications are incorporated herein by reference. Particularly the named examples of these patent applications are incorporated herein by reference. More particularly claim 1 of these patent application are incorporated herein by reference.

Other suitable classes of IBAT inhibitors for use in combination with compounds of the present invention are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity for use in combination with compounds of the present invention is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl □-D-glucopyranosiduronic acid (EP 864 582).

A further suitable compound possessing IBAT inhibitory activity for use in combination with compounds of the present invention is S-8921 (EP 597 107).

A further suitable IBAT inhibitor for use in combination with compounds of the present invention is the compound:



WO 99/32478

A particular IBAT inhibitor for use in combination with compounds of the present invention is selected from any one of Examples 1-120 of WO 02/50051, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-120 are incorporated herein by reference. Claims 1-15 of WO 02/50051 are also incorporated herein by reference. A particular IBAT inhibitor selected from WO 02/50051 for use in combination with compounds of the present invention is selected from any one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(5-carboxypentyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-((ethoxy)(methyl)phosphoryl-methyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(ethyl) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(hydroxy) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
and
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A particular IBAT inhibitor for use in combination with compounds of the present invention is selected from any one of Examples 1-44 of WO 03/020710, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-44 are incorporated herein by reference. Claims 1-10 of WO 03/020710 are also incorporated herein by reference. A particular IBAT inhibitor selected from WO 03/020710 for use in combination with compounds of the present invention is selected from any one of:
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-((S)-1-carbamoyl-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(hydroxycarbamoylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[2-(*N'*-pyrimidin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[2-(*N'*-pyridin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(1-*t*-butoxycarbonylpiperidin-4-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2,3-dihydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[2-(3,4-dihydroxyphenyl)-2-methoxyethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-aminoethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(piperidin-4-ylmethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; or

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-*N*,*N*-dimethylaminosulphamoylethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A particular IBAT inhibitor for use in combination with compounds of the present invention is selected from any one of Examples 1-7 of WO 03/022825, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-7 are incorporated herein by reference. Claims 1-8 of WO 03/022825 are also incorporated herein by reference. A particular IBAT inhibitor selected from WO 03/022825 for use in combination with compounds of the present invention is selected from any one of:

1,1-dioxo-3(R)-3-butyl-3-ethyl-5-(R)-5-phenyl-8-[*N*-((R)-α-carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,4-benzothiazepine;

1,1-dioxo-3(S)-3-butyl-3-ethyl-5-(S)-5-phenyl-8-[*N*-((R)-α-carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,4-benzothiazepine;

1,1-dioxo-3(R)-3-butyl-3-ethyl-5-(R)-5-phenyl-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

1,1-dioxo-3(S)-3-butyl-3-ethyl-5-(S)-5-phenyl-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3,5-*trans*-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-bromo-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3,5-*trans*-1,1-dioxo-3-(S)-3-ethyl-3-butyl-4-hydroxy-5-(S)-5-phenyl-7-bromo-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine

3,5-*trans*-1,1-dioxo-3-(R)-3-ethyl-3-butyl-4-hydroxy-5-(R)-5-phenyl-7-bromo-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3,5-*trans*-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3,5-*trans*-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine ammonia salt;

1,1-dioxo-3-(S)-3-ethyl-3-butyl-5-(S)-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine diethylamine salt; and

1,1-dioxo-3-(R)-3-ethyl-3-butyl-5-(R)-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine diethylamine salt;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A particular IBAT inhibitor for use in combination with compounds of the present invention is selected from any one of Examples 1-4 of WO 03/022830, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-4 are incorporated herein by reference. Claims 1-8 of WO 03/022830 are also incorporated herein by reference. A particular IBAT inhibitor selected from WO 03/022830 for use in combination with compounds of the present invention is selected from any one of:

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine ammonia salt

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{*N*-[α-(carboxy)-2-fluorobenzyl]carbamoylmethylthio}-2,3,4,5-tetrahydrobenzothiepine; and

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{*N*-[1-(carboxy)-1-(thien-2-yl)methyl]carbamoylmethylthio}-2,3,4,5-tetrahydrobenzothiepine

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A particular IBAT inhibitor for use in combination with compounds of the present invention is selected from any one of Examples 1-39 of WO 03/022286, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-39 are incorporated herein by reference. Claims 1-10 of WO 03/022286 are also incorporated herein by reference. A particular IBAT inhibitor selected from WO 03/022286 for use in combination with compounds of the present invention is selected from any one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-{(*S*)-1-[*N*-((*S*)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A particular IBAT inhibitor for use in combination with compounds of the present invention is selected from any one of Examples 1-7 of WO 03/091232, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-7 are incorporated herein by reference. Claims 1-10 of WO 03/091232 are also incorporated herein by reference. A particular IBAT inhibitor selected from WO 03/091232 for use in combination with compounds of the present invention is selected from any one of:

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R/S)-α-{*N*-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N*-{2-(S)-[*N*-(carbamoylmethyl) carbamoyl]pyrrolidin-1-ylcarbonylmethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N*-[2-(3,4,5-trihydroxyphenyl)ethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(R)-3-(S)-4-(S)-5-(R)-3,4,5,6-tetrahydroxytetrahydropyran-2-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Further suitable compounds possessing IBAT inhibitory activity for use in combination with compounds of the present invention are disclosed in WO 03/106482.

Suitable IBAT inhibitors as disclosed in WO 03/106482 for use in combination with compounds of the present invention are selected from any one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxybutyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-mesylethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-

mesylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxyethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-hydroxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylsulphinylethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-mesylethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methoxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-

benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N*'-((*S*)-1-carboxy-3-methylthiopropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N*'-((*S*)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N*'-((*S*)-1-carboxy-3-mesylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N*'-((*S*)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; or

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N*'-((*S*)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine.

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Further suitable IBAT inhibitors for use in combination with compounds of the present invention are those disclosed in WO 04/076430.

In a particular aspect of the invention an IBAT inhibitor or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof is an IBAT inhibitor or a pharmaceutically acceptable salt thereof.

Therefore in an additional feature of the invention, there is provided a combination of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing a cholesterol lowering effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of a cholesterol lowering effect in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the

simultaneous, sequential or separate administration of an effective amount of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, WO03/051821, WO03/051822, WO03/051826, PCT/GB03/02584, PCT/GB03/02591, PCT/GB03/02598, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to WY-14643, clofibrate, fenofibrate, bezafibrate, GW 9578, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, NN622/Ragaglitazar, BMS 298585, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy) phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

Therefore in an additional feature of the invention, there is provided a combination of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing a cholesterol lowering effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in producing a cholesterol lowering effect in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the

simultaneous, sequential or separate administration of an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

In another aspect of the invention, there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an -agonists to the receptor HM74A (nicotinic acid receptor). HM74A agonists may be nicotine acid derivates. As used herein "nicotinic acid derivative" means a compounds comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure. Examples of nicotinic acid derivatives include nicotinic acid, niceritrol, nicofuranose, NIASPAN® and acipimox.

Therefore, in an additional feature of the invention, there is provided a combination of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a nicotinic acid derivative or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing a cholesterol lowering effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a nicotinic acid derivative, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a nicotinic acid derivative, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a nicotinic acid derivative, or a pharmaceutically acceptable salt, solvate,

solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of a cholesterol lowering effect in a warm-blooded animal, such as man.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a bile acid sequestrant or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. Suitable bile acid sequestrants include cholestyramine, cholestipol and cosevelam hydrochloride.

Therefore, in an additional feature of the invention, there is provided a combination of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid sequestrant or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing a cholesterol lowering effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a bile acid sequestrant, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid sequestrant, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid sequestrant, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of a cholesterol lowering effect in a warm-blooded animal, such as man.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier,

with the simultaneous, sequential or separate administration one or more of the following agents selected from Group X:

- an antihypertensive compound (for example althiazide, benzthiazide, captopril, carvedilol, chlorothiazide sodium, clonidine hydrochloride, cyclothiazide, delapril hydrochloride, dilevalol hydrochloride, doxazosin mesylate, fosinopril sodium, guanfacine hydrochloride, methyidopa, metoprolol succinate, moexipril hydrochloride, monatepil maleate, pelanserin hydrochloride, phenoxybenzemine hydrochloride, prazosin hydrochloride, primidolol, quinapril hydrochloride, quinaprilat, ramipril, terazosin hydrochloride, candesartan, candesartan cilexetil, telmisartan, amlodipine besylate, amlodipine maleate and bevantolol hydrochloride);
- an angiotensin converting enzyme inhibitor (for example alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopnl, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat);
- an angiotensin II receptor antagonist (for example candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan);
- an andrenergic blocker (for example bretylium tosylate, dihydroergotamine so mesylate, phentolamine mesylate, solypertine tartrate, zolertine hydrochloride, carvedilol or labetalol hydrochloride); an alpha andrenergic blocker (for example fenspiride hydrochloride, labetalol hydrochloride, proroxan and alfuzosin hydrochloride); a beta andrenergic blocker (for example acebutolol, acebutolol hydrochloride, alprenolol hydrochloride, atenolol, bunolol hydrochloride, carteolol hydrochloride, celiprolol hydrochloride, cetamolol hydrochloride, cicloprolol hydrochloride, dexpropranolol hydrochloride, diacetolol hydrochloride, dilevalol

hydrochloride, esmolol hydrochloride, exaprolol hydrochloride, flestolol sulfate, labetalol hydrochloride, levobetaxolol hydrochloride, levobunolol hydrochloride, metalol hydrochloride, metoprolol, metoprolol tartrate, nadolol, pamatolol sulfate, penbutolol sulfate, practolol, propranolol hydrochloride, sotalol hydrochloride, timolol, timolol maleate, tiprenolol hydrochloride, tolamolol, bisoprolol, bisoprolol fumarate and nebivolol); or a mixed alpha/beta andrenergic blocker;

- an andrenergic stimulant (for example combination product of chlorothiazide and methyldopa, the combination product of methyidopa hydrochlorothiazide and methyldopa, clonidine hydrochloride, clonidine, the combination product of chlorthalidone and clonidine hydrochloride and guanfacine hydrochloride);
- channel blocker, for example a calcium channel blocker (for example clentiazem maleate, amlodipine besylate, isradipine, nimodipine, felodipine, nilvadipine, nifedipine, teludipine hydrochloride, diltiazem hydrochloride, belfosdil, verapamil hydrochloride or fostedil);
- a diuretic (for example the combination product of hydrochlorothiazide and spironolactone and the combination product of hydrochlorothiazide and triamterene);
- anti-anginal agents (for example amlodipine besylate, amlodipine maleate, betaxolol hydrochloride, bevantolol hydrochloride, butoprozine hydrochloride, carvedilol, cinepazet maleate, metoprolol succinate, molsidomine, monatepil maleate, primidolol, ranolazine hydrochoride, tosifen or verapamil hydrochloride);
- vasodilators for example coronary vasodilators (for example fostedil, azaclorzine hydrochloride, chromonar hydrochloride, clonitrate, diltiazem hydrochloride, dipyridamole, droprenilamine, erythrityl tetranitrate, isosorbide dinitrate, isosorbide mononitrate, lidoflazine, mioflazine hydrochloride, mixidine, molsidomine, nicorandil, nifedipine, nisoldipine, nitroglycerine, oxprenolol hydrochloride, pentrinitrol, perhexiline maleate, prenylamine, propatyl nitrate, terodiline hydrochloride, tolamolol and verapamil);
- anti-coagulants (selected from argatroban, bivalirudin, dalteparin sodium, desirudin, dicumarol, Iyapolate sodium, nafamostat mesylate, phenprocoumon, tinzaparin sodium and warfarin sodium);
- antithrombotic agents (for example anagrelide hydrochloride, bivalirudin, cilostazol, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, fluretofen, ifetroban, ifetroban sodium, lamifiban, lotrafiban

hydrochloride, napsagatran, orbofiban acetate, roxifiban acetate, sibrafiban, tinzaparin sodium, trifenagrel, abciximab and zolimomab aritox);

- fibrinogen receptor antagonists (for example roxifiban acetate, fradafiban, orbofiban, lotrafiban hydrochloride, tirofiban, xemilofiban, monoclonal antibody 7E3 and sibrafiban)
- platelet inhibitors (for example cilostezol, clopidogrel bisulfate, epoprostenol, epoprostenol sodium, ticlopidine hydrochloride, aspirin, ibuprofen, naproxen, sulindae, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone and piroxicam, dipyridamole);
- platelet aggregation inhibitors (for example acadesine, beraprost, beraprost sodium, ciprostene calcium, itezigrel, lifarizine, lotrafiban hydrochloride, orbofiban acetate, oxagrelate, fradafiban, orbofiban, tirofiban and xemilofiban)
- hemorrheologic agents (for example pentoxifylline);
- lipoprotein associated coagulation inhibitors;
- Factor VIIa inhibitors;
- Factor Xa inhibitors;
- low molecular weight heparins (for example enoxaparin, nardroparin, dalteparin, certroparin, parnaparin, reviparin and tinzaparin);
- squalene synthase inhibitors;
- squalene epoxidase inhibitors;
- liver X receptor (LXR) agonists for example GW-3965 and those described in WO00224632, WO00103705, WO02090375 and WO00054759 (claim 1 and the named examples of these four application are incorporated herein by reference);
- microsomal triglyceride transfer protein inhibitors for example implitapide and those described in WO03004020, WO03002533, WO02083658 and WO 00242291 (claim 1 and the named examples of these four application are incorporated herein by reference);

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore, in an additional feature of the invention, there is provided a combination of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a

salt or a prodrug thereof and a compound from Group X or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing a cholesterol lowering effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from Group X, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from Group X, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from Group X, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of a cholesterol lowering effect in a warm-blooded animal, such as man.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of inhibitors of cholesterol absorption in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

Many of the intermediates described herein are novel and are thus provided as a further feature of the invention. For example compounds of formula (VI) show cholesterol absorption inhibitory activity when tested in the above referenced *in vitro* test assay and are thus claimed as a further feature of the invention.

Thus in a further feature of the invention, there is provided a compound of formula (VI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy] phenyl}azetidin-2-one.

Therefore according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (VI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in association with a pharmaceutically-acceptable diluent or carrier, with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one.

According to an additional aspect of the present invention there is provided a compound of the formula (VI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man, with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one.

Thus according to this aspect of the invention there is provided a compound of the formula (VI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, for use as a medicament, with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one.

According to another feature of the invention there is provided the use of a compound of the formula (VI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man, with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy] phenyl}azetidin-2-one.

According to another feature of the invention there is provided the use of a compound of the formula (VI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man, with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy] phenyl}azetidin-2-one.

According to a further feature of this aspect of the invention there is provided a method for producing a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (VI), or a pharmaceutically acceptable salt,

solvate, solvate of such a salt or a prodrug thereof, with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy] phenyl}azetidin-2-one.

According to a further feature of this aspect of the invention there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (VI), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated in the following non limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise stated:
(i) evaporations were carried out by rotary evaporation *in vacuo* and work up procedures were carried out after removal of residual solids such as drying agents by filtration;
(ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;
(iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63 μm (Merck);
(iv) yields are given for illustration only and are not necessarily the maximum attainable;
(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic resonance chemical shift values were measured in deuterated $CDCl_3$ (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer unless otherwise stated data was recorded at 400MHz; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet;

m, multiplet; br, broad; ABq, AB quartet; ABd, AB doublet, ABdd, AB doublet of doublets; dABq, doublet of AB quartets;

Mass spectra were recorded on one of the following instruments: LCT, QTOF, ZQ Mass spectrometer, all from Waters.

LC-MS:

Separation was performed using Agilent 1100 Series Modules or Waters 1525 pump on a Synergi MAX-RP (Phenomenex) C12 3x50 mm 4μm with gradient elution.

Samples were injected using Waters 2700 Sample Manager.

Mobile phases:

Generic gradients were applied from 5% to 95% acetonitrile.

Buffers containing 10 mM ammonium acetate or 5 mM ammonium formiate/5mM formic acid were used.

The mass spectra were recorded with a Waters ZQ2000 or Waters ZMD equipped with an electrospray interface, swithing positive and negative ionization mode. UV spectra were collected by a Agilent 1100 PDA or Waters 2996 DAD and the evaporative light scattering (ELS) signal by a Sedere Sedex 55 or 75.

Data collection and evaluation were performed using the MassLynx software.

Accurate mass data were determined using either a LCT or QTOF MS (Waters) with leucine enkephaline (m/z 556.2771) as lockmass. Unless otherwise stated the mass ion quoted is (MH^+).

Unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Cromasil C_8, 7 μm, (Akzo Nobel); MeCN and de-ionised water 10 mM ammonium acetate as mobile phases, with suitable composition;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;

(viii) where solutions were dried sodium sulphate was the drying agent; and

(ix) the following abbreviations may be used hereinbefore or hereinafter:-

DCM dichloromethane;

DMF *N,N*-dimethylformamide;

TBTU	o-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate;
EtOAc	ethyl acetate,
MeCN	acetonitrile;
TFA	trifluoroacetic acid;
DMAP	4-(dimethylamino)pyridine;
BSA	*N,O*-Bis(trimethylsilyl)acetamide; and
TBAF	tetrabutylammonium fluoride;
NMM	*N*-methyl morpholine;
TEA	triethylamine;
DBN	1,5-diazabicyclo-[4,3,0]-non-5-ene.

Example 1

(2R)-[(N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino](phenyl)acetic acid

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (44 mg, 0.081 mmol), N-methylmorpholine (18 ul, 0.16 mmol), *tert*-butyl (2*R*)-amino(phenyl)acetate (23 mg, 0.11 mmol) and TBTU (36 mg, 0.11 mmol) were added to methylene chloride (3 ml) and the reaction mixture was sirred at ambient temperature for 1.5 h. The mixture was purified by column chromatography on silica gel using methylene chloride/ethylacetate (1/1) as eluent. The resulting intermediate ester was dissolved in formic acid (2 ml) and the mixture was stirred overnight at 45 °C. The solvent was evaporated under reduced pressure and was co-evaporated with toluene. The residue was dissolved in methanol (2 ml) and NaBH4 10 mg, 0.26 mmol) was added. The reaction mixture was stirred at ambient temperature for 15 min. A small amount of ammoniumacetate buffer was added and the methanol was evaporated off. The residue was purified by preparativ

HPLC using acetonitril/ammonium acetat buffer (45:55) as eluent. The collected fractions were lyophilized to obtain 39 mg (71%, 3 steps) of the title compound. (^{1}H-NMR, 400 MHz, CD_3OD): 1.8-2.0 (m, 2H), 3.75 (d, 2H), 4.3 (d, 1H), 4.55 (s, 2H), 4.65-4.80 (m, 2H), 5.05 (d, 1H), 7.0-7.4 (m, 17 H), 7.95 (dd, 1H) 8.25 (t, 1H)

Example 2

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-N^6-acetyl-D-lysine

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (20 mg, 0.037 mmol), N-methylmorpholine (18 ul, 0.16 mmol) and TBTU (13 mg, 0.041 mol) were added to CH2Cl2 (2 ml) and the reaction mixture was stirred at 30 °C for 1.5 h. To the mixture were N^6-acetyl-D-lysine (14 mg, 0.074 mmol) and DMF (5 drops) added and the mixture was stirred at ambient temperature. overnight. The solvent was evaporated under reduced pressure and methanol (2 ml) and NaBH4 (30 mg, 0.79 mmol) were added to the residue. The reaction mixture was stirred at ambient temperature for 1 h.. A small amount of ammoniumacetate buffer was added and the methanol was evaporated off. The residue was purified by preparativ HPLC using acetonitril/ammonium acetat buffer (40:60) as eluent. The collected fractions were lyophilized, solved in tert-butanol and lyophilized again to obtain 4 mg (15 % 2 steps) of the title compound. (^{1}H-NMR, 400 MHz, DMSO-d_6): 1.2-1.8 (m, 11H), 2.85-2.95 (m, 2H), 3.7-3.8 (m, 2H), 4.0-4.1 (bs, 1H), 4.25-4.3 (m, 1H), 4.5 (s, 2H), 4.7-4.8 (m, 1H), 5.05 (dd, 1H), 6.95-7.4 (m, 12H), 7.7-7.8 (m, 1H), 7.95-8.05 (m, 1H, 8.25-8.3 (m, 1H)

Example 3

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanyl-D-phenylalanine

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanine (12 mg, 0.022 mmol), *tert*-butyl D-phenylalaninate hydrochloride (7 mg, 0.028 mmol) and 4-methylmorpholine (7mg, 0.065 mmol were dissolved in 0.5 ml DCM. The mixture was stirred at room temperature for 5 minutes. TBTU (9 mg, 0.028mmol) was added and the reaction mixture was stirred overnight and then purified on silica (2g), first with DCM and then with DCM:MeOH, 10:1 as eluent. The fractions containing the product were concentrated and formic acid (1 ml) was added and the solution was stirred overnight. The formic acid was evaporated whereafter residual formic acid was removed by addition of toluene and evaporation. The residue was stirred in methanol: triethylamine, 40:1, (2 ml) for 2.5 days (hydrolysis of the formed formic acid ester), the mixture wasconcentrated and the residue was purified by preparative HPLC using a gradient from 20 % to 100% CH3CN in 0.1% ammonium acetate buffer as eluent. Freeze-drying gave 7.3 mg (48 %) of the title product. M/z: 702.3 (M - 1), NMR (DMSO, 400 MHz): 1.18 (d,3H), 2.85-2.96 (m,3H), 3.00-3.07 (m,1H), 4.05-4.12 (m,1H), 4.19-4.32 (m,2H), 4.48 (dd,2H), 4.68-4.76 (m,1H), 5.0-5.07 (m,1H), 6.89-6.95 (m,2H), 7.05-7.17 (m,10H), 7.19-7.25 (m,2H), 7.30-7.36 (m,4H), 7.65-7.75 (m,1H),8.12-8.18 (m,1H).

Example 4

N^2-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]-D-lysine

(2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (10 mg, 0.016mmol), *tert*-butyl N^6-(*tert*-butoxycarbonyl)-D-lysinate hydrochloride (7mg, 0.021mmol) and N-methylmorpholine (5mg, 0.048mmol) were dissolved in DCM (0.5ml). The mixture was stirred and after 5 min TBTU (7mg, 0.021) was added and the reaction mixture was stirred for two hours. The product was purified on a silica plug with DCM:MeOH, 100:5 as the eluent.

Formic acid (0.5ml) was added to the purified product and the mixture was stirred two hours at 40 °C and then at ambient temperature overnight. The formic acid was removed under reduced pressure and toluene was added whereafter the solvent was removed. The residue was dissolved in MeOH and a small amount of triethylamine and stirred overnight at ambient temperature. The product was purified by preparative HPLC (CH3CN/ 0.1%ammonium acetate 20:80-100:0). The fractions containing the product were lyophilized and 4.0mg (33%) of the title compound was obtained. M/z: 745.4 (M - 1). NMR (DMSO, 400 MHz): 1.19-2.30 (m,2H), 1.30-1.40 (m,2H), 1.40-1.52 (m,2H), 1.52-1.68 (m,2H), 2.63-2.75 (m,2H), 2.83-2.95 (m,2H), 3.7-3.8 (m,1H), 4.28 (dd,1H), 4.60 (dd, 2H), 4.68-4.76 (m,1H), 5.04 (dd,1H), 5.48 (d,1H), 6.95 (d, 2H), 7.05-7.17 (m,4H), 7.19-7.28 (m,5H), 7.30-7.40 (m,6H), 7.88 (d,1H), 8.55 (d,1H).

Example 5

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-tryptophyl-D-phenylalanine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-tryptophan (0.015 g, 0.022 mmol) was dissolved in CH_2Cl_2 (2 ml). H-D-Phe-OTBU hydrochloride (0.007 g, 0.027 mmol) and N-Methylmorpholine (0.007 g, 0.067 mmol) were added. After 10 minutes TBTU (0.009 g, 0.029 mmol) was added. The reaction mixture was stirred at room temperature for 2h. The mixture was then passed through a short pad of silica gel and eluted with EtOAc/CH_2Cl_2 25/75. The pure fractions were collected and concentrated. The resulting tert-butyl ester was hydrolysed by the addition of formic acid (0.5 ml) followed by stirring at room temperature overnight. The resulting product was concentrated and dissolved in 2 ml of MeOH. Et3N (0.1ml) was added in order to hydrolyze the formylated product. The mixture was allowed to stir overnight. The solvent was evaporated and the residue was purified by preparative HPLC using a gradient of 20-60% CH_3CN in 0.1 M NH_4OAc buffer as mobile phase. Freeze-drying afforded the title product (0.004 g, 22%) as a colourless solid. M/z: 817.3 (M - 1). ^1H NMR (CD_3CN, 400 MHz) δ 2.82-3.20 (m, 6H), 4.07-4.15 (m, 1H), 4.29-4.39 (m, 2H), 4.54-4.89 (m, 4H), 6.74-7.53 (m, 22H), 9.14-9.20 (m, 1H).

Example 6

***N*-((2*R*)-2-{[(4-{(2*R*,3*R*)-3-[(2-hydroxy-2-phenylethyl)thio]-4-oxo-1-phenylazetidin-2-yl}phenoxy)acetyl]amino}-2-phenylacetyl)glycine**

[4-((2*R*,3*R*)-3-{[(5,5-Dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-4-oxo-1-phenylazetidin-2-yl)phenoxy]acetic acid (0.050 g, 0.094 mmol) was dissolved in CH_2Cl_2 (5 ml). *tert*-Butyl *N*-[(2*R*)-2-amino-2-phenylacetyl]glycinate (0.030 g, 0.112 mmol) and N-methylmorpholine (0.028 g, 0.281 mmol) were added. After 5 minutes TBTU (0.039 g, 0.122 mmol) was added. After 1h, HPLC showed a full conversion to the corresponding tert-butylester. The reaction mixture was purified by chromatography on silica gel and eluted with EtOAc/CH_2Cl_2 (25/75). Pure fractions were collected and concentrated. The residue was dissolved in 3 ml CH_2Cl_2 and 1 ml trifluoroacetic acid was added. The reaction mixture was allowed to stir at room temperature for 2h after which the resulting acid was concentrated in vacuo. The remaining TFA was removed through co-evaporation with toluene (2 ml). The acid was dissolved in 3 ml of MeOH and sodiumborohydride (10 mg, 0.264 mmol) was added. After 5 minutes, HPLC showed a full conversion to the corresponding alcohol. The reaction was quenched by the addition of 1 ml of 0.1M NH_4OAc buffer followed by concentration of the mixture. Purification by preparative HPLC of the residue using a gradient of 20-60% CH_3CN in 0.1 M NH_4OAc buffer as mobile phase and lyophilisation afforded the title product (0.032 g, 54%) as a colourless solid. M/z: 638.5 (M - 1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.90-2.94 (m, 2H), 3.45-3.65 (m, 2H), 4.25-4.27 (m, 1H), 4.59 (d, 1H), 4.64 (d, 1H), 4.68-4.75 (m, 1H), 5.02-5.05 (m, 1H), 5.57 (d, 1H), 6.94-7.41 (m, 19H), 8.28 (s, br, 1H), 8.55 (d, 1H).

Example 7

***N*-[(4-{(2*R*,3*R*)-3-[(2-hydroxy-2-phenylethyl)thio]-4-oxo-1-phenylazetidin-2-yl}phenoxy)acetyl]glycyl-D-phenylalanine**

N-[(4-{(2*R*,3*R*)-4-Oxo-3-[(2-oxo-2-phenylethyl)thio]-1-phenylazetidin-2-yl}phenoxy)acetyl]glycine was dissolved in CH_2Cl_2 (3 ml). (R)-Phenylalanine tert-butyl ester hydrochloride (0.012 g, 0.045 mmol) and N-methylmorpholine (0.011 g, 0.113 mmol) were added. After 5 minutes TBTU (0.016 g, 0.049 mmol) was added. After 1 h, full conversion to the corresponding tert-butyl ester was obtained. The reaction mixture purified by chromatography on silica gel and eluted with EtOAc/ CH_2Cl_2 25/75. Pure fractions were collected and concentrated. The residue was dissolved in 3 ml CH_2Cl_2 and 0.5 ml trifluoroacetic acid and the reaction was allowed to stir at room temperature overnight. The resulting acid was concentrated and dissolved in 3 ml of MeOH. Sodiumborohydride (0.010 g, 0.264 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 1 ml of 0.1M NH_4OAc buffer. Concentration followed by preparative HPLC using a gradient of 20-60% CH_3CN in 0.1M NH_4OAc buffer as mobile phase afforded the title product (0.021 g, 84%) as a colourless solid after freeze-drying. M/z: 652.3 (M - 1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.85-3.05 (m, 4H), 3.62-3.80 (m, 2H), 4.18-4.35 (m, 2H), 4.48 (d, 1H), 4.51 (d, 1H), 4.68-4.78 (m, 1H), 4.99-5.03 (m, 1H), 6.93-7.35 (m, 19H), 7.65-7.80 (m, 1H), 8.23-8.29 (m, 1H).

Example 8

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]-L-alanine**

(2*R*)-({[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.040 g, 0.065 mmol) was dissolved in CH_2Cl_2 (5 ml). *tert*-Butyl L-alaninate hydrochloride (0.014 g, 0.078 mmol) and

N-methyl-morphiline (0.020 g, 0.195 mmol) were added. After 5 minutes TBTU (0.027 g, 0.084 mmol) was added. The reaction was allowed to stir for 1 h after which the resulting tert-butyl ester was purified by chromatography on silica gel and eluted with EtOAc/ CH_2Cl_2 25/75. Pure fractions were concentrated and dissolved in CH_2Cl_2 (4 ml) and trifluoroacetic acid (0.5 ml). After 1.5 h at room temperature, full conversion to the corresponding acid was obtained. The reaction mixture was concentrated and the residue of TFA was removed by co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.010 g, 0.260 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml). The mixture was concentrated and the residue was purified by preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as mobile phase. Freeze-drying afforded the title compound (0.020 g, 45%) as a colourless solid. M/z: 688.4 (M - 1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.30-2.35 (m, 3H), 2.86-2.94 (m, 2H), 3.15-3.31 (m, 1H), 4.26-4.28 (m, 1H), 4.59 (d, 1H), 4.64 (d, 1H), 4.70-4.76 (m, 1H), 5.04-5.07 (m, 1H), 5.46 (d, 1H), 6.94-7.36 (m, 17H), 8.43-8.55 (m, 2H).

Example 9

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]-D-alanine**

(2*R*)-({[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.040 g, 0.065 mmol) was dissolved in CH_2Cl_2 (5 ml). *tert*-Butyl D-alaninate hydrochloride (0.014 g, 0.078 mmol) and N-methyl-morphiline (0.020 g, 0.195 mmol) were added. After 5 minutes TBTU (0.027 g, 0.084 mmol) was added. The reaction was allowed to stir overnight and the resulting tert-butyl ester was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). The pure fractions were concentrated. The residue was dissolved in CH_2Cl_2 (4 ml) and trifluoroacetic acid (0.5 ml). After 1.5h at room temperature, full conversion to the corresponding acid was obtained. The reaction mixture was concentrated and the remaining TFA was removed

through co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.010 g, 0.260 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml). The mixture was concentrated and the residue was purified by preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as mobile phase. Freeze-drying gave the title compound (0.024 g, 54%) as a colourless solid. M/z: 688.6 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.10-1.24 (m, 3H), 2.89-2.94 (m, 2H), 3.99-4.08 (m, 1H), 4.26-4.30 (m, 1H), 4.60 (d, 1H), 4.64 (d, 1H), 4.70-4.78 (m, 1H), 5.02-5.08 (m, 1H), 5.53-5.56 (d, 1H), 6.94-7.40 (m, 17H), 8.39-8.59 (m, 2H).

Example 10

(2*R*)-{[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]amino}(phenyl)acetic acid

(2*R*)-({[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.040 g, 0.065 mmol) was dissolved in CH_2Cl_2 (5 ml) and *tert*-butyl (2*R*)-amino(phenyl)acetate (0.016 g, 0.078 mmol) and N-methyl-morphiline (0.020 g, 0.195 mmol) were added. After 5 minutes TBTU (0.027 g, 0.084 mmol) was added. The reaction was allowed to stir at room temperature for 3 h after which the resulting tert-butyl ester was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 25/75. Pure fractions were concentrated. The residue was dissolved in CH_2Cl_2 (3 ml) and TFA (0.5 ml). The reaction mixture was allowed to stir overnight at room temperature. The resulting acid was concentrated and the remaining trace of TFA was removed by co-evaporation with toluene (3 ml). The acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.010 g, 0.260 mmol) was added. After 5 minutes, full conversion to the corresponding alcohol was obtained. The reaction was quenched by the addition of 1 ml of 0.1M NH_4OAc buffer. Concentration followed by purification on preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as mobile phase and freeze-drying of the pure fractions

afforded the title compound (0.034 g, 70%) as a colourless solid. M/z: 750.4 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.88-2.94 (m, 2H), 4.23-4.29 (m, 1H), 4.56-4.65 (m, 2H), 4.70-4.78 (m, 1H), 4.91-5.06 (m, 2H), 5.65-5.75 (m, 1H), 6.93-7.42 (m, 22H), 8.54-8.69 (m, 2H).

Example 11

(2*S*)-{[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]amino}(phenyl)acetic acid

(2*R*)-({[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.040 g, 0.065 mmol) was dissolved in CH_2Cl_2 (5 ml). *tert*-Butyl (2*S*)-amino(phenyl)acetate (0.016 g, 0.078 mmol) and N-methyl-morphiline (0.020 g, 0.195 mmol) were added. After 5 minutes, TBTU (0.027 g, 0.084 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The resulting tert-butyl ester was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). The pure fractions were concentrated. The residue was dissolved in CH_2Cl_2 (3 ml) and TFA (0.5 ml). The reaction mixture was stirred overnight at room temperature. The resulting acid was concentrated and the remaining trace of TFA was removed by co-evaporation with toluene (3 ml). The acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.010 g, 0.260 mmol) was added. After 5 minutes, full conversion to the corresponding alcohol was obtained. The reaction was quenched by the addition of 1 ml of 0.1M NH_4OAc buffer. Concentration followed by purification on preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as mobile phase and freeze-drying of the pure fractions afforded the title compound (0.037 g, 76%) as a colourless solid. M/z: 750.6 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.87-2.94 (m, 2H), 4.25-4.28 (m, 1H), 4.58-4.78 (m, 3H), 5.01-5.07 (m, 2H), 5.65-5.74 (m, 1H), 6.94-7.39 (m, 22H), 8.53-8.72 (m, 2H).

Example 12

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]-D-serine**

(2*R*)-({[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.040 g, 0.065 mmol), *tert*-butyl *O*-(*tert*-butyl)-D-serinate hydrochloride (0.020 g, 0.078 mmol) and N-methyl-morpholine (0.020 g, 0.195 mmol) were dissolved in CH_2Cl_2 (5 ml) at room temperature. After 5 minutes, TBTU (0.027 g, 0.084 mmol) was added. After 1h, full conversion to the corresponding tert-butyl ester was obtained. The reaction mixture was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). Pure fractions were collected and concentrated. The residue was dissolved in 3 ml CH_2Cl_2 and 1 ml TFA. The reaction mixture was stirred for 1.5h and concentrated. The remaining trace of TFA was azeotropically removed by co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.010 g, 0.260 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). Purification on preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as mobile phase followed by freeze-drying of the pure fractions afforded the title compound (0.032 g, 71%) as a colourless solid. M/z: 704.7 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.88-2.94 (m, 2H), 3.42-3.46 (m, 1H), 3.58-3.61 (m, 1H), 3.85-3.90 (m, 1H), 4.26-4.29 (m, 1H), 4.59 (d, 1H), 4.64 (d, 1H), 4.70-4.77 (m, 1H), 5.04-5.07 (m, 1H), 5.57-5.65 (m, 1H), 6.95-7.41 (m, 17H), 8.08-8.20 (m, 1H), 8.53-8.56 (m, 1H).

Example 13

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]-L-threonine**

(2*R*)-({[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.030 g, 0.049 mmol), *tert*-butyl

O-(*tert*-butyl)-L-threoninate (0.014 g, 0.058 mmol) and N-methyl-morpholine (0.015 g, 0.146 mmol) were dissolved in CH_2Cl_2 (4 ml). After 5 minutes, TBTU (0.020 g, 0.063 mmol) was added. Full conversion to the corresponding tert-butyl ester was obtained after 1 h. The reaction mixture was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). Pure fractions were collected and concentrated. The residue was dissolved in 3 ml CH_2Cl_2 and 1 ml TFA and the mixture was stirred for 1.5 h. The resulting acid was concentrated. The remaining trace of TFA was azeotropically removed by co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.007 g, 0.195 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). Purification by preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as eluent followed by freeze-drying of the pure fractions afforded the title compound (0.025 g, 71%) as a colourless solid. M/z: 721.1. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.69 (d, 3H), 2.88-2.93 (m, 2H), 3.79-3.85 (m, 1H), 3.96-4.01 (m, 1H), 4.27-4.30 (m, 1H), 4.60 (d, 1H), 4.64 (d, 1H), 4.71-4.79 (m, 1H), 5.02-5.08 (m, 1H), 5.65-5.69 (m, 1H), 6.95-7.42 (m, 17H), 8.01-8.09 (m, 1H), 8.51-8.59 (m, 1H).

Example 14

N^2-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]-L-asparagine

(2*R*)-({[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.030 g, 0.049 mmol), *tert*-butyl L-asparaginate hydrochloride (0.013 g, 0.058 mmol) and N-methyl-morpholine (0.015 g, 0.146 mmol) were dissolved in CH_2Cl_2 (4 ml). TBTU (0.020 g, 0.063 mmol) was added after 5 minutes. Full conversion to the corresponding tert-butyl ester was obtained after 1 h. The reaction mixture was purified on silica gel and eluted with EtOAc. The pure fractions were collected and concentrated. The residue was dissolved in 3 ml CH_2Cl_2 and 1 ml TFA and the mixture was stirred for 0.5h. The resulting acid was concentrated. The remaining trace of

TFA was azeotropically removed by co-evaporation with toluene (3 ml). The crude acid was dissolved MeOH (3 ml) and $NaBH_4$ (0.007 g, 0.195 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). Purification by preparative HPLC using a gradient of 20-40% CH_3CN in 0.1M NH_4OAc buffer as eluent followed by freeze-drying of the pure fractions afforded the title compound (0.024 g, 67%) as a colourless solid. M/z: 731.6 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.16-2.23 (m, 1H), 2.32-2.42 (m, 1H), 2.87-2.95 (m, 2H), 4.20-4.30 (m, 2H), 4.59-4.78 (m, 3H), 5.03-5.07 (m, 1H), 5.54-5.59 (m, 1H), 6.68-6.73 (m, 1H), 6.94-7.38 (m, 17H), 7.78-7.83 (m, 1H), 8.22-8.37 (m, 1H), 8.50-8.58 (m, 1H).

Example 15

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]-L-aspartic acid**

(2*R*)-({[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.020 g, 0.032 mmol), di-*tert*-butyl L-aspartate hydrochloride (0.011 g, 0.039 mmol) and N-methyl-morpholine (0.010 g, 0.097 mmol) were dissolved in CH_2Cl_2 (3 ml). After 5 minutes, TBTU (0.014 g, 0.042 mmol) was added. Full conversion to the corresponding tert-butyl ester was obtained after 1 h. The reaction mixture was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). The pure fractions were collected and concentrated. The residue was dissolved in 3 ml of CH_2Cl_2 and 1 ml of TFA. The reaction mixture was stirred for 2h and the resulting acid was concentrated. The remaining trace of TFA was azeotropically removed by co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.005 g, 0.130 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). Purification by preparative HPLC using a gradient of 10-40% CH_3CN in 0.1M NH_4OAc buffer as eluent followed by freeze-drying of the pure fractions afforded the title compound (0.018 g, 76%) as a colourless solid. M/z: 715.7 (M-18). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.00-2.08 (m, 1H), 2.31-2.50 (m, 1H), 2.88-2.94 (m, 2H), 4.18-4.22 (m, 1H), 4.27-4.30 (m, 1H), 4.60-4.78 (m,

3H), 5.03-5.08 (m, 1H), 5.55-5.65 (m, 1H), 6.94-7.40 (m, 17H), 8.22-8.39 (m, 1H), 8.50-8.59 (m, 1H).

Example 16

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]-D-valine**

(2*R*)-({[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.010 g, 0.016 mmol), *tert*-butyl D-valinate hydrochloride (0.004 g, 0.020 mmol) and N-methyl-morpholine (0.005 g, 0.049 mmol) were dissolved in CH_2Cl_2 (3 ml).After 5 minutes, TBTU (0.007 g, 0.021 mmol) was added. Full conversion to the corresponding tert-butyl ester was obtained after 1h. The reaction mixture was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). The pure fractions were collected and concentrated. The residue was dissolved in 3 ml CH_2Cl_2 and 0.5 ml TFA. The reaction mixture was stirred for 1.5 h and concentrated. The remaining trace of TFA was azeotropically removed by co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (2 ml) and $NaBH_4$ (0.002 g, 0.065 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). Purification by preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as mobile phase followed by freeze-drying of the pure fractions afforded the title compound (0.004 g, 34%) as a colourless solid. M/z: 716.6 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.81-0.85 (m, 6H), 1.98-2.09 (m, 1H), 2.88-2.93 (m, 2H), 3.92-3.98 (m, 1H), 4.22-4.30 (m, 1H), 4.60 (d, 1H), 4.64 (d, 1H), 4.70-4.78 (m, 1H), 5.02-5.07 (m, 1H), 5.62 (d, 1H), 6.94-7.40 (m, 17H), 8.18-8.22 (m, 1H), 8.52 (d, 1H).

Example 17

N-[(2R)-2-({[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)-2-phenylacetyl]-L-valine

(2R)-({[4-((2R,3R)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid (0.020 g, 0.032 mmol), *tert*-butyl L-valinate hydrochloride (0.008 g, 0.039 mmol) and N-methyl-morpholine (0.010 g, 0.097 mmol) were dissolved in CH_2Cl_2 (4 ml). After 5 minutes, TBTU (0.014 g, 0.042 mmol) was added. Full conversion to the corresponding tert-butyl ester was obtained after 1 h. The reaction mixture was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). The pure fractions were collected and concentrated. The residue was dissolved in 3 ml CH_2Cl_2 and 1 ml TFA. The reaction mixture was stirred for 1.5h and concentrated. The remaining trace of TFA was azeotropically removed by co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.005 g, 0.130 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). Purification by preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as eluent followed by freeze-drying of the pure fractions afforded the title compound (0.011 g, 47%) as a colourless solid. M/z: 716.5 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.60 (d, 3H), 0.68 (d, 3H), 1.95-2.05 (m, 1H), 2.88-2.94 (m, 2H), 4.00-4.08 (m, 1H), 4.27-4.30 (m, 1H), 4.61 (d, 1H), 4.64 (d, 1H), 4.70-4.78 (m, 1H), 5.02-5.09 (m, 1H), 5.64-5.75 (m, 1H), 6.94-7.44 (m, 17H), 8.39-8.45 (m, 1H), 8.50-8.58 (m, 1H).

Example 18

N-((2R)-2-{[(4-{(2R,3R)-3-[(2-hydroxy-2-phenylethyl)thio]-4-oxo-1-phenylazetidin-2-yl}phenoxy)acetyl]amino}-2-phenylacetyl)-L-serine

[4-((2*R*,3*R*)-3-{[(5,5-Dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-4-oxo-1-phenylazetidin-2-yl)phenoxy]acetic acid (0.030 g, 0.056 mmol), *tert*-butyl *N*-[(2*R*)-2-amino-2-phenylacetyl]-*O*-(*tert*-butyl)-L-serinate (0.024 g, 0.068 mmol) and N-methyl-morpholine (0.017 g, 0.169 mmol) were dissolved in CH_2Cl_2 (5 ml). After 5 minutes, TBTU (0.023 g, 0.073 mmol) was added. Full conversion to the corresponding tert-butyl ester was obtained after 1 h. The reaction mixture was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). The pure fractions were collected and concentrated. The residue was dissolved in 3 ml CH_2Cl_2 and 1 ml TFA. The reaction mixture was stirred overnight and concentrated. The remaining trace of TFA was azeotropically removed by co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (4 ml) and $NaBH_4$ (0.009 g, 0.225 mmol) ws added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). Purification by preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as mobile phase followed by freeze-drying of the pure fractions afforded the title compound (0.022 g, 58%) as a colourless solid. M/z: 668.5 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.89-2.94 (m, 2H), 3.30-3.35 (m, 1H), 3.46-3.50 (m, 1H), 3.94-4.00 (m, 1H), 4.25-4.27 (m, 1H), 4.60 (d, 1H), 4.65 (d, 1H), 4.69-4.77 (m, 1H), 5.00-5.05 (m, 1H), 5.59-5.66 (m, 1H), 6.94-7.39 (m, 19H), 8.20-8.25 (m, 1H), 8.50-8.58 (m, 1H).

Example 19

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanyl-D-valine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanine (0.040g, 0.072 mmol) was dissolved in CH_2Cl_2 (5 ml). *tert*-Butyl D-valinate hydrochloride (0.018 g, 0.087 mmol), N-methylmorpholine (0.022 g, 0.216 mmol) and TBTU (0.030 g, 0.094 mmol) were added. The *tert*-butyl ester was obtained after 1.5 h. The reaction mixture was purified on silica gel and eluted with CH_2Cl_2/EtOAc (75/25). The pure fractions were collected and concentrated. The residue was dissolved in CH_2Cl_2 (4

ml) and TFA (1 ml). The reaction mixture was stirred for 3 h and concentrated. The crude acid was dissolved in MeOH (4 ml) and $NaBH_4$ (0.011 g, 0.289 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml). The reaction mixture was concentrated and the residue was purified by preparative HPLC using an eluent of 20-50% CH_3CN in 0.1M NH_4OAc buffer. This gave the title compound (0.039 g, 82%) as a colourless solid. M/z: 654.5 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.79 (d, 6H), 1.21 (d, 3H), 1.96-2.05 (m, 1H), 2.85-2.95 (m, 2H), 3.91-3.97 (m, 1H), 4.22-4.29 (m, 1H), 4.35-4.42 (m, 1H), 4.48 (d, 1H), 4.53 (d, 1H), 4.70-4.78 (m, 1H), 5.02-5.04 (m, 1H), 6.94-7.36 (m, 12H), 7.70-7.77 (m, 1H), 8.15 (d, 1H).

Example 20

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanyl-D-alanine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanine (0.040g, 0.072 mmol) was dissolved in CH_2Cl_2 (5 ml). *tert*-Butyl D-alaninate hydrochloride (0.016 g, 0.087 mmol), N-methylmorpholine (0.022 g, 0.216 mmol) and TBTU (0.030 g, 0.094 mmol) were added. Full conversion to the *tert*-butyl-ester was obtained after 1.5 h. The reaction mixture was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). The pure fractions were collected and concentrated. The residue was dissolved in CH_2Cl_2 (3 ml) and TFA (1 ml). Full conversion to the acid was obtained after 2 h at room temperature. The reaction mixture was concentrated and the remaining trace of TFA was azeotropically removed by co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.011 g, 0.289 mmol) was added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml). The reaction mixture was concentrated and the

residue purified by preparative HPLC using a gradient of 20-50% CH_3CN in 0.1M NH_4OAc buffer as mobile phase. Freeze-drying of the pure fractions gave the title compound (0.039 g, 86%) as a colourless solid. M/z: 626.4 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.17-1.22 (m, 6H), 2.82-2.96 (m, 2H), 3.90-3.98 (m, 1H), 4.25-4.35 (m, 2H), 4.48-4.54 (m, 2H), 4.70-4.78 (m, 1H), 5.02-5.06 (m, 1H), 6.94-7.37 (m, 12H), 7.85-7.92 (m, 1H), 8.16 (d, 1H).

Example 21

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanyl-D-lysine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanine (0.040g, 0.072 mmol) was dissolved in CH_2Cl_2 (5 ml). *tert*-Butyl N^6-(*tert*-butoxycarbonyl)-D-lysinate hydrochloride (0.029 g, 0.087 mmol), *N*-methylmorpholine (0.022 g, 0.216 mmol) and TBTU (0.030 g, 0.094 mmol) were added. After 1.5 h full conversion to the ester was obtained. The reaction mixture was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). The pure fractions were collected and concentrated. The residue was dissolved in CH_2Cl_2 (3 ml) and TFA (1 ml) and stirred overnight and the corresponding acid was formed. The reaction mixture was concentrated and the remaining trace of TFA was azeotropically removed by co-evaporation with toluene (3 ml). The crude acid was dissolved in MeOH (3 ml) and $NaBH_4$ (0.011 g, 0.288 mmol) was added. The reduction was completed after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml). The mixture was concentrated and the residue purified by preparative HPLC using a gradient of 10-50% CH_3CN in 0.1M NH_4OAc buffer as eluent. Freeze-drying of the pure fractions afforded the title compound (0.039 g, 79%) as a colourless solid. M/z: 685.1. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.21 (d, 3H), 1.22-1.69 (m, 6H), 2.62-2.70 (m, 2H), 2.82-2.93 (m, 2H), 3.78-3.84 (m, 1H), 4.22-4.33 (m, 2H), 4.48 (d, 1H), 4.52 (d, 1H), 4.70-4.78 (m, 1H), 5.01-5.06 (m, 1H), 6.95-7.37 (m, 12H), 7.56-7.63 (m, 1H), 8.27 (d, 1H).

Example 22

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valyl-D-serine**

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valine (11 mg, 18.9 μmol) was dissolved in DCM (2 ml). *tert*-Butyl *O*-(*tert*-butyl)-D-serinate hydrochloride (6.3 mg, 24.8 μmol) and *N*-methylmorpholine (10 μl, 91 μmol) were added. After 5 minutes, TBTU (8.2 mg, 25.5 μmol) was added and the reaction mixture, a white suspension, was stirred overnight. The formation of the ester was confirmed. M/z: 780.5 (M-H). The solvent was removed under reduced pressure. The residue was dissolved in formic acid (1 ml) and stirred at 50°C for 5 h and at ambient temperature overnight. LC-MS analysis showed the formation of the formiate adduct of the product. M/z: 698.2 (M+H) and 696.2 (M-H). The formic acid was removed under reduced pressure, toluene (3x1 ml) was used to assist this removal. The yellowish oily residue was dissolved in methanol (1 ml) and triethylamine (150 μl, 0.12 mmol) was added. The reaction mixture was stirred for 1 h. The formiate was hydrolyzed; M/z: 670.1 (M+1) and 668.0 (M-1). Sodium borohydride (8.4 mg, 0.22 mmol) was added to the methanol solution. The mixture was stirred for 5 minutes. Ammonium acetate (7 mg) was added and the solvent was removed under reduced pressure. The residue was purified with preparative HPLC on a C8 column. A gradient from 20 to 50 % MeCN in 0.1M ammonium acetate buffer was used as eluent. After freeze-drying, the title compound was obtained as a white solid (3.8 mg, 30 %). H-NMR (400 MHz, DMS-d_6): 0.80 (m, 6H), 1.95-2.05 (m, 1H), 2.87-2.93 (m, 2H), 3.46-3.60 (m, 2H), 3.86 (brs, 1H), 4.19-4.32 (m, 2H), 4.59 (br, 2H), 4.69-4.77 (m, 1H), 5.05 (m, 1H), 6.96 (d, 2H), 7.06-7.18 (m, 4H), 7.20-7.26 (m, 2H), 7.30-7.39 (m, 4H), 7.70-7.77 (brs, 1H), 7.96-8.01 (d, 1H). M/z: 670.1(M-H).

Example 23

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine (0.022 g, 0.034 mmol) was dissolved in methanol (2 ml). $NaBH_4$ (0.0025 g, 0.066 mmol) was added and when the reaction was complete according to LC-MS a few drops of acetic acid was added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 35% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.015 g (68 %) of the title product was obtained. NMR (400 MHz,CD_3COOD) 0.90 (d, 3H), 0.93 (d, 3H), 2.10-2.20 (m, 1H), 2.90-3.06 (m, 2H), 3.99 (s, 2H), 4.03 (d, 0.5H), 4.05 (d, 0.5H), 4.27-4.34 (m, 1H), 4.60 (s, 2H), 4.79-4.84 (m,1H), 4.89 (d, 0.5H), 4.91 (d, 0.5H), 6.95-7.03 (m, 4H), 7.06 (d, 2H), 7.25-7.30 (m, 2H); 7.30-7.37 (m, 4H).

Example 24

(2R)-cyclohexyl[(N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino]acetic acid

(2R)-cyclohexyl[(N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino]acetic acid (0.0085 g, 0.013 mmol) was dissolved in methanol (2 ml). $NaBH_4$ (0.006 g, 0.159 mmol) was added and when the reaction was complete according to LC-MS a few drops of acetic acid was added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a stepwise gradient of 35%, 40% then 50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.007 g (82 %) of the title product was obtained. NMR (500 MHz,CD_3COOD) 1.05-1.33 (m, 5H), 1.60-1.87 (m, 6H), 2.91-3.07 (m, 2H), 3.94-4.06 (m, 3H), 4.32 (d, 1H),4.60 (s, 2H), 4.79-4.86 (m,1H), 4.90 (d,

0.5H), 4.92 (d, 0.5H), 6.96-7.03 (m, 4H), 7.03-7.08 (brd, 2H), 7.25-7.31 (m, 2H), 7.31-7.38 (m, 4H)

Example 25

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-(trimethylsilyl)alanine**

Ethyl 3-(trimethylsilyl)alaninate (20mg, 0.106mmol) was dissolved in 1.5ml Et_3N, 0.2ml MeOH and 0.2ml H_2O and stirred for 5 days. The solvent was evaporated under reduced pressure at 40°C. Et_3N, 1ml, was added and evaporated. *N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (20mg, 0.037mmol) was dissolved in 1.5ml dry DMF. N-Methylmorpholine (0.010ml, 0.109mmol) and TBTU (15mg, 0.047mmol) were added and the mixture was stirred for 1.5h. The Et_3N-salt of the above hydrolyzed amino acid was added and the mixture was stirred for 3h. A few drops of water were added and the mixture was stirred for 15 min. MeOH (2ml) and $NaBH_4$ (ca 15mg) were added. After 15 min ca 20mg NH_4Ac was added. The mixture was left overnight and was purified using preparative HPLC on a C8 column. A gradient from 20-50% MeCN in 0.1M ammonium acetate was used as mobile phase. A pure product fraction was collected and lyophilized. Mass: 14.5mg. The solid was placed in the vacuum oven at 40°C for 5h. M/z: 684 (M-1). NMR (400 MHz, DMSO-*d6*): 8.23 (t, 1H), 7.88-7.98 (m, 1H), 7.30-7.38 (m, 4H), 7.20-7.25 (m, 2H), 7.05-7.18 (m, 4H), 6.98 (d, 2H), 5.02-5.07 (m, 1H), 4.67-4.76 (m, 1H), 4.51 (s, 2H), 4.24-4.33 (m, 1H), 4.05-4.15 (m, 1H), 3.65-3.80 (m, 2H), 2.82-2.98 (m, 2H), 0.85-1.03 (m, 2H), 0.04 (s, 9H).

Example 26

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-tyrosine

A mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.0227g, 0.042 mmol), (R)-tyrosine *tert*-butylester (0.0144g, 0.061 mmol), N-methylmorpholin (0.012 ml,0.111 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.018 g, 0.056 mmol) was added and the mixture was stirred overnight. Trifluoroacetic acid (0.65 ml) was added and after a couple of hours the hydrolysis was complete. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. After removing the solvent under reduced pressure the compound (M/z 704.1) was dissolved in methanol (2 ml). $NaBH_4$ (0.004 g, 0.105 mmol) was added and when the reaction was complete a few drops of acetic acid was added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 35% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.021 g (71 %) of the title product was obtained. NMR (400 MHz,CD_3COOD) 2.85-3.10 (m, 4H), 3.90 (ABq, 2H), 4.03 (d, 0.5H), 4.05 (d, 0.5H), 4.51 (dd, 1H),4.55 (ABq, 2H), 4.79-4.84 (m,1H), 4.89 (d, 0.5H), 4.90 (d, 0.5H), 6.62-6.67 (m, 2H), 6.95-7.05 (m, 8H), 7.25-7.37 (m, 6H)

Example 27

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-proline

A mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.0197g, 0.036 mmol), (R)-proline *tert*-butylester (0.0118 g, 0.069 mmol), N-methylmorpholin (0.012 ml,0.111 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.018 g, 0.056 mmol) was added and the

mixture was stirred overnight. Trifluoroacetic acid (0.65 ml) was added and after a couple of hours the hydrolysis was complete. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. After removing the solvent under reduced pressure the compound (M/z 638.08) was dissolved in methanol (2 ml). $NaBH_4$ (0.004 g, 0.106 mmol) was added and when the reaction was complete a few drops of acetic acid was added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 35% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.020 g (85 %) of the title product was obtained. NMR (400 MHz,CD_3COOD) 1.80-1.94 (m, 1H), 1.94-2.10 (m, 1.5H), 2.12-2.35 (m, 1.5H), 2.90-3.06 (m, 2H), 3.49-3.67 (m, 2H), 3.85 (d, 0.5H), 4.00-4.07 (m, 1.5H), 4.14-4.24 (m, 1H), 4.35 (dd, 0.5H), 4.41 (brd, 0.5H), 4.57 (s, 1H),4.59 (s, 1H), 4.78-4.84 (m,1H), 4.89 (d, 0.5H), 4.91 (d, 0.5H), 6.95-7.08 (m, 6H), 7.25-7.38 (m, 6H).

Example 28

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxylacetyl}glycyl-L-threonine

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-threonine (0.014 g, 0.022 mmol) was dissolved in methanol (2 ml). $NaBH_4$ (0.003 g, 0.079 mmol) was added and when the reaction was complete a few drops of acetic acid was added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 35% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.012 g (85 %) of the title product was obtained. NMR (400 MHz,CD_3COOD) 1.14 (d 3H), 2.91-3.07 (m, 2H), 4.00-4.08 (m, 3H), 4.21-4.30 (m, 1H), 4.35 (d, 1H), 4.60 (s, 2H), 4.78-4.85 (m, 1H), 4.89 (d, 0.5H), 4.91 (d, 0.5H), 6.96-7.03 (m, 4H), 7.04-7.08 (m, 2H), 7.24-7.38 (m, 6H).

Example 29

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-lysine

A mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.0209g, 0.039 mmol), *tert*-butyl N^6-(*tert*-butoxycarbonyl)-D-lysinate hydrochloride (0.0205 g, 0.060 mmol), N-methylmorpholin (0.012 ml,0.111 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.018 g, 0.056 mmol) was added and the mixture was stirred overnight. Trifluoroacetic acid (0.65 ml) was added and after a couple of hours the hydrolysis was complete. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. After removing the solvent under reduced pressure the compound (M/z 669.13) was dissolved in methanol (2 ml). $NaBH_4$ (0.005 g, 0.132 mmol) was added and when the reaction was complete a few drops of acetic acid was added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 35% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.020 g (83%) of the title product was obtained. NMR (400 MHz,CD_3COOD) 1.34-1.47 (m 2H), 1.56-1.74 (m, 3H), 1.84-1.93 (m, 1H), 2.84-3.07 (m, 4H), 3.94 (ABq, 2H), 4.02 (d, 0.5H), 4.05 (d, 0.5H), 4.27 (dd, 1H), 4.61 (s, 2H), 4.79-4.85 (m, 1H), 4.90 (d, 0.5H), 4.91 (d, 0.5H), 6.95-7.08 (m, 6H), 7.24-7.38 (m, 6H).

Example 30

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-asparagine

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-asparagine (0.020 g, 0.031 mmol) was dissolved in methanol (2 ml). $NaBH_4$ (0.004 g, 0.106 mmol) was added and when the reaction was complete according to LC-MS a few drops of acetic acid were added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using

35% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.016 g (80%) of the title product was obtained. NMR (400 MHz,CD_3COOD) 2.62 (dd 1H), 2.73 (dd, 1H), 2.90-3.07 (m, 2H), 3.89-4.08(m, 3H), 4.55 (dd, 1H), 4.60 (ABq, 2H), 4.78-4.85 (m, 1H), 4.90 (d, 0.5H), 4.92 (d, 0.5H), 6.96-7.09 (m, 6H), 7.24-7.38 (m, 6H).

Example 31

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-methionine

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-methionine (0.015 g, 0.022 mmol) was dissolved in methanol (2 ml). $NaBH_4$ (0.004 g, 0.106 mmol) was added and when the reaction was complete a few drops of acetic acid were added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 35% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.015 g (99%) of the title product was obtained. NMR (400 MHz,CD_3COOD) 1.86-2.00 (m, 1H), 2.04 (s, 3H); 2.07-2.18 (m, 1H),2.45-2.51 (m, 2H), 2.90-3.08 (m, 2H), 3.97 (s, 2H), 4.04 (d, 0.5H), 4.06 (d, 0.5H), 4.36-4.43 (m, 1H), 4.60 (s, 2H), 4.77-4.85 (m, 1H), 4.90 (d, 0.5H), 4.92 (d, 0.5H), 6.95-7.08 (m, 6H), 7.25-7.38 (m, 6H).

Example 32

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-hydroxy-2-(4-methoxyphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine (0.015g, 0.023 mmol) was dissolved in methanol (3 ml). $NaBH_4$ (0.006 g, 0.158 mmol) was added and when the reaction was complete a few drops of acetic acid were added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 25% MeCN in 0.1M

ammonium acetate buffer as eluent. After freeze-drying, 0.014 g (93%) of the title product was obtained. NMR (500 MHz,CD_3COOD) 0.93 (d, 3H), 0.95 (d, 3H), 2.12-2.22 (m, 1H), 2.91-3.07 (m, 2H), 3.75 (s, 1.5H), 3.76 (s, 1.5H), 3.94-4.06 (m, 3H), 4.33 (d, 1H), 4.60 (s, 2H), 4.72-4.78 (m, 1H), 4.81-4.88 (m, 1H), 6.79-6.83 (m, 2H), 6.97-7.08 (m, 4H), 7.20-7.36 (m, 6H).

Example 33

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-leucine

A mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.015g, 0.028 mmol), *tert*-butyl D-leucinate hydrochloride (0.010g, 0.045 mmol), N-methylmorpholin (0.0092 ml,0.083 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.012 g, 0.037 mmol) was added and the mixture was stirred overnight. Trifluoroacetic acid (1.0 ml) was added and after 2 h the solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. After removing the solvent under reduced pressure the compound (M/z 654.25) was dissolved in methanol (2 ml). $NaBH_4$ (0.005 g, 0.132 mmol) was added and the mixture was stirred for 5 minutes. A few drops of acetic acid was added and the solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 35% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.014 g (76 %) of the title product was obtained. NMR (400 MHz,CD_3COOD) 0.90-0.94 (m, 6H), 1.52-1.74 (m, 3H), 2.90-3.07 (m, 2H), 3.97 (s 2H), 4.02 (d, 0.5H), 4.04 (d, 0.5H), 4.40 (d, 0.5H), 4.42 (d, 0.5H), 4.59 (s, 2H), 4.78-4.84 (m, 1H), 4.89 (d, 0.5H), 4.91 (d, 0.5H), 6.95-7.08 (m, 6H), 7.24-7.37 (m, 6H).

Example 34

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-hydroxy-2-(4-methoxyphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-lysine

A mixture of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.0177g, 0.032 mmol *tert*-butyl N^6-(*tert*-butoxycarbonyl)-D-lysinate hydrochloride (0.0141 g, 0.042 mmol), N-methylmorpholin (0.0106 ml,0.096 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.013 g, 0.042 mmol) was added and the mixture was stirred for 2 h. Additional *tert*-butyl N^6-(*tert*-butoxycarbonyl)-D-lysinate hydrochloride (0.004 g, 0.012 mmol) was added and after 0.5 h. TBTU (0.008g, 0.025 mmol) was added and the mixture was stirred for additional 10 minutes. Trifluoroacetic acid (0. 65 ml) was added and after 3 h the solvent was removed under reduced pressure. The residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% 1M ammonium acetate buffer as eluent. After removing the solvents under reduced pressure, the intermediate (M/z 681.4) was dissolved in methanol (3 ml). $NaBH_4$ (0.008 g, 0.211mmol) was added and when the reaction was complete a few drops of acetic acid was added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 35% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.020 g (91 %) of the title product was obtained. NMR (500 MHz,CD_3COOD) 1.41-1.52 (m, 2H), 1.58-1.78 (m, 3H), 1.90-2.02 (m 1H), 2.86-3.08 (m, 4H), 3.76 (s, 1.5H), 3.77 (s, 1.5H), 3.90-4.06 (m, 3H), 4.48 (dd, 1H), 4.60-4.62 (m, 2H), 4.73-4.78 (m, 1H), 4.83-4.89 (m, 1H), 6.80-6.84 (m, 2H), 6.98-7.08 (m, 4H), 7.21-7.31 (m, 4H), 7.31-7.36 (m, 2H), 8.20 (d, NH), 8.54 (t, NH).

Example 35

N^2-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-glutaminyl-D-phenylalanine

N^2-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-glutamine (15mg, 0.0244 mmol), *tert*-butyl D-phenylalaninate hydrochloride (8 mg, 0.0310 mmol) and N-methylmorpholine (10 mg, 0.099 mmol) were dissolved in methylene chloride (0.5 ml). TBTU (10 mg, 0.0313 mmol) was added and the mixture was stirred for 1 h at room temperature. The solvent was evaporated and the residue was dissolved in formic acid (0.5 ml). The mixture was heated to 45-50 °C and stirred at this temperature for 6 h. The reaction mixture was evaporated under reduced pressure. Methanol (5 ml) was added and evaporated . The residue was dissolved in methanol (1 ml). Two drops of TEA was added and the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by preparative HPLC using acetonitrile/ammonium acetate buffer (40:60) as eluent. After freeze-drying 12 mg (64%) of the title compound was obtained. ^{1}H-NMR, 300 MHz, DMSO): 1.55-1.97 (m, 4H), 2.77-3.10 (m, 4H), 4.20-4.38 (m, 3H), 4.49 (s, 2H), 4.66-4.78 (m, 1H), 4.99-5.07 (m, 1H), 6.70 (s, 1H), 6.88-7.40 (m, 19H), 8.00-8.20 (m, 2H).

Example 36

N^2-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-glutaminyl-D-tyrosine

N^2-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-glutamine (22 mg, 0.0359 mmol), *tert*-butyl D-tyrosinate hydrochloride (10 mg, 0.0421 mmol) and N-methylmorpholine (14 mg, 0.138 mmol) were dissolved in methylene chloride (0.5 ml). TBTU (14 mg, 0.0436 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was dissolved in formic acid (1 ml). The mixture was stirred at 45-50 °C for 4 h and was then evaporated under reduced pressure. Methanol (10 ml) was added and evaporated. The residue was dissolved in methanol (2 ml). Three drops of TEA were added and the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by preparative HPLC using acetonitrile/ammonium acetate buffer (40:60) as eluent. After freeze-drying 15 mg (54%) of the title compound was obtained. ^{1}H-NMR, 300 MHz, DMSO): 1.60-2.00 (m, 4H), 2.69-3.0 (m, 4H), 4.09-4.18 (m, 1H), 4.22-4.35

(m, 3H), 4.49 (s, 2H), 4.65-4.78 (m, 1H), 4.97-5.08 (m, 1H), 6.56 (d, 2H), 6.70 (s, 1H), 6.86-7.40 (m, 18H), 7.77-7.91 (m, 1H), 8.12 (d, 1H), 9.10 (bs, 1H).

Example 37

***N*-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-cyclohexyl-D-alanine**

N-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (20mg, 0.0349 mmol) and *N*-methylmorpholine (20 mg, 0.198 mmol) were dissolved in methylene chloride (0.5 ml). TBTU (17 mg, 0.0530 mmol) was added and the mixture was stirred for 15 min at room temperature. 3-Cyclohexyl-D-alanine (9 mg, 0.0526 mmol) was added and the stirring was continued for 1 h at room temperature. The solvent was evaporated and the residue was dissolved in methanol (0.5 ml). NaBH4 (10 mg, 0.264 mmol) was added and the mixture was stirred for 15 min at room temperature. Three drops of acetic acid was added to the reaction mixture. The product was isolated by preparative HPLC using acetonitrile/ammonium acetate buffer (45:55) as eluent. After freeze-drying 3 mg (12%) of the title compound was obtained.The product was analyzed by LC/Micromass Q TOF micro MS technique. M/z: 728.1973 (calc. Mass 728.1964).

Example 38

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-cyclohexyl-D-alanine**

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (30 mg, 0.0555 mmol) and N-methylmorpholine (30 mg, 0.296 mmol) were dissolved in DMF (0.5 ml). TBTU (23 mg, 0.0717 mmol) was added and the mixture was stirred for 15 min at room temperature. 3-Cyclohexyl-D-alanine (15 mg, 0.0876 mmol) was added and the stirring was continued overnight at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in methanol (1 ml). NaBH4 (10 mg, 0.264 mmol) was added and the mixture was stirred for 10 min at room temperature. Three drops of acetic acid was added to the reaction mixture. The product was isolated by preparative HPLC using acetonitrile/ammonium acetate buffer (40:60) as eluent. After freeze-drying 19 mg (49%) of the title compound was obtained. ^{1}H-NMR, 300 MHz, DMSO): 0.68-0.93 (m, 2H), 1.0-1.75 (m, 11H), 2.78-3.00 (m, 2H), 3.73 (s, 2H), 4.00-4.14 (m, 1H), 4.23-4.35 (m, 1H), 4.51 (s, 2H), 4.65-4.78 (m, 1H), 4.99-5.09 (m, 1H), 6.90-7.44 (m, 12H), 7.72-7.86 (m, 1H), 8.26 (t,1H).

Example 39

_N_-{[4-((2_R_,3_R_)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-phenylalanine

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-phenylalanine (7mg, 0.010mmol) was dissolved in 1.5ml MeOH and $NaBH_4$ (2mg, 0.053mmol) was added. The mixture was stirred for 30 min and quenched with an excess of NH_4Ac. LC/MS showed ca 15% startingmaterial. The mixture was diluted with H_2O and purified using preparative chromatography on a C8 column (25x300mm). A gradient from 20% to 40% MeCN in 0.1M ammonium acetate was used as mobile phase. The product fraction was collected and partly concentrated. The mixture was lyophilized to yield 2mg (29%). M/z: 688 (M-1). NMR (400 MHz, MeOD): 6.95-7.36 (m, 17H), 4.90 (dd, 1H), 4.53-4.59 (m, 4H), 4.03 (dd, 1H), 3.90 (q, 2H), 3.17 (dd, 1H), 2.90-3.05 (m, 3H).

Example 40

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-4-methylleucine**

tert-Butyl *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio} -4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-4-methylleucinate (ca 26mg, 0.036mmol) was dissolved in 1.5 ml formic acid and heated at 40°C for 1.5 h. The formic acid was evaporated under reduced pressure. The intermediate acid was confirmed by LC/MS analysis. M/z: 668. The crude mixture was dissolved in 2 ml MeOH. $NaBH_4$ (15mg, 0.40mmol) was added and the mixture was stirred for 10 min. NH_4Ac (30mg) was added. The crude mixture was diluted with 1ml water and purified using preparative HPLC on a C8 column (50x300mm). A gradient from 20% to 40% MeCN in 0.1M ammonium acetate buffer was used as mobile phase. Lyophilization yielded 36mg white solid. NMR showed the presence of water and HOAc. The product was dried in the vacuum oven for 1.5h at 40°C. Mass 13mg (52%). M/z: 668 (M-1). NMR (400 MHz, DMSO): 8.22 (t, 1H), 7.53-7.65 (m, 1H), 7.30-7.38 (m, 4H), 7.20-7.25 (m, 2H), 7.05-7.17 (m, 4H), 6.98 (d, 2H), 5.02-5.06 (m, 1H), 4.68-4.76 (m, 1H), 4.51 (s, 2H), 4.24-4.32 (m, 1H), 4.01-4.09 (m, 1H), 3.60-3.77 (m, 2H), 2.82-2.98 (m, 2H), 1.64 (dd, 1H), 1.33 (dd, 1H), 0.83 (s, 9H).

Example 41

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-seryl-D-phenylalanine**

A solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-serine (diastereomeric mixture) (0.008 g, 0.014 mmol), D-phenylalanine tert-butyl ester hydrochloride (0.005 g, 0.018 mmol) and N-Methylmorpholine (0.006 ml, 0.055 mmol) in DCM (3 ml) was stirred at RT for 5 min.

TBTU (0.008 g, 0.025 mmol) was added. After 3 days the conversion to the ester (M/z: 776.1) was complete and the mixture was concentrated under reduced pressure. The residue was dissolved in formic acid (3 ml) and the solution was stirred for 25 h. The mixture was concentrated under reduced pressure and the residue was dissolved in MeOH (4ml) and TEA (1 ml). The solution was stirred at 40°C for 6 h. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.005 g (53 % yield) of the title product was obtained as a white solid. M/z: 720.1. 1H NMR (DMSO, 400 MHz): δ 2.78-2.96 (m, 3H), 3.03-3.11 (m, 1H), 3.44-3.60 (m, 2H), 4.20-4.36 (m, 3H), 4.51 (s, 2H), 4.67-4.76 (m, 1H), 5.01-5.06 (m, 1H), 5.70 (bs, 1H), 6.90-6.98 (m, 2H), 7.05-7.25 (m, 11H), 7.29-7.37 (m, 4H), 7.84-8.00 (m, 2H).

Example 42

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-seryl-D-serine**

A solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-serine (0.008 g, 0.014 mmol), O-tert-butyl-D-serine tert-butyl ester hydrochloride (0.005 g, 0.019 mmol) and N-Methylmorpholine (0.006 ml, 0.055 mmol) in DCM (3 ml) was stirred for 5 min. TBTU (0.008 g, 0.025 mmol) was added. After 3 days the conversion to the ester (M/z: 772.5) was complete and the mixture was concentrated under reduced pressure. The residue was dissolved in formic acid (3 ml) and the solution was stirred at RT for 26h. The mixture was concentrated under reduced pressure and the residue was dissolved in MeOH (4ml) and TEA (1 ml). The solution was stirred at 40°C for 6 h. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.005 g (52 % yield) of the title compound was obtained as a white solid. M/z: 660.1. 1H NMR (DMSO, 400 MHz): δ 2.83-2.95 (m, 2H), 3.42-3.66 (m, 4), 3.91-4.01 (m, 1H), 4.25-4.31 (m, 1H), 4.32-4.39 (m, 1H),

4.54 (ABq, 2H), 4.68-4.76 (m, 1H), 5.02-5.06 (m, 1H), 5.68 (bs, 1H), 6.94-7.00 (m, 2H), 7.05-7.18 (m, 4H), 7.19-7.26 (m, 2H), 7.29-7.39 (m, 4H), 7.74-7.81 (m, 1H), 7.99 (d, 1H).

Example 43

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-2-butylnorleucine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-2-butylnorleucine (0.009 g, 0.012 mmol) was dissolved in MeOH (3 ml). NaBH4 (0.007 g, 0.185 mmol) was added and the mixture was stirred for 10 min. Ammonium acetate buffer (0.1M, 3 ml) was added and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC, using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.008 g (94 % yield) of the title compound was obtained as a white solid. M/z: 712.1. ^{1}H NMR (DMSO, 400 MHz): δ 0.73-0.83 (m, 6H), 0.89-1.22 (m, 8H), 1.59-1.71 (m, 2H), 1.94-2.06 (m, 2H), 2.83-2.96 (m, 2H), 3.73 (d, 2H), 4.23-4.28 (m, 1H), 4.51 (s, 2H), 4.68-4.76 (m, 1H), 5.02-5.07 (m, 1H), 5.68 (bs, 1H), 6.94-7.00 (m, 2H), 7.05-7.18 (m, 4H), 7.19-7.26 (m, 2H), 7.29-7.39 (m, 4H), 7.53 (s, 1H), 8.30-8.36 (m, 1H).

Example 44

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-methyl-L-cysteine**

A solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.015 g, 0.028 mmol), *tert*-butyl *S*-methyl-L-cysteinate (0.014 g, 0.073 mmol)) and N-methylmorpholine (0.012 ml, 0.109 mmol) in DCM (5 ml) was stirred for 5 min. TBTU (0.013 g, 0.042 mmol) was added. After 20 h, the

conversion to the ester (M/z: 714.1) was complete and the mixture was concentrated under reduced pressure. The residue was dissolved in formic acid (3 ml) and the solution was stirred at 40°C for 22 h. The mixture was diluted with toluene (2 ml) and the solvent was again removed under reduced pressure. The residue was dissolved in MeOH (4 ml) and $NaBH_4$ was added in small portions to the solution (a total of 0.035 g, 0.925 mmol) until the reduction was complete. Ammonium acetate buffer (0.1M, 3 ml) was added and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC, using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.013 g (72 % yield) of the title compound was obtained as a white solid. M/z: 660.3. 1H NMR (DMSO, 400 MHz): δ 2.66-2.74 (m, 1H), 2.82-3.02 (m, 3H), 3.67-3.82 (m, 2H), 4.02-4.12 (m, 1H), 4.24-4.31 (m, 1H), 4.52 (s, 2H), 4.68-4.77 (m, 1H), 5.01-5.07 (m, 1H), 6.95-7.02 (m, 2H), 7.05-7.18 (m, 4H), 7.19-7.26 (m, 2H), 7.29-7.40 (m, 4H), 7.73-7.82 (m, 1H), 8.30-8.37 (m, 1H).

Example 45

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-isoleucine**

A solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.015 g, 0.028 mmol), L-isoleucine t-butyl ester hydrochloride (0.008 g, 0.036 mmol) and N-methylmorpholine (0.012 ml, 0.109 mmol) in DCM (5 ml) was stirred for 5 min. TBTU (0.012 g, 0.036 mmol) was added. After 22 h, the conversion to the ester (M/z: 710.2) was complete and the mixture was concentrated under reduced pressure. The residue was dissolved in formic acid (3 ml) and the solution was stirred at 40°C for 20h. The mixture was diluted with toluene (2 ml) and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (4 ml) and $NaBH_4$ was added in small portions to the solution (a total of 0.060 g, 1.59 mmol) until the reduction was complete. Ammonium acetate buffer (0.1M, 3 ml) was added and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC, using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.010 g (57 % yield) of the title compound was obtained as a white solid. M/z: 656.2. 1H

NMR (DMSO, 400 MHz): δ 0.76-0.84 (m, 6H), 1.05-1.17 (m, 1H), 1.32-1.44 (m, 1H), 1.67-1.78 (m, 1H), 2.82-2.95 (m, 2H), 3.78 (d, 2H), 4.03-4.11 (m, 1H), 4.23-4.29 (m, 1H), 4.51 (s, 2H), 4.68-4.77 (m, 1H), 5.01-5.07 (m, 1H), 6.94-7.01 (m, 2H), 7.05-7.26 (m, 6H), 7.29-7.39 (m, 4H), 7.79-7.89 (m, 1H), 8.22-8.28 (m, 1H).

Example 46

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-alanyl-D-valine**

A solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-alanine (0.015 g, 0.027 mmol), D-valine *tert*-butyl ester hydrochloride (0.008 g, 0.038 mmol) and *N*-methylmorpholine (0.030 ml, 0.272 mmol) in DCM (4 ml) was stirred for 5 min. TBTU (0.013 g, 0.041 mmol) was added. After 3 h, the conversion to the ester (M/z: 710.2) was completed and TFA (3 ml) was added. After 4h, the mixture was diluted with toluene (2 ml) and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (4 ml) and $NaBH_4$ was added in small portions to the solution (a total of 0.065 g, 1.72 mmol) until the reduction was complete. Ammonium acetate buffer (0.1M, 3 ml) was added and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC, using a gradient of 20-50% MeCN in a 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.014 g (77 % yield) of the title compound was obtained as a white solid. M/z: 656.1. 1H NMR (DMSO, 400 MHz): δ 0.75-0.83 (m, 6H), 1.22 (d, 3H), 1.95-2.07 (m, 1H), 3.83-3.96 (m, 2H), 3-98-4.06 (m, 1H), 4-24-4.31 (m, 1H), 4.40-4.54 (m, 3H), 4.67-4.76 (m, 1H), 5.01-5.07 (m, 1H), 6.91-7.98 (m, 2H), 7.05-7.17 (m, 4H), 7.19-7.25 (m, 2H), 7.29-7.39 (m, 4H), 7.84-7.95 (m, 1H). 8.07 (d, 1H),

Example 47

1-[(*N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino]cyclopentanecarboxylic acid

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.015 g, 0.028 mmol), NMM (0.012 ml, 0.109 mmol) and TBTU (0.011 g, 0.034 mmol) were dissolved in DMF (2 ml) at 30°C. After 30 min 1-amino-1-cyclopentanecarboxylic acid (0.004 g, 0.030 mmol, 97 %) was added and the mixture was stirred at 30°C for 1h. The reaction was quenched with water (0.2 ml) and the mixture was diluted with MeOH (2 ml). NaBH4 (0.015 g, 0.397 mmol) was added and the mixture was stirred for 10 min. Ammonium acetate buffer (0.1M, 3 ml) was added and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC, using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, the title compound (0.009 g, 49 % yield) was obtained as a white solid. M/z: 654.0. 1H NMR (DMSO, 400 MHz): δ 1.56-1.66 (m, 4H), 1.78-1.87 (m, 2H), 1.97-2.07 (m, 2H), 2.84-2.94 (m, 2H), 3.74 (d, 2H), 4.24-4.29 (m, 1H), 4.51 (s, 2H), 4.68-4.76 (m, 1H), 5.02-5.07 (m, 1H), 6.92-7.00 (m, 2H), 7.05-7.26 (m, 6H), 7.29-7.39 (m, 4H), 8.09-8.15 (m, 2H).

Example 48

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*N*-benzylglycine**

TBTU (0.011 g, 0.034 mmol) was added to a solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.015 g, 0.028 mmol) and NMM (0.020 ml, 0.182 mmol) in DMF (2 ml) at 30°C. After 30 min, *N*-benzylglycine (0.005 g, 0.030 mmol, 98 %) was added and the mixture was stirred at 30°C for 1h. The reaction was quenched with water (0.2 ml) and the mixture was diluted with MeOH (2 ml). $NaBH_4$ (0.015 g, 0.397 mmol) was added and the mixture was stirred for 10 min. Ammonium acetate buffer (0.1M, 3 ml) was added and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC, using a

gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, the title compound (0.010 g, 53 % yield) was obtained as a white solid. M/z: 690.0. 1H NMR (DMSO, 400 MHz): δ 2.83-2.94 (m, 2H), 3.91 (s, 1H), 3.98-4.09 (m, 3H), 4.25-4.29 (m, 1H), 4.50 (s, 2H), 4.54 (s, 1H), 4.62 (s, 1H), 4.68-4.76 (m, 1H), 5.02-5.07 (m, 1H), 6.92-7.02 (m, 2H), 7.05-7.40 (m, 15H), 8.14-8.21 (m, 1H).

Example 49

[(*N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino](diphenyl)acetic acid

TBTU (0.016 g, 0.050 mmol) was added to a solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.020 g, 0.037 mmol) and NMM (0.012 ml, 0.109 mmol) in DMF (2 ml) at 30°C. After 30min, 2,2-diphenylglycine (0.009 g, 0.037 mmol, 98 %) was added and the mixture was stirred at 30°C for 2.5 h. The reaction was quenched with water (0.2 ml) and the mixture was diluted with MeOH (2 ml). $NaBH_4$ (0.020 g, 0.529 mmol) was added and the mixture was stirred for 10 min. Ammonium acetate buffer (0.1M, 3 ml) was added and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC, using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, the title compound (0.012 g, 44 % yield) was obtained as a white solid. M/z: 752.0. 1H NMR (DMSO, 400 MHz): δ 2.83-2.95 (m, 2H), 3.75 (d, 2H), 4.24-4.28 (m, 1H), 4.54 (s, 1H), 4.68-4.75 (m, 1H), 5.02-5.06 (m, 1H), 6.95-7.03 (m, 2H), 7.04-7.38 (m, 20H), 8.43-8.51 (m, 1H), 8.90 (s, 1H).

Example 50

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycylglycine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycylglycine (0.011 g, 0.018 mmol) was dissolved in MeOH (3 ml). $NaBH_4$ (0.013 g, 0.344 mmol) was added and the mixture was stirred for 10 min. Ammonium acetate buffer (0.1M, 3 ml) was added and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC, using a gradient of 20-50% MeCN in a 0.1M ammonium acetate buffer as eluent. After freeze-drying, the title compound (0.011 g, 97 % yield) was obtained as a white solid. M/z: 600.0. 1H NMR (DMSO, 400 MHz): 2.97-2.84 (m, 2H), 3.44-3.50 (m, 2H), 3.74 (d, 2H), 4.26-4.32 (m, 1H), 4.46-4.54 (m, 2H), 4.67-4.76 (m, 1H), 5.02-5.07 (m, 1H), 6.95-7.01 (m, 2H), 7.05-7.26 (m, 6H), 7.30-7.40 (m, 4H), 7.60-7.80 (m, 1H), 8.32-8.38 (m, 1H).

Example 51

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valyl-L-serine

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valine (6.9 mg, 11.8 μmol) was dissolved in DCM (3 ml). *tert*-Butyl *O*-(*tert*-butyl)-L-serinate hydrochloride (3.7 mg, 14.2 μmol) and *N*-methylmorpholine (5.5 μl, 50 μmol) were added. After 5 minutes, TBTU (4.6 mg, 14.3 μmol) was added and the reaction mixture was stirred overnight. The formation of the ester was confirmed. M/z: 780.57 (M-1). The mixture was extracted between DCM (5 ml) and aqueous $KHSO_4$ (5 ml, pH of 2). The organic phase was washed with aqueous $NaHCO_3$ (5 ml, pH of 9). The aqueous phase was extracted with DCM (2x5 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. Formic acid (1.5 ml) was added and the reaction mixture was stirred overnight. The formiate of the intermediate acid was obtained. The solvent was removed under reduced pressure, toluene (3x1 ml) was added and evaporated. The residue was dissolved in MeOH (1.5 ml) and triethylamine (90 μl, 0.65 mmol) was added and the reaction mixture was stirred for 1 hour. Sodium borohydride (4.0 mg, 0.11 mmol) was added and the reaction mixture was stirred for 1 hour. Ammonium acetate (15 mg) was added. The solvent was removed under reduced pressure and the residue was purified on preparative

HPLC using a C8 column. A gradient from 20% to 50 % MeCN in 0.1M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (5.3 mg, 67 %). HRMS calcd for $C_{33}H_{35}F_2N_3O_8S$ 671.2113, found 672.2192 $[M+H]^+$.

Example 52

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valylglycine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valine (11.8 mg, 0.02 mmol), *tert*-butyl glycinate hydrochloride (4.6 mg, 0.03 mmol) and *N*-methylmorpholine (10 µl, 0.09 mmol) were dissolved in DCM (1.5 ml). After 5 minutes, TBTU was added and the reaction mixture was stirred for 3.5 h. The formation of the ester was confirmed. M/z: 694.0 (M-H). The mixture was extracted between DCM (3 ml) and aqueous $KHSO_4$ (5 ml, pH of 3). The aqueous phase was extracted with DCM (2x5 ml). The combined organic phases were washed with water (2x5 ml), dried over Na_2SO_4, filtered and concentrated. Formic acid (3 ml) was added and the solution was heated at 40°C overnight. The solvent was removed under reduced pressure, toluene was added and evaporated. The residue was dissolved in methanol (3 ml) and sodium borohydride (8.5 mg, 0.23 mmol) was added. The rection mixture was stirred for 15 minutes. The solvent was removed under reduced pressure. The residue was purified on preparative HPLC on a C8 column. A gradient from 20% to 50 % MeCN in 0.1M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (6.2 mg, 48 %). HRMS calcd for $C_{32}H_{33}F_2N_3O_7S$ 641.2007, found 642.2086 $[M+H]^+$.

Example 53

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valyl-L-valine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valine (11.5, 0.02 mmol), *tert*-butyl L-valinate hydrochloride (5.3 mg, 0.025 mmol) and *N*-methylmorpholine (10 µl, 0.091 mmol) were dissolved in DCM (1.5 ml). After 5 minutes, TBTU (7.8 mg, 0.024 mmol) was added and the reaction mixture was stirred overnight. Additional *tert*-butyl L-valinate hydrochloride (1.5 mg, 7.2 µmol), *N*-methylmorpholine (6.5 µl, 58 µmol) and TBTU (2.0 mg, 6.2µmol, 0.31 eq) were added and the mixture was stirred for 2.5 h. The formation of the ester was confirmed. M/z: 736.1 (M-H). The reaction mixture was extracted between aqueous $KHSO_4$ (5 ml, pH of 3) and DCM (5 ml). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in formic acid (2 ml) and heated at 40 °C overnight. The solvent was removed under reduced pressure. Toluene was added and removed under reduced pressure. The residue was dissolved in MeOH (2 ml) and sodium borohydride (8.1 mg, 0.21 mmol) was added. The mixture was stirred for 30 minutes. Ammonium acetate (16 mg) was added and the solvent was removed under reduced pressure. The residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 50 % MeCN in 0.1 M NH_4OAc buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (7.3 mg, 54 %) H-NMR (400 MHz, DMSO-d_6): 0.70 (d, 3H), 0.79 (d, 3H), 0.83 (d, 6H), 2.00 (m, 2H), 2.86-2.92 (m, 2H), 4.07 (brs, 1H), 4.25-4.29 (m, 1H), 4.40 (m, 1H), 4.59 (brs, 2H), 4.72 (m, 1H) 5.03 (d, 0.5H), 5.05 (d, 0.5H), 5.68 (brs, 1H), 6.95 (d, 2H), 7.06-7.16 (m, 4H), 7.19-7.24 (m, 2H), 7.29-7.37 (m, 4H), 7.80 (d, 1H), 8.05-8.15 (brs, 1H). M/z: 682.1 (M-H).

Example 54

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valyl-D-valine**

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-Fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valine (11.9 mg, 0.02 mmol), *tert*-butyl D-valinate hydrochloride (5.6 mg, 0.027 mmol) and *N*-methylmorpholine (10 µl, 0.092 mmol) were dissolved in DCM (1.5

ml). After 5 minutes, TBTU (8.2 mg, 0.0255 mmol) was added and the reaction mixture was stirred overnight. Additional *tert*-butyl D-valinate hydrochloride (1.7 mg, 8.1 μmol), *N*-methylmorpholine (6.5 μl, 58 μmol), TBTU (2 mg, 6.2 μmol) were added and the mixture was stirred for 3 h. The formation of the ester was confirmed. M/z: 736.2 (M-H). The solvent was removed under reduced pressure and the residue was purified on silica gel (1 g) using DCM: MeOH (8:2) as eluent. The fractions were collected and concentrated. The residue was dissolved in formic acid (1 ml) and the resulting solution was stirred at 25-30 °C overnight. The solvent was evaporated and toluene was added and removed under reduced pressure. The residue was dissolved in methanol (1 ml) and sodium borohydride (8.8 mg, 0.23 mmol) was added. The mixture was stirred for 30 minutes. Ammonium acetate (18 mg) was added and the solvent was removed under reduced pressure. The residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 50 % MeCN in 0.1 M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (2.5 mg, 18%). H-NMR (400 MHz, DMSO-d_6): 0.75 (d, 3H), 0-79-0.87 (m, 9H), 1.92-2.06 (m, 2H), 2.86-2.92 (m, 2H), 4.01 (brs, 1H), 4.25 (d, 0.5H), 4.28 (d, 0.5H), 4.32 (t, 1H), 4.57 (d, 2H), 4.67-4.76 (m, 1H), 5.03 (d, 0.5H), 5.05 (d, 0.5H), 5.69 (brs, 1H), 6.93 (d, 2H), 7.04-7.17 (m, 4H), 7.18-7.25 (m, 2H), 7.29-7.38 (m, 4H), 7.85 (d, 1H), 7.96 (brs, 1H). M/z: 682.1 (M-H).

Example 55

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valyl-L-methionine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valine (13.3 mg, 0.023 mmol), *tert*-butyl L-methioninate hydrochloride (7.4 mg, 0.031 mmol) and *N*-methylmorpholine (10 μl, 0.091 mmol) were dissolved in 1 ml. After 5 minutes, TBTU (8.9 mg, 0.028 mmol) was added and the resulting suspension was stirred overnight. Additional *tert*-butyl L-methioninate hydrochloride (2.1 mg, 0087 mmol), *N*-methylmorpholine (5 μl, 45 μmol) and TBTU (2.1 mg, 6.54 μmol) were added and the

mixture was stirred for 2 h. The formation of the ester was confirmed. M/z 768.1 (M-H) and 770.0 (M+H). The yellow suspension was purified on silica gel (1g) and eluted with EtOAc:DCM (15:85). The pure fractions were concentrated and formic acid (1.5 ml) was added. The solution was stirred at 50°C overnight. The solvent was removed under reduced pressure. Toluene was added and removed under reduced pressure. The residue was dissolved in methanol (1 ml) and sodium borohydride (9.9 mg, 0.26 mmol) was added. The resulting reaction mixture was stirred for 10 minutes. Ammonium acetate (18.9 mg) was added and the solvent was removed under reduced pressure. The residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 40 % MeCN in 0.1 M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid was obtained (4.6 mg, 28%). 1H-NMR (400 MHz, DMSO-d_6): 0.75 (d, 3H), 0.79 (d, 3H), 1.79-1.97 (m, 3H), 1.99 (s, 3H), 2.36-2.44 (m, 2H), 2.86-2.92 (m, 2H), 2.24-4.35 (m, 3H), 4.58 (d, 2H), 4.67-4.76 (m, 1H), 5.03 (d, 0.5H), 5.5 (d, 0.5H), 5.63 (t, 1H), 6.95 (d, 2H), 7.05-7.16 (m, 4H), 7.18-7.24 (m, 2H), 7.30-7.38 (m, 2H), 7.82 (d, 1H), 7.37 (d, 1H). M/z: 714.0 (M-1) and 716.1 (M+H).

Example 56

***N*-[(4-{(2*R*,3*R*)-1-(4-fluorophenyl)-3-[(2-hydroxy-2-phenylethyl)thio]-4-oxoazetidin-2-yl}phenoxy)acetyl]glycyl-D-valine**

(4-{(2*R*,3*R*)-1-(4-Fluorophenyl)-4-oxo-3-[(2-oxo-2-phenylethyl)thio]azetidin-2-yl}phenoxy)acetic acid (15 mg, 0.043 mmol), *tert*-butyl glycyl-D-valinate hydrochloride, (14.3 mg, 0.054 mmol) and *N*-methylmorpholine (14 µl, 0.13 mmol) were dissolved in DCM (2 ml). After 5 minutes, TBTU (16.9 mg, 0.053 mmol) was added and the reaction mixture was stirred for 2.5 h. The formation of the ester was confirmed. M/z: 678.35 (M+H). The solvent was removed under reduced pressure. The residue was dissolved in EtOAc:DCM (1:3) and purified on silica gel (1 g) using EtOAc:DCM (1:3) as eluent. The fractions were collected and concentrated. The residue (0.029 g) was dissolved in DCM (3 ml) and TFA (0.5 ml) was added. The reaction mixture was stirred overnight. The solvent was removed under

reduced pressure and toluene was added and removed under reduced pressure. The yellowish residue was dissolved in MeOH (2 ml) and sodium borohydride (16.2 mg, 0.43 mmol) was added. The reaction mixture was stirred for 10 minutes. Ammonium acetate (31.4 mg) was added and the solvent was removed under reduced pressure. The residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 50 % MeCN in 0.1 M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (7.6 mg, 28 %). H-NMR (400 MHz, DMSO-d_6): 0.79 (d, 3H), 0.81 (d, 3H) 1.95-2.05 (m, 1H), 2.84-2.96 (m, 2H), 3.79 (d, 2H), 3.98-4.04 (m, 1H), 4.27 (d, 0.5H), 4.30 (d, 0.5H), 4.51 (s, 2H), 4.66-4.75 (m, 1H), 5.02 (d, 0.5H), 5.04 (d, 0.5H), 6.98 (d, 2H), 7.10-7.17 (m, 2H), 7.19-7.32 (m, 7H), 7.36 (d, 2H), 7.77 (t, 1H), 8.26 (t, 1H). M/z: 622.1 (M-H) and 624.2 (M+H).

Example 57

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-hydroxy-2-(4-methylphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine**

[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-methylphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (15.0 mg, 0.043 mmol), *tert*-butyl glycyl-D-valinate hydrochloride (10.8 mg, 0.04 mmol), *N*-methylmorpholine (10 µl, 0.09mmol) were dissolved in DCM (2 ml). After 5 minutes, TBTU (12.1 mg, 0.04 mmol) was added and the reaction mixture was stirred overnight. The formation of the ester was confirmed. M/z: 690.13 (M-H) and 692.15 (M+H).The reaction mixture was purified on silica gel (1 g) and eluted with EtOAc:DCM (1:4). The collected fractions were concentrated. The oily residue was dissolved in DCM (1.5 ml) and TFA (1 ml) was added. The reaction mixture was stirred for 2.5 h. The solvent was evaporated. Toluene was added and evaporated to assist the removal of TFA. The residue was dissolved in methanol (1.5 ml) and sodium borohydride (12.2 mg, 0.32 mmol) was added. Additional sodium borohydride (4.2 mg, 0.11 mmol) was added and the mixture was stirred for 15 minutes. The solvent was removed under reduced pressure and the residue was purified on preparative HPLC on a C8 column. A gradient from 20% to 50 % MeCN in 0.1M

ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (10.4 mg, 52 %). H-NMR (400 MHz, DMSO-d_6): 0.80 (d, 6H), 1.95-2.05 (m, 1H), 2.24 (brs, 3H), 2.80-2.94 (m, 2H), 3.78 (d, 2H), 4.00 (brs, 1H), 4.23 (d, 0.5H), 4.27 (brs, 0.5H) 4.51 (s, 2H), 4.61-4.70 (m, 1H), 5.00 (m, 1H), 6.97 (d, 2H) 7.06 (d, 2H), 7.10-7.18 (m, 4H), 7.19-7.25 (m, 2H), 7.34 (d, 2H), 7.76 (brs, 1H), 8.26 (t, 1H). M/z: 636.1 (M-H) and 638.1(M+H).

Example 58

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valyl-D-tyrosine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valine (14.7 mg, 0.025 mmol), added *tert*-butyl D-tyrosinate hydrochloride (10.5 mg, 0.038 mmol) and *N*-methylmorpholine (10 µl, 91 µmol) were dissolved in DCM (1.5 ml). After 5 minutes, TBTU (9.9 mg, 0.031 mmol) was added and the reaction mixture was stirred overnight. Additional *tert*-butyl D-tyrosinate hydrochloride (3.6 mg, 0.013 mmol), *N*-methylmorpholine (10 µl, 91 µmol) and TBTU (3.1 mg, 9.7 µmol) were added. The mixture was stirred for 3 h. The formation of the ester was confirmed. M/z. 800.07 (M-H) and 802.08 (M+H). Aqueous $KHSO_4$ (3 ml) was added and the mixture (pH of 2) was extracted with DCM (3x5 ml). The combined organic phases were washed with water (2x10 ml), dried over Na_2SO_4, filtered and concentrated. The oily residue (22.4 mg) was dissolved in DCM (1.5 ml) and TFA (1.0 ml) was added. The mixture was stirred overnight. The solvent was evaporated. Toluene was added and removed under reduced pressure. The residue was dissolved in methanol (2 ml) and sodium borohydride (14 mg) was added. The solution was stirred for 10 minutes. Ammonium acetate (15 mg) was added and the solvent was removed under reduced pressure. The residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 50 % MeCN in 0.1M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (8.4 mg, 45 %). 1H-NMR (400 MHz, DMSO-d_6): 0.70 (d, 3H), 0.76 (d, 3H), 1.90-1.99 (m, 1H), 2.73-2.80 (m, 1H), 2.86-2.95 (m, 3H), 3.96-4.04 (m, 1H), 4.06-4.12 (m, 1H), 4.27 (d, 0.5H), 4.29 (d, 0.5H),

4.50-4.61 (m, 2H), 4.67-4.76 (m, 1H), 5.02 (d, 0.5H), 5.04 (d, 0.5H), 6.53 (d, 2H), 6.91 (q, 4H), 7.04-7.15 (m, 4H), 7.18-7.25 (m, 2H), 7.30-7.38 (m, 4H), 7.58-7.65 (brs, 1H), 7.91 (d, 1H). M/z: 746.0 (M-H).

Example 59

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valyl-D-lysine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valine (14.7, 0.025 mmol), *tert*-butyl N^6-(*tert*-butoxycarbonyl)-D-lysinate hydrochloride (10.3, 0.03 mmol) and *N*-methylmorpholine (10 µl, 91 µmol) were dissolved in DCM (1.5 ml). After 5 min, TBTU (9.8 mg, 0.03 mmol) was added and the reaction mixture was stirred overnight. Additional N^6-(*tert*-butoxycarbonyl)-D-lysinate hydrochloride (3.4 mg, 0.01 mmol), *N*-methylmorpholine (5 µl, 45 µmol) and TBTU (3.3 mg, 0.01 mmol) were added and the mixture was stirred for 2 h. Aqueous $KHSO_4$ (3 ml) was added and the mixture (pH of 3) was extracted with DCM (3x5 ml).The combined organic phases were washed with water (2x5 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude residue (17.1 mg) was dissolved in DCM (1.5 ml) and TFA (1ml). The solution was stirred for 1.5 h. The solvent was removed under reduced pressure. Toluene was added and evaporated to assist the removal of TFA. The residue was dissolved in methanol (2 ml) and sodium borohydride (11.5 mg, 0.30 mmol) was added. The mixture was for ca 15 minutes. After removal of the solvent under reduced pressure, the residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 50 % MeCN in 0.1M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid. (7.8 mg, 43 %). 1H-NMR (400 MHz, DMSO-d_6): 0.75 (d, 3H), 0.79 (d, 3H), 1.17-1.63 (m, 4H), 1.96-2.06 (m,1H), 2.61-2.69 (m, 2H), 2.85-2.93 (m, 2H), 3.72-3.80 (m, 1H), 4.12 (t, 1H), 4.27 (s, 0.5H), 4.30 (s, 0.5H), 4.53-5.64 (m, 2H), 4.67-4.76 (m, 1H), 5.01-5.05 (m, 1H), 6.94 (d, 2H), 7.03-7.16 (m, 4H), 7.29-7.39 (m, 4H), 7.50-7.57 (brs, 1H), 8.05 (d, 1H). M/z: 713.1.

Example 60

N-[(4-{(2R,3R)-3-[(2-hydroxy-2-phenylethyl)thio]-4-oxo-1-phenylazetidin-2-yl}phenoxy)acetyl]glycyl-D-valine

[4-((2*R*,3*R*)-3-{[(5,5-Dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-4-oxo-1-phenylazetidin-2-yl)phenoxy]acetic acid (12.6 mg, 0.024 mmol) and *N*-methylmorpholine (15 µl, 0.14 mmol) were dissolved in DCM (2 ml). Additional DCM (2 ml), *N*-methylmorpholine (20 µl, 0.18 mmol) and *tert*-butyl glycyl-D-valinate hydrochloride, (9.0 mg, 0.034 mmol) were added after 0.5 h and the mixture was stirred for 10 minutes. TBTU (10.5 mg, 0.033 mmol) was added and the mixture was stirred overnight. The formation of the ester was confirmed. M/z: 746.1. The solvent was removed under reduced pressure and the residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 50% MeCN in 0.1 M ammonium acetate buffer was used as eluent. After lyophilisation, the obtained compound was dissolved in DCM (2 ml) and TFA (1 ml) was added. The reaction mixture was stirred for 2.5 h. The hydrolysis of the ester was confirmed. M/z: 604.2. The solvent was removed under reduced pressure. Co-evaporation with toluene was performed to assist the removal of TFA. The residue was dissolved in methanol (2 ml) and sodium borohydride (9.2 mg, 0.24 mmol) was added. After 15 minutes, the solvent was evaporated off and the residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 50 % MeCN in 0.1 M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid was (4.0 mg, 28%). H-NMR (400 MHz, DMSO-d_6): 0.78 (d, 6H), 1.95-2.04 (m, 1H), 2.83-2.97 (m, 2H), 3.76 (d, 2H), 3.89-3.95 (m, 1H), 4.26 (d, 0.5H), 4.30 (d, 0.5H), 4.51 (s, 2H), 4.67-4.75 (m, 1H), 5.01 (d, 0.5H), 5.03 (d, 0.5H), 6.98 (d, 2H), 7.03 (t, 1H), 7.17-7.22 (m, 3H), 7.23-7.32 (m, 6H), 7.36 (d, 2H), 7.55-7.65 (m, 1H), 8.29 (t, 1H). M/z: 603.96 (M-H).

Example 61

N-{[4-((2R,3R)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine

[4-((2*R*,3*R*)-1-(4-Chlorophenyl)-3-{[2-(4-chlorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (15.3 mg, 0.03 mmol), *N*-methylmorpholine (10 µl, 0.091 mmol) and *tert*-butyl glycyl-D-valinate hydrochloride, (10.4 mg, 0.039 mmol) were dissolved in DCM (2 ml). After 10 minutes, TBTU (11.9 mg, 0.037 mmol) was added and the mixture was stirred overnight. The intermediate *tert*-butylester was confirmed. M/z: 727.8 (M-H). The reaction mixture was extracted between water (10 ml, acidified to pH of 3 with $KHSO_4$ (2M)) and DCM (3x10 ml). The combined organic phases were washed with water (2x20 ml), dried over Na_2SO_4, filtered and concentrated. The oily residue was dissolved in DCM (2 ml) and TFA (1.3 ml) was added. The mixture was stirred overnight. The solvent was evaporated and co-evaporation with toluene was performed to assist the removal of TFA. The residue was dissolved in methanol (2 ml) and sodium borohydride (12.3 mg, 0.33 mmol) was added. After 15 minutes, ammonium acetate (17mg) was added and the solvent was removed under reduced pressure. The residue was purified on preparative HPLC on C8 column. A gradient from 20% to 50 % MeCN in 0.1M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (15.1 mg, 77 %). H-NMR (400 MHz, DMSO-d_6): 0.78 (d, 3H), 0.80 (d, 3H), 0.95-1.03 (m, 1H), 2.83-3.00 (m, 2H), 3.75-3.80 (m, 2H), 3.93-4-00 (t, 1H), 4.30 (d, 0.5H), 4.36-4.38 (brs, 0.5H), 4.52 (s, 2H), 4.69-4.77 (m, 1H), 5.02 (d, 0.5H), 5.06 (d, 0.5H), 6.96-7.00 (m, 2H), 7.18-7.22 (m, 2H), 7.31-7.38 (m, 8H), 7.60-7.74 (m, 1H), 8.28 (t, 1H). M/z: 671.9 (M+H).

Example 62

N-{[4-((2R,3R)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-lysine

N-{[4-((2*R*,3*R*)-1-(4-Chlorophenyl)-3-{[2-(4-chlorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (14.6 mg, 0.026 mmol) and *N*-methylmorpholine (20 µl, 0.18 mmol) were dissolved in DCM (2 ml). *tert*-Butyl N^6-(*tert*-butoxycarbonyl)-D-lysinate hydrochloride (11.1 mg, 0.033 mmol) was added and after 5 minutes TBTU (9.8 mg, 0.031 mmol) was added to the suspension. The mixture was stirred overnight. Additional *tert*-butyl N^6-(*tert*-butoxycarbonyl)-D-lysinate (4.8 mg, 0.014 mmol), *N*-methylmorpholine (10 µl, 91 µmol) and TBTU (4.6 mg, 0.014 mmol) were added and the mixture was stirred for 2.5 h. The formation of the ester was confirmed. M/z: 855.4 (M-H). DCM (3 ml) and water (5 ml) were added and the solution was acidified to pH 3 with $KHSO_4$ (2M). The organic phase was washed with water (2x5 ml). The combined water phases were extracted with DCM (2x5 ml). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was dissolved in DCM (1.5 ml) and TFA (1 ml) was added. The mixture was stirred for 2.5 h. The mixture was concentrated and co-evaporation with toluene was performed to assist the removal of TFA. The residue was dissolved in methanol (2 ml) and sodium borohydride (10.4 mg, 0.027 mmol) was added. After 15 minutes, ammonium acetate buffer (0.1M, 1.5 ml) was added and the solvent was removed under reduced pressure. The residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 50 % MeCN in 0.1M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (10.8 mg, 59 %). H-NMR (400 MHz, DMSO-d_6): 1.18-1.36 (m, 2H), 1.41-1.70 (m, 4H), 2.71 (t, 2H), 2.84-2.97 (m, 2H), 3.72-3.75 (brd, 2H), 3.93 (m, 1H), 4.30 (d, 0.5H), 4.34 (d, 0.5H), 4.52 (s, 2H), 4.68-4.77 (m, 1H), 5.03 (d, 0.5H), 5.07 (d, 0.5H), 6.98 (d, 2H), 7.20 (d, 2H), 7.31-7.38 (m, 8H), 7.63-7.72 (m, 1H), 8.34 (t, 1H). M/z: 705.1.

Example 63

(2*R*)-2-[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino]-4-phenylbutanoic acid

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (14.4 mg, 0.027 mmol) and *N*-methylmorpholine (15 µl, 0.14 mmol) were dissolved in DMF (3 ml). After 5 minutes, TBTU (10.3 mg, 0.032 mmol) was added and the mixture was stirred at 30°C for 20 minutes. (2*R*)-2-Amino-4-phenylbutanoic acid (5.7 mg, 0.032 mmol) was added and the mixture was stirred at ambient temperature for 1.5 hors. The formation of the intermediate acid was confirmed. M/z: 702.0. MeOH (2.5 ml) and sodium borohydride were added and the mixture was stirred for 20 minutes. Ammonium acetate (31 mg) was added. The mixture was concentrated and purified with preparative HPLC on a C8 column. A gradient from 20% to 45% MeCN in 0.1M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (9.4 mg, 50 %). H-NMR (400 MHz, DMSO-d_6): 1.74-1.87 (m, 1H), 1.89-1.99 (m, 1H), 2.49-2.53 (m, 2H), 2.82-2.98 (m, 2H), 3.77 (d, 2H), 3.94-4.01 (m, 1H), 4.27 (d, 0.5H), 4.31 (d, 0.5H), 4.53 (s, 2H), 4.68-4.77 (m, 1H), 5.02 (d, 0.5H), 5.05 (d, 0.5H), 6.99 (d, 2H), 7.05-7.16 (m, 7H), 7.19-7.26 (m, 4H), 7.30-7.38 (m, 4H), 7.78-7.88 (dd, 1H), 8.35 (t, 1H). M/z: 702.0 (M-H).

Example 64

(2*R*)-2-[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino]-4-(4-hydroxyphenyl)butanoic acid

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (15.2 mg, 0.028 mmol) and *N*-methylmorpholine (15 µl, 0.14 mmol) were dissolved in DMF (2 ml). TBTU (10.5 mg, 0.033 mmol) was added and after 20 minutes (2*R*)-2-amino-4-(4-hydroxyphenyl)butanoic acid hydrobromide (9.2 mg, 0.033 mmol) was added. The reaction mixture was stirred for 1.5 h. The formation of the intermediate acid was confirmed. M/z: 718.3. MeOH (2 ml) and sodium borohydride (10.7 mg, 0.28 mmol) were added and the mixture was stirred for 20 minutes. Ammonium acetate (34 mg) was addded and the methanol was removed under reduced pressure. The residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 45% MeCN in 0.1M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound

was obtained as a white solid (9.6 mg, 47%). H-NMR (400 MHz, DMSO-d_6): 1.75-1.86 (m, 1H), 1.89-1.98 (m, 1H), 2.41 (t, 2H), 2.81-2.98 (m, 2H), 3.78 (d, 2H), 3.97-4.05 (m, 1H), 4.27 (d, 0.5H), 4.31 (d, 0.5H), 4.53 (s, 2H), 4.67-4.76 (m, 1H), 5.02 (d, 0.5H), 5.05 (d, 0.5H), 6.62 (d, 2H), 6.91 (d, 2H), 6.98 (d, 2H), 7.05-7.16 (m, 4H), 7.20-7.25 (m, 2H), 7.30-7.39 (m, 4H), 7.87-7.97 (m, 1H), 8.30 (t, 1H), 8.91-9.30 (br, 1H). M/z: 718.0 (M-H).

Example 65

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-hydroxy-2-(4-methoxyphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-alanine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.04 g, 0.072 mmol) and N-methylmorpholine (0.022 g, 0.217 mmol) were dissolved in CH_2Cl_2 (4 ml). *tert*-Butyl D-alaninate hydrochloride (0.016 g, 0.087 mmol) and TBTU (0.030 g, 0.094 mmol) were added. After 2 h, the reaction mixture was purified on silica gel and eluted with EtOAc/ CH_2Cl_2 (25/75). Pure fractions were collected and concentrated. The residue was dissolved in CH_2Cl_2 (3 ml) and TFA (2 ml). The hydrolysis was completed after 2h. The reaction mixture was concentrated and MeOH (3 ml) and $NaBH_4$ (0.011 g, 0.290 mmol) were added. The mixture was stirred for 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml) and the solvent evaporated. The residue was purified by preparative HPLC using an eluent of 0-50% CH_3CN in 0.1M NH_4OAc buffer. Freeze-drying of the pure fractions afforded the title compound (0.030 g, 66%) as a colourless solid. M/z: 624.2, (M -1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.16 (d, 3H), 2.83-2.93 (m, 2H), 3.68-3.74 (m, 5H), 3.88-3.95 (m, 1H), 4.23-4.26 (m, 1H), 4.51 (s, 2H), 4.60-4.70 (m, 1H), 5.00-5.03 (m, 1H), 6.81-7.37 (m, 12H), 7.74-7.79 (m, 1H), 8.29-8.34 (m, 1H).

Example 66

1-[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino]cyclopropanecarboxylic acid

N-Methyl morpholine (0.037 g, 0.370 mmol) and TBTU (0.039 g, 0.120 mmol) were added to a solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.025 g, 0.046 mmol) in DMF (2 ml) at 30 °C. After 1h, 1-aminocyclopropane carboxylic acid (0.019 g, 0.185 mmol) was added. After 1h, the reaction was quenched by the addition of water (1 ml). After 10 minutes, MeOH (2 ml) and $NaBH_4$ (0.035 g, 0.925 mmol) were added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). The product was purified by preparative HPLC (eluent 0-50% CH_3CN in 0.1M NH_4OAc buffer). Freeze-drying of the pure fractions afforded the title compound (0.045 g, 78%) as a colourless solid. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.78-0.88 (m, 2H), 1.08-1.22 (m, 2H), 2.84-2.94 (m, 2H), 3.63-3.72 (m, 2H), 4.24-4.29 (m, 1H), 4.48-4.52 (m, 2H), 4.68-4.75 (m, 1H), 5.03-5.06 (m, 1H), 6.96-7.37 (m, 12H), 7.78-8.36 (m, 2H).

Example 67

***N*-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-methyl-D-valine**

TBTU (0.020 g, 0.063 mmol) was added to a solution of *N*-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.030 g, 0.052 mmol) and N-methylmorpholine (0.016 g, 0.157 mmol) in CH_2Cl_2 (5 ml) at 30 °C. After 30 minutes, D-tert-leucine (0.008 g, 0.063 mmol) was added and the mixture was stirred for 30 minutes. The reaction mixture was concentrated. Toluene (2 ml) was added and evaporated. MeOH (3 ml) and sodium borohydride (0.020 g, 0.523 mmol) were added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc (1 ml) buffer and the mixture was concentrated. The residue was purified by preparative HPLC using an eluent of 0-50% CH_3CN in 0.1M

NH_4OAc buffer. Freeze-drying of the pure fractions afforded the title compound (0.021 g, 58%) as a colourless solid. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.85 (s, 9H), 2.82-2.98 (m, 2H), 3.75-3.81 (m, 2H), 3.91-3.96 (m, 1H), 4.29-4.37 (m, 1H), 4.52 (s, 2H), 4.70-4.78 (m, 1H), 5.01-5.06 (m, 1H), 6.97-6.99 (m, 2H), 7.19-7.21 (m, 2H), 7.32-7.36 (m, 8H), 7.52-7.63 (m, 1H), 8.27-8.32 (m, 1H).

Example 68

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-tryptophan**

TBTU (0.016 g, 0.051 mmol) was added to a solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.025 g, 0.046 mmol) and N-methylmorpholine (0.014 g, 0.139 mmol) in DMF (2 ml) at 30 °C. After 1h, DMSO (1 ml) and D-tryptophan (0.019 g, 0.092 mmol) were added. After 10 minutes, the reaction was quenched by the addition of water (1ml). The mixture was stirred for 10 minutes and MeOH (1 ml) and $NaBH_4$ (0.035 g, 0.925 mmol) were added. After 5 minutes, full conversion to the corresponding alcohol was obtained. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml). The reaction mixture was concentrated and the residue was purified by preparative HPLC using an eluent of 0-50% CH_3CN in 0.1M NH_4OAc buffer. This gave the title compound (0.028 g, 83%) as a colurless solid. M/z: 727.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.79-3.18 (m, 4H), 3.61-3.80 (m, 2H), 4.26-4.34 (m, 2H), 4.43-4.54 (m, 2H), 4.68-4.78 (m, 1H), 4.97-5.04 (m, 1H), 6.84-7.55 (m, 17H), 7.65-7.82 (m, 1H), 8.22-8.25 (m, 1H), 10.73 (s, 1H).

Example 69

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-histidine**

TBTU (0.016 g, 0.051 mmol) was added to a solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.025 g, 0.046 mmol) and N-methylmorpholine (0.014 g, 0.139 mmol) in DMF (2 ml) at 30 °C. After 1 h, D-histidine (0.014 g, 0.092 mmol) and tetrabutylammoniumbromide (0.003 g, 0.009 mmol) were added. The reaction mixture was stirred overnight (30% conversion) and the reaction was quenched by the addition of water (2 ml). Purification by preparative HPLC using an eluent of 0-50% CH_3CN in 0.1M NH_4OAc buffer afforded the intermediate ketone, which was reduced by the addition of MeOH (3 ml) and $NaBH_4$ (0.005 g, 0.139 mmol). Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml) and the mixture was concentrated. Purification by preparative HPLC using an eluent of 0-40% CH_3CN in 0.1M NH_4OAc buffer afforded the title compound (0.001 g, 4.5%) as a colourless solid. M/z: 680.0. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.82-2.93 (m, 4H), 3.71-3.80 (m, 2H), 4.11-4.30 (m, 2H), 4.52 (s, 2H), 4.68-4.73 (m, 1H), 5.04-5.07 (m, 1H), 6.68-7.50 (m, 14H), 7.90-7.96 (m, 1H), 8.27-8.33 (m, 1H).

Example 70

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-(2-naphthyl)-D-alanine**

TBTU (0.019 g, 0.060 mmol) was added to a solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.025 g, 0.046 mmol) and N-methylmorpholine (0.014 g, 0.139 mmol) in CH_2Cl_2 (5 ml) at 30 °C. After 1h, DMF (3 ml), DMSO (1 ml) and D-(2-naphtyl)alanine (0.011 g, 0.051 mmol) were added. The reaction was quenched by the addition of water (1 ml) after 1 h. $NaBH_4$ (0.035 g, 0.925 mmol) was added. After 5 minutes, full conversion to the corresponding alcohol was obtained. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml) and the mixture was concentrated. Purification by preparative HPLC using an eluent of 0-55%

CH_3CN in 0.1M NH_4OAc buffer afforded the title compound (0.017 g, 48%) as a colourless solid. M/z: 738.0 (M–1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.75-3.27 (m, 4H), 3.55-3.83 (m, 2H), 4.25-4.55 (m, 4H), 4.68-4.79 (m, 1H), 4.92-5.02 (m, 1H), 6.72-7.80 (m, 20H), 8.26-8.30 (m, 1H).

Example 71

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-methyl-D-valine**

TBTU (0.021 g, 0.067 mmol) was added to a solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.030 g, 0.056 mmol) and N-methyl morpholine (0.017 g, 0.166 mmol) in CH_2Cl_2 (5 ml) at 30 °C. After 1.5h, D-tert-leucine (0.011 g, 0.083 mmol) was added. Full conversion to the corresponding amide was obtained after 30 minutes. The reaction was quenched by the addition of water (1 ml). After 10 minutes, MeOH (3 ml) and $NaBH_4$ (0.042 g, 1.11 mmol) were added. After 5 minutes, the reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml). The reaction mixture was concentrated and purified by preparative HPLC using an eluent of 0-50% CH_3CN in 0.1M NH_4OAc buffer. The title compound (0.025 g, 69%) was obtained as a colourless solid. M/z: 654.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.86 (s, 9H), 2.82-2.98 (m, 2H), 3.76-3.81 (m, 2H), 3.92-3.96 (m, 1H), 4.26-4.33 (m, 1H), 4.52 (s, 2H), 4.68-4.76 (m, 1H), 5.02-5.07 (m, 1H), 6.97-7.37 (m, 12H), 7.58-7.63 (m, 1H), 8.29-8.34 (m, 1H).

Example 72

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-(3*R*,4*S*,5*R*)-3,4,5,6-tetrahydroxy-D-norleucine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.025 g, 0.046 mmol) was dissolved in DMSO (2 ml) at 30 °C. N-Methylmorpholine (0.014 g, 0.139 mmol) and TBTU (0.018 g, 0.056 mmol) were added. After 1h, D-glucosaminic acid (0.018 g, 0.092 mmol) and tetrabutylammoniumbromide (0.001 g, 0.005 mmol) were added. The mixture was stirred for 15 minutes. Additional TBTU (18 mg, 0.056 mmol) was added. After 30 minutes, approximately 30% amide formation had occured. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). The intermediate ketone was purified by preparative HPLC using an eluent of 0-50% CH_3CN in 0.1M NH_4OAc buffer and freeze-dried. MeOH (3 ml) and $NaBH_4$ (0.005 g, 0.139 mmol) were added. After 5 minutes, the reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml). Concentration of the mixture and purification by preparative HPLC using an eluent of 0-50% CH_3CN in 0.1M NH_4OAc buffer gave the title compound (0.005 g, 16%) as a colourless solid. M/z: 718.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.82-2.94 (m, 2H), 3.34-3.56 (m, 4H), 3.76-3.80 (m, 2H), 3.87-3.90 (m, 1H), 4.07-4.11 (m, 1H), 4.27-4.32 (m, 1H), 4.52 (s, 2H), 4.68-4.76 (m, 1H), 5.02-5.05 (m, 1H), 6.97-7.39 (m, 12H), 7.63-7.70 (m, 1H), 8.28-8.35 (m, 1H).

Example 73

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-β-phenyl-D-phenylalanine**

TBTU (0.018 g, 0.056 mmol) was added to a solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine(0.025 g, 0.046 mmol) and N-methylmorpholine (0.023 g, 0.231 mmol) in CH_2Cl_2 (5 ml) at 30 °C. After 1.5h, β-phenyl-D-phenylalanine trifluoro acetic acid salt (0.033 g, 0.092 mmol) was added. The mixture was stirred for 5 minutes. Water (1 ml) was added and the mixture was concentrated. MeOH (3 ml) and $NaBH_4$ (0.017 g, 0.462 mmol) were added. After 5 minutes, the reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml) followed by concentration of the mixture. Purification by preparative HPLC using an eluent of 0-45% CH_3CN in 0.1M NH_4OAc buffer and lyophilisation gave the title compound (0.021 g, 59%)

as a colourless solid. M/z: 764.1 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.82-2.95 (m, 2H), 3.42-3.49 (m, 1H), 3.66-3.74 (m, 1H), 4.25-4.33 (m, 2H), 4.42 (d, 1H), 4.47 (d, 1H), 4.69-4.76 (m, 1H), 5.03-5.12 (m, 2H), 6.94-7.38 (m, 22H), 8.10-8.14 (m, 1H), 8.18-8.24 (m, 1H).

Example 74

(2*R*)-4-cyclohexyl-2-[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino]butanoic acid

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.025 g, 0.046 mmol) was dissolved in DMF (2 ml) at 30 °C. N-Methyl morpholine (0.034 g, 0.333 mmol) and TBTU (0.043 g, 0.133 mmol) were added. After 1h, sodium (2*R*)-2-amino-4-cyclohexylbutanoate (0.039 g, 0.189 mmol), DMSO (2 ml) and tetrabutylammoniumbromide (0.004 g, 0.011 mmol) were added. The mixture was stirred for 1 h and water (1 ml) was added. After 1h, MeOH (2 ml) and $NaBH_4$ (0.084 g, 2.220 mmol) were added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). The mixture was purified by preparative HPLC (eluent 0-50% CH_3CN in 0.1M NH_4OAc buffer). Freeze-drying of the pure fractions gave the title compound (0.034 g, 43%) as a colourless solid. M/z: 708.1 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.75-1.62 (m, 15H), 2.82-2.99 (m, 2H), 3.68-3.78 (m, 2H), 3.90-3.96 (m, 1H), 4.23-4.35 (m, 1H), 4.50 (s, 2H), 4.69-4.75 (m, 1H), 5.01-5.07 (m, 1H), 6.95-7.39 (m, 12H), 7.68-7.80 (m, 1H), 8.20-8.34 (m, 1H).

Example 75

(2*R*)-cyclopentyl[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino]acetic acid

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.035 g, 0.065 mmol) was dissolved in DMF (2 ml) at 30 °C. N-Methyl morpholine (0.026 g, 0.259 mmol) and TBTU (0.027 g, 0.084 mmol) were added. After 1h, (2*R*)-amino(cyclopentyl)acetic acid (0.014 g, 0.097 mmol) was added. The mixture was stirred for 1 h and water (1 ml) was added. After 10 minutes, MeOH (2 ml) and $NaBH_4$ (0.037 g, 0.971 mmol) were added. Full conversion to the corresponding alcohol was obtained after 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml). The mixture was purified by preparative HPLC (eluent 0-50% CH_3CN in 0.1M NH_4OAc buffer). Freeze-drying of the pure fractions gave the title compound (0.018 g, 42%) as a colourless solid. M/z: 666.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.19-1.62 (m, 8H), 2.09-2.19 (m, 1H), 2.83-2.95 (m, 2H), 3.78 (d, 2H), 4.06-4.10 (m, 1H), 4.25-4.30 (m, 1H), 4.51 (s, 2H), 4.68-4.75 (m, 1H), 5.03-5.06 (m, 1H), 6.97-7.37 (m, 12H), 7.95-8.00 (m, 1H), 8.22 (t, 1H).

Example 76

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-methyl-D-isovaline

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.035 g, 0.065 mmol) was dissolved in DMF (2 ml) at 30 °C. N-Methyl morpholine (0.026 g, 0.259 mmol) and TBTU (0.027 g, 0.084 mmol) were added. After 1h, 3-methyl-D-isovaline (0.013 g, 0.097 mmol) was added. The mixture was stirred for 2 h and water (1 ml) was added. After 10 minutes, MeOH (2 ml) and $NaBH_4$ (0.037 g, 0.971 mmol) were added. Full conversion to the corresponding alcohol was obtained after 5 minutes and 0.1M NH_4OAc buffer (2 ml) was added. The mixture was purified by preparative HPLC (eluent 0-50% CH_3CN in 0.1M NH_4OAc buffer). Freeze-drying of the pure fractions afforded the title compound (0.020g, 47%) as a colourless solid. M/z: 654.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.79 (d, 3H), 0.87 (d, 3H), 1.29 (s, 3H), 2.00-2.07 (m, 1H), 2.84-2.94 (m, 2H), 3.73 (d, 2H), 4.25-4.28 (m, 1H), 4.51 (s, 2H), 4.69-4.75 (m, 1H), 5.03-5.06 (m, 1H), 6.97-7.37 (m, 12H), 7.82 (s, 1H), 8.24 (t, 1H).

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Example 77

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-(*tert*-butyl)-D-cysteine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (20 mg, 0.037 mmol) and *N*-methylmorpholine (20 µl, 0.18 mmol) were dissolved in DMF (3 ml). TBTU (14.6mg, 0.046mmol) was added and the mixture was stirred at 30°C for 45 minutes. *S*-(*tert*-Butyl)-D-cysteine hydrochloride (9.7 mg, 0.045 mmol) was added and the reaction mixture was stirred for 1.5 h. The formation of the ketone of the title compund was confirmed. M/z: 700.0. Methanol (2 ml) and sodium borohydride (14.3 mg, 0.38 mmol) were added and the mixture was stirred for 30 minutes. Ammonium acetate buffer (0.1M, 2 ml) was added and the mixture was concentrated. The residue was purified with preparative HPLC on a C8 column. A gradient from 20% to 45 % MeCN in 0.1M NH_4OAc buffer was used as eluent. The MeCN was removed from the collected fraction under reduced pressure. The remaining water solution was acidified to pH 1 with HCl (1M) and extracted with DCM. The organic phase was concentrated under reduced pressure and the residue was dissolved in MeCN and water. After lyophilisation, the title compound was obtained as a white solid (16.5 mg, 65%). H-NMR (400 MHz, DMSO-d_6): 1.21 (s, 9H), 2.71-2.78 (m, 1H), 2.82-2.86 (m, 3H), 2.74-2.80 (m, 2H), 2.18-2.26 (m, 1H), 4.27 (d, 0.5H), 4.30 (d, 0.5H), 4.51 (s, 2H), 2.67-2.76 (m, 1H), 5.03 (d, 0.5H), 5.05 (d, 0.5), 6.98 (d, 2H), 7.05-7.17 (m, 4H), 7.20-7.25 (m, 2H), 7.30-7.39 (m, 4H), 7.94-8.06 (b, 1H), 8.26 (t, 1H). M/z: 700.0 (M-H) and 702.1 (M+H).

Example 78

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*N*,2-dimethylalanine**

To mixture of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.020g, 0.037 mmol) and NMM (0.012ml, 0.109mmol) in DMF (3 ml) at 30°C was added TBTU (0.018 g, 0.056 mmol). The reaction mixture was stirred for 20 min after which 2-(methylamino)isobutyric acid (0.005 g, 0.038 mmol) was added. The mixture was stirred at 30°C for 20h before the reaction was quenched by the addition of water (1 ml). The mixture was diluted with MeOH (2 ml) and NaBH4 (0.018 g, 0.486 mmol) was added. After 10 min the reaction was quenched by the addition of a 0.1M ammonium acetate buffer (2 ml) and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC using a gradient of 20-50% MeCN in a 0.1M ammonium acetate buffer as eluent. Freeze-drying of the pure fractions gave the desired product as a white solid (0.012 g, 50 % yield).

Accurate mass: 642.211 $(M+1)^+$

Example 79

(2*R*)-3-(4-cyanophenyl)-2-{[({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)acetyl]amino}propanoic acid

(2*R*)-3-(4-cyanophenyl)-2-{[({[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)acetyl]amino}propanoic acid (0.006 g, 0.0084 mmole) was dissolved in methanol (1.5 ml). $NaBH_4$ (0.0035 g, 0.092 mmole) was added and when the reaction was complete according to LC-MS a few drops of acetic acid was added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a stepwise gradient of 33.5%, 43% and then 55.5% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.005 g (83 %) of the desired product was obtained.

NMR (500 MHz,CD_3COOD) 2.91-3.12 (m, 3H), 3.26-3.32 (m, 1H), 3.91 (ABq, 2H), 4.03-4.07 (m, 1H),4.57 (s, 2H), 4.65 (brt, 1H), 4.80-4.85 (m,1H), 4.90-4.93 (m, 1H), 6.97-7.08 (m, 6H), 7.26-7.32 (m, 2H), 7.32-7.41 (m, 6H), 7.60 (d, 2H)

Example 80

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-hydroxy-2-(4-pentylphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-cyclohexyl-D-alanine**

To a solution of [4-((2*R*,3*R*)-1-(4-fluorophenyl)-4-oxo-3-{[2-oxo-2-(4-pentylphenyl)ethyl]thio}azetidin-2-yl)phenoxy]acetic acid (0.020 g, 0.037 mmol) and NMM (0.012 ml, 0.109 mmol) in DMF (2 ml) at 30°C was added TBTU (0.019 g, 0.059 mmol). After 15 min glycyl-3-cyclohexyl-D-alanine (0.009 g, 0.039 mmol) was added and the mixture was stirred at 30°C for 22 h. The reaction was quenched by the addition of water (1 ml) before the mixture was diluted with MeOH (2 ml). To this solution was added NaBH4 (0.020 g, 0.529 mmol) and the mixture was stirred for 10 min. This reaction was quenched by the addition of a 0.1M ammonium acetate buffer (3 ml) and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC using a gradient of 20-60% MeCN in a 0.1M ammonium acetate buffer as eluent. Freeze-drying of the pure fractions gave the desired product as a white solid (0.009 g, 32 % yield).

1H NMR (CD3OD, 400 MHz) δ: 0.82-1.03 (m, 5H), 1.10-1.45 (m, 8H), 1.48-1.74 (m, 8H), 1.75-1.85 (m, 1H), 2.51-2.60 (m, 2H), 2.89-3.08 (m, 2H), 3.91-4.04 (m, 3H), 4.42-4.49 (m, 1H), 4.56-4.60 (m, 2H), 4.71-4.87 (m, 2H), 6.95-7.10 (m, 6H), 7.18-7.35 (m, 6H).

Example 81

***N*-({4-[(2*R*,3*R*)-1-(4-Fluorophenyl)-3-({2-hydroxy-2-[4-(methylthio)phenyl]ethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetyl)glycyl-3-cyclohexyl-D-alanine**

To a solution of {4-[(2*R*,3*R*)-1-(4-fluorophenyl)-3-({2-hydroxy-2-[4-(methylthio)phenyl]ethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetic acid (0.020 g, 0.039 mmol) and NMM (0.025 ml, 0.227 mmol) in DMF (3 ml) at RT was added TBTU (0.025 g, 0.078 mmol). The reaction mixture was stirred for 90 min after which glycyl-3-cyclohexyl-D-alanine (0.010 g, 0.044 mmol) was added. The mixture was stirred for 22 h before the reaction was quenched by the addition of water (1 ml). The mixture was diluted with MeOH (1 ml) and then NaBH4 (0.016 g, 0.423 mmol) was added. After 10 min the reaction was quenched by the addition of a 0.1M ammonium acetate buffer (2 ml) and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC using a gradient of 20-60% MeCN in a 0.1M ammonium acetate buffer as eluent. Freeze-drying of the pure fractions gave the desired product as a white solid (0.009 g, 32 % yield).

ES- m/z: 723.1 $(M-1)^-$. 1H NMR (DMSO, 500 MHz) δ: 0.75-0.95 (m, 2H), 1.05-1.35 (m, 4H), 1.42-1.72 (m, 7H), 2.43-2.47 (m, 3H), 2.85-2.97 (m, 2H), 4.15-4.23 (m, 1H), 4.26-4.32 (m, 1H), 4.53 (s, 2H), 4.65-4.74 (m, 1H), 5.01-5.07 (m, 1H), 5.66 (bs, 1H), 6.97-7.03 (m, 2H), 7.13-7.29 (m, 8H), 7.35-7.41 (m, 2H), 7.96-8.06 (m, 1H), 8.22-8.29 (m, 1H).

Example 82

***N*-({4-[(2*R*,3*R*)-1-(4-Fluorophenyl)-3-({2-hydroxy-2-[4-(methylthio)phenyl]ethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetyl)glycyl-D-valine**

A solution of {4-[(2*R*,3*R*)-1-(4-fluorophenyl)-3-({2-hydroxy-2-[4-(methylthio)phenyl]ethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetic acid (0.015g, 0.029mmol), *tert*-butyl glycyl-D-valinate hydrochloride (0.009g, 0.034mmol) and N-Methylmorpholine (0.013ml, 0.118mmol) in DCM (3 ml) was stirred at RT for 10 min, after which TBTU (0.014g, 0.044 mmol) was added. After 17 h the conversion to the intermediate (m/z: 724.7, M+1) was completed. The solution was diluted with TFA (2 ml) and the mixture was allowed to stir for 2 h. The resulting acid (m/z: 668.6, M+1) was concentrated and the residue was dissolved in MeOH (3 ml). To this solution was added NaBH4 (80 mg, 2.11 mmol) in

portions until the reduction of the ketone was completed (LC/MS). The reaction was quenched by the addition of a 0.1M ammonium acetate buffer (3 ml) before most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC, using a gradient of 20-50% MeCN in a 0.1M ammonium acetate buffer as eluent. Freeze-drying of the pure fractions gave the desired product (0.014g, 70%) as a white solid.

ES- m/z: 669.0 $(M-1)^-$. 1H NMR (CD3OD, 400 MHz) δ: 0.88-0.98 (m, 6H), 2.10-2.23 (m, 1H), 2.40-2.47 (m, 3H), 2.89-3.08 (m, 2H), 3.93-4.06 (m, 3H), 4.31 (d, 1H), 4.59 (s, 2H), 4.73-4.84 (m, 2H), 6.95-7.07 (m, 4H), 7.13-7.18 (m, 2H), 7.21-7.34 (m, 6H).

Example 83

***N*-({4-[(2*R*,3*R*)-1-(4-Fluorophenyl)-3-({2-hydroxy-2-[4-(methylthio)phenyl]ethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetyl)glycyl-3-methyl-D-valine**

To a solution of {4-[(2*R*,3*R*)-1-(4-fluorophenyl)-3-({2-hydroxy-2-[4-(methylthio)phenyl]ethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetic acid (0.020 g, 0.039 mmol) and NMM (0.020 ml, 0.182 mmol) in DMF (3 ml) at RT was added TBTU (0.020 g, 0.062 mmol). The reaction mixture was stirred for 60 min after which glycyl-3-methyl-D-valine (0.008 g, 0.043 mmol) was added. The mixture was stirred for 18 h before the reaction was quenched by the addition of water (1 ml). The mixture was diluted with MeOH (1 ml) and NaBH4 (0.040 g, 1.06 mmol) was added. After 10 min the reaction was quenched by the addition of a 0.1M ammonium acetate buffer (2 ml) and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC using a gradient of 20-60% MeCN in a 0.1M ammonium acetate buffer as eluent. Freeze-drying of the pure fractions gave the desired product as a white solid (0.006 g, 22 % yield).

ES- m/z: 683.0 $(M-1)^-$. 1H NMR (DMSO, 500 MHz) δ: 0.88-0.94 (m, 9H), 2.44-2.46 (m, 3H), 2.85-2.98 (m, 2H), 3.80-3.87 (m, 2H), 4.01-4.07 (m, 1H), 4.27-4.35 (m, 1H), 4.55 (s, 2H), 4.66-4.75 (m, 1H), 5.01-5.07 (m, 1H), 6.97-7.03 (m, 2H), 7.14-7.29 (m, 8H), 7.36-7.41 (m, 2H), 7.70-7.85 (m, 1H), 8.28-8.33 (m, 1H).

Example 84

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-4-methyl-D-leucine**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (20mg, 0.037mmol) was dissolved in 1.5 ml DMF. *N*-Methylmorpholine (13μl, 118mmol) and TBTU (15mg, 0.047mmol) were added and the mixture was stirred for 1h. *β-tert*-Butyl-D-alanine (11mg, 0.076mmol) was added and the mixture was stirred for 3h. Water (0.2ml) was added and the mixture was stirred for 15 min. MeOH (2ml) and $NaBH_4$ (15mg) were added. NH_4Ac (ca 20mg) was added after 15 min. Purification was performed using preparative HPLC on a C8 column. A gradient from 20-50% MeCN in 0.1M NH_4Ac was used as mobile phase. Lyophilization yielded 17.5mg (70%) of the title compound. M/z: 668 (M-1). NMR (400 MHz, DMSO): 8.24 (t, 1H), 7.77-7.87 (m, 1H), 7.32-7.40 (m, 4H), 7.22-7.27 (m, 2H), 7.07-7.19 (m, 4H), 6.99 (d, 2H), 5.06 (dd, 1H), 4.70-4.78 (m, 1H), 4.53 (s, 2H), 4.31 (dd, 1H), 4.09-4.17 (m, 1H), 3.65-3.81 (m, 2H), 2.84-3.00 (m, 2H), 1.65 (dd, 1H), 1.42 (dd, 1H), 0.86 (s, 9H).

Example 85

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-cyclopentyl-D-alanine**

To a solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.05 g, 0.092 mmol) and N-methyl morpholine (0.037 g, 0.37 mmol) in DMF (2 ml), under an atmosphere of nitrogen, was added TBTU (0.039 g, 0.12 mmol). After 1.5 h, 3-cyclopentyl-D-alanine (0.022 g, 0.139 mmol) was added. The reaction was allowed to stir for 1 h after which water (1 ml) was added. After 10 minutes, MeOH (2 ml) and $NaBH_4$ (0.035 g, 0.925 mmol) were added. Full conversion to the corresponding alcohol was achieved within 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml) and the product was isolated by preparative HPLC of

the mixture (eluent 0-50% CH_3CN in 0.1M NH_4OAc buffer). Freeze drying of pure fractions afforded the desired compound (0.031 g, 49%) as a colourless solid. m/z: 680.7 (M – 1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.97-1.10 (m, 2H), 1.38-1.81 (m, 9H), 2.84-2.94 (m, 2H), 3.77 (d, 2H), 4.11-4.16 (m, 1H), 4.25-4.28 (m, 1H), 4.51 (s, 2H), 4.69-4.75 (m, 1H), 5.03-5.06 (m, 1H), 6.97-7.37 (m, 12H), 8.02-8.06 (m, 1H), 8.22 (t, 1H).

Example 86

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-hydroxy-2-(4-methoxyphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-methyl-D-valine**

To a solution of [4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (0.04 g, 0.081 mmol) and N-methyl morpholine (0.033 g, 0.323 mmol) in DMF (2 ml), under an atmosphere of nitrogen, was added TBTU (0.034 g, 0.105 mmol). After 1.5 h, glycyl-3-methyl-D-valine trifluoroacetate salt (0.037 g, 0.121 mmol) was added. The mixture was allowed to stir for 1 h after which water (1 ml) was added. After 10 minutes, MeOH (2 ml) and $NaBH_4$ (0.031 g, 0.807 mmol) were added. Full conversion to the corresponding alcohol was achieved within 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml) and the product was isolated by preparative HPLC of the mixture (eluent 0-50% CH_3CN in 0.1M NH_4OAc buffer). Freeze drying of pure fractions afforded the desired compound (0.027 g, 50%) as a colourless solid. m/z: 666.7 (M – 1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.88 (s, 9H), 2.81-2.93 (m, 2H), 3.69-3.70 (m, 3H), 3.82 (d, 2H), 4.03-4.07 (m, 1H), 4.22-4.25 (m, 1H), 4.51 (s, 2H), 4.61-4.68 (m, 1H), 5.01-5.03 (m, 1H), 6.81-7.36 (m, 12H), 7.81-7.86 (m, 1H), 8.25 (t, 1H).

Example 87

***N*-({4-[(2*R*,3*R*)-3-{[2-(4-ethoxyphenyl)-2-hydroxyethyl]thio}-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetyl)glycyl-3-methyl-D-valine**

To a solution of {4-[(2*R*,3*R*)-3-{[2-(4-ethoxyphenyl)-2-oxoethyl]thio}-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetic acid (0.04 g, 0.078 mmol) and N-methyl morpholine (0.032

g, 0.314 mmol) in DMF (2 ml) under an atmosphere of nitrogen was added TBTU (0.033 g, 0.102 mmol). After 45 minutes, glycyl-3-methyl-D-valine trifluoroacetate salt (0.031 g, 0.102 mmol) was added. The mixture was allowed to stir for 15 minutes after which water (1 ml) was added. After 10 minutes, MeOH (2 ml) and $NaBH_4$ (0.030 g, 0.785 mmol) were added. Full conversion to the corresponding alcohol was achieved within 5 minutes. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (2 ml) and the product was isolated by preparative HPLC of the mixture (eluent 0-50% CH_3CN in 0.1M NH_4OAc buffer). Freeze drying of pure fractions afforded the desired compound (0.027 g, 50%) as a colourless solid. m/z: 680.8 (M – 1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.89 (s, 9H), 1.26-1.30 (m, 3H), 2.81-2.92 (m, 2H), 3.82 (d, 2H), 3.93-3.99 (m, 2H), 4.05-4.08 (m, 1H), 4.22-4.25 (m, 1H), 4.51 (s, 2H), 4.60-4.67 (m, 1H), 5.01-5.03 (m, 1H), 6.79-7.36 (m, 12H), 7.82-7.87 (m, 1H), 8.25 (t, 1H).

Example 88

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-(4-methoxybenzyl)-D-cystein**

To a stirred solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine, (21.3 mg, 0.039 mmol) in DMF (3 ml) was added *N*-methylmorpholine (20 µl, 0.18 mmol). TBTU (15.1 mg, 0.047 mmol) was added and the mixture was stirred at 30°C for 35 minutes. *S*-(4-methoxybenzyl)-D-cysteine (12.8 mg, 0.053 mmol) was added and the mixture was stirred 1 hour at 30°C and 1.5 hours at ambient temperature. The formation of the ketone of the title compound was confirmed. M/z: 764.11 (M+1) and 762.06 (M-1). Methanol (3 ml) and sodium borohydride (15 mg, 0.40 mmol) were added and the mixture was stirred for 20 minutes. Ammonium acetate (25 mg) was added and the methanol was removed under reduced pressure. The remaining DMF-solution was purified with preparative HPLC on a C8 column, UV 240/260 nm. A gradient from 20 to 47% MeCN in 0.1M NH_4OAc was used as eluent. The MeCN was removed from the collected fractions under reduced pressure. The remaining water solution was acidified to pH 1 with $KHSO_4$ (2M) and extracted with DCM. The organic phase was concentrated under reduced pressure and the residue was dissolved in MeCN and water. After

lyophilisation, the title compound was obtained as a white solid (10.7 mg, 36 %). H-NMR (400 MHz, DMSO-d_6): 2-60-2.80 (m, 2H), 2.83-2.97 (m, 2H), 3.63-3.66 (bd, 2H), 3.69 (s, 3H), 3.77-3.81 (bd, 2H), 4.24-4.33 (m, 2H), 4.52 (s, 2H), 4.67-4.76 (m, 1H), 5.03 (d, 0.5H), 5.06 (d, 0.5H), 5.60-5.90 (b, 1H), 6.82 (d, 2H), 6.98 (d, 2H), 7.05-7.25 (m, 8H), 7.30-7.38 (m, 4H), 8.00-8.10 (b, 1H), 8.30 (t, 1H). M/z: 764.07 (M-1).

Example 89

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*O*-benzyl-L-serine**

To a stirred solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine, (20.3 mg, 0.038 mmol) in DMF (2 ml) was added *N*-methylmorpholine (15 µl, 0.14 mmol). TBTU (14.8 mg, 0.046 mmol) was added the mixture was stirred at 30°C for 1.5 hours. *O*-benzyl-L-serine (8.8 mg, 0.045 mmol) was added and the mixture was stirred overnight. The formation of the ketone of the title compound was confirmed. M/z: 718.04 (M+1) and 716.02 (M-1). Methanol (3 ml) and sodium borohydride (10.3 mg, 0.27 mmol) were added and the mixture was stirred for 1.5 hours. Ammonium acetate (20 mg) was added and the methanol was removed under reduced pressure. The remaining DMF-solution was purified by preparative HPLC on a C8 column, UV 240/260 nm. A gradient from 20 to 45 % MeCN in 0.1M NH_4OAc buffer was used as eluent. The pure fractions were collected and the MeCN was removed under reduced pressure. The remaining water solution was acidified to pH 1 with HCl (1M) and extracted with DCM. The combined organic phases were concentrated and the residue was dissolved in MeCN and water. After lyophilisation, the title compound was obtained as a white solid (2.3 mg, 8.5 %). H-NMR (400 MHz, DMSO-d_6): 2.85-2.94 (m, 2H), 3.58-3.63 (m, 1H), 3.69-3.75 (m, 1H), 3.83 (d, 2H), 4.25 (d, 0.5 H), 4.27 (d, 0.5H), 4.39-4.44 (m, 1H), 4.46 (d, 2H), 4.51 (s, 2H), 4.68-4.75 (m, 1H), 5.03 (d, 0.5H), 5.06 (d, 0.5), 6.98 (d, 2H), 7.05-7.17 (m, 4H), 7.20-7.26 (m, 3H), 7.28-7.39 (m, 8H), 8.20 (d, 1H), 8.25 (t, 1H). M/z: 718.10 (M-1).

Example 90

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-(4-methylbenzyl)-D-cysteine**

To a stirred solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine, (19.9 mg, 0.037 mmol) in DMF (2.0 ml) was added *N*-methylmorpholine (15 µl, 0.14 mmol). TBTU (14.4 mg, 0.045 mmol) was added and the mixture was stirred at 30 °C for 45 minutes. *S*-(4-methylbenzyl)-D-cysteine (10.5 mg, 0.047 mmol) was added and the mixture was stirred at 30 °C for 1 hour. The formation of the ketone of the title compound was confirmed. M/z: 748.02 (M+1). Methanol (2 ml) and sodium borohydride (14.7 mg, 0.39 mmol) were added the mixture was stirred for 30 minutes. Ammonium acetate (20 mg) was added and the methanol was removed under reduced pressure. The remaining DMF-solution was purified with preparative HPLC on a C8 column, UV-detection 240/260 nm. A gradient from 20 to 50% MeCN in 0.1M NH_4OAc buffer was used as eluent. The pure fractions were collected and the MeCN was removed under reduced pressure. The remaining water solution was acidified to pH 1 with HCl (1M) and extracted with DCM. The combined organic phases were concentrated and the residue was dissolved in MeCN and water. After lyophilisation, the title compound was obtained as a white solid (8.7 mg, 31.5 %). H-NMR (400 MHz, DMSO-d_6): 2.24 (s, 3H), 2.60-2.68 (m, 1H), 2.72-2.79 (m, 1H), 2.86-2.94 (m, 2H), 3.68 (s, 2H), 3.82 (d, 2H), 4.25 (d, 0.5H), 4.27 (d, 0.5H), 4.39-4.46 (m, 1H), 4.52 (s, 2H), 4.67-4.77 (m, 1H), 5.03 (d, 0.5H), 5.06 (d, 0.5H), 5.60-5.67 (bs, 1H), 6.98 (d, 2H), 7.05-7.18 (m, 8H), 7.20-7.25 (m, 2H), 4.30-4.39 (m, 4H), 8.23-8.32 (m, 2H), 12.80-12.95 (bs, 1H). M/z: 748.04 (M-1).

Example 91

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-ornithine**

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-ornithine (0.021 g, 0.032 mmole) was dissolved in methanol (1.5 mL). $NaBH_4$ (0.0032 g, 0.085 mmole) was added and after about 15 min the reaction was complete according to LC-MS. A few drops of acetic acid was added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a

Kromasil C8- column using 37% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.018 g (85%) of the desired product was obtained.

NMR (500 MHz,CD_3COOD) 1.62-1.80 (m, 3H), 1.91-2.00 (m, 1H), 2.92-3.10 (m, 4H), 3.98 (ABq, 2H), 4.05 (d, 0.5H), 4.08 (d, 0.5H), 4.27-4.32 (m, 1H), 4.64 (s, 2H), 4.82-4.87 (m, 1H), 4.93 (d, 0.5H), 4.94 (d, 0.5H), 6.99-7.06 (m, 4H), 7.09 (d, 2H), 7.28-7.33 (m, 2H), 7.33-7.41 (m, 4H)

Example 92

_N_-{[4-((2_R_,3_R_)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-N^6,N^6-dimethyl-L-lysine acetate

_N_-{[4-((2_R_,3_R_)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-N^6,N^6-dimethyl-L-lysine (0.05 g, 0.007 mmole) was dissolved in methanol (1.5 mL). $NaBH_4$ (0.0065 g, 0.0172 mmole) was added and after about 15 min the reaction was complete according to LC-MS. A few drops of acetic acid were added. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using 33.5% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.004g (73%) of the desired product as the acetate-salt was obtained.

NMR (500 MHz,CD_3COOD) 1.33-1.43 (m, 2H), 1.62-1.78 (m, 3H), 1.85-1.98 (m, 4H), 2.83 (s, 6H), 2.91-3.08 (m, 4H), 3.94 (s, 2H), 4.02 (d, 0.5H), 4.05 (d, 0.5H), 4.25-4.30 (m, 1H), 4.61 (s, 2H), 4.79-4.85 (m, 1H), 4.90 (d, 0.5H), 4.92 (d, 0.5H), 6.96-7.08 (m, 6H), 7.25-7.30 (m, 2H), 7.30-7.38 (m, 4H)

Example 93

_N_-{[4-((2_R_,3_R_)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-b,b-dimethyl-D-phenylalanine

To a stirred solution of *N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (25.2 mg, 0.047 mmol) in DMF (2 ml) was added *N*-methylmorpholine (30 µl, 0.027 mmol). TBTU (18.0 mg, 0.056 mmol) was added and the mixture was stirred at 30 °C for 1 hour. β, β -dimethyl-D-phenylalanine trifluoroacetate was added and the mixture was stirred at 30 °C for 1.25 hours. The formation of the ketone of the title compound was confirmed. M/z: 716.07 (M+1) and 714.05 (M-1). Water (0.5 ml) was added. Methanol (2 ml) and sodium borohydride (18.2 mg, 0.48 mmol) were added the mixture was stirred for 25 minutes. Ammonium acetate (30 mg) was added and the methanol was removed under reduced pressure. The remaining DMF-solution was purified with preparative HPLC. A gradient from 20 to 48 % MeCN in 0.1M NH_4OAc buffer was used as eluent. The MeCN was removed under reduced pressure and the remaining water solution was acidified to pH 1 with HCl (1M) and extracted with DCM. The organic phase was concentrated under reduced pressure and the residue was dissolved in MeCN and water. After lyophilisation, the title compound was obtained as a white solid (20.5 mg, 62 %). H-NMR (400 MHz, DMSO-d_6): 1.27-1.32 (m, 6H), 2.75-3.05 (m, 2H), 3.55-3.67 (m, 1H), 3.79 (dd, 1H), 4.25-4.30 (m, 0.5H), 4.40 (s, 0.5H), 4.45-4.53 (m, 3H), 4.68-4.78 (m, 1H), 4.99 (d, 0.5H), 4.05 (d, 0.5H), 6.88-6.98 (m, 2H), 7.05-7.17 (m, 5H), 7.20-7.40 (m, 10H) 7.45-7.75 (m, 1H) 8.22 (t, 1H). M/z: 718.09 (M+1) and 716.07 (M-1).

Example 94

1-(4-Fluorophenyl)-3-(R)-[2-(4-fluorophenyl)-2-hydroxyethylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(hydroxy)-1-(S)-(carboxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one

To a solution of 1-(4-fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(hydroxy)-1-(S)-(carboxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl} azetidin-2-one (0.039 g, 0.055 mmol) in MeOH (3 ml) was added $NaBH_4$ (0.005 g, 0.135 mmol). After 10 min, water (2 ml) and acetic acid (2 drops) were added before most of the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a gradient of 20-60% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying the desired product was obtained in 0.038 g (96%) as a white solid. NMR (DMSO, 500 MHz): 2.90-3.00 (m, 2H), 3.50 (dd, 1H), 3.60 (dd, 1H), 4.15-4.30 (m, 2H), 4.60 (ABq, 2H),

4.70-4.80 (m, 1H), 5.00-5.05 (m, 1H), 5.65 (d, 1H), 6.95-7.45 (m, 17H), 8.30-8.45 (m, 2H); m/z: 706.4.

Example 95

1-(4-Fluorophenyl)-3-(R)-[2-(4-fluorophenyl)-2-hydroxyethylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxy)-1-(S)-(carboxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one

To a solution of 1-(4-fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxy)-1-(S)-(carboxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl} azetidin-2-one (0.002 g, 0.003 mmol) in MeOH (3 ml) was added $NaBH_4$ (0.004 g, 0.108 mmol). After 10 min, the solution was added water (1 ml) and acetic acid (2 drops) before most of the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a gradient of 20-60% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying the desired product was obtained in 0.002 g (~quantitative yield) as a white solid. NMR (DMSO, 500 MHz): 1.00 (s, 9H), 2.90-3.00 (m, 2H), 3.40-3.55 (m, 2H), 4.20-4.30 (m, 2H), 4.60 (ABq, 2H), 4.70-4.80 (m, 1H), 5.00-5.05 (m, 1H), 5.70 (d, 1H), 6.95-7.45 (m, 17H), 8.20 (bs, 1H), 8.35 (d, 1H); m/z: 762.5.

Example 96

1-(4-Fluorophenyl)-3-(R)-[2-(4-fluorophenyl)-2-hydroxyethylthio]-4-(R)-{4-[*N*-{*N*-[2-(hydroxy)-1-(R)-(carboxy)ethyl]carbamoylmethyl}carbamoylmethoxy]phenyl}azetidin-2-one

To a solution of 1-(4-fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-{*N*-[2-(hydroxy)-1-(R)-(carboxy)ethyl]carbamoylmethyl}carbamoylmethoxy]phenyl} azetidin-2-one (0.028 g, 0.045 mmol) in MeOH (3 ml) was added $NaBH_4$ (0.010 g, 0.264 mmol). After 10 minutes the solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying the desired product was obtained in 0.014 g (50 %) as a white solid. NMR (CD_3COOD, 400 MHz): 3.00-3.20 (m, 2H), 3.95 (dd, 1H), 4.00-4.15 (m,

2H), 4.25 (ABq, 2H), 4.70 (s, 2H), 4.70-4.80 (m, 1H), 4.85-5.00 (m, 2H), 6.95-7.10 (m, 6H), 7.25-7.45 (m, 6H); m/z: 630.1.

Example 97

1-(4-Fluorophenyl)-3-(R)-[2-(4-fluorophenyl)-2-hydroxyethylthio]-4-(R)-{4-[*N*-{*N*-[2-(phenyl)-1-(R)-(carboxy)ethyl]carbamoylmethyl}carbamoylmethoxy]phenyl}azetidin-2-one

1-(4-Fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-{*N*-[2-(phenyl)-1-(R)-(carboxy)ethyl]carbamoylmethyl}carbamoylmethoxy]phenyl}azetidin-2-one (15mg, 0.022mmol) was dissolved in methanol (1 ml) and sodium borohydride (4mg) was added. The solvent was evaporated and the residue was purified by preparative HPLC using a gradient from 10% to 100 % MeCN in 0.1 M ammonium acetate buffer as mobile phase. Lyophilisation of the product fraction gave 8 mg (53 %) of the desired product. NMR (400 MHz,CD_3COOD): 3.02-3.17 (m,3H), 3.19-3.25 (m, 1H), 4.06-4.17 (m, 3H), 4.66 (s, 2H), 4.87-4.96 (m, 3H), 6.97-7.05 (m, 6H), 7.10-7.40 (m, 12H); m/z 688.3 (m-H).

Examples 98-136

The following compounds could be prepared by the procedure of Example 97, but wherein different protecting groups may be used.

Ex	R^1	R^2	R^3	R^4
98	H	Me	F	H
99	Ph	Me	F	H
100	H	Me	F	F
101	H	Me	H	H
102	Ph	Me	H	H
103	H	-$CH(Me)_2$	F	H
104	Ph	-$CH(Me)_2$	F	H
105	Ph	-$CH(Me)_2$	H	H
106	H	-$CH_2CH(Me)_2$	F	H
107	Ph	-$CH_2CH(Me)_2$	F	H

Ex	R^1	R^2	R^3	R^4
108	Ph	-$CH_2CH(Me)_2$	F	F
109	H	-$CH_2CH(Me)_2$	H	H
110	Ph	-$CH_2CH(Me)_2$	H	H
111	H	Ph	F	H
112	Ph	Ph	F	H
113	H	Ph	H	H
114	Ph	Ph	H	H
115	H	-CH_2Ph	F	H
116	Ph	-CH_2Ph	F	H
117	Ph	-CH_2Ph	F	F
118	Ph	-CH_2Ph	H	H
119	H	-CH_2(4-HOPh)	F	H
120	Ph	-CH_2(4-HOPh)	F	H
121	Ph	-CH_2(4-HOPh)	F	F
122	H	-CH_2(4-HOPh)	H	H
123	Ph	-CH_2(4-HOPh)	H	H
124	H	-CH_2OH	H	H
125	H	-CH_2COOH	F	F
126	H	-CH_2CH_2COOH	F	F
127	H	-$CH_2CH_2CH_2CH_2NHC(=NH)NH_2$	F	F
128	H	4-HOPh	F	F
129	Ph	-CH_2CH_2COOH	F	F
130	Ph	-$CH_2CH_2CH_2CH_2NHC(=NH)NH_2$	F	F
131	Ph	4-HOPh	F	F
132	Ph	-CH_2indol-3-yl	F	F
133	Ph	-CH_2imidazol-4-yl	F	F
134	Ph	-CH_2CH_2SMe	F	F
135	Ph	cyclohexyl	F	F
136	Ph	-CH_2cyclohexyl	F	F

Preparation of starting materials for the above Examples

Methods

Method 1

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanine**

[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (50 mg, 0.1mmol), *tert*-butyl D-alaninate (23 mg, 0.12mmol) and 4-methylmorpholine (31 mg, 0.31 mmol) were dissoved in DCM (1.5 ml) and stirred at room temperature for 5 minutes. TBTU (40 mg, 0.12 mmol) was added and the reaction mixture was stirred for 2 h. TFA (0.7 ml) was added and the solution was stirred for 90 minutes. TFA and DCM were removed under reduced pressure and the residue was dissolved in DCM and washed with water. The organic layer was dried over sodium sulphate and the solvent was removed under reduced pressure giving 55 mg (95 %) of the title product. M/z: 553.0 (M-1).

Method 2

[4-((2*R*,3*R*)-3-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-4-oxo-1-phenylazetidin-2-yl)phenoxy]acetic acid

To a solution of ethyl [4-((2*R*,3*R*)-3-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-4-oxo-1-phenylazetidin-2-yl)phenoxy]acetate (0.86 g, 1.53 mmol) in MeOH (25 ml) was added water (2.5 ml) and triethylamine (1.55 g). The reaction was stirred for 48 h at 50 °C. The solvent was evaporated and the residue was purified by preparative HPLC using a gradient of 20-70% CH_3CN in 0.1M NH_4OAc buffer. Freeze-drying of the pure fractions gave the title compound as a colourless solid. ^1H NMR [$(CD_3)_2SO$), 400 MHz] □ 0.50 (s, 3H), 1.15

(s, 3H), 2.93 (d, 1H), 2.96 (d, 1H), 3.21-3.37 (m, 4H), 4.13 (d, 1H), 4.28 (s, 2H), 4.97 (d, 1H), 6.83-7.41 (m, 14H).

Method 3

N-[(4-{(2R,3R)-4-oxo-3-[(2-oxo-2-phenylethyl)thio]-1-phenylazetidin-2-yl}phenoxy)acetyl]glycine

Glycine tert-butyl ester (0.015 g, 0.112 mmol) and N-Methylmorpholine (0.028 g, 0.281 mmol) were added to a solution of [4-((2R,3R)-3-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-4-oxo-1-phenylazetidin-2-yl)phenoxy]acetic acid (0.050 g, 0.094 mmol) in CH_2Cl_2 (5 ml). After 10 minutes, TBTU (0.039 g, 0.122 mmol) was added. The reaction was stirred overnight. The resulting tert-butyl ester was purified on silica gel and eluted with EtOAc/CH_2Cl_2 (25/75). The pure fractions were collected and concentrated. CH_2Cl_2 (4 ml) and TFA (1 ml) were added. The solvent was evaporated after 2 h and the residue was purified by preparative HPLC using an eluent of 20-70% CH_3CN in 0.1M NH_4OAc buffer. Freeze-drying of the pure fractions gave the title product as a colourless solid. M/z: 503.5 (M-1). ^1H NMR (CD_3CN), 400 MHz] δ 3.84 (d, 2H), 4.18 (d, 1H), 4.24 (s, 2H), 4.50 (s, 2H), 5.04 (d, 1H), 6.99-7.12 (m, 3H), 7.25-7.66 (m, 9H), 7.94-7.96 (m, 2H).

Method 4

(2R)-({[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}amino)(phenyl)acetic acid

[4-((2R,3R)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (0.40 g, 0.827 mmol) was dissolved in CH_2Cl_2 (40 ml) and *tert*-butyl (2R)-amino(phenyl)acetate (0.206 g, 0.993 mmol) and N-methylmorpholine (0.251 g, 2.48 mmol) were added. After 10 minutes, TBTU (0.345 g, 1.076 mmol) was added. The reaction was stirred overnight. The resulting tert-butyl ester was concentrated and purified on silica gel (eluted with EtOAc/CH2Cl2 25/75). The pure fractions were collected and concentrated.

CH_2Cl_2 (25 ml) and TFA (3 ml) were added. The mixture was stirred for 5 days and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a gradient of 20-70% CH_3CN in 0.1M NH_4OAc buffer. Freeze-drying of the pure fractions gave the title compound as a colourless solid. M/z: 615.50 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 4.35 (d, 1H), 4.36 (d, 1H), 4.40 (d, 1H), 4.53 (d, 1H), 4.58 (d, 1H), 4.94 (d, 1H), 5.19 (d, 1H), 6.97-7.40 (m, 15H), 8.02-8.06 (m, 2H), 8.26-8.32 (m, 1H).

Method 5

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-valine**

[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid, (50.0 mg, 0.10 mmol) was dissolved in DCM (2 ml). *tert*-Butyl D-valinate hydrochloride (28.4 mg, 0.14 mmol) and *N*-methylmorpholine (3.0 µl, 0.31 mmol) were added. After 5 minutes, TBTU (43.7 mg, 0.14 mmol) was added and the mixture was stirred overnight. The intermediate *tert*-butylester of the title compound was confirmed. M/z: 637.1 (M-H). The solvent was removed under reduced pressure. The yellow residue was dissolved in formic acid (1.5 ml) and heated at 50°C for 5 h. The solvent was evaporated and the residue was purified by preparative HPLC on a C8 column. A gradient from 20 to 50% MeCN in 0.1 M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (30.5 mg, 51 %). 1H-NMR (400 MHz, DMS-d_6): 0.74 (t, 6H), 1.98-2.07 (m, 1H), 3.84 (brs, 1H), 4.32 (d, 1H), 4.35 (s, 1H), 4.36 (s, 1H), 4.50 (brs, 2H), 5.16 (d, 1H), 6.96 (d, 2H), 7.10-7.17 (m, 2H), 7.19-7.24 (m, 2H), 7.31-7.38 (m, 4H), 7.66 (brs, 1H), 7.99-8.04 (m, 2H). M/z: 583.0 (M+H) and 581.0 (M-H).

Method 6

(N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine

A mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.0229g, 0.042 mmol), (R)-valin *tert*-butylester hydrochloride (0.0121 g, 0.058 mmol) and N-methylmorpholine (0.012 ml,0.111 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.018 g, 0.056 mmol) was added and the mixture was stirred overnight. Trifluoroacetic acid (0.65 ml) was added and after a couple of hours the hydrolysis was complete according to LC-MS. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. The solvent was removed under reduced pressure and 0.022 g (81 %) of the title product was obtained. M/z 640.06.

Method 7

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-threonine**

A mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.0188g, 0.035 mmol), *tert*-butyl *O*-(*tert*-butyl)-L-threoninate (0.0151 g, 0.065 mmol) and N-methylmorpholine (0.012 ml,0.111 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.018 g, 0.056 mmol) was added and the mixture was stirred overnight. Trifluoroacetic acid (0.65 ml) was added and after a couple of hours the hydrolysis was complete according to LC-MS. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. The solvent was removed under reduced pressure and 0.014 g (63 %) of the title product was obtained. M/z 641.92.

Method 8

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-asparagine**

A mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.0213g, 0.039 mmol), tert-butyl L-asparaginate hydrochloride (0.0141 g, 0.063 mmol) and N-methylmorpholine (0.012 ml,0.111 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.018 g, 0.056 mmol) was added and the mixture was stirred overnight. Trifluoroacetic acid (0.65 ml) was added and after a couple of hours the hydrolysis was complete according to LC-MS. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. The solvent was removed under reduced pressure and 0.020 g (77 %) of the title product was obtained. M/z 655.11.

Method 9

_N_-{[4-((2_R_,3_R_)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-methionine

A mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.0197g, 0.036 mmol), *tert*-butyl L-methioninate hydrochloride (0.0144 g, 0.060 mmol) and N-methylmorpholine (0.012 ml,0.111 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.018 g, 0.056 mmol) was added and the mixture was stirred overnight. Trifluoroacetic acid (0.65 ml) was added and after a couple of hours the hydrolysis was complete according to LC-MS. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. The solvent was removed under reduced pressure and 0.015 g (61 %) of the title product was obtained. M/z 672.10.

Method 10

***tert*-butyl _N_-[(benzyloxy)carbonyl]glycyl-D-valinate**

A mixture of *N*-[(benzyloxy)carbonyl]glycine (, 2.4g, 11.5 mmol), *tert*-butyl D-valinate hydrochloride (2.4 g, 11.4 mmol) and N-methylmorpholine (2.53 ml,22.9 mmol) in DCM (20ml) was stirred at room temperature. TBTU (4.79 g, 14.9 mmol) was added and the mixture was stirred for three days. The solvent was removed under reduced pressure. Water was added and the mixture was extracted two times with toluen. The organic layer was washed with brine, dryed (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography using DCM:EtOAc:aceton 4:1:1 as eluent to give 3.92 g (94%) of the title compound. NMR (500 MHz,CD_3COOD) 0.88-0.99 (m, 6H), 1.48 (s, 9H), 2.08-2.19 (m 1H), 3.85 (ABq, 2H), 4.24 (d, 1H), 5.12 (ABq, 2H), 7.28-7.41 (m, 5H).

Method 11

***tert*-butyl glycyl-D-valinate hydrochloride**

tert-Butyl *N*-[(benzyloxy)carbonyl]glycyl-D-valinate (3.89g, 10.7 mmol) and Pd on charcoal (95%, 0.3g) were mixed in EtOH (95%, 80 ml) and stirred under H_2-atmosphere for 2 h. The mixture was filtered through Celite 521 and the solvent was evaporated under reduced pressure. MeCN (25 ml) and pyridine hydrochloride (1.25g, 10.8 mmol) were added. The solvent was evaporated under reduced pressure to give 2.3g (81%) of the title product. NMR (500 MHz,CD_3COOD) 0.96-1.01 (m, 6H), 1.49 (s, 9H), 2.13-2.23 (m 1H), 3.76 (AB, 2H), 4.28-4.33 (m, 1H).

Method 12

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine**

A mixture of [4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (0.0153g, 0.031 mmol), *tert*-butyl glycyl-D-valinate

hydrochloride (0.0099 g, 0.037 mmol) and N-methylmorpholine (0.010 ml,0.091 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.016 g, 0.050 mmol) was added and the mixture was stirred for 3.5 h. Trifluoroacetic acid (0. 5 ml) was added and after 3.5 h the solvent was removed under reduced pressure. The residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. The solvent was removed under reduced pressure and 0.015 g (74 %) of the title product was obtained. M/z 652.20.

Method 13

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine**

A mixture of [4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (0.150g, 0.30 mmol), *tert*-butyl glycinate hydrochloride (0.0635 g, 0.38 mmol) and N-methylmorpholine (0.10 ml,0.91 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.128 g, 0.40 mmol) was added and the mixture was stirred overnight. Trifluoroacetic acid (4.0 ml) was added and after 2 h the solvent was removed under reduced pressure. The residue was purified by preparative HPLC on a Kromasil C8- column using 35% MeCN in 0.1M ammonium acetate buffer as eluent. The solvent was removed under reduced pressure and 0.159 g (95 %) of the title product was obtained. M/z 553.02.

Method 14

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-2-butylnorleucine**

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (0.020 g, 0.037 mmol) and NMM (0.040 ml, 0.363 mmol) were dissolved in DCM (5 ml) at 30°C. TBTU (a total of 0.016 g, 0.050 mmol) were added in

portions and the mixture was stirred for 1 h. 2-Butylnorleucine (0.007 g, 0.037 mmol) was added and the mixture was stirred at 30°C for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC, using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.009 g (34 % yield) of the title product was obtained as a white solid. M/z: 710.1. 1H NMR (DMSO, 400 MHz): δ 0.73-0.82 (m, 6H), 0.88-1.22 (m, 8H), 1.56-1.69 (m, 2H), 1.96-2.07 (m, 2H), 3.71 (d, 2H), 4.32 (d, 1H), 4.36 (ABq, 2H), 4.52 (s, 2H), 5.16 (d, 1H), 6.95-7.01 (m, 2H), 7.11-7.26 (m, 4H), 7.30-7.40 (m, 4H), 7.61 (s, 1H), 7.98-8.06 (m, 2H), 8.25-8.42 (m, 1H).

Method 15

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-alanine**

A solution of [4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (0.020 g, 0.041 mmol), L-Alanine tert-butyl ester hydrochloride (0.009 g, 0.050 mmol) and N-Methylmorpholine (0.018 ml, 0.163 mmol) in DCM (4 ml) was stirred for 5 min. TBTU (0.017 g, 0.053 mmol) was added. The formation of the ester was confirmed after 3 h. M/z: 611.1. TFA (3 ml) was added. After 2h, the mixture was diluted with toluene (2 ml) and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC, using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.023 g (>98%) of the title product was obtained as a white solid. M/z: 555.1. 1H NMR (DMSO, 400 MHz): δ 1.17 (d, 3H), 3.73-3.82 (m, 1H), 4.33 (d, 1H), 4.35 (ABq, 2H), 4.43 (s, 2H), 5.15 (d, 1H), 6.92-7.98 (m, 2H), 7.10-7.24 (m, 4H), 7.29-7.39 (m, 4H), 7.84 (d, 1H), 7.97-8.04 (m, 2H).

Method 16

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-phenylalanine

Methyl N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-phenylalaninate (20 mg, 0.029 mmol) was dissolved in 1.6 ml MeOH and 0.2 ml H_2O. Et_3N (0.2 ml, 1.44 mmol) was added and the mixture was stirred overnight. The mixture was heated to 80°C for 7 h. The mixture was purified by preparative HPLC using a C8 column (25x300mm). A gradient from 20% to 40% MeCN in 0.1 M ammonium acetate was used as mobile phase. The product fraction was concentrated and lyophilized to yield 7 mg (36%). M/z: 688.

Method 17

methyl N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-L-phenylalaninate

N-{[4-((2R,3R)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (66 mg, 0.12 mmol) was dissolved in 2 ml DCM. N-methylmorpholine (40 ul, 0.36 mmol), L-(S)-phenylalanine methyl ester hydrochloride (33 mg, 0.15 mmol) and finally TBTU (45 mg, 0.14 mmol) were added. The mixture was stirred overnight. The crude mixture was purified by flash chromatography on 5g SiO_2. EtOAc:Hex (1:1), DCM and finally DCM:Acetone (4:1) were used as eluents. The collected fraction was concentrated to yield 67mg (78%) of the title compound. M/z: 702 (M+1).

Method 18

***tert*-butyl N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio} -4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-4-methylleucinate**

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine (20 mg, 0.037 mmol) was dissolved in 3 ml DCM. N-Methylmorpholine (9 µl, 0.082 mmol) and TBTU (14 mg, 0.044 mmol) were added. After 5 minutes, *tert*-butyl 4-methylleucinate (9 mg, 0.045 mmol) was added and the mixture was stirred for 2 h. Additional *tert*-butyl 4-methylleucinate (ca 3 mg, 0.015 mmol) was added. After 15 min, water (2 ml) was added and the mixture was acidified to a pH of 2 using 2M $KHSO_4$. The aqueous phase was extracted with 2 ml DCM and the combined organic phases were washed with 3 ml water, dried over Na_2SO_4 and filtered. Removal of the solvent under reduced pressure gave the title compound. M/z: 724.

Method 19

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycylglycine

A solution of of [4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (0.200 g, 0.414 mmol), glycylglycine methyl ester hydrochloride (0.090 g, 0.493 mmol) and N-methylmorpholine (0.150 ml) in DCM (5 ml) was stirred for 10 min. TBTU (0.170 g) was added and the mixture was stirred for 20 h. The formation of the ester was confirmed. M/z: 612.0. The solvent was removed under reduced pressure. The residue was dissolved in a mixture of MeOH (5 ml), water (1 ml) and Et_3N (0.5 ml). The solution was stirred at 50°C for 18 h. DBN (0.050 ml, 0.405 mmol) was added and the mixture was stirred for 2 h at 50°C. Ammonium acetate buffer (0.1 M, 3 ml) was added and the mixture was concentrated. The residue was purified by preparative HPLC, using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, the title product (0.094 g, 38 % yield) was obtained as a white solid. M/z: 598.2. 1H NMR (DMSO, 400 MHz): 3.50 (d, 2H), 3.75 (d, 2H), 4.32 (d, 1H), 4.35 (ABq, 2H), 4.46-4.53 (m, 2H), 5.15 (d, 1H), 6.94-7.00 (m, 2H), 7.10-7.25 (m, 4H), 7.29-7.39 (m, 4H), 7.68-7.81 (m, 1H), 7.98-8.04 (m, 2H), 8.30-8.36 (m, 1H).

Method 20

Ethyl {[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}acetate

Ethyl [(2-oxo-2-phenylethyl)thio]acetate (10.8 g, 45.3 mmol) was dissolved in toluene (250 ml). 2,2-Dimethyl-1,3-propanediol (37.6 g, 0.36 mol) and p-toluene sulfonic acid (cat., 500 mg) were added. The mixture was stirred at reflux in a Dean-Stark apparatus for two hours and at room temperature overnight. The mixture was concentrated under reduced pressure. The crude oil was purified by flash-chromatography (hexane:EtOAc-7:1) to give 11.2 g (70 %) of the title compound as a colourless oil. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2-1.3 (t, 3H), 1.4 (s, 3H), 3.0 (s, 2H), 3.2 (s, 2H), 3.5 (s, 4H), 4.1-4.2 (q, 2H), 7.3-7.6 (m, 5H).

Method 21

{[(5,5-Dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}acetic acid

Ethyl {[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}acetate (11.2 g, 34.3 mmol) was dissolved in THF (150 ml) and cooled to 0°C. LiOH (2.88 g, 68.7 mmol) in water (40 ml) was added and the mixture was stirred for 19 h. The solvents were evaporated. The crude product was extracted between water and diethyl ether. The aqueous layer was acidified to a pH of 6 using 2M HCl and extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 9.8 g (96 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.4 (s, 3H), 3.0 (s, 2H), 3.3 (s, 2H), 3.5 (s, 4H), 7.3-7.6 (m, 5H).

Method 22

(4*S*)-3-({[(5,5-Dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}acetyl)-4-phenyl-1,3-oxazolidin-2-one

{[(5,5-Dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}acetic acid (9.9 g, 33.0 mmol) was dissolved in dry CH_2Cl_2 (250 ml) and cooled to 0°C. N,N'-Dicyclohexylcarbodiimide (DCC, 7.63 g, 37.0 mmol) and 4-(dimethylamino)pyridine (DMAP, 8.57 g, 70.0 mmol) were added and the mixture was stirred at 0°C for 20 minutes. (S)-(+)-4-Phenyl-2-oxazolidinone (5.38 g, 33.0 mmol) was added and the mixture was stirred at room temperature for 70 h. The mixture was filtered, concentrated under reduced pressure and purified by flash-chromatography (hexane:EtOAc-7:3). This afforded 10.2 g (70 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): 0.6 (s, 3H), 1.3 (s, 3H), 2.8 (s, 2H), 3.4 (s, 4H), 3.8 (s, 2H), 4.1-4.15 (dd, 1H), 4.6-4.8 (t, 1H), 5.35-5.45 (dd, 1H), 7.25-7.45 (m, 9H).

<u>Method 23</u>

Ethyl (4-{(1*S*,2*R*)-1-anilino-2-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate

Tetraisopropyl orthotitanate (0.5 ml, 1.7 mmol) was added to a solution of $TiCl_4$ (1M in CH_2Cl_2, 5.1 ml, 5.1 mmol) in CH_2Cl_2 (50 ml) at 0°C under inert atmosphere. The mixture was stirred for ten minutes. (4*S*)-3-({[(5,5-Dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}acetyl)-4-phenyl-1,3-oxazolidin-2-one (3.0 g, 6.8 mmol) in dry CH_2Cl_2 (60 ml) was added dropwise over 20 minutes and the mixture was stirred for ten minutes. Ethyl {4-[(phenylimino)methyl]phenoxy}acetate (3.8 g, 13.6 mmol) in dry CH_2Cl_2 (60 ml) was added dropwise over 30 minutes and the mixture was cooled to -40°C and stirred for 20 minutes. Ethyl diisopropyl amine (2.3 ml, 13.6 mmol) was added dropwise over ten minutes and the mixture was stirred at -40°C for six hours. The mixture was cooled to -78°C and isopropanol (90 ml) was added. The mixture was slowly warmed to room temperature overnight. H_2O (100 ml) was added and the mixture was stirred for 35 minutes at room temperature. NH_4Cl (10%) was added and the mixture was extracted twice with diethyl ether.

The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash-chromatography (hexane:EtOAc 5:1 then 7:3 then 6:4) gave 2.13 g (43 %) of the title compound as a yellow solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2-1.4 (m, 6H), 2.8-3.0 (m, 2H), 3.3-3.5 (m, 4H), 4.5-4.7 (m, 3H), 5.3-5.5 (m, 1H), 5.7-5.8 (d, 1H), 6.4-6.5 (d, 2H), 6.6-6.9 (m, 4H), 6.9-7.0 (d, 2H), 7.0-7.5(m, 7H). M/z: 747.3 (M^+ + Na)

Method 24

Ethyl [4-((2*R*,3*R*)-3-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-4-oxo-1-phenylazetidin-2-yl)phenoxy]acetate

Ethyl (4-{(1*S*,2*R*)-1-anilino-2-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate (2.1 g, 2.9 mmol) was dissolved in dry toluene (200 ml) and heated to 90°C under inert atmosphere. N,O-Bis(trimethylsilyl)acetamide (BSA, 2.1 ml, 8.7 mmol) was added and the mixture was stirred at 90°C for one hour. At 45°C tetrabutylammonium fluoride (TBAF, cat., 0.1 g) was added and the mixture was stirred at 45°C for 18 h. The mixture was concentrated under reduced pressure. The residue was purified by flash-chromatography (hexane:EtOAc 5:1). This afforded 0.98 g (60 %) of the title compound as a yellow oil. ^{1}H-NMR ($CDCl_3$, 200 MHz): 0.6 (s, 3H), 1.2-1.4 (m, 6H), 3.0-3.2 (t, broad, 2H), 3.3-3.5 (m, 4H), 3.95 (d, 1H), 4.2-4.4 (q, 2H), 4.6 (s, 2H), 4.8 (d, 1H), 6.9-7.1 (m, 3H), 7.2-7.6 (m, 11H). MS (CI) M/z: 584.2 (M^+ + Na).

Method 25

***tert*-Butyl (4-{(1*S*,2*R*)-2-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-1-[(4-fluorophenyl)amino]-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate**

Tetraisopropyl orthotitanate (0.51 ml, 1.8 mmol) was added to a solution of $TiCl_4$ (1M in CH_2Cl_2, 5.1 ml, 5.1 mmol) in CH_2Cl_2 (50 ml) at 0°C under inert atmosphere. The mixture was stirred for ten minutes. (4*S*)-3-({[(5,5-Dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}acetyl)-4-phenyl-1,3-oxazolidin-2-one (3.0 g, 6.8 mmol) in dry CH_2Cl_2 (50 ml) was added dropwise over 20 minutes. After ten minutes, *tert*-butyl (4-{[(4-fluorophenyl)imino]methyl}phenoxy)acetate (4.5 g, 13.6 mmol) in dry CH_2Cl_2 (50 ml) was added dropwise over 30 minutes. The mixture cooled to -30°C and stirred for 20 minutes. Ethyl diisopropyl amine (2.3 ml, 13.4 mmol) in 20 ml dry CH_2Cl_2 was added dropwise over ten minutes and the mixture was stirred at -30°C for six hours. The mixture was cooled to -78°C. Isopropanol (60 ml) was added and the temperature was risen overnight. H_2O (100 ml) was added and the mixture was stirred for 35 minutes at room temperature. The mixture was extracted twice with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash-chromatography (hexane:EtOAc 5:1) afforded 2.95 g (56 %) of the title compound as a yellow solid. M/z: 793.3 (M^+ + Na).

Method 26

***tert*-Butyl {4-[(2*R*,3*R*)-3-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetate**

tert-Butyl (4-{(1*S*,2*R*)-2-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-1-[(4-fluorophenyl)amino]-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate (2.6 g, 3.4 mmol) was dissolved in dry toluene (250 ml) and heated to 90°C under inert atmosphere. N,O-Bis(trimethylsilyl)acetamide (BSA, 2.5 ml, 10.3 mmol) was added and the mixture was stirred at 90°C for one hour. The mixture was cooled to 45°C and tetrabutylammonium fluoride (TBAF, cat., 0.5 g) was added. The mixture was stirred at 45°C for two hours. The mixture was concentrated under reduced pressure and purified by flash-chromatography (hexane:EtOAc 7:1). This afforded 0.65 g (31 %) of the title compound as a yellow solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2 (s, 3H), 1.5

(s, 9H), 2.9-3.1 (q, broad, 2H), 3.4 (q, 4H), 4.0 (s, 1H), 4.5 (s, 2H), 4.8 (s, 1H), 6.9-7.0 (m, 4H), 7.2-7.3 (m, 5H), 4.3-4.4 (m, 4H).

Method 27

(4-{(2*R*,3*R*)-1-(4-Fluorophenyl)-4-oxo-3-[(2-oxo-2-phenylethyl)thio]azetidin-2-yl}phenoxy)acetic acid

tert-butyl {4-[(2*R*,3*R*)-3-{[(5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)methyl]thio}-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetate(1.34 g, 2.21 mmol) was dissolved in formic acid (20 ml) and stirred for 90 minutes. The mixture was concentrated under reduced pressure (temperature < 30°C). The crude oil was purified by flash-chromatography (hexane:acetone:formic acid 60:40:0.1) to afford 0.7 g (68 %) of the title compound as a pale yellow solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 4.15 (d, 1H), 4.22 (d, 2H), 4.71 (s, 2H), 4.91 (d, 1H), 6.92-7.00 (m, 4H), 7.24-7.30 (m, 4H), 7.46-7.63 (m, 3H), 7.94-7.99 (d, 2H). MS (CI) M/z: 464.2 (M-1).

Method 28

Ethyl ({[2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetate

Ethyl {[2-(4-methoxyphenyl)-2-oxoethyl]thio}acetate (9.57 g, 35.7 mmol) was dissolved in benzene (250 ml). 2,2-Dimethyl-1,3-propanediol (29.7 g, 0.29 mol) and p-toluene sulfonic acid (500 mg) were added. The mixture was stirred at reflux in a Dean-Stark apparatus for three hours and at room temperature overnight. The mixture was concentrated under reduced pressure. CH_2Cl_2 was added and the solution was washed twice with H_2O and with brine. The organic phase was dried ($MgSO_4$) and filtered. Concentration under reduced pressure afforded a crude oil which was purified by flash-chromatography (hexane:EtOAc 7:1) to afford 5.95 g (47 %) of the title compound as a colorless oil. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2-1.4 (m, 6H), 3.0 (s, 2H), 3.2 (s, 2H), 3.4 (s, 4H), 3.8 (s, 3H), 4.2 (q, 2H), 6.9 (d, 2H), 7.4 (d, 2H).

Method 29

({[2-(4-Methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetic acid

Ethyl ({[2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetate (5.95 g, 16.8 mmol) was dissolved in THF (75 ml) and cooled to 0°C. LiOH (2.11 g, 50.4 mmol) in water (40 ml) was added and the mixture was stirred for 90 minutes. Water was added and the mixture was extracted twice with diethyl ether. The aqueous layer was acidified using 2M HCl until pH=4 and extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford 5.4 g (>98%) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.4 (s, 3H), 3.0 (s, 2H), 3.4 (s, 2H), 3.5 (s, 4H), 3.9 (s, 3H), 6.9 (d, 2H), 7.4 (d, 2H).

Method 30

(4*S*)-3-[({[2-(4-Methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetyl]-4-phenyl-1,3-oxazolidin-2-one

({[2-(4-Methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetic acid (5.4 g, 16.5 mmol) was dissolved in dry CH_2Cl_2 (80 ml) and cooled to 0°C. N,N'-dicyclohexylcarbodiimide (DCC, 3.76 g, 18.2 mmol) in 20 ml of CH_2Cl_2 and 4-(dimethylamino)pyridine (DMAP, 4.04 g, 33.1 mmol) were added and the mixture was stirred at 0°C for 30 minutes. (S)-(+)-4-Phenyl-2-oxazolidinone (2.69 g, 16.5 mmol) was added and the mixture was stirred at room temperature for 17 h. The mixture was filtered, concentrated under reduced pressure and purified by flash-chromatography (hexane:EtOAc 4:1 then 2:1). This afforded 5.69 g (73 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 2.8 (s, 2H), 3.4 (s, 4H), 3.8 (s, 2H), 3.8 (s, 3H), 4.3 (dd, 1H), 4.7 (t, 1H), 5.4 (dd, 1H), 6.9 (d, 2H), 7.3 (m, 7H).

Method 31

***tert*-Butyl (4-{(1*S*,2*R*)-1-[(4-fluorophenyl)amino]-2-({[2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate**

Tetraisopropyl orthotitanate (0.31 ml, 1.06 mmol) was added to a solution of $TiCl_4$ (1M in CH_2Cl_2, 3.18 ml, 3.18 mmol) in CH_2Cl_2 (50 ml) at 0°C under inert atmosphere. The mixture was stirred for ten minutes. (4*S*)-3-[({[2-(4-Methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetyl]-4-phenyl-1,3-oxazolidin-2-one (2.00 g, 4.24 mmol) in dry CH_2Cl_2 (50 ml) was added dropwise over 20 minutes. The mixture was stirred for ten minutes. *tert*-Butyl (4-{[(4-fluorophenyl)imino]methyl}phenoxy)acetate (2.79 g, 8.48 mmol) in dry CH_2Cl_2 (50 ml) was added dropwise over 30 minutes. The mixture was cooled to -30°C and stirred for 20 minutes. Ethyl diisopropyl amine (1.45 ml, 8.48 mmol) in 10 ml dry CH_2Cl_2 was added dropwise over ten minutes and the mixture was stirred at -30°C for five hours. The mixture was cooled to -78°C. Isopropanol (60 ml) was added and the temperature was allowed to rise overnight. H_2O (100 ml) was added and the mixture was stirred for 20 minutes and extracted twice with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash-chromatography (hexane:EtOAc 3:1) afforded 2.00 g (59 %) of the title compound as a yellow solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 1.5 (s, 9H), 2.6-2.9 (m, 2H), 3.3-3.5 (m, 4H), 3.8 (s, 3H), 4.1-4.3 (m, 2H), 4.5 (s, 2H), 4.6-4.8 (m, 2H), 5.0-5.4 (s, broad, 1H), 5.4 (m, 1H), 5.7 (d, 1H), 6.4 (m, 2H), 6.6-6.8 (m, 4H), 6.8-7.0 (m, 4H), 7.1-7.4 (m, 7H).

Method 32

***tert*-Butyl {4-[(2*R*,3*R*)-1-(4-fluorophenyl)-3-({[2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetate**

tert-Butyl (4-{(1*S*,2*R*)-1-[(4-fluorophenyl)amino]-2-({[2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-

yl]propyl}phenoxy)acetate (2.0 g, 2.5 mmol) was dissolved in dry toluene (200 ml) and heated to 90°C under inert atmosphere. N,O-Bis(trimethylsilyl)acetamide (BSA, 1.8 ml, 7.5 mmol) was added and the mixture was stirred at 90°C for one hour. The mixture was cooled to 45°C and tetrabutylammonium fluoride (TBAF, 150 mg) was added and the mixture was stirred at 45°C for two hours. The mixture was concentrated under reduced pressure and filtered through a short column of silica (hexane:EtOAc 4:1). Purification of the crude oil by flash-chromatography (hexane:EtOAc 5:1) gave 0.65 g (41 %) of the title compound as a yellow solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 1.5 (s, 9H), 3.0-3.2 (m, 2H), 3.3-3.5 (m, 4H), 3.8 (s, 3H), 4.0 (d, 1H), 4.5 (s, 2H), 4.8 (d, 1H), 6.8-7.0 (m, 6H), 7.2-7.4 (m, 6H).

Method 33

[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid

tert-Butyl {4-[(2*R*,3*R*)-1-(4-fluorophenyl)-3-({[2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetate(0.65 g, 1.02 mmol) was dissolved in formic acid (10 ml) and stirred for 90 minutes. The mixture was concentrated under reduced pressure (temperature < 30°C) and the crude oil was purified by flash-chromatography (hexane:acetone:formic acid 60:40:0.1) to afford 0.45 g (88 %) of the title compound as a pale yellow solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 3.9 (s, 3H), 4.1 (d, 1H), 4.1 (s, 2H), 4.7 (s, 2H), 4.9 (d, 1H), 6.9-7.1 (m, 6H), 7.2-7.4 (m, 4H), 7.9-8.0 (d, 2H). MS (CI) M/z: 494.1 ($M^+ - 1$), 495.1 (M^+)

Method 34

Ethyl ({[5,5-dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)acetate

Ethyl {[2-(4-methylphenyl)-2-oxoethyl]thio}acetate (12.2 g, 48.4 mmol) was dissolved in benzene (350 ml). 2,2-Dimethyl-1,3-propanediol (40.3 g, 0.387 mol) and p-toluene sulfonic

acid (1g) were added. The mixture was stirred at reflux in a Dean-Stark apparatus for two hours, cooled and concentrated under reduced pressure. CH_2Cl_2 was added and the organic phase was washed twice with brine and dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded a.crude oil, which was purified by flash-chromatography (hexane:EtOAc 8:1) to afford 10.0 g (61 %) of the title compound as a clear oil. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2-1.4 (m, 6H), 2.4 (s, 3H), 3.0 (s, 2H), 3.2 (s, 2H), 3.4-3.5 (m, 4H), 4.2 (q, 2H), 7.2-7.4 (m, 4H).

Method 35

({[5,5-Dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)acetic acid

Ethyl ({[5,5-dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)acetate (10.1 g, 29.8 mmol) was dissolved in THF (150 ml) and cooled to 0°C. LiOH (3.76 g, 89.5 mmol) in water (50 ml) was added and the mixture was stirred for two hours at room temperature. The mixture was concentrated under reduced pressure. Water was added and the mixture was extracted with diethyl ether. The aqueous layer was acidified using 2M HCl to pH 3 and extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford 8.7 g (94 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2 (s, 3H), 2.4 (s, 3H), 3.0 (s, 2H), 3.4 (s, 2H), 3.4 (s, 4H), 7.2-7.4 (m. 4H).

Method 36

(4*S*)-3-[({[5,5-Dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)acetyl]-4-phenyl-1,3-oxazolidin-2-one

({[5,5-Dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)acetic acid (8.7 g, 28.0 mmol) was dissolved in dry CH_2Cl_2 (120 ml) and cooled to 0°C. N,N'-Dicyclohexylcarbodiimide (DCC, 6.35 g, 30.8 mmol) in 30 ml of CH_2Cl_2 and 4-

(dimethylamino)pyridine (DMAP, 6.85 g, 56.1 mmol) were added. The mixture was stirred at 0°C for 30 minutes. (S)-(+)-4-Phenyl-2-oxazolidinone (4.57 g, 28.0 mmol) was added and the mixture was stirred at room temperature for 19 h. The mixture was filtered, concentrated under reduced pressure and purified by flash-chromatography (hexane:EtOAc 5:1 then 4:1). This afforded 7.07 g (55 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2 (s, 3H), 2.4 (s, 3H), 2.8 (s, 2H), 3.4 (s, 4H), 3.8 (s, 2H), 4.3 (dd, 1H), 4.7 (t, 1H), 5.4 (dd ,1H), 7.2-7.5 (m, 9H).

Method 37

tert-Butyl (4-{(1*S*,2*R*)-2-({[5,5-dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)-1-[(4-fluorophenyl)amino]-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate

Tetraisopropyl orthotitanate (0.37 ml, 1.23 mmol) was added to a solution of $TiCl_4$ (1M in CH_2Cl_2, 3.3 ml, 3.3 mmol) in CH_2Cl_2 (50 ml) at 0°C under inert atmosphere. The mixture was stirred for ten minutes. (4*S*)-3-[({[5,5-Dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)acetyl]-4-phenyl-1,3-oxazolidin-2-one (2.0 g, 4.4 mmol) in dry CH_2Cl_2 (50 ml) was added dropwise over 20 minutes and the mixture was stirred for ten minutes. *tert*-Butyl (4-{[(4-fluorophenyl)imino]methyl}phenoxy)acetate (2.9 g, 8.8 mmol) in dry CH_2Cl_2 (50 ml) was added dropwise over 30 minutes. The mixture was cooled to -30°C and stirred for 20 minutes. Ethyl diisopropyl amine (1.5 ml, 8.8 mmol) in 10 ml dry CH_2Cl_2 was added dropwise over ten minutes. The mixture was stirred at -30°C for four hours. The mixture was cooled to -78°C and isopropanol (60 ml) was added. The temperature was allowed to reach room temperature over two hours. H_2O (100 ml) was added and the mixture was stirred for 20 minutes and extracted twice with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash-chromatography (hexane:EtOAc 5:1 then 4:1) afforded 2.55 g (74 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 1.5 (s, 9H), 2.4 (s, 3H), 2.6-2.9 (m, 2H), 3.3-3.5 (m, 4H), 4.1-4.3 (m, 1H), 4.5 (s, 2H), 4.6-4.8 (m, 2H), 5.0-5.3 (s, broad, 1H), 5.2 (m, 1H), 5.7 (d, 1H), 6.4 (m, 2H), 6.6-6.8 (m, 4H), 6.9 (m, 2H), 7.1-7.4 (m, 9H).

Method 38

***tert*-Butyl {4-[(2*R*,3*R*)-3-({[5,5-dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetate**

tert-Butyl (4-{(1*S*,2*R*)-2-({[5,5-dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)-1-[(4-fluorophenyl)amino]-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate (2.55 g, 3.25 mmol) was dissolved in dry toluene (250 ml) and heated to 90°C under inert atmosphere. N,O-Bis(trimethylsilyl)acetamide (BSA, 2.38 ml, 9.75 mmol) was added and the mixture was stirred at 90°C for one hour. The mixture was cooled to 45°C and tetrabutylammonium fluoride (TBAF, 0.25 g) was added and the mixture was stirred at 45°C for one hour. The mixture was concentrated under reduced pressure and purified by flash-chromatography (hexane:EtOAc 6:1). This afforded 1.06 g (52 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 1.5 (s, 9H), 2.4 (s, 3H), 3.0-3.2 (m, 2H), 3.3-3.5 (m, 4H), 3.9 (d, 1H), 4.5 (s, 2H), 4.8 (d, 1H), 6.8-7.0 (m, 6H), 7.1-7.4 (m, 6H).

Method 39

[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-methylphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid

tert-Butyl {4-[(2*R*,3*R*)-3-({[5,5-dimethyl-2-(4-methylphenyl)-1,3-dioxan-2-yl]methyl}thio)-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetat (1.04 g, 1.67 mmol) was dissolved in formic acid (20 ml) and stirred for 60 minutes. The mixture was concentrated under reduced pressure (temperature < 30°C) and the crude oil was purified by flash-chromatography (hexane:acetone:formic acid 60:40:0.1) to afford 0.72 g (90 %) of the title compound as a pale yellow solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.4 (s, 3H), 4.1 (d, 1H), 4.2 (s, 2H), 4.7 (s, 2H), 4.9 (d, 1H), 6.9 (m, 6H), 7.2-7.4 (m, 4H), 7.8 (d, 2H). MS (CI) M/z: 478.1 (M^+ - 1).

Method 40

tert-Butyl (4-{(*E*)-[(4-chlorophenyl)imino]methyl}phenoxy)acetate

A suspension of NaH (60 % in mineral oil, 3.69 g, 92.2 mmol) in dry DMF (70 ml) was cooled to 0°C. A solution of 4-hydroxybenzaldehyde (10.0 g, 82.0 mmol) in dry DMF (35 ml) was added dropwise. The mixture was stirred at 0°C for 40 minutes. tert-Butyl bromoacetate (12.1 ml, 82.5 mmol) was added and the mixture was stirred at room temperature for 17 h. The mixture was concentrated under reduced pressure. Diethyl ether was added and the mixture was washed with 10% NH_4Cl, water and brine. The organic phase was dried ($MgSO_4$), concentrated under reduced pressure and purified by flash-chromatography (10% - 20% EtOAc in hexane). This gave *tert*-butyl (4-formylphenoxy)acetate (17.4 g, 73.4 mmol, 90 % yield) as an colourless oil. This intermediate was dissolved in dry toluene (120 ml) and 4-chloroaniline (9.37 g, 73.4 mmol) was added. The mixture was refluxed in a Dean-Stark apparatus for 20 h, cooled and concentrated under reduced pressure. Hexane was added and the formed precipitate was filtered, washed twice with cold hexane and dried. This afforded 20.0 g (79%) of the title compound as a yellow solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.5 (s, 9H), 4.6 (s, 2H), 7.0 (d, 2H), 7.2 (d, 2H), 7.4 (d, 2H), 7.8 (d, 2H), 8.4 (s, 1H). MS (CI) M/z: 368.0 (M^++Na, 100), 369.0 (20), 370.0 (30), 371.0 (10).

Method 41

Ethyl ({[2-(4-chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetate

Ethyl {[2-(4-chlorophenyl)-2-oxoethyl]thio}acetate (8.15 g, 29.9 mmol) was dissolved in toluene (165 ml). 2,2-Dimethyl-1,3-propanediol (24.8 g, 238 mmol) and p-toluene sulfonic acid (300 mg) were added. The mixture was stirred at reflux in a Dean-Stark apparatus for 2.5 h and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2. The mixture was washed with H_2O (3x), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash-chromatography (Hexane:EtOAc 9:1) to give 3.36

g (31 %) of the title compound as an yellow oil. MS (CI) M/z: 381.0 (M^+ + Na, 100), 382.0 (15), 383.0 (30), 384 (5)

Method 42

({[2-(4-Chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetic acid

Ethyl ({[2-(4-chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetate(3.36 g, 9.36 mmol) was dissolved in THF (45 ml) and cooled to 0°C. LiOH (0.79 g, 18.8 mmol) in water (12 ml) was added and the mixture was stirred for 18 h at room temperature. The solvents were evaporated. The crude product was extracted between water and diethyl ether. The aqueous layer was acidified using 2M HCl to pH 6 and extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford 2.98 g (96 %) of the title compound as an yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.62 (s, 3H), 1.34 (s, 3H), 2.95 (s, 2H), 3.34 (s, 2H), 3.45 (s, 4H), 7.4 (m, 4H)

Method 43

(4*S*)-3-[({[2-(4-Chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetyl]-4-phenyl-1,3-oxazolidin-2-one

({[2-(4-Chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetic acid (2.00 g, 6.05 mmol) was dissolved in dry CH_2Cl_2 (45 ml) and cooled to 0°C. N,N'-Dicyclohexylcarbodiimide (DCC, 1.43 g, 6.93 mmol) and 4-(dimethylamino)pyridine (DMAP, 1.70 g, 10.4 mmol) were added and the mixture was stirred at 0°C for 20 minutes. (S)-(+)-4-Phenyl-2-oxazolidinone (1.40 g, 11.5 mmol) was added and the mixture was stirred at room temperature for 70 h. The mixture was filtered, concentrated under reduced pressure and purified by flash-chromatography (20% - 30% EtOAc in hexane). This afforded 1.27 g (44 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.62 (s, 3H), 1.34 (s, 3H), 2.78 (s, 2H), 3.42 (s, 4H), 3.85 (s, 2H), 4.27-4.33 (dd, 1H), 4.69-4.78 (t, 1H), 5.34-5.42 (dd, 1H), 7.29-7.38 (m, 9H).

Method 44

tert-Butyl (4-{(1*S*,2*R*)-1-[(4-chlorophenyl)amino]-2-({[2-(4-chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate

Tetraisopropyl orthotitanate (0.23 ml, 0.77 mmol) was added to a solution of $TiCl_4$ (1M in CH_2Cl_2, 2.25 ml, 2.25 mmol) in CH_2Cl_2 (22 ml) at 0°C under inert atmosphere. The mixture was stirred for ten minutes. (4*S*)-3-[({[2-(4-Chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)acetyl]-4-phenyl-1,3-oxazolidin-2-one (1.44 g, 3.03 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise over 45 minutes and the mixture was stirred for ten minutes. *tert*-Butyl (4-{(*E*)-[(4-chlorophenyl)imino]methyl}phenoxy)acetate (2.09 g, 6.04 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise over 80 minutes. The mixture was cooled to -40°C and stirred for 20 minutes. Ethyl diisopropyl amine (1.03 ml, 6.02 mmol) was added dropwise over 40 minutes and the mixture was stirred at -40°C for ten minutes. The mixture was cooled to -78°C and isopropanol (80 ml) was added. The temperature was allowed to reach room temperature over three hours. NH_4Cl (10%, 80 ml) was added and the mixture was stirred for 35 minutes. Brine (200 ml) was added and the mixture was extracted extracted twice with 400 ml diethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash-chromatography (10% - 20% EtOAc in hexane) afforded 1.69 g (65 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.65 (s, 3H), 1.3 (s, 3H), 1.5 (s, 9H), 2.6-2.9 (m, 2H), 3.4 (m, 4H), 4.2 (m, 1H), 4.5 (s, 2H), 4.6-4-8 (m, 2H), 5.3 (m, 1H), 5.7 (d, 1H), 6.4 (m, 2H), 6.7-7.4 (m, 15H).

Method 45

tert-Butyl {4-[(2*R*,3*R*)-1-(4-chlorophenyl)-3-({[2-(4-chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetate

tert-Butyl (4-{(1*S*,2*R*)-1-[(4-chlorophenyl)amino]-2-({[2-(4-chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate(1.69 g, 2.06 mmol) was dissolved in dry toluene (140 ml) and heated to 90°C under inert atmosphere. N,O-Bis(trimethylsilyl)acetamide (BSA, 1.48 ml, 6.05 mmol) was added and the mixture was stirred at 90°C for one hour. The mixture was cooled to 45°C and tetrabutylammonium fluoride (TBAF, 0.1 g) was added and the mixture was stirred at 45°C for one hour and at room temperature overnight. The mixture was concentrated under reduced pressure and purified by flash-chromatography (10% - 20% EtOAc in hexane). This afforded 0.84 g (61 %) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2 (s, 3H), 1.5 (s, 9H), 2.9-3.1 (t, broad, 2H), 3.4 (s, 4H), 4.0 (s, 1H), 4.5 (s, 2H), 4.8 (s, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 10H).

Method 46

[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-4-oxo-3-{[2-oxo-2-(4-pentylphenyl)ethyl]thio}azetidin-2-yl)phenoxy]acetic acid

tert-Butyl (4-{(2*R*,3*R*)-1-(4-fluorophenyl)-3-[(3-nitropyridin-2-yl)dithio]-4-oxoazetidin-2-yl}phenoxy)acetate (0.20 g, 0.36 mmol) was dissolved in acetone (10 ml) at room temperature. Water (2.5 ml) and triphenyl phosphine (0.094 g, 0.36 mmol) were added. The mixture was stirred at room temperature for 30 minutes and then concentrated under reduced pressure to afford the crude thiol as a brown oil. This crude thiol was immediately dissolved in CH_2Cl_2 (10 ml) and 2-bromo-1-(4`-penthyl phenyl)ethan-1-one (0.19 g, 0.72 mmol) was added, followed by Et_3N (0.10 ml, 0.72 mmol). The mixture was stirred at room temperature for 20 hours, concentrated under reduced pressure and purified by flash-chromatography (Hex : EtOAc 4:1). This afforded 0.21 g of a mixture of *tert*-butyl [4-((2*R*,3*R*)-1-(4-fluorophenyl)-4-oxo-3-{[2-oxo-2-(4-pentylphenyl)ethyl]thio}azetidin-2-yl)phenoxy]acetate and 2-[(3-nitropyridin-2-yl)thio]-1-(4-pentylphenyl)ethanone. This mixture was dissolved in HCOOH (10 ml) and stirred at room temperature for 18 hours. Concentration under reduced pressure

and purification by flash-chromatography (hex : acetone : HCOOH 60 : 40 : 0.1) afforded 0.11 g (61 %) of the desired compound as a pale yellow solid.

^{1}H-NMR (CD_3Cl, 300 MHz): δ 0.8-1.0 (m, 3H), 1.2-1.5 (m, 4H), 1.6-1.8 (m, 2H), 2.7 (t, 2H), 4.1 (d, 1H), 4.2 (s, 2H), 4.7 (s, 2H), 4.9 (d, 1H) 6.9-7.1 (m, 4H), 7.2-7.4 (m, 6H), 7.9 (d, 2H).

Method 47

Sodium (2*R*)-2-amino-4-cyclohexylbutanoate

Ethyl (2*R*)-2-amino-4-cyclohexylbutanoate hydrochloride (4.00 g, 18.75 mmol) was dissolved in MeOH/Water (10/5 ml). Sodium hydroxide (1.50 g, 37.50 mmol) was added. The reaction mixture was stirred for 1 h and concentrated to give the title compound as a colourless solid (containing 100 mol% of sodium chloride). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.83-0.97 (m, 2H), 1.10-1.33 (m, 6H), 1.48-1.78 (m, 7H), 3.15 (dd, 1H).

Method 48

***N*-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine**

[4-((2*R*,3*R*)-1-(4-Chlorophenyl)-3-{[2-(4-chlorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid, 302.1 mg, 0.585 mmol) was dissolved in DCM (6 ml). *N*-Methylmorpholine (190 µl, 1.728 mmol) and *tert*-butyl glycinate hydrochloride (133.4 mg, 0.80 mmol) were added. After 10 minutes, TBTU (224.3 mg, 0.67 mmol) was added and the reaction mixture was stirred for 60 h. The intermediate *tert*-butylester of the title compound was confirmed. M/z: 626.88 (M-H). DCM (10 ml) and water (15 ml) were added and the mixture was acidified to pH of 3 using $KHSO_4$ (2M). The organic phase was washed with water (2x15 ml). The combined aqueous phases were extracted with DCM (10 ml), dried over Na_2SO_4, filtered and concentrated. A solution of the residue (500 mg) in DCM (10 ml) and

TFA (4 ml) was stirred overnight. The solvent was removed under reduced presssure. Toluene was added and evaporated to assist the removal of TFA. The residue was purified with preparative HPLC on a C8 column. A gradient from 20 to 50 % MeCN in 0.1M ammonium acetate buffer was used as eluent. After lyophilisation, the title compound was obtained as a white solid (166.9 mg, 50 %). H-NMR (400 MHz, DMS-d_6): 3.51 (d, 2H), 4.33 (d, 1H), 4.34 (s, 1H), 4.36 (s, 1H), 4.47 (s, 2H), 5.17 (d, 1H), 6.96 (d, 2H), 7.16-7.21 (m, 2H), 7.35 (d, 4H), 7.54-7.59 (m, 2H), 7.83-7.90 (brs, 1H), 7.91-7.95 (m, 2H). M/z: 571.04 (M-H) and 572.88 (M+H).

Method 49

(2*R*)-cyclohexyl[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl)amino]acetic acid

TBTU (0.0092 g, 0.029 mmol) was added to a mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.016g, 0.030 mmol) and N-methylmorpholin (0.101 ml,0.98 mmol) in DMF (2ml). The mixture was stirred overnight under N_2-atmosphere. Additional TBTU (0.0092 g, 0.029 mmol) was added and the mixture was stirred at 35°C for 2 h.(2*R*)-amino(cyclohexyl)acetic acid hydrochloride (0.0068 g, 0.035
mmol) was added. The mixture was stirred at 35°C for 2 h and at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid buffer as eluent. The solvent was removed under reduced pressure and 0.009 g (47 %) of the title product was obtained.
M/z 680.01

Method 50

***tert*-butyl N^2-[(benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-D-ornithinate**

N^2-[(benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-D-ornithine (1g, 2.73 mmole) was dissolved in toluene (5mL) and kept at 100°C. N,N-dimethylformamide di-tert-butyl acetal (1.5 mL, 6.25 mmole) was added drop wise. After 40 minutes the mixture was allowed to cool down to room temperature and kept there for three days. The organic layer was washed with $NaHCO_3$-solution and brine, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. 0.67 g (58 %) of the desired product was obtained.

NMR (500 MHz, CD3COOD) 1.35-1.71 (m, 21H), 1.72-1.85 (m, 1H), 3.06 (t, 2H), 4.05 (dd, 1H), 5.11 (ABq, 2H), 7.29-7.40 (m, 5H)

Method 51

***tert*-butyl N^5-(*tert*-butoxycarbonyl)-D-ornithinate**

tert-butyl N^2-[(benzyloxy)carbonyl]-N^5-(*tert*-butoxycarbonyl)-D-ornithinate (0.67g, 1.83 mmole) and Pd on charcoal (95%, 0.115g) were mixed in EtOH (95%, 20 mL) and stirred under H_2-atmosphere for 5 hours and 15 minutes. The mixture was filtered through Celite 521 and the solvent was evaporated under reduced pressure to give 0.45g (85%) of the desired product.

NMR (500 MHz, CD3COOD) 1.41-1.76 (m22H), 3.07 (t, 2H), 3.32-3.36 (m 1H)

Method 52

Glycyl-3-cyclohexyl-D-alanine

N-(*tert*-butoxycarbonyl)glycine (2.0 g, 11.4 mmol) and DIPEA (4.0 g, 31 mmol) were dissolved in methylene chloride (25 ml). TBTU (4.1 g, 12.8 mmol) was added and the mixture was stirred for 15 min at room temperature. 3-cyclohexyl-D-alanine (2.1 g, 12.2 mmol) was added and the reaction mixture was stirred over night at room temperature. The reaction mixture was transferred to a separation funnel and was then extracted with a

water/acetic acid solution (100ml 5% acetic acid). The organic layer was separated and evaporated under reduced pressure. The residue was dissolved in formic acid (20 ml) and the mixture was stirred over night at 40 °C. The formic acid was removed under reduced pressure.The residue was washed with water (50 ml) and then stirred in aceton (25 ml) for 1 h at room temperature. The solid material was filtered off and washed with aceton (20 ml). 530 mg (20%) of the title compound was obtained.

^{1}H-NMR, 300 MHz, CD3COOD): 0.8-1.9 (m, 13H), 3.9-4.1 (m, 2H), 4.55-4.65 (m, 1H).

Method 53

β, β -dimethyl-D-phenylalanine trifluoroacetate

N-(*tert*-butoxycarbonyl)-b,b-dimethyl-D-phenylalanine *tert*-butyl ammonium salt (51.2 mg, 0.14 mmol) was dissolved in DCM (15 ml). Water (10 ml) was added and the mixture was acidified to pH 1 with HCl (1M). The organic phase was washed with water (3x10 ml) and the water phase extracted with DCM (3x10 ml). The solvent was removed under reduced pressure. The residue was dissolved in DCM (4 ml) and TFA (2.5 ml) was added and the mixture was stirred for 2 hours. The solvent was removed under reduced pressure and the residue was dried under vacuum overnight. The title compound was obtained as a white solid (36.1 mg, 85 %). M/z: 194.18 (M+1).

Method 54

Glycyl-3-methyl-D-valine trifluoroacetate

To a 30 °C solution of *N*-(*tert*-butoxycarbonyl)glycine (0.450 g, 2.569 mmol) and N-methylmorpholine (1.30 g, 12.84 mmol) in CH_2Cl_2 (50 ml) was added TBTU (0.99 g, 3.08 mmol). After 1.5 h, D-tert-leucine (0.303 g, 2.31 mmol) was added. After 30 minutes, the reaction was quenched by the addition of water (1 ml). The mixture was concentrated and the residue was purified through preparative HPLC using an eluent of 0-40% CH_3CN in 0.1M

NH_4OAc buffer. Pure fractions were collected and concentrated. To the residue were added CH_2Cl_2 (10 ml) and TFA (3 ml). Full conversion to the corresponding aminoacid was obtained after 30 minutes. The reaction mixture was concentrated to give the desired compound (0.359 g, 46%) as a colourless solid. ^1H NMR [$(CD_3)_2SO$), 400 MHz] □0.94 (s, 9H), 3.60-3.67 (m, 2H), 4.16 (d, 1H), 7.90-8.00 (m, 3H), 8.47 (d, 1H).

Method 55

{4-[(2*R*,3*R*)-3-{[2-(4-*tert*-Butylphenyl)-2-oxoethyl]thio}-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetic acid

tert-Butyl (4-{(2*R*,3*R*)-1-(4-fluorophenyl)-3-[(3-nitropyridin-2-yl)dithio]-4-oxoazetidin-2-yl}phenoxy)acetate (0.20 g, 0.36 mmol) was dissolved in acetone (10 ml) at room temperature, then water (2.5 ml) and triphenyl phosphine (0.094 g, 0.36 mmol) was added. The mixture was stirred at room temperature for 15 minutes and then concentrated under reduced pressure to afford the crude thiol as a brown oil. This crude thiol was immediately dissolved in CH_2Cl_2 (8 ml) and 2-bromo-1-(4´-tert-butyl-phenyl)-ethan-1-one (0.15 g, 0.72 mmol) was added, followed by Et_3N (0.10 ml, 0.72 mmol). The mixture was stirred at room temperature for 1.5 hours, concentrated under reduced pressure and purified by flash-chromatography (Hex : EtOAc 4.1). This afforded 0.26 g of a mixture of *tert*-butyl {4-[(2*R*,3*R*)-3-{[2-(4-*tert*-butylphenyl)-2-oxoethyl]thio}-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetate and 1-(4-*tert*-butylphenyl)-2-[(3-nitropyridin-2-yl)thio]ethanone. This mixture was dissolved in formic acid (10 ml) and stirred at room temperature for 17 hours. Concentration under reduced pressure and purification by flash-chromatography (hex : acetone : formic acid 70 : 30 : 0.1) afforded 0.08 g (43 %) of the desired product as a white solid.

^1H-NMR (CD_3Cl, 200 MHz): δ 1.30 (s, 9H), 4.10 (s, 1H), 4.15 (s, 2H), 4.60 (s, 2H), 4.85 (s, 1H), 6.80-7.00 (m, 4H), 7.15-7.30 (m, 4H), 7.60-7.70 (m, 2H), 7.80-7.90 (m, 2H).

Method 56

_N_-({4-[(2_R_,3_R_)-3-{[2-(4-_tert_-Butylphenyl)-2-hydroxyethyl]thio}-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetyl)glycyl-3-cyclohexyl-D-alanine

To a solution of {4-[(2_R_,3_R_)-3-{[2-(4-_tert_-butylphenyl)-2-oxoethyl]thio}-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetic acid (0.020 g, 0.038 mmol) and NMM (0.013 ml, 0.118 mmol) in DMF (3 ml) at RT was added TBTU (0.019 g, 0.059 mmol). After 90 min glycyl-3-cyclohexyl-D-alanine (0.009 g, 0.039 mmol) was added and the mixture was stirred for 18 h before the reaction was quenched by the addition of water (1 ml). The mixture was diluted with MeOH (1 ml) and NaBH4 (0.025 g, 0.661 mmol) was added. After 10 min the reaction was quenched by the addition of a 0.1M ammonium acetate buffer (2 ml) and most of the methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC using a gradient of 20-60% MeCN in a 0.1M ammonium acetate buffer as eluent. Freeze-drying of the pure fractions gave the desired product as a white solid (0.010 g, 36 % yield).

ES- m/z: 733.2 $(M-1)^-$. 1H NMR (DMSO, 500 MHz) δ: 0.70-0.93 (m, 2H), 1.00-1.35 (m, 13H), 1.35-1.71 (m, 7H), 2.84-2.96 (m, 2H), 3.72-3.80 (m, 2H), 4.12-4.22 (m, 1H), 4.22-4.28 (m, 1H), 4.50 (s, 2H), 4.60-4.72 (m, 1H), 4.98-5.03 (m, 1H), 6.94-7.01 (m, 2H), 7.09-7.39 (m, 10H), 7.94-8.03 (m, 1H), 8.19-8.27 (m, 1H).

Method 57

{4-[(2_R_,3_R_)-3-{[2-(4-Ethoxyphenyl)-2-oxoethyl]thio}-1-(4-fluorophenyl)-4-oxoazetidin-2-yl]phenoxy}acetic acid

tert-Butyl (4-{(2_R_,3_R_)-1-(4-fluorophenyl)-3-[(3-nitropyridin-2-yl)dithio]-4-oxoazetidin-2-yl}phenoxy)acetate (0.25 g, 0.45 mmol) was dissolved in acetone (10 ml) at room temperature. Water (2.5 ml) and triphenyl phosphine (0.12 g, 0.45 mmol) were added. The mixture was stirred at room temperature for 15 minutes and then concentrated under reduced pressure to afford the crude thiol as a brown oil. This crude thiol was immediately dissolved

in CH_2Cl_2 (10 ml) and (2-bromo-3`-ethoxy acetophenone (0.22 g, 0.90 mmol) was added, followed by Et_3N (0.13 ml, 0.90 mmol). The mixture was stirred at room temperature for 19 hours, concentrated under reduced pressure and purified by flash-chromatography (Hex : EtOAc 3:1). This afforded a colourless oil that was dissolved in formic acid (10 ml) and stirred at ambient temperature for 18 hours. Concentration under reduced pressure and purification by flash-chromatography (hex : acetone : formic acid 60 : 40 : 0.1) afforded 0.13 g (57 %) of the desired product as a pale yellow solid.

^{1}H-NMR (CD_3Cl, 200 MHz): δ 1.4 (t, 3H), 4.0-4.1 (m, 5H), 4.5 (s, 2H), 4.8 (d, 2H), 6.8-7.0 (m, 6H), 7.1-7.3 (m, 4H), 7.9 (d, 2H).

Method 58

***tert*-Butyl (4-{[(4-fluorophenyl)imino]methyl}phenoxy)acetate**

tert-Butyl (4-formylphenoxy)acetate (21.6 g, 0.09 mol) was dissolved in dry toluene (150 ml) and 4-fluoroaniline (8.8 ml, 0.091 mol) was added. The mixture was refluxed in a Dean-Stark apparatus for 23 hours, cooled and concentrated under reduced pressure. Addition of hexane and concentration under reduced pressure afforded 30.0 g (quant. yield) of the title compound as an off-white solid. NMR (200 MHz): 1.5 (s, 9H), 4.6 (s, 2H), 7.0-7.2 (m, 6H), 7.8 (d, 2H), 8.4 (s, 1H).

Method 59

(4*S*)-3-{[(4-Methoxybenzyl)thio]acetyl}-4-phenyl-1,3-oxazolidin-2-one

(4-Methoxy-benzylsulfanyl)-acetic acid (1.3 g, 6.1 mmol) was dissolved in dry DCM (40 ml) and cooled to 0°C. N,N'-dicyclohexylcarbodiimide (6.1 g, 6.1 mmol) and DMAP (1.6 g, 12.9 mmol) were added and the mixture was stirred for 30 minutes. (S)-(+)-4-Phenyl-2-oxazolidinone (1,0 g, 6.1 mol) was added and the mixture was stirred at room temperature for 24 hours. The mixture was filtrated, concentrated under reduced pressure and purified by flash-chromatography (Hex : EtOAc 8:2 then 1:1). This afforded 1.7 g (77 %) of the title

compound as a white solid. NMR (200 MHz): 3.46-3.59 (m, 3H), 3.74-3.76 (m, 4H), 4.23-4.28 (m, 1H), 4.68 (t, 1H), 5.38-5-42 (m, 1H), 6.78 (d, 2H), 7.14 (d, 2H), 7.32-7.40 (m, 5H).

Method 60

tert-Butyl (4-{(1*R*)-1-(4-fluoroanilino)-2-[(4-methoxybenzyl)thio]-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate

$TiCl_4$ (1M in DCM, 7.2 ml, 7.2 mmol) was added to a solution of tetraisopropyl orthotitanate (0.71 ml 2.4 mmol) in DCM (40 ml) held at 0°C under inert atmosphere. The mixture was stirred for 15 minutes, then (4*S*)-3-{[(4-methoxybenzyl)thio]acetyl}-4-phenyl-1,3-oxazolidin-2-one (3.4 g, 9.6 mmol) in dry DCM (20 ml) was added and the mixture was stirred for five minutes. Then *tert*-butyl (4-{[(4-fluorophenyl)imino]methyl} phenoxy)acetate (6.3 g, 19.0 mmol) in dry DCM (30 ml) was added and the mixture was given -40°C and stirred for 20 minutes. Ethyl diisopropyl amine (3.3 ml, 19.0 mmol) was added and the mixture was stirred at -40°C for 19 hours. The mixture was then given -78°C, added isopropanol (50 ml) and slowly given room temperature over night. Water (100 ml) was added and the mixture was stirred for 35 minutes at room temperature and then extracted twice with diethyl ether. The combined organic layer was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was dissolved in methanol and an off-white precipitate formed. Filtration and drying afforded 1.7 g (26 %) of the title compound as an off-white solid. NMR (200 MHz): 1.5 (s, 9H), 3.65 (s, 1H), 3.8 (s, 3H), 4.1 (m, 1H), 4.4-4.6 (m, 4H), 5.0-5.2 (m, 2H), 5.4 (m, 1H), 6.4-6.6 (m, 2H), 6.7-7-4 (m, 15H).

Method 61

3-(R)-4-(R)-1-(4-Fluorophenyl)-3-(4-methoxybenzylsulphanyl)-4-[4-(*t*-butoxycarbonyl methoxy)phenyl]azetidin-2-one

tert-Butyl (4-{(1*R*)-1-(4-fluoroanilino)-2-[(4-methoxybenzyl)thio]-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]propyl}phenoxy)acetate (1.3 g, 1.9 mmol) was dissolved in dry toluene (140 ml) and heated to 90°C under inert atmosphere. BSA (1.4 ml, 5.7 mmol) was added and the mixture was stirred at 90°C for one hour. The mixture was then cooled to 45°C and TBAF (dried, 0.1 g) was added. After 18 hours, additional BSA was added (0.5 ml, 2.0

mmol) and the temperature was kept at 45°C for another six hours. After cooling, the mixture was concentrated under reduced pressure and purified by flash-chromatography (Hex : EtOAc 5:1). This afforded 0.55 g (55 %) of the title compound as a white solid. MR (200 MHz): 1.5 (s, 9H), 3.7 (s, 3H), 3.9 (m, 3H), 4.5 (m, 3H), 6.7 (d, 2H), 6.8-7.0 (m, 4H), 7.0-7.2 (m, 6H).

Method 62

3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(3-nitropyridin-2-yl)dithio]-4-[4-(*t*-butoxycarbonyl methoxy)phenyl]azetidin-2-one

3-(R)-4-(R)-1-(4-Fluorophenyl)-3-(4-methoxybenzylsulphanyl)-4-[4-(*t*-butoxycarbonyl methoxy)phenyl]azetidin-2-one (0.65 g, 1.24 mmol) was dissolved in DCM (50 ml) and given 0°C under inert atmosphere. 3-Nitro-2-pyridinesulfenyl chloride (0.28 g, 1.49 mmol) was added and the mixture was stirred for 75 minutes at 0°C. Then additional 3-nitro-2-pyridinesulfenyl chloride (0.05 g, 0.27 mmol) was added and the mixture was stirred for an additional 45 minutes at 0°C. Concentration under reduced pressure and purification by flash-chromatography (Hex : EtOAc 4:1 then 2:1) afforded 0.67 g (97 %) of the desired product as a yellow oil. NMR (200 MHz): 1.6 (s. 9H), 4.3 (d, 1H), 4.5 (s, 2H), 5.2 (d, 1H), 6.8-7.0 (m, 4H), 7.1-7.3 (m, 4H), 7.4 (m, 1H) 8.5 (d, 1H), 8.9 (d, 1H).

Method 63

3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-[4-(*t*-butoxycarbonyl methoxy)phenyl]azetidin-2-one

3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(3-nitropyridin-2-yl)dithio]-4-[4-(*t*-butoxycarbonyl methoxy)phenyl]azetidin-2-one (0.67 g, 1.2 mmol) was dissolved in acetone (50 ml) at room temperature, then water (10 ml) and tributyl phosphine (0.30 ml, 1.2 mmol) was added. The mixture was stirred at room temperature for 30 minutes and then concentrated under reduced pressure to afford the crude thiol as a brown oil. This crude thiol was immediately dissolved in DCM (40 ml) and 2-bromo-4'-fluoroacetophenone (0.29 g, 1.3 mmol) was added, followed by Et_3N (0.20 ml, 1.4 mmol). The mixture was stirred at room temperature for 90 minutes, concentrated under reduced pressure and purified by flash-chromatography (Hex : EtOAc

4:1). This afforded 0.42 g (65 % total over two steps) of the title compound as a white solid. NMR (200 MHz) 1.44 (s, 9H), 4.06 (d, $J \approx 2.4$ Hz, 1H), 4.13 (d, $J = 3.8$ Hz, 2H), 4.48 (s, 2H), 4.81 (d, $J = 2.2$ Hz, 1H), 6.83-6.93 (m, 4H), 7.05-7.21 (m, 6H), 7.90-7.97 (m, 2H).

Method 64

3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-[4-(carboxymethoxy) phenyl]azetidin-2-one

3-(R)-4-(R)-1-(4-fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-[4-(*t*-butoxycarbonylmethoxy)phenyl]azetidin-2-one (0.42 g, 0.78 mmol) was dissolved in DCM (30 ml) at 0°C and TFA (7.5 ml) was added dropwise. The mixture was slowly given room temperature over several hours and then stirred at room temperature over night. Concentration under reduced pressure and purification by flash-chromatography (EtOAc, then 5% MeOH in EtOAc) afforded 0.32 g (85 %) of the title compound as a white solid. NMR (CD_3OD, 300 MHz): 4.1 (d, 1H), 4.2 (s, 2H), 4.5 (s, 2H), 5.0 (d, 1H), 6.9-7.0 (m, 4H), 7.1-7.3 (m, 6H), 8.0 (m, 2H).

Method 65

***tert*-Butyl *N*-[(2*R*)-2-amino-2-phenylacetyl]-*O*-(*tert*-butyl)-L-serinate**

tert-Butyl *N*-((2*R*)-2-{[(benzyloxy)carbonyl]amino}-2-phenylethanoyl)-*O*-(*tert*-butyl)-L-serinate (Method 15; 3.3 g, 6.8 mmol) was dissolved in EtOH (95%, 30 ml) and a cat amount of Pd/C (5%)(50% in water) was added and hydrogenation was performed at atmospheric pressure for 3 hours. at room temperature. The reaction mixture was filtered through diatomaceous earth and the solvent was evaporated to give the title compound (2.35 g, 98 %). NMR (500 MHz, CD_3OD): 1.1 (s, 9H), 1.45 (s, 9H), 3.45-3.8 (m, 2H), 4.5 (t, 1H), 4.55 (s, 1H), 4.85 (s, 2H), 7.3-7.5 (m, 5H).

Method 66

1-(4-Fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxy)-1-(S)-(*t*-butoxycarbonyl)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl} azetidin-2-one

A solution of 3-(R)-4-(R)-1-(4-fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-[4-(carboxymethoxy) phenyl]azetidin-2-one (0.090 g, 0.186 mmol), *tert*-Butyl *N*-[(2*R*)-2-amino-2-phenylacetyl]-*O*-(*tert*-butyl)-L-serinate (Method 8; 0.098 g, 0.280 mmol) and N-methylmorpholine (0.062 ml, 0.563 mmol) in DMF (6 ml) was stirred at room temperature for 10 minutes, after which TBTU (0.096 g, 0.299 mmol) was added. After 22 hours, the reaction mixture was added water (15 ml) and extracted three times with ether (3x10 ml). The combined organic layers where washed with brine (10 ml), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel, using Hept:EtOAc (6:4) as eluent. The desired product was obtained in 0.053 g (35 %) as a white solid. NMR (400 MHz): 0.90 (s, 9H), 1.45 (s, 9H), 3.35 (dd, 1H), 3.65 (dd, 1H), 4.10 (d, 1H), 4.15 (ABq, 2H), 4.50 (ABq, 2H), 4.50-4.60 (m, 1H), 4.85 (d, 1H), 5.55 (d, 1H), 6.40 (d, 1H), 6.90-7.00 (m, 4H), 7.10-7.40 (m, 11H), 7.90-8.00 (m, 3H); m/z: 816.7.

Method 67

1-(4-Fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(hydroxy)-1-(S)-(carboxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one

and

Method 68

1-(4-Fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxy)-1-(S)-(carboxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one

TFA (2 ml) was added to a solution of 1-(4-fluorophenyl)-3-(R)-[(4-fluorobenzoyl) methylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxy)-1-(S)-(*t*-butoxycarbonyl)ethyl]carbamoyl} benzyl)carbamoylmethoxy]phenyl}azetidin-2-one (0.050 g, 0.061 mmol) in DCM (5 ml) at

room temperature. After 2.5 hours the solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-60% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 1-(4-fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(hydroxy)-1-(S)-(carboxy)ethyl] carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one was obtained in 0.039g (90%). NMR (DMSO, 400 MHz): 3.35 (dd, 1H), 3.50 (dd, 1H), 3,95-4.05 (m, 1H), 4.30 (d, 1H), 4.35 (ABq, 2H), 4.60 (ABq, 2H), 5.15 (d, 1H), 5.65 (d, 1H), 6.90-7.00 (m, 2H), 7.10-7.40 (m, 13H), 7.95-8.05 (m, 2H), 8.25 (d, 1H), 8.55 (d, 1H); m/z: 704.5. 1-(4-fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxy)-1-(S)-(carboxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl} azetidin-2-one was obtained in 0.002g (4%). NMR (CD_3COOD, 400 MHz): 1.00 (s, 9H), 3.50 (dd, 1H), 3.80 (dd, 1H), 4.20-4.30 (m, 3H), 4.70 (s, 2H), 4.80-4.85 (m, 1H), 5.00-5.05 (m, 1H), 5.90-6.00 (m, 1H), 6.95-7.05 (m, 4H), 7.15-7.50 (m, 11H), 8.00-8.10 (m, 2H); m/z: 760.5. Both were white solids.

Method 69

3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one

A solution of 3-(R)-4-(R)-1-(4-fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-[4-(carboxymethoxy)phenyl]azetidin-2-one (0.200 g, 0.414 mmol), glycine tert-butyl ester hydrochloride (0.113 g, 0.674 mmol) and N-methylmorpholine (0.180 ml, 1.63 mmol) in DCM (5 ml) was stirred at room temperature for 10 minutes, after which TBTU (0.193 g, 0.601 mmol) was added. After 25 hours, the conversion to the ester (m/z: 597.43 $(M+1)^+$) was completed and TFA (2 ml) was added to the solution. After 1 hour, the solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, the desired product was obtained in 0.093 g (41 %) as a white solid. NMR (DMSO, 500 MHz): 3.65 (d, 2H), 4.35 (d, 1H), 4.40 (ABq, 2H), 4.50 (s, 2H), 5.20 (d, 1H), 6.95-7.05 (m, 2H), 7.15-7.40 (m, 8H), 8.00-8.15 (m, 3H); m/z: 541.3.

Method 70

1-(4-Fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-{*N*-[2-(hydroxy)-1-(R)-(carboxy)ethyl]carbamoylmethyl}carbamoylmethoxy]phenyl}azetidin-2-one

A solution of 3-(R)-4-(R)-1-(4-fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.030 g, 0.056 mmol), D-serine tert-butyl ester hydrochloride (0.017 g, 0.067 mmol) and N-methylmorpholine (0.019 ml, 0.172 mmol) in DCM (4 ml) was stirred at room temperature for 10 minutes, after which TBTU (0.023 g, 0.072 mmol) was added. After 22 hours, the conversion to the ester (m/z: 740.58 $(M+1)^+$) was complete. TFA (1.5 ml) was added to the solution and after 2 hours, the solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, the desired product was obtained in 0.035 g (~quantitative) as a white solid. NMR (CD_3COOD, 400 MHz): 3.95 (dd, 1H), 4.10 (dd, 1H), 4.20-4.30 (m, 5H), 4.65 (s, 2H), 4.70-4.80 (m, 1H), 5.00 (d, 1H), 6.95-7.10 (m, 4H), 7.15-7.45 (m, 6H), 8.00-8.10 (m, 2H); m/z: 628.4.

Method 71

1-(4-Fluorophenyl)-3-(R)-[(4-fluorobenzoyl)methylthio]-4-(R)-{4-[*N*-{*N*-[2-(phenyl)-1-(R)-(carboxy)ethyl]carbamoylmethyl}carbamoylmethoxy]phenyl}azetidin-2-one

3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one (21 mg, 0.039 mmol), *tert*-butyl D-phenylalaninate HCl (12 mg, 0.047 mmol) and 4-methylmorpholine (12 mg, 0.12 mmol) were mixed in DCM (1 ml). TBTU (15 mg, 0.046 mmol) was added after 5 minutes and the mixture was stirred for 20 hours. The solvent was removed under reduced pressure and the residue purified by chromatography on silica with hexane: EtOAc 1:1 as the eluent. The product was dissolved in formic acid and stirred for 20 hours. The formic acid was removed under reduced pressure where after toluene was added and evaporated giving (21 mg 64%). M/z 686.3 $(M-H)^-$.

Method 72

{4-[(2*R*,3*R*)-1-(4-Fluorophenyl)-3-({2-hydroxy-2-[4-(methylthio)phenyl]ethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetic acid

tert-Butyl (4-{(2*R*,3*R*)-1-(4-fluorophenyl)-3-[(3-nitropyridin-2-yl)dithio]-4-oxoazetidin-2-yl}phenoxy)acetate (0.25 g, 0.45 mmol) was dissolved in acetone (10 ml) at room temperature, then water (2.5 ml) and triphenyl phosphine (0.12 g, 0.45 mmol) was added. The mixture was stirred at room temperature for 15 minutes and then concentrated under reduced pressure to afford the crude thiol as a brown oil. This crude thiol was immediately dissolved in CH_2Cl_2 (10 ml) and (2-bromo-3`-thiomethyl acetophenone (0.22 g, 0.90 mmol) was added, followed by Et_3N (0.13 ml, 0.90 mmol). The mixture was stirred at room temperature for 19 hours, concentrated under reduced pressure and purified by flash-chromatography (Hex : EtOAc 4:1 then 3:1). This afforded 0.4 g of a mixture of *tert*-butyl {4-[(2*R*,3*R*)-1-(4-fluorophenyl)-3-({2-[4-(methylthio)phenyl]-2-oxoethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetate and 1-[4-(methylthio)phenyl]-2-[(3-nitropyridin-2-yl)thio]ethanone. This mixture was dissolved in HCOOH (15 ml) and stirred at room temperature for 19 hours. Concentration under reduced pressure and purification by flash-chromatography (hex : acetone : HCOOH 60 : 40 : 0.1) afforded 0.16 g (70 %) of the desired compound as a pale yellow solid.

^{1}H-NMR (CD_3Cl, 200 MHz): δ 2.5 (s, 3H), 4.0 (d, 1H), 4.1 (s, 2H), 4.6 (s, 2H), 4.8 (d, 1H), 6.8-7.0 (m, 4H), 7.1-7.3 (m, 6H), 7.8 (d, 2H).

Method 73

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-ornithine**

A mixture of 3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.020g, 0.037 mmole) *tert*-butyl N^5-(*tert*-butoxycarbonyl)-D-ornithinate (0.012 g, 0.042 mmole), and N-methylmorpholine (0.012 mL, 0.111 mmole) in DCM (3mL) was stirred at room temperature. TBTU (0.018 g, 0.056 mmole) was added and the mixture was stirred over night. Trifluoroacetic acid (1.0 mL) was added and after 6 hours the solvent was removed under reduced pressure. The residue

was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.1M ammonium acetate -buffer as eluent. After removing the solvent under reduced pressure, 0.021 g (87 %) of the desired product was obtained. M/z 655.21

Method 74

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-N^6,N^6-dimethyl-L-lysine

3-(R)-4-(R)-1-(4-Fluorophenyl)-3-[(4-fluorobenzoyl)methylthio]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (0.010g, 0.018 mmole) and N-methylmorpholin (0.006 mL, 0.055 mmole) were dissolved in DMF (0.5mL). TBTU (0.0099 g, 0.031 mmole) was added. The mixture was stirred at 30-40°C for 30 minutes under N_2-atmosphere. N^6,N^6-dimethyl-L-lysine hydrochloride (0.0045 g, 0.021 mmole) was added and the mixture was stirred at 30-40°C for some hours then at room temperature over night. A few drops of water were added and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.1M ammonium acetate buffer as eluent. After removing the solvent under reduced pressure, 0.005 g (39 %) of the desired product was obtained.

M/z 697.31

Method 75

N-{[4-((2R,3R)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycine

A mixture of [4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (0.0153g, 0.031 mmol), *tert*-butyl glycyl-D-valinate hydrochloride (0.0099 g, 0.037 mmol) and N-methylmorpholine (0.010 ml,0.091 mmol) in DCM (2ml) was stirred at room temperature. TBTU (0.016 g, 0.050 mmol) was added and the mixture was stirred for 3.5 h. Trifluoroacetic acid (0. 5 ml) was added and after 3.5 h the solvent was removed under reduced pressure. The residue was purified by preparative HPLC on a Kromasil C8- column using a gradient of 5-100% MeCN in 0.15% trifluoroacetic acid

buffer as eluent. The solvent was removed under reduced pressure and 0.015 g (74 %) of the title product was obtained. M/z 652.20.

Method 76

[4-((2*R*,3*R*)-1-(4-Chlorophenyl)-3-{[2-(4-chlorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid

tert-Butyl {4-[(2*R*,3*R*)-1-(4-chlorophenyl)-3-({[2-(4-chlorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]methyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetate(1.69 g, 2.57 mmol) was dissolved in formic acid (25 ml) and stirred for two hours. The mixture was concentrated under reduced pressure (temperature < 30°C) and the crude oil was purified by flash-chromatography (hexane:acetone:formic acid 60:40:0.1) to afford 1.08 g (81 %) of the title compound as a pale yellow solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 4.0-4.2 (m, 3H), 4.7 (s, 2H), 4.9 (d, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 6H), 7.5 (d, 2H), 7.9 (d, 2H). MS (CI) M/z: 514.2 (M$^+$), 515.2 (30), 516.1 (70), 517.2 (20).

Examples of intermediates of formula (VI) and XV

Method 77

***N*-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanine**

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-alanine was dissolved in methanol (1.5 ml). Sodium borohydride was added and the mixture was stirred for 30 minutes. An ammonium acetate/H2O solution (2 ml) was added and the methanol was evaporated. The product was purified by preparative HPLC (CH3CN/ 0.1 % ammoniumacetate buffer 20:80-100:0). The fractions containing product were lyophilized and 27 mg (48%) of the title product was obtained. M/z: 555.0 (M-1).

Method 78

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-tryptophan

[4-((2R,3R)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (0.050 g, 0.103 mmol) was dissolved in CH_2Cl_2 (5 ml). Tryphtophane tert-butyl ester hydrochloride (0.037g, 0.12 mmol) and N-methylmorpholine (31 mg, 0.31 mmol) were added. After 10 minutes, TBTU (43 mg, 0.13 mmol) was added and the mixture was stirred for 4 h. The crude ester was purified on silica gel and eluted with EtOAc/CH_2Cl_2, 25/75. The fractions containing pure ester were concentrated. CH_2Cl_2 (5 ml) and TFA (1 ml) were added and the reaction was stirred for 4 h. The mixture was concentrated and the remaining trace of TFA was azeotropically removed by co-evaporation with toluene (2 X 5 ml). The residue was dissolved in 5 ml of MeOH and sodium borohydride (0.016 g, 0.414 mmol) was added. The reaction was quenched by the addition of 0.1M NH_4OAc buffer (1 ml) after 5 minutes. The mixture was concentrated and purified by preparative HPLC (gradient 20-50% CH_3CN in 0.1M ammonium acetate buffer). Freeze-drying of the pure fractions gave the title compound as a colourless solid (0.040 g, 58%). M/z: 670.3 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.85-2.95 (m, 2H), 3.07-3.12 (m, 1H), 3.22-3.27 (m, 1H), 4.24-4.27 (m, 1H), 4.34-4.38 (m, 1H), 4.41 (s, 2H), 4.70-4.76 (m, 1H), 5.01-5.04 (m, 1H), 6.80-7.35 (m, 16H), 7.50-7.53 (m, 1H), 7.85-7.92 (m, 1H), 10.76 (s, 1H).

Method 79

N^2-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-glutamine

[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (50 mg, 0.103 mmol), tert-butyl L-glutaminate hydrochloride (30 mg, 0.124 mmol) and N-metylmorpholine (40 mg, 0.396 mmol) were dissolved in methylene chloride (1 ml). TBTU (40 mg, 0.125 mmol) was added and the mixture was stirred for 90 min. The solvent was evaporated and the residue was dissolved in formic acid (1 ml). The mixture was heated to 45-50 °C for 4 h. The reaction mixture was evaporated under reduced

pressure. Toluene (5 ml) was added and evaporated. The residue was dissolved in methanol (1 ml). NaBH4 (30 mg, 0.793 mmol) was added and the mixture was stirred for 15 min. Acetic acid (50 mg, 0.83mmol) was added and the rection mixture was evaporated under reduced pressure. The residue was purified by preparative HPLC using acetonitrile/ammonium acetate buffer (35:65) as eluent. After freeze-drying 47 mg (74%) of the title compound was obtained. ^{1}H-NMR, 300 MHz, DMSO): 1.72-2.16 (m, 4H), 2.81-2.95 (m,2H), 4.08-4.20 (m, 1H), 4.26-4.31 (m, 1H), 4.50 (s, 2H), 4.65-4.78 (m, 1H), 5.03-5.08 (m, 1H), 6.68 (s, 1H), 6.89-7.44 (m, 14H), 8.29 (d, 1H).

Method 80

N-{[4-((2R,3R)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-D-serine

A solution of [4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-oxoethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetic acid (0.050 g, 0.103 mmol), O-(tert-butyl)-D-serine tert-butyl ester hydrochloride (0.032 g, 0.147 mmol) and N-methylmorpholine (0.035 ml, 0.318 mmol) in DCM (4 ml) was stirred for 5 min. TBTU (0.044 g, 0.137 mmol) was added. The formation of the ester was confirmed after 3 h. M/z: 683.1. TFA (2 ml) was added and the mixture was stirred for 22 h. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (4 ml) and NaBH4 (totally 0.130 g, 3.44 mmol) was added in small portions. The reaction was quenched by the addition of 0.1M ammonium acetate buffer (3 ml). The methanol was removed under reduced pressure. The remaining solution was purified by preparative HPLC using a gradient of 20-60% MeCN in 0.1M ammonium acetate buffer as eluent. After freeze-drying, 0.021 g (36 % yield) of the title product was obtained as a white solid. M/z: 573.1. 1H NMR (DMSO, 400 MHz): δ 2.84-2.96 (m, 2H), 3.47 (dd, 1H), 3.69 (dd, 1H), 3.97-4.06 (m, 1H), 4.27-4.32 (m, 1H), 4.52 (ABq, 2H), 4.68-4.77 (m, 1H), 5.04-5.09 (m, 1H), 5.65 (bs, 1H), 6.99 (d, 2H), 7.07-7.41 (m, 10H), 7.89 (d, 1H).

It will be appreciated by those skilled in the art that the examples may be modified within the realms of the invention, why the invention is not limited to particular embodiments.

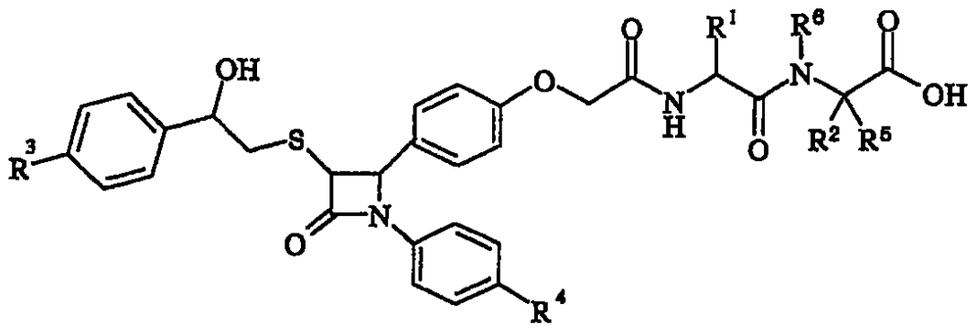
Absorption

Absorption of the compounds of formula (I) was tested in a Caco-2 cells model (Gastroenterology 1989, 96, 736):

Compound (I)	**Caco value (10^{-6}cm/sec)**
N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine	0.06
N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-tyrosine	0.07
N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-lysine	0.2
1-(4-Fluorophenyl)-3-(R)-[2-(4-fluorophenyl)-2-hydroxyethylthio]-4-(R)-{4-[*N*-{*N*-[2-(phenyl)-1-(R)-(carboxy)ethyl]carbamoylmethyl}carbamoylmethoxy]phenyl}azetidin-2-one	0.09

Claims

1. A compound of formula (I):



(I)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, guanidino, carbamoyl, carboxy, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_1-C_6 alkylcarbonylamino C_{1-6}alkylS(O)$_a$ wherein a is 0-2, C_{3-6}cycloalkyl or aryl; and wherein any aryl group may be optionally substituted by one or two substituents selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^2 and R^5 are independently hydrogen, a branched or unbranched C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, guanidino, cyano, carbamoyl, carboxy, C_{1-6}alkoxy, aryl C_{1-6}alkoxy,$(C_1$-$C_4)_3$Si, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$, C_{3-6}cycloalkyl, aryl or aryl C_{1-6} alkylS(O)$_a$ wherein a is 0-2; and wherein any aryl group may be optionally substituted by one or two substituents selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^3 is hydrogen, alkyl, halo, C_{1-6}alkoxy or C_{1-6} alkylS-;

R^4 is hydrogen, C_{1-6} alkyl, halo or C_{1-6}alkoxy;

R^6 is hydrogen, C_{1-6} alkyl, or arylC_{1-6} alkyl;

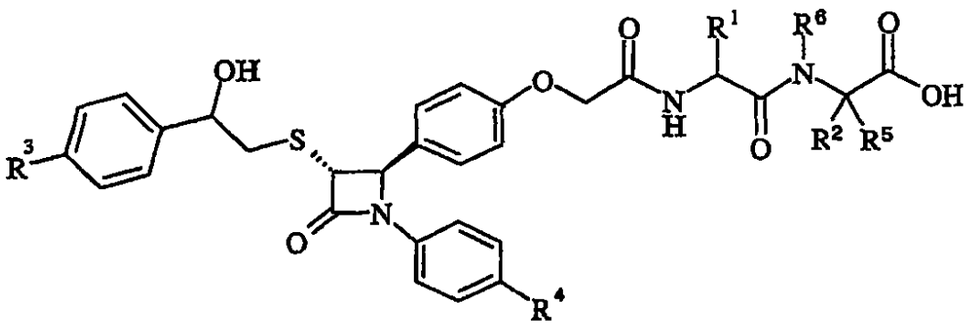
wherein R^5 and R^2 may form a ring with 2-7 carbon atoms and wherein R^6 and R^2 may form a ring with 3-6 carbon atoms;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof;

with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-[4-(*N*-{*N*-[(R)-1-(carboxy)-2-(hydroxy)ethyl]carbamoylmethyl} carbamoylmethoxy)phenyl]azetidin-2-one; or 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-

2-hydroxyethylsulphanyl]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy) ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one.

2. A compound of formula (I2):



(I2)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, guanidino, carbamoyl, carboxy, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_1-C_6 alkylcarbonylamino C_{1-6}alkylS(O)$_a$ wherein a is 0-2, C_{3-6}cycloalkyl or aryl; and wherein any aryl group may be optionally substituted by one or two substituents selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^2 and R^5 are independently hydrogen, a branched or unbranched C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, guanidino, cyano, carbamoyl, carboxy, C_{1-6}alkoxy, aryl C_{1-6}alkoxy,(C_1-C_4)$_3$Si, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$, C_{3-6}cycloalkyl, aryl or aryl C_{1-6} alkylS(O)$_a$, wherein a is 0-2; and wherein any aryl group may be optionally substituted by one or two substituents selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^3 is hydrogen, alkyl, halo, C_{1-6}alkoxy or C_{1-6} alkylS-;

R^4 is hydrogen, C_{1-6} alkyl, halo or C_{1-6}alkoxy;

R^6 is hydrogen, C_{1-6} alkyl, or arylC_{1-6} alkyl;

wherein R^5 and R^2 may form a ring with 2-7 carbon atoms and wherein R^6 and R^2 may form a ring with 3-6 carbon atoms;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof;

with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-[4-(*N*-{*N*-[(R)-1-(carboxy)-2-(hydroxy)ethyl]carbamoylmethyl} carbamoylmethoxy)phenyl]azetidin-2-one; or 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy) ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one.

3. A compound according to claim 1 or 2, wherein:
R^1 is hydrogen or phenyl.

4. A compound according to any of the preceding claims, wherein:
R^2 is hydrogen, a branched or unbranched C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, acylamino, C_{1-6}alkyl$S(O)_a$ wherein a is 0-2, C_{3-6}cycloalkyl or aryl; and wherein any aryl group may be optionally substituted by hydroxy, alkyl, alkoxy or cyano.

5. A compound according to any of the preceding claims, wherein:
R^3 is hydrogen, C_1-C_2alkyl, halo or methoxy.

6. A compound according to any of the preceding claims, wherein:
R^3 is hydrogen, methyl, chlorine, fluorine, C_{1-6} alkylS-, or methoxy.

7. A compound according to any of the preceding claims, wherein:
R^4 is hydrogen or halo.

8. A compound according to any of the preceding claims, wherein:
R^4 is chlorine or fluorine.

9. A compound according to any of the preceding claims, wherein:
R^6 is hydrogen, C_{1-6} alkyl, arylC_{1-6}alkyl or R^6 and R^2 form a ring with 3-6 carbon atoms.

10. A compound according to claim 1, wherein:
R^1 is hydrogen;

R^2 is a branched or unbranched C_{1-4}alkyl, optionally substituted by a C_{3-6}cycloalkyl, alkylS-, aryl optionally substituted by hydroxy or cyano, amino, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino or aryl C_{1-6} alkylS(O)$_a$, wherein a is 0-2

R^3 and R^4 are halo;
R^5 is hydrogen or C_{1-6} alkyl; and
R^6 is hydrogen.

11. One or more compounds chosen from:

N-{[4-((2R,3R)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-N^6-acetyl-D-lysine;

1-(4-Fluorophenyl)-3-(R)-[2-(4-fluorophenyl)-2-hydroxyethylthio]-4-(R)-{4-[*N*-{*N*-[2-(phenyl)-1-(R)-(carboxy)ethyl]carbamoylmethyl}carbamoylmethoxy]phenyl}azetidin-2-one;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-tyrosine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-proline;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-lysine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-hydroxy-2-(4-methoxyphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-2-butylnorleucine;

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-methyl-L-cysteine;

N-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-cyclohexyl-D-alanine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-cyclohexyl-D-alanine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-4-methylleucine;

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}-L-alanyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-hydroxy-2-(4-methylphenyl)ethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-chlorophenyl)-3-{[2-(4-chlorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-methyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-(2-naphthyl)-D-alanine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-3-methyl-D-valine;

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-(3*R*,4*S*,5*R*)-3,4,5,6-tetrahydroxy-D-norleucine.

N-{[4-((2*R*,3*R*)-1-(4-Fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*N*,2-dimethylalanine

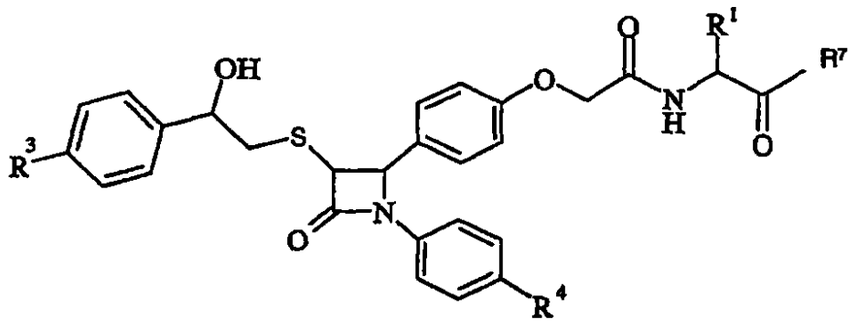
N-({4-[(2*R*,3*R*)-1-(4-Fluorophenyl)-3-({2-hydroxy-2-[4-(methylthio)phenyl]ethyl}thio)-4-oxoazetidin-2-yl]phenoxy}acetyl)glycyl-3-methyl-D-valine

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-(4-methylbenzyl)-D-cysteine

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-*S*-(*tert*-butyl)-D-cysteine

N-{[4-((2*R*,3*R*)-1-(4-fluorophenyl)-3-{[2-(4-fluorophenyl)-2-hydroxyethyl]thio}-4-oxoazetidin-2-yl)phenoxy]acetyl}glycyl-b,b-dimethyl-D-phenylalanine.

12. A compound of the formula (XV) or hydrolysable esters or amides thereof:



(XV)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, guanidino, carbamoyl, carboxy, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N*,*N*-(C_{1-6}alkyl)$_2$amino, C_1-C_6 alkylcarbonylamino C_{1-6}alkyl$S(O)_n$ wherein a is 0-2, C_{3-6}cycloalkyl or aryl; and wherein any aryl group may be optionally substituted by one or two substituents selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^2 and R^5 are independently hydrogen, a branched or unbranched C_{1-6}alkyl, C_{3-6}cycloalkyl or aryl; wherein said C_{1-6}alkyl may be optionally substituted by one or more hydroxy, amino, guanidino, carbamoyl, carboxy, C_{1-6}alkoxy, aryl C_{1-6}alkoxy,$(C_1-C_4)_3Si$, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_{a,\ aryl}$ C_{1-6} alkylS(O)$_a$, wherein a is 0-2, C_{3-6}cycloalkyl or aryl; and wherein any aryl group may be optionally substituted by one or two substituents selected from halo, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

R^3 is hydrogen, alkyl, halo, C_{1-6}alkoxy or C_{1-6} alkylS-;

R^4 is hydrogen, C_{1-6} alkyl, halo or C_{1-6}alkoxy;

R^6 is hydrogen, C_{1-6} alkyl, or arylC_{1-6} alkyl;

R^7 is an hydroxy group or a C_{1-3} alkoxy group;

wherein R^5 and R^2 may form a ring with 2-7 carbon atoms and wherein R^6 and R^2 may form a ring with 3-6 carbon atoms;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof;

with the proviso that said compound is not 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-[4-(*N*-{*N*-[(R)-1-(carboxy)-2-(hydroxy)ethyl]carbamoylmethyl} carbamoylmethoxy)phenyl]azetidin-2-one; or 3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy) ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one.

13. A method of treating or preventing hyperlipidemic conditions comprising the administration of an effective amount of a compound according to any one of claims 1 to 12 to a mammal in need thereof.

14. A method of treating or preventing atherosclerosis comprising the administration of an effective amount of a compound according to any one of claims 1 to 12 to a mammal in need thereof.

15. A method for treating or preventing Alzheimers' disease comprising the administration of an effective amount of a compound according to any one of claims 1 to 12 to a mammal in need thereof.

16. A method for treating or preventing cholesterol associated tumors comprising the administration of an effective amount of a compound according to any one of claims 1 to 12 to a mammal in need thereof.

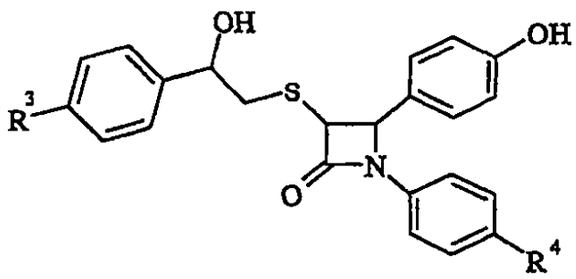
17. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 12 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

18. A combination of a compound according to formula (I) or (I2) with a PPAR alpha and/or gamma agonist.

19. A combination of a compound according to formula (I) or (I2) with an HMG Co-A reductase inhibitor.

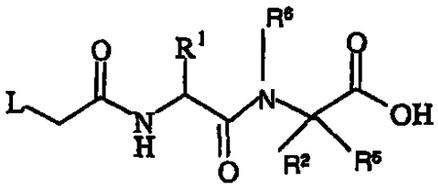
20. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

Process 1) reacting a compound of formula (II):



(II)

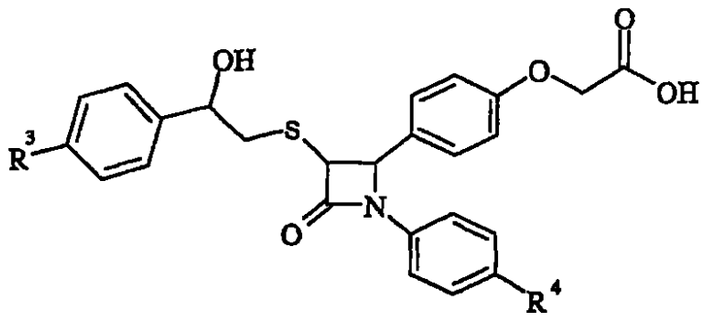
with a compound of formula (III):



(III)

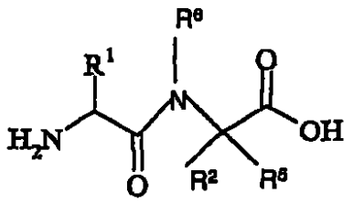
wherein L is a displaceable group;

Process 2) reacting an acid of formula (IV):



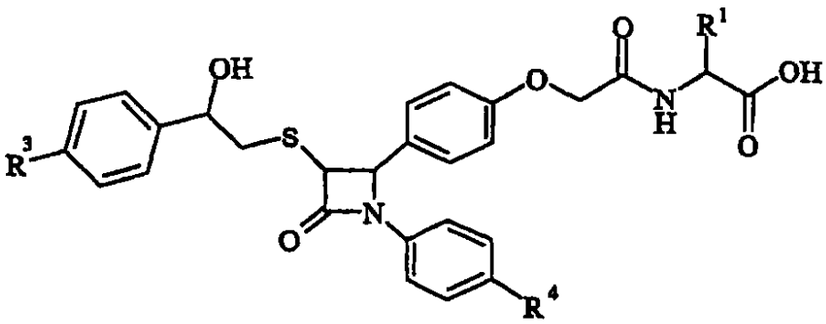
(IV)

or an activated derivative thereof; with an amine of formula (V):



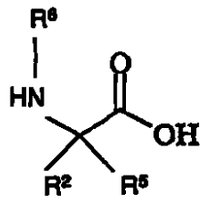
(V)

Process 3): reacting an acid of formula (VI):



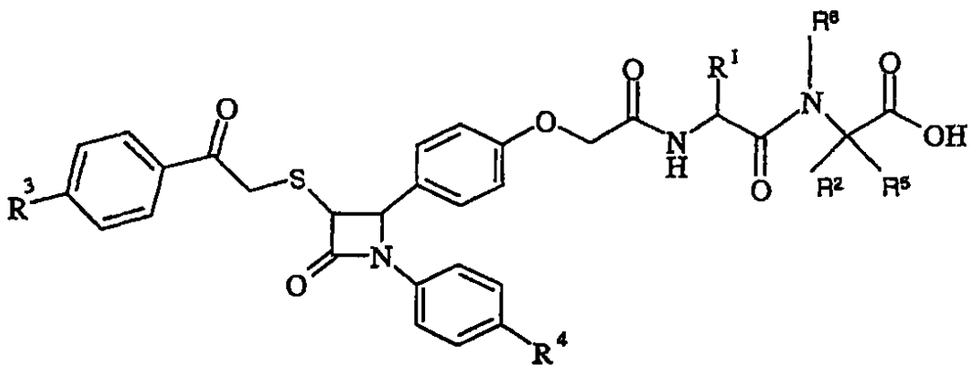
(VI)

or an activated derivative thereof, with an amine of formula (VII):



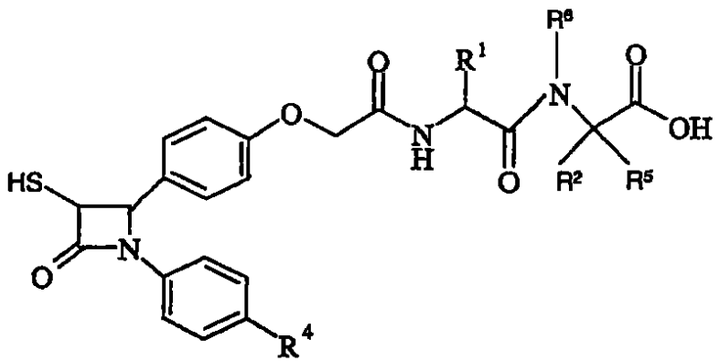
(VII)

Process 4): reducing a compound of formula (VIII):



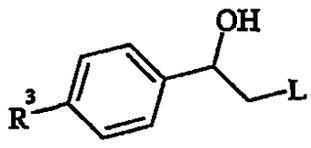
(VIII)

Process 5): reacting a compound of formula (IX):



(IX)

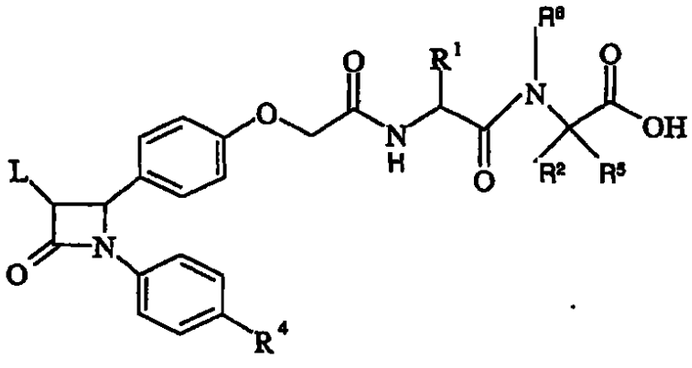
with a compound of formula (X):



(X)

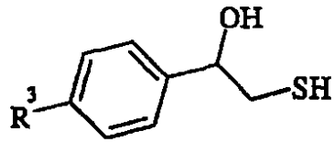
wherein L is a displaceable group;

Process 6): reacting a compound of formula (XI):



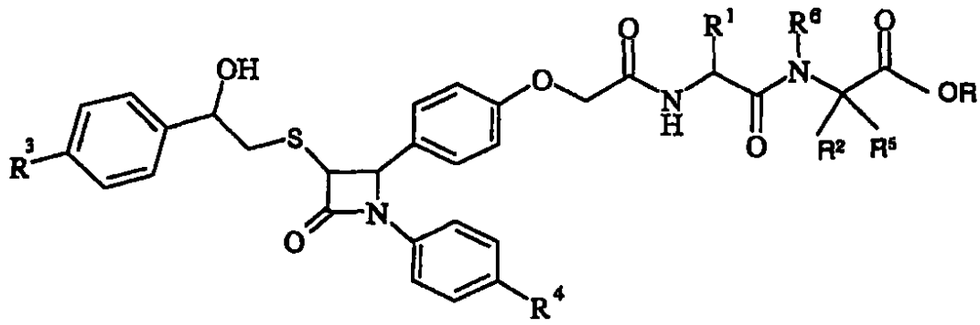
(XI)

wherein L is a displaceable group; with a compound of formula (XII):



(XII)

Process 7): De-esterifying a compound of formula (XIII)



(XIII)

wherein the group C(O)OR is an ester group;

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug; or

iv) separating two or more enantiomers.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

C(O)OR is an ester group, suitable values for C(O)OR are methoxycarbonyl, ethoxycarbonyl, *t*-butoxycarbonyl and benzyloxycarbonyl.

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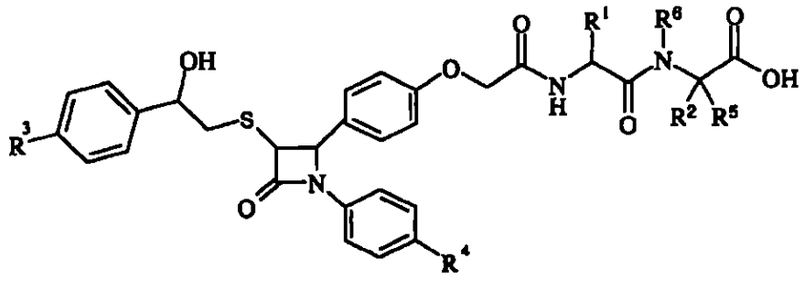
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(54) Título: DERIVADOS DE DIFENILAZETIDINONA QUE POSEEN ACTIVIDAD INHIBIDORA DE LA ABSORCIÓN DE COLESTEROL



(I)

(57) Extracto Se describen compuestos de fórmula (I) (en donde los grupos variables son como se definen allí), sales, solvatos de tales sales y sus profármacos farmacéuticamente aceptables, y su uso como inhibidores de la absorción de colesterol para el tratamiento de hiperlipidemia Se describen asimismo procesos para su manufactura y composiciones farmacéuticas que los contienen

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Derivados de Difenilazetidinona que Poseen Actividad Inhibidora de la Absorción de Colesterol

Esta invención se refiere a derivados de 2-azetidinona, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales y profármacos. Estas 2-azetidinonas poseen actividad inhibidora de absorción de colesterol y, en consecuencia, son útiles en el tratamiento de estados patológicos asociados con afecciones hiperlipidémicas. Por lo tanto, son de utilidad en métodos de tratamiento de un animal de sangre caliente, tal como el hombre. La invención se refiere igualmente a procesos para la manufactura de dichos derivados de 2-azetidinona, a composiciones farmacéuticas que los contienen y a su uso en la manufactura de medicamentos para inhibir la absorción del colesterol en un animal de sangre caliente, tal como el hombre. Un aspecto adicional de esta invención se relaciona con el uso de los compuestos de la invención en el tratamiento de afecciones dislipidémicas.

La arteriopatía coronaria ateroesclerótica es una causa importante de muerte y morbilidad en el mundo occidental, así como de un significativo drenaje de recursos para asistencia médica. Es bien conocido que las afecciones hiperlipidémicas, asociadas con concentraciones elevadas de colesterol total y colesterol de lipoproteína de baja densidad (LDL), son los principales riesgos de la enfermedad ateroesclerótica cardiovascular (por ejemplo, "Coronary Heart Disease: Reducing the Risk; a Worldwide View" Assman G., Carmena R. Cullen P. *et al*, Circulation 1999, 100, 1930-1938 y "Diabetes and Cardiovascular Disease: A Statement for Healthcare Professionals from the American Heart Association" Grundy S., Benjamin I., Burke G., *et al*; Circulation, 1999, 100, 1134-46).

La concentración de colesterol en el plasma depende del balance integrado de rutas endógenas y exógenas del metabolismo del colesterol. En la ruta endógena, el colesterol es sintetizado por el hígado y tejidos extrahepáticos y entra en la circulación en forma de lipoproteínas o es secretado en la bilis. En la ruta exógena el colesterol de fuentes dietéticas y

biliares es absorbido en el intestino y entra en la circulación como un componente de quilomicrones. La alteración de una cualquiera de las rutas afectará la concentración del colesterol en el plasma.

Sin embargo, no es claro el mecanismo preciso por el cual el colesterol es absorbido del intestino. La hipótesis original ha sido que el colesterol atraviesa el intestino mediante difusión no específica. Pero estudios más recientes sugieren que hay transportadores específicos involucrados en la absorción intestinal del colesterol. (Véase, por ejemplo, New molecular targets for cholesterol-lowering therapy Izzat, N.N., Deshazer, M.E. and Loose-Mitchell D.S. JPET 293:315-320, 2000.)

Se ha establecido una clara asociación entre la reducción del colesterol total y el colesterol (LDL) y la disminución en los casos de arteriopatía coronaria, y se emplean varias clases de agentes farmacéuticos para controlar el colesterol sérico. Las principales opciones para regular el colesterol en el plasma incluyen (i) bloquear la síntesis del colesterol por agentes tales como inhibidores de HMG-CoA reductasa, por ejemplo estatinas tales como simvastatina y fluvastatina, las cuales, mediante la regulación por incremento de receptores de LDL, promoverán la eliminación del colesterol del plasma; (ii) bloquear la reabsorción de ácido biliar por agentes específicos, lo que resulta en una excreción mayor de ácido biliar y síntesis de ácidos biliares del colesterol con agentes tales como captadores de ácidos biliares (***"bile acid binders"***), tales como resinas, por ejemplo colestiramina y colestipol; y (iii) bloquear la absorción intestinal de colesterol mediante inhibidores selectivos de la absorción del colesterol. Asimismo se han empleado agentes que elevan la lipoproteína de alta densidad (HDL) tales como fibratos y análogos del ácido nicotínico.

Incluso con la diversa gama actual de agentes terapéuticos, una significativa proporción de la población hipercolesterolémica es incapaz de alcanzar niveles diana de colesterol, o las interacciones de los medicamentos o la seguridad de los mismos impiden el uso a largo plazo, necesario para alcanzar los niveles diana. Por lo tanto, subsiste una

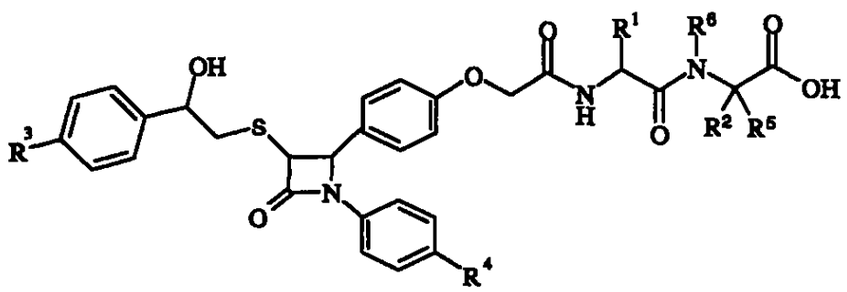
necesidad de desarrollar agentes adicionales que sean más eficaces y mejor tolerados.

Se han descrito compuestos que poseen tal actividad inhibidora de la absorción de colesterol; véase, por ejemplo, los compuestos descritos en WO 93/02048, WO 94/17038, WO 95/08532, WO 95/26334, WO 95/35277, WO 96/16037, WO 96/19450, WO 97/16455, WO 02/50027, WO 02/50060, WO 02/50068, WO 02/50090, WO 02/66464, WO 04/000803, WO 04/000804, WO 04/000805, WO 04/043457, WO 04/081002, US 5756470, US 5767115, US 20040180860, US20040180861 y US RE37721.

La presente invención se basa en el descubrimiento de que ciertos derivados de 2-azetidinona inhiben sorpresivamente la absorción del colesterol. Se espera que tales propiedades seán útiles en el tratamiento de estados patológicos asociados con afecciones hiperlipidémicas. Los compuestos de la presente invención no se divulgan en ninguna de las solicitudes mencionadas, y nosotros hemos descubierto sorpresivamente que los compuestos de la presente invención poseen perfiles metabólicos y toxicológicos benéficos, eficaces, que los hacen particularmente apropiados para administración *in vivo* a un animal de sangre caliente, tal como el hombre. En particular, ciertos compuestos de la presente invención tienen un bajo grado de absorción comparados con los compuestos del arte previo, conservando al mismo tiempo su capacidad de inhibir la absorción del colesterol.

Por consiguiente se provee un compuesto de fórmula (I):

(I)



(I)

en donde:

R^1 es hidrógeno, C_{1-6}alquilo, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, guanidino, carbamoilo, carboxi, C_{1-6}alcoxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_1-C_6 alquilcarbonilamino C_{1-6}alquil$S(O)_a$ en donde **a** es 0-2, C_{3-6}cicloalquilo o arilo; y en donde cualquier grupo arilo puede sustituirse en forma opcional por uno o dos sustituyentes seleccionados de halo, hidroxi, C_{1-6}alquilo o C_{1-6}alcoxi ;

R^2 y **R^5** son independientemente hidrógeno, un C_{1-6}alquilo ramificado o no ramificado, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, guanidino, ciano, carbamoilo, carboxi, C_{1-6}alcoxi, arilC_{1-6}alcoxi, $(C_1$-$C_4)_3$Si, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquil$S(O)_a$, C_{3-6}cicloalquilo, arilo o arilC_{1-6}alquil$S(O)_a$, en donde a es 0-2; y en donde cualquier grupo arilo puede sustituirse en forma opcional por uno o dos sustituyentes seleccionados de halo, hidroxi, C_{1-6}alquilo o C_{1-6}alcoxi;

R^3 es hidrógeno, alquilo, halo, C_{1-6}alcoxi o C_{1-6} alquilS-;

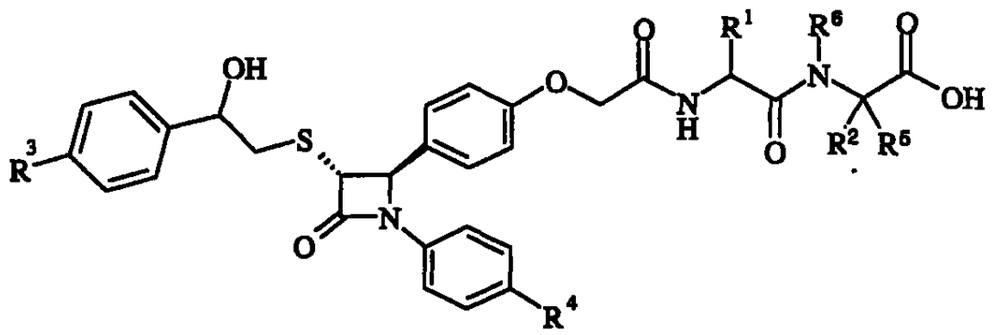
R^4 es hidrógeno, C_{1-6} alquilo, halo o C_{1-6}alcoxi;

R^6 es hidrógeno, C_{1-6} alquilo, o arilC_{1-6} alquilo;

En donde **R^5** y **R^6** pueden formar un anillo con 2-7 átomos de carbono y en donde **R^6** y **R^2** pueden formar un anillo con 3-6 átomos de carbono;

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco; con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-[4-(*N*-{*N*-[(R)-1-(carboxi)-2-(hidroxi)etil]carbamoilmetil}carbamoilmetoxi)fenil]azetidin-2-ona; o 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi) etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona.

En un aspecto de la invención se contempla un compuesto de fórmula **(I2)**:



I2

en donde son como se definen más arriba para la fórmula (I). Lo que se dice además para fórmula (I), aparte de los siguientes esquemas de proceso, se aplicará también a fórmula (I2).

En un aspecto de la invención R^1 es hidrógeno. De acuerdo con otro aspecto de la invención, R^2 es hidrógeno, un C_{1-6}alquilo ramificado o no ramificado, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, C_{1-6}alquilS(O)$_a$ en donde **a** es 0-2, C_{3-6}cicloalquilo o arilo; y en donde cualquier grupo arilo puede sustituirse en forma opcional por hidroxi. De acuerdo con un aspecto adicional de la invención, R^3 es hidrógeno, metoxi, o alquilo, por ejemplo un C_1-C_2alquilo, es decir, metilo o etilo, por ejemplo metilo, o un halógeno, por ejemplo cloro o flúor.
De acuerdo con todavía otro aspecto de la invención R^4 es hidrógeno o halo, por ejemplo cloro o flúor. De acuerdo con un aspecto adicional de la invención, R^6 es hidrógeno, arilC_{1-6} o R^6 y R^2 forman un anillo con 3-6 átomos de carbono.

De acuerdo con un aspecto de la invención R^1 es hidrógeno, R^2 es un C_{1-4}alquilo ramificado o no ramificado, sustituido de manera opcional por un C_{3-6}cicloalquilo, R^3 y R^4 son halo, R^5 es hidrógeno o C_{1-6} alquilo, y R^6 es hidrógeno.

La invención contempla además uno o más compuestos seleccionados de:
N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}6-acetil}glicil-N^6-acetil-D-lisina;

1-(4-Fluorofenil)-3-(R)-[2-(4-fluorofenil)-2-hidroxietiltio]-4-(R)-{4-[*N*-{*N*-[2-(fenil)-1-(R)-(carboxi)etil]carbamoilmetil}
carbamoilmetoxi]fenil}azetidin-2-ona;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-tirosina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-prolina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-lisina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-hidroxi-2-(4-metoxifenil)etil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-2-butilnorleucina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*S*-metil-L-cisteína;

N-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-ciclohexil-D-alanina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-ciclohexil-D-alanina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-4-metil-leucina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-alanil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-hidroxi-2-(4-metilfenil)etil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-metil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-(2-naftil)-D-alanina;

N-{[4-(2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-metil-D-valina;

N-{[4-(2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-(3*R*,4*S*,5*R*)-3,4,5,6-tetrahidroxi-D-norleucina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*N*,2-dimetilalanina;

N-({4-[(2*R*,3*R*)-1-(4-fluorofenil)-3-({2-hidroxi-2-[4-(metiltio)fenil] etil}tio)-4-oxoazetidin-2-il]fenoxi}acetil)glicil-3-metil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*S*-(4-metilbencil)-D-cisteína;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*S*-(*terc*-butil)-D-cisteína;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-b,b-dimetil-D-fenilalanina.

En esta especificación el término "alquilo" incluye los dos grupos alquilo de cadena recta y ramificada, pero referencias a grupos alquilo individuales tales como "propilo" son específicos de la versión de cadena recta únicamente. Por ejemplo, "C_{1-6}alquilo" y "C_{1-4}alquilo" incluyen propilo, isopropilo y *t*-butilo. Sin embargo, referencias a grupos alquilo individuales tales como 'propilo' son específicos de la versión de cadena recta únicamente y referencias a grupos alquilo individuales de cadena ramificada tales como 'isopropilo' son específicos de la versión de cadena ramificada únicamente. Una convención similar se aplica a otros radicales, por ejemplo "fenilC_{1-6}alquilo" incluiría bencilo, 1-feniletilo y 2-feniletilo. El término "halo" se refiere a fluoro, cloro, bromo y yodo.

Donde sustituyentes opcionales se escogen de "uno o más" grupos hay que entender que esta definición incluye todos los sustituyentes que se escogen de uno de los grupos especificados o los sustituyentes que se escogen de dos o más de los grupos especificados.

El término "arilo" se refiere a un anillo mono o bicíclico de 4-10 miembros que contiene 0 a 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre. Ejemplos de arilos incluyen fenilo, pirrolilo, furanilo, imidazolilo, triazolilo, tetrazolilo, pirazinilo, pirimidinilo, piridazinilo, piridilo, isoxazolilo, oxazolilo, 1,2,4 oxadiazolilo,

isotiazolilo, tiazolilo, 1,2,4-triazolilo, tienilo, naftilo, benzofuranilo, benzimidazolilo, benztienilo, benztiazolilo, benzisotiazolilo, benzoxazolilo, benzisoxazolilo, 1,3-benzodioxolilo, indolilo, piridoimidazolilo, pirimidoimidazolilo, quinolilo, isoquinolilo, quinoxalinilo, quinazolinilo, ftalazinilo, cinnolinilo y naftiridinilo. Particularmente, "arilo" se refiere a fenilo, tienilo, piridilo, imidazolilo o indolilo. El término "arilo" incluye anillos aromáticos sustituidos y no sustituidos.

Ejemplos de "C_{1-6}alcoxi" incluyen metoxi, etoxi y propoxi. Ejemplos de "C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2" incluyen metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo y etilsulfonilo. Ejemplos de "*N*-(C_{1-6}alquil)amino" incluyen metilamino y etilamino. Ejemplos de "*N*,*N*-(C_{1-6}alquil)$_2$amino" incluyen di-*N*-metilamino, di-(*N*-etil)amino y *N*-etil-*N*-metilamino. "C_{3-6}cicloalquilo" se refiere a ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

Una sal apropiada, farmacéuticamente aceptable de un compuesto de la invención, u otros compuestos divulgados aquí, es, por ejemplo, una sal de adición de ácido de un compuesto de la invención, que es suficientemente básica, por ejemplo, una sal de adición de ácido con, por ejemplo, un ácido orgánico o inorgánico, por ejemplo ácido clorhídrico, bromhídrico, sulfúrico, fosfórico, trifluoroacético, cítrico, acetato o ácido maleico. Adicionalmente, una sal apropiada, farmacéuticamente aceptable de un compuesto de la invención, que es suficientemente ácida es una sal de metal alcalino, por ejemplo una sal de sodio o potasio, una sal de metal alcalinotérreo, por ejemplo una sal de calcio o magnesio, una sal de amonio o una sal con una base orgánica que suministre un catión fisiológicamente aceptable, por ejemplo una sal con metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina.

Los compuestos de la fórmula (I), u otros compuestos divulgados aquí, pueden administrarse en la forma de un profármaco que se descompone en el cuerpo humano o animal para producir un compuesto de la fórmula (I). Ejemplos de profármacos incluyen ésteres hidrolizables *in vivo* y amidas hidrolizables *in vivo* de un compuesto de la fórmula (I).

Un éster hidrolizable *in vivo* de un compuesto de la fórmula (I), u otros compuestos divulgados aquí, que contienen un grupo carboxi o hidroxi es, por ejemplo, un éster farmacéuticamente aceptable que se hidroliza en el cuerpo humano o animal para producir el ácido original o alcohol. Ésteres apropiados farmacéuticamente aceptables para carboxi incluyen C_{1-6}alcoximetil ésteres por ejemplo metoximetilo, C_{1-6}alcanoiloximetil ésteres por ejemplo pivaloiloximetilo, ftalidil ésteres, C_{3-8}cicloalcoxicarboniloxiC_{1-6}alquil ésteres por ejemplo 1-ciclohexilcarboniloxietilo; 1,3-dioxolen-2-onilmetil ésteres por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo; y C_{1-6} alcoxicarboniloxietil ésteres por ejemplo 1-metoxicarboniloxietilo, y pueden formarse en cualquier grupo carboxi en los compuestos de esta invención.

Un éster hidrolizable *in vivo* de un compuesto de la fórmula (I), u otros compuestos divulgados aquí, que contienen un grupo hidroxi incluye ésteres inorgánicos tales como ésteres de fosfato y α-aciloxialquil éteres y compuestos relacionados los cuales, como resultado de la hidrólisis *in vivo* del éster se descomponen para producir el grupo hidroxi original. Ejemplos de α-aciloxialquil éteres incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi. Una selección de grupos formadores de éster hidrolizable *in vivo* para hidroxi incluyen alcanoilo, benzoilo, fenilacetilo y benzoilo sustituido y fenilacetilo, alcoxicarbonilo (para producir ésteres de alquil carbonato), dialquilcarbamoilo y *N*-(dialquilaminoetil)-*N*-alquilcarbamoilo (para producir carbamatos), dialquilaminoacetilo y carboxiacetilo. Ejemplos de sustituyentes en benzoilo incluyen morfolino y piperazino enlazados desde un átomo de nitrógeno del anillo mediante un grupo metileno a la posición 3 ó 4 del anillo benzoilo.

Un valor apropiado para una amida hidrolizable *in vivo* de un compuesto de la fórmula (I), u otros compuestos divulgados aquí, que contienen un grupo carboxi es, por ejemplo, una *N*-C_{1-6}alquil o *N*,*N*-di-C_{1-6}alquil amida tales como *N*-metil, *N*-etil, *N*-propil, *N*,*N*-dimetil, *N*-etil-*N*-metil o *N*,*N*-dietil amida.

Algunos compuestos de la fórmula (I) pueden tener centros quirales y/o centros isoméricos geométricos (E- y Z-isómeros), y hay que entender que la invención abarca la totalidad de tales, diastereoisómeros e isómeros geométricos, ópticos que poseen actividad inhibidora de absorción de colesterol.

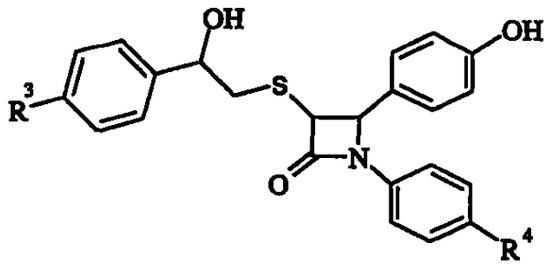
La invención se refiere a cualquiera y todas las formas tautoméricas de los compuestos de la fórmula (I) que poseen actividad inhibidora de absorción de colesterol.

Hay que entender igualmente que ciertos compuestos de la fórmula (I) pueden existir en formas solvatadas y no solvatadas tales como, por ejemplo, formas hidratadas. Hay que entender que la invención abarca la totalidad de tales formas solvatadas que poseen actividad inhibidora de absorción de colesterol.

Aspectos preferidos de la invención son los que se relacionan con el compuesto de fórmula (I) o su sal farmacéuticamente aceptable.

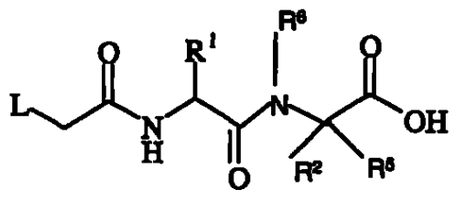
Otro aspecto de la presente invención provee un proceso para preparar un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, proceso que (en donde hay grupos variables, a menos que se especifique lo contrario, como se define en la fórmula (I)), comprende:

Proceso 1) hacer reaccionar un compuesto de fórmula (II):



(II)

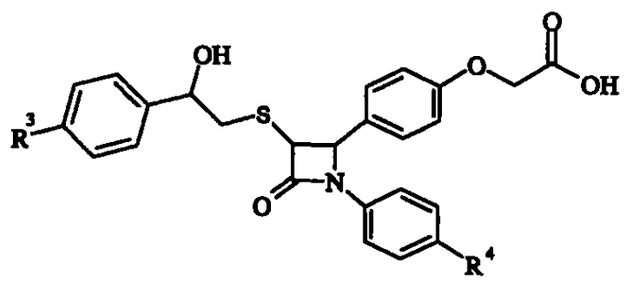
con un compuesto de fórmula (III):



(III)

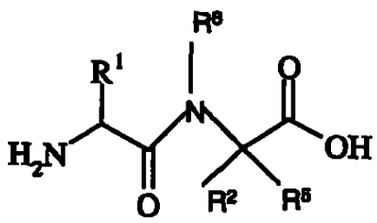
en donde L es un grupo desplazable;

Proceso 2) hacer reaccionar un ácido de fórmula (IV):



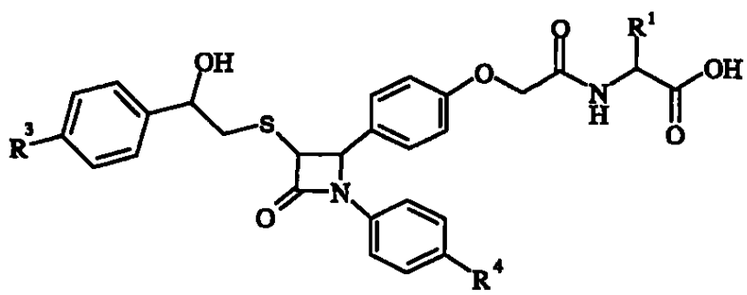
(IV)

o su derivado activado; con una amina de fórmula (V):



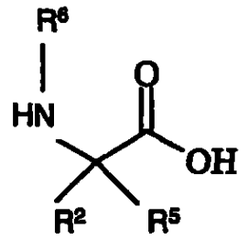
(V)

Proceso 3) hacer reaccionar un ácido de fórmula (VI):



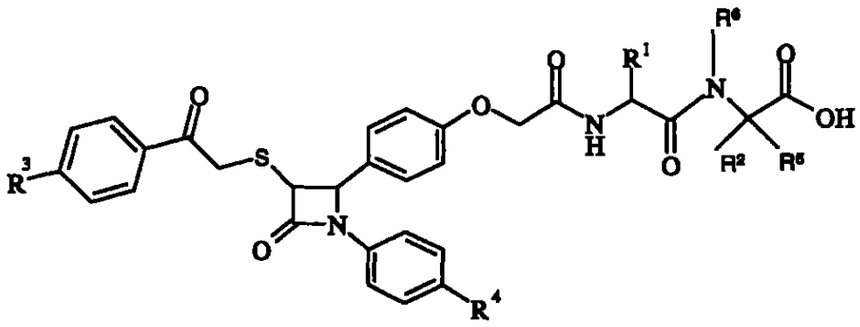
(VI)

o su derivado activado; con una amina de fórmula (VII):



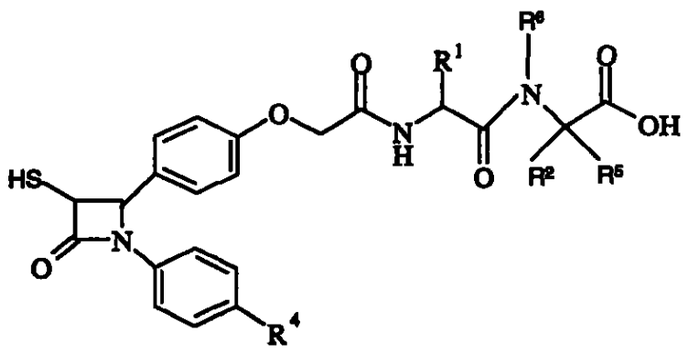
(VII)

Proceso 4): reducir un compuesto de fórmula (VIII):



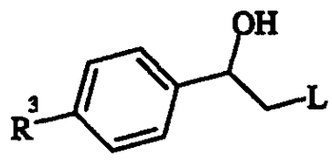
(VIII)

Proceso 5): hacer reaccionar un compuesto de fórmula (IX):



(IX)

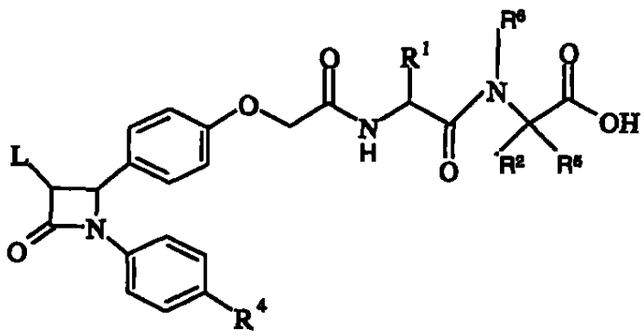
con un compuesto de fórmula (X):



(X)

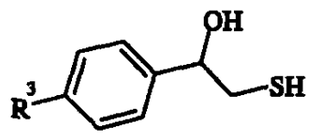
en donde L es un grupo desplazable;

Proceso 6): hacer reaccionar un compuesto de fórmula (XI):



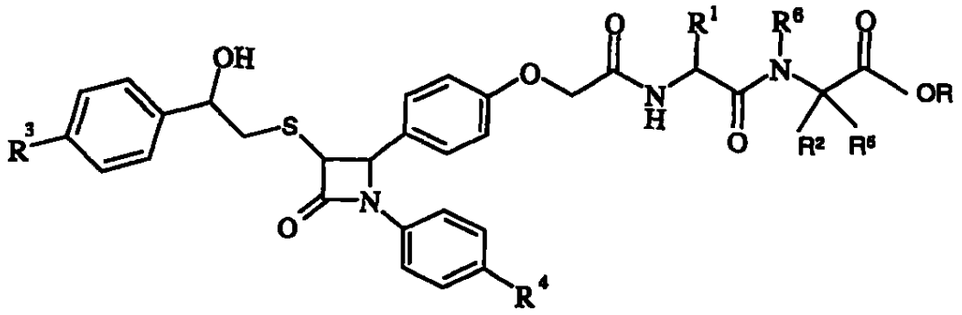
(XI)

en donde L es un grupo desplazable; con un compuesto de fórmula **(XII)**:



(XII)

Proceso 7): des-esterificar un compuesto de fórmula (XIII)



(XIII)

en donde el grupo C(O)OR es un grupo éster;

y posteriormente, si es necesario o deseable:

i) convertir un compuesto de la fórmula **(I)** en otro compuesto de la fórmula **(I)**;

ii) retirar cualesquiera grupos protectores;

iii) formar una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco; o

iv) separar dos o más enantiómeros.

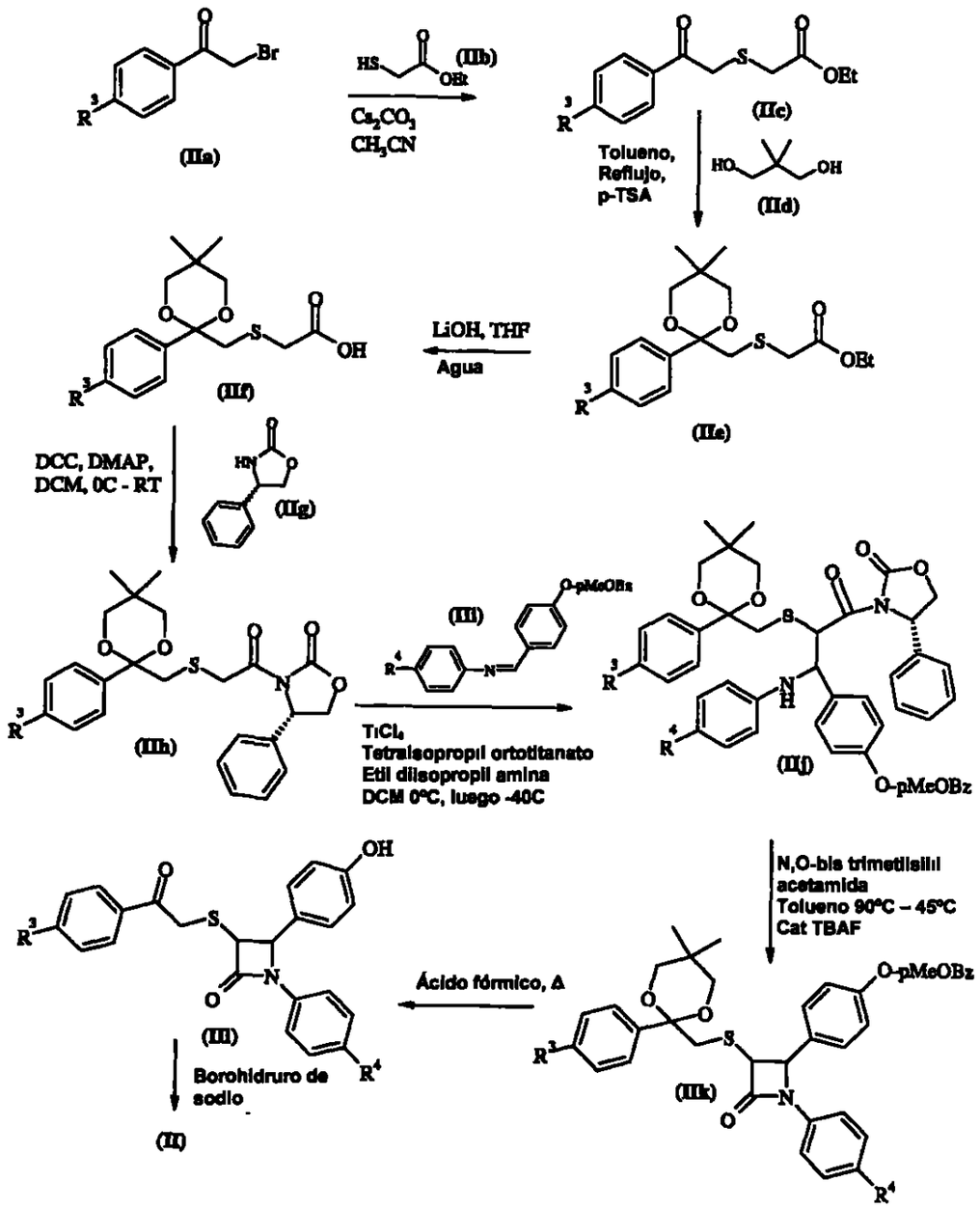
L es un grupo desplazable; valores apropiados para L son por ejemplo, un halógeno o grupo sulfoniloxi, por ejemplo un grupo cloro, bromo, metanosulfoniloxi o tolueno-4-sulfoniloxi.

C(O)OR es un grupo éster; valores apropiados para C(O)OR son metoxicarbonilo, etoxicarbonilo, *t*-butoxicarbonilo y benciloxicarbonilo.

Los materiales de partida usados en la presente invención pueden prepararse por modificaciones de las rutas descritas en EP 0 792 264 B 1. Alternativamente, los materiales de partida pueden prepararse por las siguientes reacciones.

Proceso 1): Alcoholes de fórmula **(II)** pueden hacerse reaccionar con compuestos de fórmula **(III)** en la presencia de una base por ejemplo una base inorgánica tal como carbonato de sodio, o una base orgánica tal como una base de Hünig, en la presencia de un disolvente apropiado tal como acetonitrilo, diclorometano o tetrahidrofurano a una temperatura en el rango de 0°C a reflujo, preferiblemente a reflujo o cerca de él.

Compuestos de fórmula **(II)** pueden prepararse de acuerdo con el siguiente esquema:



Esquema 1

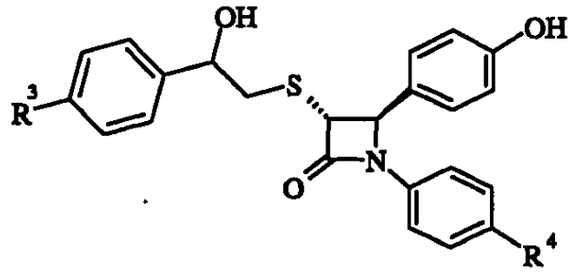
en donde pMeOBz es *para* metoxi bencilo.

Compuestos de fórmula **(IIb)**, **(IId)**, **(IIg)** y **(III)** son compuestos disponibles en el comercio, o se conocen en la literatura, o se preparan por procesos estándar conocidos en el arte.

Otro aspecto de la presente invención provee un proceso para preparar un compuesto de fórmula **(I2)** o su sal farmacéuticamente aceptable,

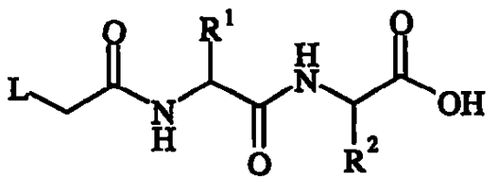
solvato, solvato de tal sal o profármaco, proceso (en donde grupos variables son, a menos que se especifique otra cosa, como se definen en fórmula (I)) que consta de:

Proceso 1) hacer reaccionar un compuesto de fórmula (II2):



(II2)

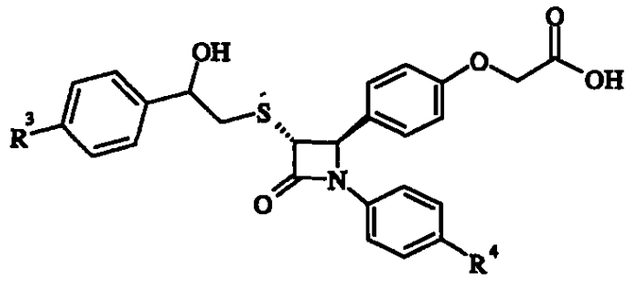
con un compuesto de fórmula (III):



(III)

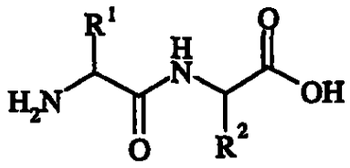
en donde L es un grupo desplazable;

Proceso 2) hacer reaccionar un ácido de fórmula (IV2):



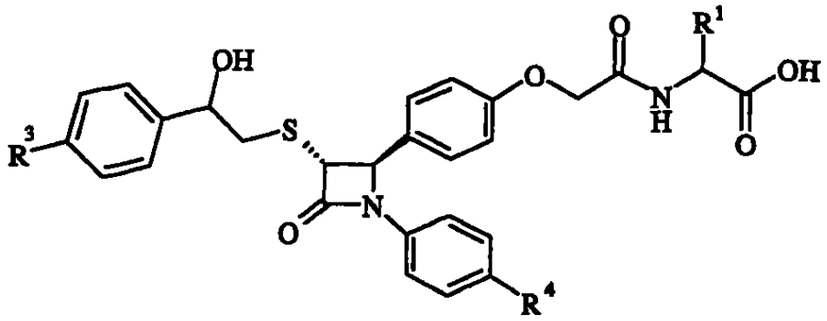
(IV)

o su derivado activado; con una amina de fórmula (V):



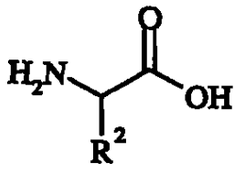
(V)

Proceso 3): hacer reaccionar un ácido de fórmula (VI2):



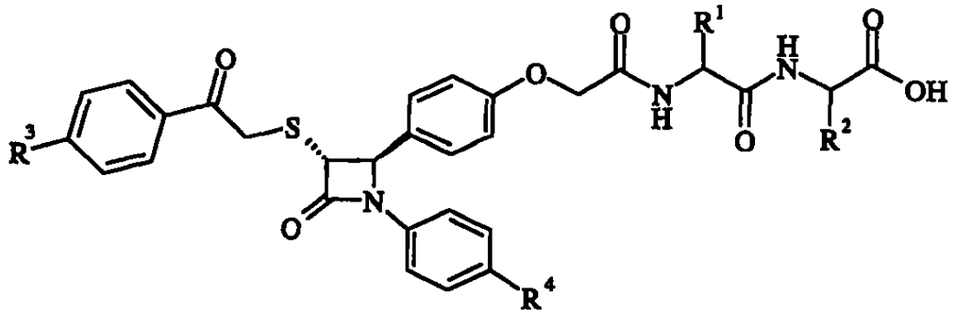
(VI2)

o su derivado activado; con una amina de fórmula (VII):



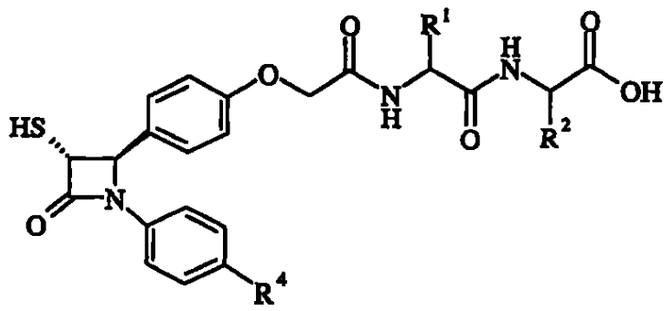
(VII)

Proceso 4): reducir un compuesto de fórmula (VIII2):



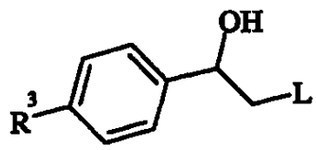
(VIII2)

*Proceso*5): hacer reaccionar un compuesto de fórmula (IX2):



(IX2)

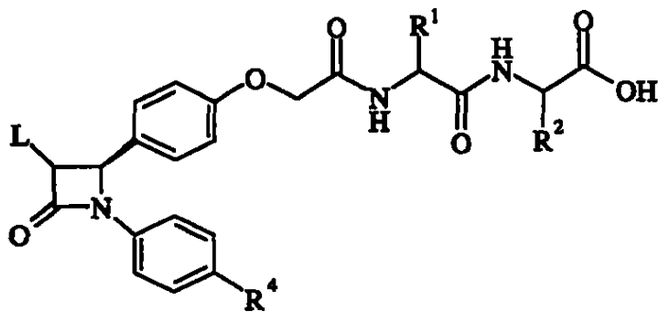
con un compuesto de fórmula (X):



(X)

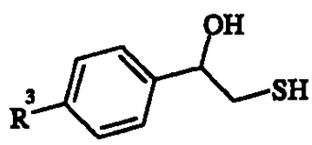
en donde L es un grupo desplazable;

Proceso 6): hacer reaccionar un compuesto de formula **(XI2)**:



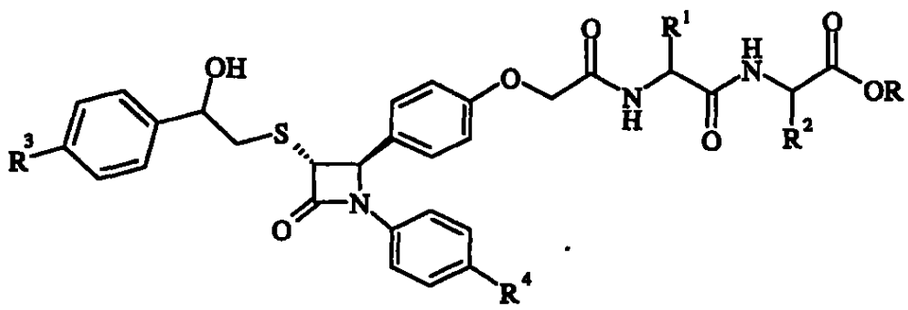
(XI2)

en donde L es un grupo desplazable; con un compuesto de fórmula **(XII)**:



(XII)

Proceso 7): des-esterificar un compuesto de fórmula **(XIII2)**



(XIII2)

en donde el grupo C(O)OR es un éster grupo;

y posteriormente, si es necesario o deseable;

i) convertir un compuesto de la fórmula **(I2)** en otro compuesto de la fórmula **(I2)**;

ii) retirar cualesquiera grupos protectores;

iii) formar una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco; o

iv) separar dos o más enantiómeros.

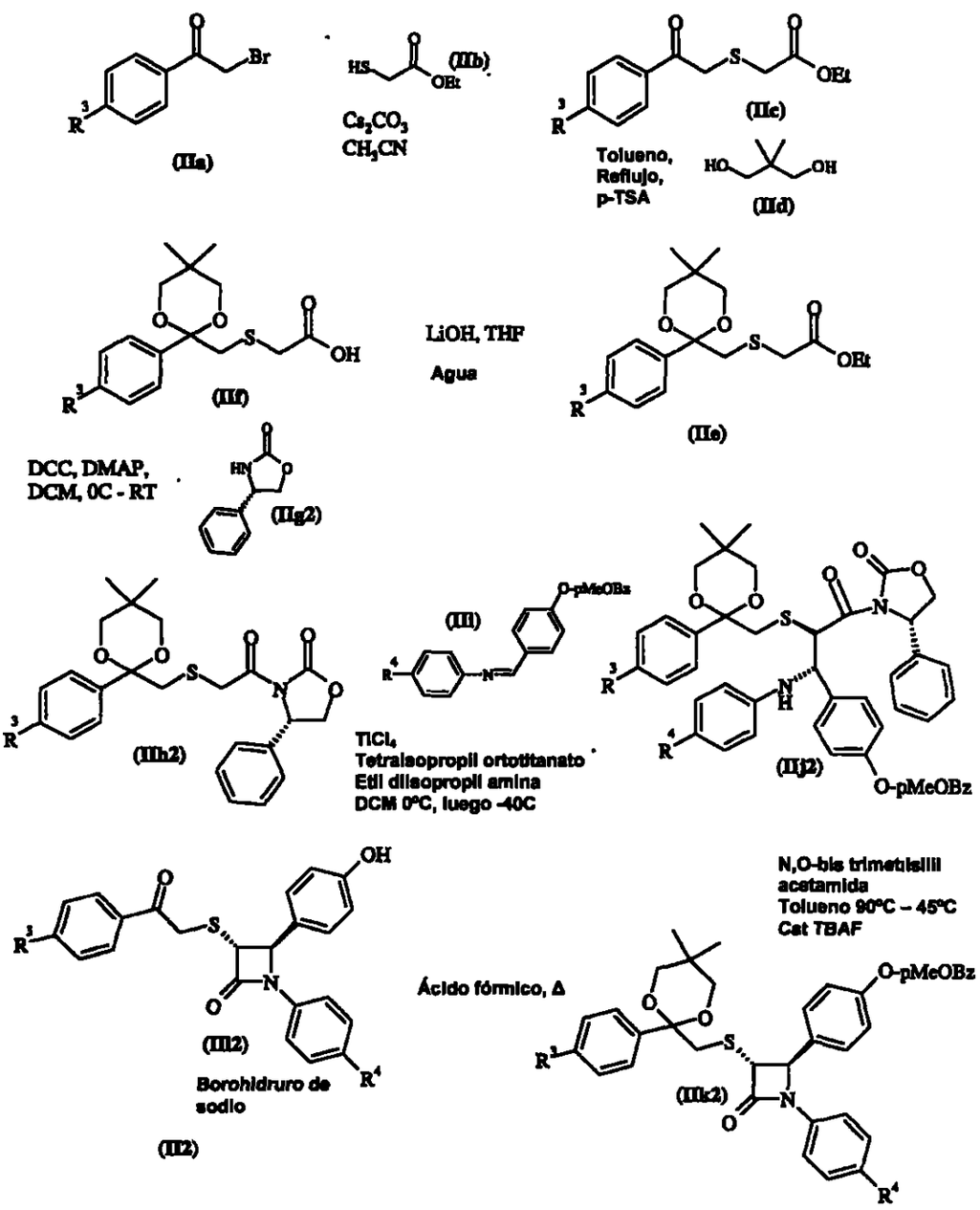
L es un grupo desplazable; valores apropiados para L son por ejemplo, un halógeno o grupo sulfoniloxi, por ejemplo un grupo cloro, bromo, metanosulfoniloxi o tolueno-4-sulfoniloxi.

C(O)OR es un grupo éster; valores apropiados para C(O)OR son metoxicarbonilo, etoxicarbonilo, *t*-butoxicarbonilo y benciloxicarbonilo.

Los materiales de partida usados en la presente invención pueden prepararse por modificaciones de las rutas descritas en EP 0 792 264 B1. Alternativamente, pueden prepararse por las siguientes reacciones.

Proceso 1): Alcoholes de fórmula **(II2)** pueden hacerse reaccionar con compuestos de fórmula **(III)** en la presencia de una base por ejemplo una base inorgánica tal como carbonato de sodio, o una base orgánica tal como una base de Hünig, en la presencia de un disolvente apropiado tal como acetonitrilo, diclorometano o tetrahidrofurano a una temperatura en el rango de 0°C a reflujo, preferiblemente a reflujo o cerca de él.

Compuestos de fórmula **(II2)** pueden prepararse de acuerdo con el siguiente esquema:



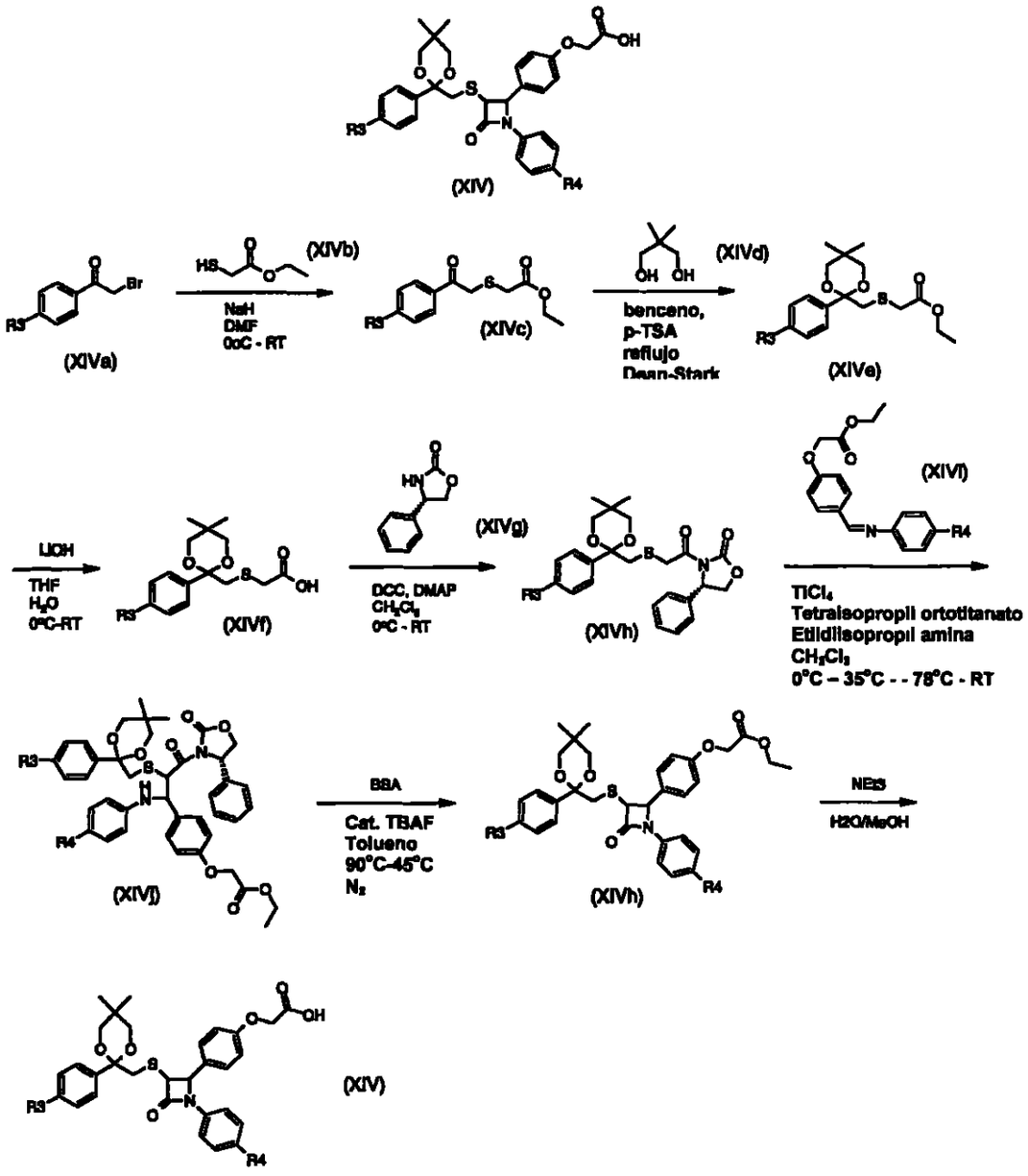
Esquema 1

en donde pMeOBz es **para** metoxi bencilo.

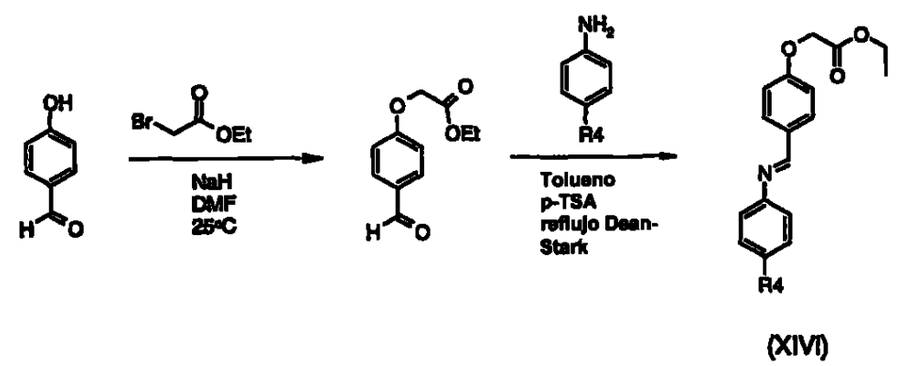
Compuestos de fórmula **(IIb)**, **(IId)**, **(Iig2)** y **(III2)** se encuentran disponibles en el comercio, o se conocen en la literatura, o se preparan por procesos estándar conocidos en el arte.

Asimismo, un compuesto de fórmula **(III)** puede hacerse reaccionar con un compuesto de fórmula (XIV).

Compuestos de fórmula **(XIV)** pueden prepararse de acuerdo con la siguiente ruta:

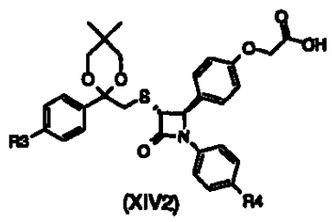


Compuestos de fórmula XIVi pueden prepararse por la siguiente ruta:

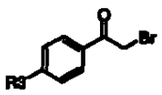


Un compuesto de fórmula **(III2)** pude hacerse reaccionar además con un compuesto de fórmula **(XIV2)**.

Compuestos de fórmula **(XIV2)** pueden prepararse de acuerdo con la siguiente ruta:

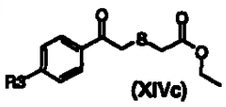


(XIV2)



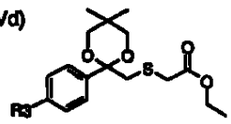
(XIVa)

(XIVb)



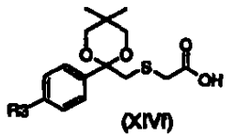
(XIVc)

(XIVd)

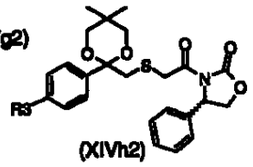


(XIVe)

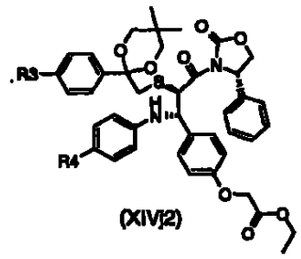
(XIVf)



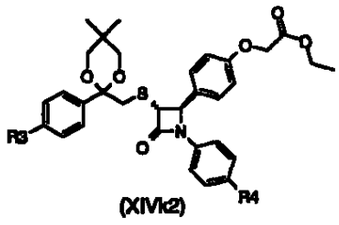
(XIVg2)



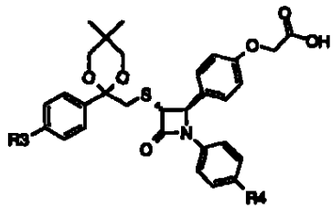
(XIVh2)



(XIVj2)

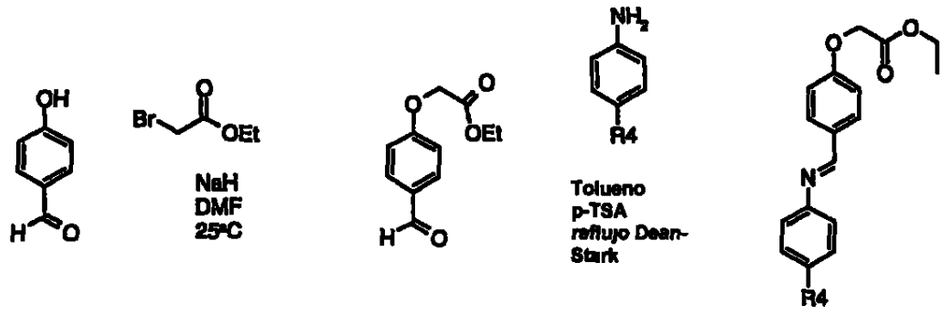


(XIVk2)



(XIV2)

Compuestos de fórmula **XIVi** pueden prepararse por la siguiente ruta:



(XIVI)

Para ambas, XIV y XIV2, se aplica lo siguiente:

Proceso 2) y *Proceso 3*): Ácidos y aminas pueden acoplarse entre sí en la presencia de un reactivo apropiado de acoplamiento. Reactivos de acoplamiento peptídico estándar conocidos en el arte pueden emplearse como reactivos de acoplamiento apropiado, por ejemplo carbonildiimidazol y diciclohexil-carbodiimida, de manera opcional en la presencia de un catalizador tal como dimetilaminopiridina o 4-pirrolidinopiridina, de manera opcional en la presencia de una base por ejemplo trietilamina, piridina, o 2,6-di-*alquil*-piridinas tales como 2,6-lutidina o 2,6-di-*terc*-butilpiridina. Disolventes apropiados incluyen dimetilacetamida, diclorometano, benceno, tetrahidrofurano y dimetilformamida. La reacción de acoplamiento puede realizarse convenientemente a una temperatura en el rango de -40 a 40°C.

Derivados apropiados de ácido activados incluyen halogenuros de ácido, por ejemplo cloruros de ácido, y ésteres activos, por ejemplo pentafluorofenil ésteres. La reacción de estos tipos de compuestos con aminas es bien conocida en el arte, por ejemplo pueden hacerse reaccionar en la presencia de una base, tal como las descritas anteriormente, y en un disolvente apropiado, tal como los ya descritos. La reacción puede llevarse convenientemente a cabo a una temperatura en el rango de -40 a 40°C.

Ácidos de fórmula **(IV)** y **(VI)** pueden prepararse de compuestos de fórmula **(II)** haciéndolos reaccionar con la cadena lateral, apropiada, protegida de manera opcional, usando las condiciones del *Proceso 1*).

Alternativamente, ácidos de fórmula **(IV)** y **(VI)** pueden prepararse por una modificación de *Esquema 1.*

Aminas de fórmula **(V)** y **(VII)** son compuestos disponibles en el comercio, o se conocen en la literatura, o pueden prepararse por procesos estándar conocidos en el arte.

Proceso 4): La reducción de compuestos de fórmula **(VIII)** podrían llevarse a cabo con un reactivo hidruro tal como borohidruro de sodio en un disolvente tal como metanol a temperaturas apropiadas entre -20-40°C.

Compuestos de fórmula **(VIII)** pueden prepararse de compuestos de fórmula **(III)**, desprotegiendo el grupo bencilo y realizando *Proceso 1.* Alternativamente, el compuesto **(IIk)** podría desbencilarse, *Proceso 1* podría llevarse a cabo y el compuesto resultante desprotegerse para revelar la cetona.

Proceso 5) y *Proceso 6*): Estos compuestos pueden hacerse reaccionar juntos en la presencia de una base por ejemplo una base inorgánica tal como carbonato de sodio, o una base orgánica tal como una base de Hunigs, en la presencia de un disolvente apropiado tal como acetonitrilo, diclorometano, o tetrahidrofurano a una temperatura en el rango de 0°C a reflujo, preferiblemente a reflujo o cerca de él.

Compuestos de fórmula **(IX)** y **(XI)** pueden prepararse por una modificación apropiada de *Esquema 1.*

Compuestos de fórmula **(X)** y **(XII)** son compuestos disponibles en el comercio, o se conocen en la literatura, o pueden prepararse por procesos estándar conocidos en el arte.

Proceso 7): Ésteres de fórmula **(XIII)** pueden desprotegerse bajo condiciones estándar, tales como las descritas a continuación; por ejemplo un éster metílico o etílico puede desprotegerse con hidróxido de sodio en metanol a temperatura ambiente.

Compuestos de fórmula **(XIII)** pueden prepararse por una modificación de cualquiera de los procesos descritos aquí para la preparación de compuestos de fórmula **(I)**.

Se observará que algunos de los diferentes sustituyentes del anillo en los compuestos de la presente invención pueden introducirse por reacciones estándar de sustitución aromática o generarse por modificaciones convencionales del grupo funcional ya sea antes o inmediatamente después de los procesos mencionados más arriba, y como tales se incluyen en el aspecto de los procesos de la invención. Tales reacciones y modificaciones incluyen, por ejemplo, la introducción de un sustituyente por medio de una reacción de sustitución aromática, reducción de sustituyentes, alquilación de sustituyentes y oxidación de sustituyentes. Los reactivos y condiciones de reacción para tales procedimientos son bien conocidos en el arte químico. Ejemplos particulares de reacciones de sustitución aromática incluyen la introducción de un grupo nitro usando ácido nítrico concentrado, la introducción de un grupo acilo usando, por ejemplo, un halogenuro de acilo y un ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; la introducción de un grupo alquilo usando un halogenuro de alquilo y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; y la introducción de un grupo halógeno. Ejemplos particulares de modificaciones incluyen la reducción de un grupo nitro a un grupo amino mediante, por ejemplo, hidrogenación catalítica con un catalizador de níquel o tratamiento con hierro en la presencia de ácido clorhídrico con calentamiento; oxidación de alquiltio en alquilsulfinilo o alquilsulfonilo.

Se apreciará igualmente que en algunas de las reacciones mencionadas aquí puede ser necesario/deseable proteger cualesquiera grupos sensibles en los compuestos. Los casos en donde la protección es necesaria o deseable y los métodos apropiados para la protección son conocidos por los expertos en el arte. Grupos protectores convencionales pueden usarse se acuerdo con la práctica estándar (para efectos de ilustración véase T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999). Por lo tanto, si los reactivos incluyen grupos tales como amino, carboxi o hidroxi, puede ser deseable proteger el grupo en algunas de las reacciones mencionadas aquí.

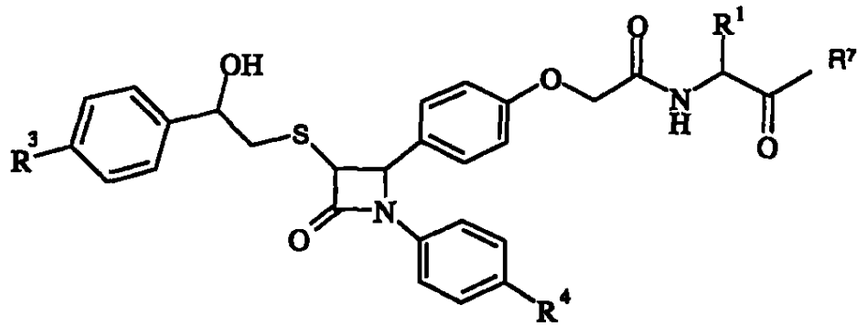
Un grupo protector adecuado para un grupo amino o alquilamino es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como un grupo acetilo, un grupo alcoxicarbonilo, por ejemplo un grupo metoxicarbonilo, etoxicarbonilo o *t*-butoxicarbonilo, un grupo arilmetoxicarbonilo, por ejemplo benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo. Las condiciones de desprotección para los anteriores grupos protectores varían necesariamente con la elección del grupo protector. Así, por ejemplo, un grupo acilo tal como un grupo alcanoilo o alcoxicarbonilo o un grupo aroilo pueden retirarse por ejemplo, mediante hidrólisis con una base adecuada tal como un hidróxido de metal alcalino, por ejemplo hidróxido de litio o sodio. Alternativamente un grupo acilo tal como un grupo *t*-butoxicarbonilo puede retirarse, por ejemplo, mediante tratamiento con un ácido adecuado tal como ácido clorhídrico, sulfúrico o fosfórico o ácido trifluoroacético, y un grupo arilmetoxicarbonilo tal como un grupo benciloxicarbonilo puede retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbón, o mediante tratamiento con un ácido de Lewis por ejemplo tris(trifluoroacetato) de boro. Un grupo protector alternativo adecuado para un grupo amino primario es, por ejemplo, un grupo ftaloilo que puede retirarse mediante tratamiento con una alquilamina, por ejemplo dimetilaminopropilamina, o con hidrazina.

Un grupo protector adecuado para un grupo hidroxi es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como acetilo, un grupo aroilo, por ejemplo benzoilo, o un grupo arilmetilo, por ejemplo bencilo. Las condiciones de desprotección para los grupos protectores anteriores variarán necesariamente con la elección del grupo protector. Así, por ejemplo, un grupo acilo tal como un alcanolilo o un grupo aroilo pueden retirarse, por ejemplo, mediante hidrólisis con una base apropiada tal como un hidróxido de metal alcalino, por ejemplo hidróxido de litio o de sodio. Alternativamente, un grupo arilmetilo tal como un grupo bencilo pueden retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbón.

Un grupo protector adecuado para un grupo carboxi, por ejemplo, un grupo esterificante, por ejemplo un grupo metilo o etilo que puede retirarse, por ejemplo, mediante hidrólisis con una base tal como hidróxido de sodio, o por ejemplo un grupo *t*-butilo que puede retirarse, por ejemplo, mediante tratamiento con un ácido, por ejemplo un ácido orgánico tal como ácido trifluoroacético, o por ejemplo un grupo bencilo que puede retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbón.

Los grupos protectores pueden retirarse en cualquier fase convencional en la síntesis usando técnicas convencionales bien conocidas en el arte químico.

La invención provee además un compuesto de fórmula **(XV)** o sus ésteres hidrolizables o amidas:



(XV)

en donde $\mathbf{R^7}$ es un hidroxi o un grupo C_{1-3} alcoxi. $\mathbf{R^1}$, $\mathbf{R^3}$ y $\mathbf{R^4}$ son como ya se definieron con respecto a la fórmula **(I)**. Un compuesto de fórmula **(XV)** puede ser un intermedio a fórmula **(I)**.

Como ya se afirmó anteriormente en el texto, los compuestos definidos en la presente invención poseen actividad inhibidora de absorción del colesterol. Estas propiedades pueden avaluarse, por ejemplo, usando la siguiente prueba biológica.

Análisis *in vivo* de los inhibidores de absorción del colesterol (A)

Ratones hembra C57BL/6 se mantuvieron en una dieta regular de comida y se albergaron en jaulas individuales para recoger las heces. Se hizo ayunar a los ratones durante 3 horas y luego se alimentaron mediante sonda gástrica con vehículo o compuesto. Media hora después los ratones se recibieron colesterol radiomarcado a través de la sonda gástrica. Seis horas después de la administración de ^{14}C-colesterol con sonda gástrica, se tomaron muestras de sangre de la cola y se preparó el plasma para determinar la cantidad de colesterol que se había absorbido. 24 horas después de la administración de ^{14}C-colesterol con sonda gástrica, los ratones se desangraron y se preparó el plasma para análisis. Se recogieron las heces durante 24 horas para evaluar la eficiencia de la absorción.

Análisis *in vivo* de los inhibidores de absorción del colesterol (B).

Ratones hembra C57BL/6 se mantuvieron en una dieta regular de comida y se albergaron en jaulas individuales para recoger las heces. Se hizo ayunar a los ratones durante 3 horas y luego se alimentaron mediante sonda gástrica con vehículo o compuesto. Una a diez horas después los ratones se recibieron colesterol radiomarcado a través de la sonda gástrica. Seis horas después de la administración de ^{14}C-colesterol con sonda gástrica, se tomaron muestras de sangre de la cola y se preparó el plasma para determinar la cantidad de colesterol que se había absorbido. 24 horas después de la administración de ^{14}C-colesterol con sonda gástrica, los ratones se desangraron, y el plasma se analizó con respecto a radioactividad. Se recogieron las heces durante 24 horas para evaluar la eficiencia de la absorción.

Referencias

1. E. A. Kirk, G. L. Moe, M. T. Caldwell, J. Å. Lemmark, D. L. Wilson, R. C. LeBoeuf. Hiper- and hypo-responsiveness to dietary fat and cholesterol among inbred mice: searching for level and variability genes. J. Lipid Res. 1995 36:1522-1532.

2. C. P. Carter, P. N. Howles, D. Y. Hui. Genetic variation in cholesterol absorption efficiency among inbred strains of mice. J. Nutr. 1997 127:1344-1348.

3. C. D. Jolley, J. M. Dietschy, S.D. Turley. Genetic differences in cholesterol absorption in 129/Sv and C57BL/6 mice: effect on cholesterol responsiveness. Am. J. Physiol. 1999 276:G1117-G1124.

Administración de 5 μmol/kg de Ejemplo 96 produjo 87% de inhibición de la absorción de ^{14}C-colesterol (procedimiento A). Administración de 5 μmol/kg de Ejemplo 94 produjo 89% de inhibición de absorción de ^{14}C-colesterol (procedimiento A).

Administración de 0.2 μmol/kg de Ejemplo 91 produjo 58% de inhibición de absorción de ^{14}C-colesterol (procedimiento A). Administración de 0.2 μmol/kg de Ejemplo 85 produjo 47% de inhibición de absorción de ^{14}C-colesterol (procedimiento A).

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto en asociación con un diluyente o vehículo farmacéuticamente aceptables.

La composición puede estar en una forma apropiada para administración oral, por ejemplo como una tableta o cápsula, para inyección parenteral (incluida intravenosa, subcutánea, intramuscular, intravascular o infusión) como una solución estéril, suspensión o emulsión, para administración local como un ungüento o crema o para administración rectal como un supositorio.

En general, las composiciones anteriores pueden prepararse un una manera convencional usando excipientes convencionales.

El compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, se administrarán normalmente a un animal de sangre caliente en una dosis unitaria en el rango de

aproximadamente 0.02-100 mg/kg, preferiblemente 0.02 -50 mg/kg, y ésta proporciona normalmente una dosis terapéuticamente eficaz. Una forma de dosis unitaria tal como una tableta o cápsula contendrá usualmente, por ejemplo 1-250 mg de ingrediente activo. Preferiblemente se emplea una dosis diaria en el rango de 1-50 mg/kg, particularmente 0.1-10 mg/kg. En otro aspecto se emplea una dosis diaria en el rango de 0.01-20 mg/kg. En un aspecto de la invención la dosis diaria de un compuesto de fórmula (I) es menor o igual a 100mg. No obstante, la dosis diaria variará necesariamente dependiendo del anfitrión tratado, la vía particular de administración, y la gravedad de la enfermedad que se está tratando. En consecuencia, la posología óptima puede determinarse por el profesional médico que este tratando un paciente particular.

De acuerdo con un aspecto adicional de la presente invención se provee un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto para uso en un método de tratamiento terapéutico o profiláctico de un animal de sangre caliente, tal como el hombre.

Hemos descubierto que los compuestos definidos en la presente invención, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, son inhibidores efectivos de la absorción del colesterol y, en consecuencia, son de utilidad en el tratamiento de estados patológicos asociados con afecciones hiperlipidémicas.

Por consiguiente, de acuerdo con este aspecto de la invención se provee un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto para uso como un medicamento.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto en la producción de un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre.

En este caso, donde se especifica la producción de un efecto inhibidor de absorción de colesterol o un efecto reductor del colesterol, convenientemente éste se refiere al tratamiento de afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre. Adicionalmente se refiere al tratamiento de afecciones dislipidémicas y trastornos tales como hiperlipidemia, hipertrigliceridemia, hiperbetalipoproteinemia (LDL alta), hiperprebetalipoproteinemia (VLDL alta), hiperquilomicronemia, hipolipoproteinemia, hipercolesterolemia, hiperlipoproteinemia e hipoalfalipoproteinemia (HDL baja) en un animal de sangre caliente, tal como el hombre. Más aún, se refiere al tratamiento de diferentes afecciones clínicas tales como ateroesclerosis, arteriosclerosis, arritmia, afecciones hipertrombóticas, disfunción vascular, disfunción endotelial, insuficiencia cardíaca, cardiopatías coronarias, enfermedades cardiovasculares, infarto del miocardio, angina pectoris, enfermedades vasculares periféricas, inflamación de tejidos cardiovasculares tales como corazón, válvulas, vasculatura, arterias y venas, aneurismas, estenosis, restenosis, placas vasculares, estrías adiposas vasculares, leucocitos, monocitos y/o infiltración de macrófagos, engrosamiento de la capa íntima, adelgazamiento de la media, trauma infeccioso y quirúrgico y trombosis vascular, apoplejía y ataques isquémicos transitorios en un animal de sangre caliente, tal como el hombre. Se refiere asimismo al tratamiento de ateroesclerosis, cardiopatías coronarias, infarto del miocardio, angina pectoris, enfermedades vasculares periféricas, apoplejía y ataques isquémicos transitorios en un animal de sangre caliente, tal como el hombre.

La producción de un efecto inhibidor de absorción de colesterol o un efecto reductor del colesterol se refiere también a un método de tratar y/o

prevenir lesiones ateroescleróticas, un método de prevenir la ruptura de placas y un método de promover la regresión de la lesión. Más aún, se refiere a un método de inhibir la acumulación de monocitos-macrófago en lesiones ateroescleróticas, un método de inhibir la expresión de metaloproteinasas de matriz en lesiones ateroescleróticas, un método de inhibir la desestabilización de lesiones ateroescleróticas, un método para prevenir la ruptura de placas ateroescleróticas y un método de trata angina inestable.

La producción de un efecto inhibidor de absorción de colesterol o un efecto reductor del colesterol se relaciona igualmente con un método de tratar sitosterolemia.

Además, los compuestos de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco pueden ser útiles en el tratamiento o prevención de la Enfermedad de Alzheimer (véase por ejemplo WO 02/096415). Por lo tanto, en un aspecto adicional de la invención, se provee un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, para uso en el tratamiento o prevención de la Enfermedad de Alzeheimer.

Compuestos de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco pueden ser también útiles en el tratamiento o prevención de tumores asociados con el colesterol. Por lo tanto, en un aspecto adicional de la invención, se provee un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, para uso en el tratamiento o prevención de tumores asociados con el colesterol.

Compuestos de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco pueden tener asimismo utilidad en el tratamiento o prevención de la inflamación vascular (véase por ejemplo WO 03/026644). Por lo tanto en un aspecto adicional de la invención, se provee un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, para uso en el tratamiento o prevención de la inflamación vascular.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para producir un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

La actividad inhibidora de absorción de colesterol definida más arriba en el texto puede aplicarse como terapia única o puede incluir, aparte de un compuesto de la invención, uno o más de otras sustancias y/o tratamientos. Tal tratamiento conjunto puede lograrse mediante la administración simultánea, consecutiva o separada de los componentes individuales del tratamiento. De acuerdo con este aspecto de la invención se provee un producto farmacéutico que comprende un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto, y una sustancia adicional inhibidora de la absorción de colesterol, como se define más arriba en el texto, y un agente hipolipidémico adicional para el tratamiento conjunto de hiperlipidemia.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, pueden administrarse en asociación con inhibidores de biosíntesis de colesterol, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos. Inhibidores apropiados de biosíntesis de colesterol incluyen inhibidores de HMG Co-A reductasa, inhibidores de la síntesis de escualeno e inhibidores de escualeno epoxidasa. Un inhibidor apropiado de la síntesis de escualeno es esqualestatina 1 y un inhibidor apropiado de escualeno epoxidasa es NB-598.

En este aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, pueden administrarse en asociación con un inhibidor de HMG Co-A reductasa, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos. Inhibidores apropiados de HMG Co-A reductasa,

sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos son estatinas son bien conocidos en el arte. Estatinas particulares son fluvastatina, lovastatina, pravastatina, simvastatina, atorvastatina, cerivastatina, bervastatina, dalvastatina, mevastatin y rosuvastatina, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco. Otra estatina particular es pitvastatina, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco. Una estatina particular es atorvastatina, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco. Una estatina más particular es sal de calcio de atorvastatina. Otra estatina particular es rosuvastatina, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco. Una estatina particular preferible es sal de calcio de rosuvastatina.

Por lo tanto en una característica adicional de la invención, se provee una combinación de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco y un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Por lo tanto en una característica adicional de la invención, se provee un método para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en administración simultánea, consecutiva o separada con una cantidad eficaz de un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptables.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende:

a) un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una primera presentación farmacéutica unitaria;

b) un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco; en una segunda presentación farmacéutica unitaria; y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende:

a) un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, conjuntamente con un diluyente o vehículo farmacéuticamente aceptables, en una primera presentación farmacéutica unitaria;

b) un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una segunda presentación farmacéutica unitaria; y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en la producción de un efecto reductor del colesterol.

De acuerdo con un aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad eficaz de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables, con la administración simultánea, consecutiva o separada de una cantidad eficaz de un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento terapéutico.

De acuerdo con otro aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad eficaz de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables, con la administración simultánea, consecutiva o separada de un inhibidor de metaloproteinasa de matriz.

De acuerdo con otro aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad eficaz de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables, con la administración simultánea, consecutiva o separada de Péptido Mimético ApoA-1.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, pueden administrarse en asociación con un inhibidor de transporte de ácido bilial en el íleon (IBAT) o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco. Se han descrito compuestos apropiados que poseen actividad inhibidora IBAT para uso en combinación con compuestos

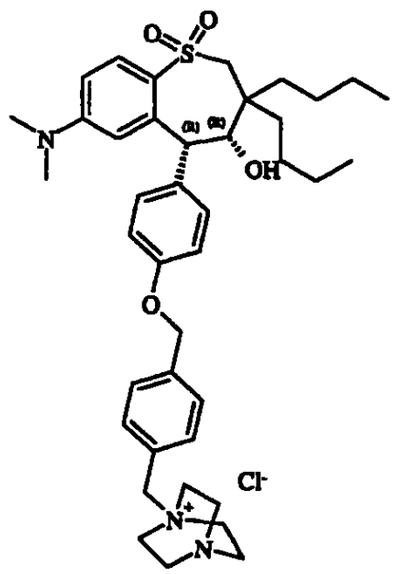
de la presente invención; véase, por ejemplo los compuestos descritos en WO 93/16055, WO 94/18183, WO 94/18184, WO 94/24087, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07749, WO 98/38182, WO 98/40375, WO 98/56757, WO 99/32478, WO 99/35135, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 00/35889, WO 01/34570, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 00/47568, WO 00/61568, WO 01/66533, WO 01/68096, WO 01/68637, WO 02/08211, DE 19825804, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 489 423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595, EP 864 582, EP 869 121 y EP 1 070 703 y los contenidos de estas solicitudes de patente se incorporan aquí por referencia. Particularmente los ejemplos mencionados de esta solicitud de patente se incorporan aquí por referencia. Más particularmente, la reivindicación 1 de esta solicitud de patente se incorpora aquí por referencia.

Otras clases apropiadas de inhibidores IBAT para uso en combinación con compuestos de la presente invención son las 1,2-benzotiazepinas, 1,4-benzotiazepinas y 1,5-benzotiazepinas. Otra clase apropiada de inhibidores IBAT son las 1,2,5-benzotiadiazepinas.

Un compuesto particular apropiado, que posee actividad inhibidora IBAT para uso en combinación con compuestos de la presente invención es ácido (3*R*,5*R*)-3-butil-3-etil-1,1-dioxido-5-fenil-2,3,4,5-tetrahidro-1,4-benzotiazepin-8-il β-D-glucopiranosidurónico (EP 864 582).

Otro compuesto apropiado que posee actividad inhibidora IBAT para uso en combinación con compuestos de la presente invención es S-8921 (EP 597 107).

Otro inhibidor IBAT apropiado para uso en combinación con compuestos de la presente invención es el compuesto:



WO 99/32478

Un inhibidor IBAT particular para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de los Ejemplo 1-120 de WO 02/50051, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y los compuestos de Ejemplos 1-120 se incorporan aquí por referencia. Igualmente, las reivindicaciones 1-15 de WO 02/50051 se incorporan aquí por referencia. Un inhibidor IBAT particular seleccionado de WO 02/50051 para uso en combinación con compuestos de la presente invención se selecciona de cualquiera de:

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N'*-(carboximetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(carboximetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N'*-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N'*-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-carboxietil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-carboxietil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(5-carboxipentil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-carboxietil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-(2-sulfoetil)carbamoil]-2-fluorobencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hidroxi-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hidroxi-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hidroxi-1-carboxietil)carbamoil]-2-hidroxietil}carbamoil)bencil] carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-(carboximetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-((etoxi)(metil) fosforil-metil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{2-[(hidroxi)(metil)fosforil]etil}carbamoil)bencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-metiltio-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{2-[(metil)(etil)fosforil]etil}carbamoil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{2-[(metil)(hidroxi)fosforil]etil}carbamoil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[(R)-*N'*-(2-metilsulfinil-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina; y

1,1-dioxo-3,3-dibutil-5-fenil-7-metoxi-8-[*N*-{(R)-α-[*N'*-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina;

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Un inhibidor IBAT particular para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de Ejemplos 1-44 de WO 03/020710, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y los compuestos de Ejemplos 1-44 se incorporan aquí por referencia. Igualmente, las reivindicaciones 1-10 de WO 03/020710 se incorporan aquí por referencia. Un inhibidor IBAT particular seleccionado de WO 03/020710 para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de:

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-((S)-1-carbamoil-2-hidroxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-(R)-α-[*N'*-(hidroxicarbamoil-metil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N'*-[2-(*N'*-pirimidin-2-ilureido)etil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N'*-[2-(*N'*-piridin-2-ilureido)etil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(1-*t*-butoxicarbonilpiperidin-4-ilmetil)carbamoil]bencil} carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2,3-dihidroxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N'*-[2-(3,4-dihidroxifenil)-2-metoxietil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-aminoetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5 -benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(piperidin-4-ilmetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina; o

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-*N*,*N*-dimetilaminosulfamoiletil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Un inhibidor IBAT particular para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de Ejemplos 1-7 de WO 03/022825, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y los compuestos de Ejemplos 1-7 se incorporan aquí por referencia. De igual manera, las reivindicaciones 1-8 de WO 03/022825 se incorporan aquí por referencia. Un inhibidor IBAT particular, seleccionado de WO 03/022825 para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de:

1,1-dioxo-3(R)-3-butil-3-etil-5-(R)-5-fenil-8-[*N*-((R)-α-carboxibencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,4-benzotiazepina;

1,1-dioxo-3(S)-3-butil-3-etil-5-(S)-5-fenil-8-[*N*-((R)-α-carboxibencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,4-benzotiazepina;

1,1-dioxo-3(R)-3-butil-3-etil-5-(R)-5-fenil-8-(*N*-{(R)-α-[*N*-(carboximetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina;

1,1-dioxo-3(S)-3-butil-3-etil-5-(S)-5-fenil-8-(*N*-{(R)-α-[*N*-(carboximetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina;

3,5-*trans*-1,1-dioxo-3-etil-3-butil-5-fenil-7-bromo-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina;

3,5-*trans*-1,1-dioxo-3-(S)-3-etil-3-butil-4-hidroxi-5-(S)-5-fenil-7-bromo-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina

3,5-*trans*-1,1-dioxo-3-(R)-3-etil-3-butil-4-hidroxi-5-(R)-5-fenil-7-bromo-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina;

3,5-*trans*-1,1-dioxo-3-etil-3-butil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina;

3,5-*trans*-1,1-dioxo-3-etil-3-butil-5-fenil-7-metiltio-8-(*N*-{(R)-α-*N*-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina sal de amoníaco;
1,1-dioxo-3-(S)-3-etil-3-butil-5-(S)-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil)carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina sal dietilamina; y
1,1-dioxo-3-(R)-3-etil-3-butil-5-(R)-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina sal dietilamina;
o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Un inhibidor IBAT particular para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de Ejemplos 1-4 de WO 03/022830, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y los compuestos de Ejemplos 1-4 se incorporan aquí por referencia. Asimismo las reivindicaciones 1-8 de WO 03/022830 se incorporan aquí por referencia. Un inhibidor IBAT particular seleccionado de WO 03/022830 para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de:
1,1-dioxo-3-butil-3-etil-4-hidroxi-5-fenil-7-(*N*-{(R)-α-[*N*-(carboximetil) carbamoil]bencil}carbamoilmetiltio)-2,3,4,5-tetrahidrobenzotiepina;
1,1-dioxo-3-butil-3-etil-4-hidroxi-5-fenil-7-(*N*-{(R)-α-[*N*-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetiltio)-2,3,4,5-tetrahidrobenzotiepina sal de amoníaco;
1,1-dioxo-3-butil-3-etil-4-hidroxi-5-fenil-7-{*N*-[α-(carboxi)-2-fluorobencil] carbamoilmetiltio}-2,3,4,5-tetrahidrobenzotiepina; y
1,1-dioxo-3-butil-3-etil-4-hidroxi-5-fenil-7-{*N*-[1-(carboxi)-1-(tien-2-il) metil]carbamoilmetiltio}-2,3,4,5-tetrahidrobenzotiepina
o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Un inhibidor IBAT particular para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de

Ejemplos 1-39 de WO 03/022286, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y los compuestos de Ejemplos 1-39 se incorporan aquí por referencia. Las reivindicaciones 1-10 de WO 03/022286 se incorporan también aquí por referencia. Un inhibidor IBAT particular seleccionado de WO 03/022286 para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de:

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxi-2-metiltio)etil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxi-2-(R)-hidroxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxi-2-metilpropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxibutil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxietil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxi-2-(R)-hidroxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3.4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxietil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxi-2-metiltioetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-{(S)-1-[*N*-((S)-2-hidroxi-1-carboxietil)carbamoil]propil}carbamoil]bencil}carbamoilmetoxi) -2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxi-2-metilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina; y

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-((R)-α-carboxi-4-hidroxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Un inhibidor IBAT particular para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de Ejemplos 1-7 de WO 03/091232, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y los compuestos de Ejemplos 1-7 se incorporan aquí por referencia. Las reivindicaciones 1-10 de WO 03/091232 se incorporan también aquí por referencia. Un inhibidor IBAT particular seleccionado de WO 03/091232 para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de:

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]-4-hidroxibencil} carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-((R/S)-α-{*N*-[1-(R)-2-(S)-1-hidroxi-1-(3,4-dihidroxifenil)prop-2-il]carbamoil}bencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N*-{2-(S)-[*N*-(carbamoilmetil)carbamoil]pirrolidin-1-ilcarbonilmetil}carbamoil) bencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;
1,1 -Dioxo-3,3 -dibutil-5-fenil-7-metiltio-8-[N-((R)-α-{*N*-[2-(3,4,5-trihidroxifenil)etil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina; y
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(2-(R)-3-(S)-4-(S)-5-(R)-3,4,5,6-tetrahidroxitetrahidropiran-2-ilmetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;
o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Otros compuestos apropiados que poseen actividad inhibidora IBAT para uso en combinación con compuestos de la presente invención se divulgan en WO03/106482.

Inhibidores IBAT apropiados como se divulga en WO 03/106482 para uso en combinación con compuestos de la presente invención se selecciona de uno cualquiera de:
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxietil) carbamoil]bencil]}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxibutil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metilbutil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-metilbutil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-hidroxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-mesiletil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-metilsulfonilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-mesilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxietil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxibutil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((S)-1-carboxi-2-metilpropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metilbutil)carbamoil]-4-hidroxibencil} carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-metilbutil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-hidroxietil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-hidroxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metiltioetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metilsulfiniletil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-mesiletil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metoxietil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-metiltiopropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((S)-1-carboxi-3-metilsulfonilpropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-mesilpropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina; ó
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Otros inhibidores IBAT apropiados para uso en combinación con compuestos de la presente invención son los divulgados en WO04/076430.

En un aspecto particular de la invención un inhibidor IBAT o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco es un inhibidor IBAT o su sal farmacéuticamente aceptable.

Por lo tanto in una característica adicional de la invención, se provee una combinación de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco y un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Por lo tanto, en una característica adicional de la invención, se provee un método para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en administración simultánea, consecutiva o separada con una cantidad eficaz de un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptables.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende:

a) un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una primera presentación farmacéutica unitaria;

b) un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco; en una segunda presentación farmacéutica unitaria; y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende:

a) un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, junto con un diluyente o vehículo farmacéuticamente aceptables, en una primera presentación farmacéutica unitaria;

b) un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una segunda presentación farmacéutica unitaria; y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso e la producción de un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre.

De acuerdo con un aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad eficaz de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables, con la administración simultánea, consecutiva o separada de una cantidad eficaz de un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento terapéutico.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, pueden administrarse en asociación con un agonista PPAR alfa y/o gamma, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos. Agonistas PPAR alfa y/o gamma apropiados, sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos son bien conocidos en el arte. Éstos incluyen los compuestos descritos en WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, WO 03/051821, WO 03/051822, WO 03/051826, PCT/GB03/02584, PCT/GB03/02591, PCT/GB03/02598, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (en particular los compuestos descritos en las solicitudes de patente enumeradas en la página 634) y J Med Chem, 2000, 43, 527, que se incorporan todos aquí por referencia. Particularmente un agonista PPAR alfa y/o gamma se refiere a WY-14643, clofibrato,

fenofibrato, bezafibrato, GW 9578, troglitazona, pioglitazona, rosiglitazona, eglitazona, proglitazona, NN622/Ragaglitazar, BMS 298585, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 y GW 2433. Particularmente un agonista PPAR alfa y/o gamma se refiere a ácido (S)-2-etoxi-3-[4-(2-{4-metanosulfoniloxifenil} etoxi)fenil]propanoico y sus sales farmacéuticamente aceptables.

Por lo tanto, en una característica adicional de la invención, se provee una combinación de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco y un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Por lo tanto, en una característica adicional de la invención, se provee un método para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en administración simultánea, consecutiva o separada con una cantidad eficaz de un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptables.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende:

a) un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una primera presentación farmacéutica unitaria;

b) un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco; en una segunda presentación farmacéutica unitaria; y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende:

a) un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, junto con un diluyente o vehículo farmacéuticamente aceptables, en una primera presentación farmacéutica unitaria;

b) un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una segunda presentación farmacéutica unitaria; y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre.

De acuerdo con un aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad eficaz de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables, con la administración simultánea,

consecutiva o separada de una cantidad eficaz de un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento terapéutico.

En otro aspecto de la invención, se provee un tratamiento de combinación que comprende la administración de una cantidad efectiva de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en forma opcional junto con un vehículo o diluyente farmacéuticamente aceptable, con la administración simultánea, consecutiva o separada de agonistas al receptor HM74A (receptor de ácido nicotínico). Los agonistas HM74A pueden ser derivados de ácido nicotínico. Tal como se usa aquí "derivado de ácido nicotínico" significa compuestos que comprenden una estructura piridin-3-carboxilato o una estructura pirazin-2-carboxilato. Ejemplos de derivados de ácido nicotínico incluyen ácido nicotínico, niceritrol, nicofuranosa, NIASPAN® y acipimox.

Por lo tanto, en una característica adicional de la invención, se provee una combinación de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco y un derivado de ácido nicotínico o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Por lo tanto, en una característica adicional de la invención, se provee un método para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en administración simultánea, consecutiva o separada con una cantidad eficaz de un derivado de ácido nicotínico, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o

profármaco, y un derivado de ácido nicotínico, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptables.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un derivado de ácido nicotínico, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en la producción de un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, pueden administrarse en asociación con un secuestrante de ácido biliar o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco. Secuestrantes apropiados de ácidos biliares incluyen colestiramina, colestipol y clorhidrato de colesevelam.

Por lo tanto, en una característica adicional de la invención, se provee una combinación de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco y un secuestrante de ácido biliar o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

Por lo tanto, en una característica adicional de la invención, se provee un método para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en administración simultánea, consecutiva o separada con una cantidad eficaz de un secuestrante de ácido biliar, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o

profármaco, y un secuestrante de ácido biliar, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptables.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un secuestrante de ácido biliar, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en la producción de un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre.

De acuerdo con otro aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad eficaz de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables, con la administración simultánea, consecutiva o separada de uno o más de los siguientes agentes seleccionados del grupo X:

- un compuesto antihipertensor (por ejemplo altiazida, benztiazida, captopril, carvedilol, clorotiazida sódica, clorhidrato de clonidina, ciclotiazida, delapril clorhidrato, dilevalol clorhidrato, doxazosina mesilato, fosinopril sódico, clorhidrato de guanfacina, metiidopa, metoprolol succinato, moexipril clorhidrato, monatepil maleato, clorhidrato de pelanserina, clorhidrato de fenoxibenzemina, clorhidrato de prazosina, primidolol, quinapril clorhidrato, quinaprilat, ramipril, clorhidrato de terazosina, candesartán, candesartán cilexetil, telmisartán, bisalato de amlodipina, maleato de amlodipina y bevantolol clorhidrato);
- un inhibidor de la enzima de conversión de angiotensina (por ejemplo alacepril, alatriopril, altiopril cálcico, ancovenina, benazepril, benazepril clorhidrato, benazeprilat, benzoilcaptopril, captopril, captopril-cisteína, captopril-glutatión, ceranapril, ceranopril,

ceranapril, cilazapril, cilazaprilat, delapril, delapril-diácido, enalapril, enalaprilat, enapril, epicaptopril, foroximitina, fosfenopril, fosenopril, fosenopril sódico, fosinopril, fosinopril sódico, fosinoprilat, ácido fosinoprílico, glicopril, hemorfin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, liciumina A, liciumina B, mixanpril, moexipril, moexiprilat, moveltipril, muraceína A, muraceína B, muraceína C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril clorhidrato, quinaprilat, ramipril, ramiprilat, spirapril, spirapril clorhidrato, spiraprilat, spiropril, spiropril clorhidrato, temocapril, temocapril clorhidrato, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril y zofenoprilat);

- un antagonista de receptor de angiotensina II (por ejemplo candesartán, candesartán cilexetil, losartán, valsartán, irbesartán, tasosartán, telmisartán y eprosartán);
- un bloqueador andrenérgico (por ejemplo bretilio tosilato, dihidroergotamina mesilato, fentolamina mesilato, solipertina tartrato, clorhidrato de zolertina, carvedilol o labetalol clorhidrato); un bloqueador alfa andrenérgica (por ejemplo fenspiride clorhidrato, labetalol clorhidrato, proroxan y alfuzosin clorhidrato); un bloqueador beta andrenérgico (por ejemplo acebutolol, acebutolol clorhidrato, alprenolol clorhidrato, atenolol, bunolol clorhidrato, carteolol clorhidrato, celiprolol clorhidrato, cetamolol clorhidrato, cicloprolol clorhidrato, dexpropranolol clorhidrato, diacetolol clorhidrato, dilevalol clorhidrato, esmolol clorhidrato, exaprolol clorhidrato, flestolol sulfato, labetalol clorhidrato, levobetaxolol clorhidrato, levobunolol clorhidrato, metalol clorhidrato, metoprolol, metoprolol tartrato, nadolol, pamatolol sulfato, penbutolol sulfato, practolol, propranolol clorhidrato, sotalol clorhidrato, timolol, timolol maleato, tiprenolol clorhidrato, tolamolol, bisoprolol, bisoprolol fumarato y nebivolol); o un bloqueador adrenérgico alfa/beta mixto;
- un estimulante andrenérgico (por ejemplo un producto de

combinación de clorotiazida y metiidopa, el producto de combinación de metiidopa hidroclorotiazida y metiidopa, clonidina clorhidrato, clonidina, el producto de combinación de clortalidona y clonidina clorhidrato y guanfacina clorhidrato);

- bloqueador de canal, por ejemplo un bloqueador de canales de calcio (por ejemplo clentiazem maleato, amlodipina besilato, isradipina, nimodipina, felodipina, nilvadipina, nifedipina, teludipina clorhidrato, diltiazem clorhidrato, belfosdil, verapamil clorhidrato o fostedil);
- un diurético (por ejemplo el producto de combinación de hidroclorotiazida y espironolactona y el producto de combinación de hidroclorotiazida y triamterene);
- agentes antianginales (por ejemplo amlodipina besilato, amlodipina maleato, betaxolol clorhidrato, bevantolol clorhidrato, butoprozina clorhidrato, carvedilol, cinepazet maleato, metoprolol succinato, molsidomine, monatepil maleato, primidolol, ranolazina clorhidrato, tosifeno o verapamil clorhidrato);
- vasodilatadores por ejemplo vasodilatadores coronarios (por ejemplo fostedil, azaclorzina clorhidrato, cromonar clorhidrato, clonitrato, diltiazem clorhidrato, dipiridamol, droprenilamina, eritritil tetranitrato, isosorbida dinitrato, isosorbida mononitrato, lidoflazina, mioflazina clorhidrato, mixidina, molsidomina, nicorandil, nifedipina, nisoldipina, nitroglicerina, oxprenolol clorhidrato, pentrinitrol, perhexilina maleato, prenilamina, propatil nitrato, terodilina clorhidrato, tolamolol y verapamil);
- anti-coagulantes (seleccionados de argatroban, bivalirudina, dalteparina sódica, desirudina, dicumarol, Iyapolato sódico, nafamostat mesilato, fenprocoumon, tinzaparina sódica y warfarina sódica);
- agentes antitrombóticos (por ejemplo anagrelide clorhidrato, bivalirudina, cilostazol, dalteparina sódica, danaparoid sódico, dazoxiben clorhidrato, efegatran sulfato, enoxaparina sódica,

fluretofen, ifetroban, ifetroban sódico, lamifiban, lotrafiban clorhidrato, napsagatran, orbofiban acetato, roxifiban acetato, sibrafiban, tinzaparina sódica, trifenagrel, abciximab y zolimomab aritox);

- antagonistas de receptor de fibrinógeno (por ejemplo roxifiban acetato, fradafiban, orbofiban, lotrafiban clorhidrato, tirofiban, xemilofiban, anticuerpo monoclonal 7E3 y sibrafiban)
- inhibidores plaquetarios (por ejemplo cilostezol, clopidogrel bisulfato, epoprostenol, epoprostenol sódico, ticlopidina clorhidrato, aspirina, ibuprofeno, naproxeno, sulindae, indometacina, mefenamato, droxicam, diclofenac, sulfinpirazona y piroxicam, dipiridamol);
- inhibidores de agregación plaquetaria (por ejemplo acadesine, beraprost, beraprost sódico, ciprostene cálcico, itezigrel, lifarizina, lotrafiban clorhidrato, orbofiban acetato, oxagrelate, fradafiban, orbofiban, tirofiban y xemilofiban)
- agentes hemorreológicos (por ejemplo pentoxifilina);
- inhibidores de coagulación asociada con lipoproteína;
- inhibidores de Factor VIIa;
- inhibidores de Factor Xa;
- heparinas de bajo peso molecular (por ejemplo enoxaparina, nardroparina, dalteparina, certroparina, parnaparina, reviparina y tinzaparina);
- inhibidores de escualeno sintasa;
- inhibidores de escualeno epoxidasa;
- agonistas de receptor hepático X (LXR) por ejemplo GW-3965 y los descritos en WO00224632, WO00103705, WO02090375 y WO00054759 (reivindicación 1 y los ejemplos mencionados de estas cuatro aplicaciones se incorporan aquí por referencia);
- inhibidores de proteína de transporte de triglicéridos microsomales por ejemplo implitapide y los descritos en WO03004020, WO03002533, WO02083658 y WO 00242291 (reivindicación 1 y los

ejemplos mencionados de estas cuatro solicitudes se incorporan aquí por referencia);

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento terapéutico.

Por lo tanto, en una característica adicional de la invención, se provee una combinación de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un compuesto del Grupo X o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Por lo tanto, en una característica adicional de la invención, se provee un método para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en administración simultánea, consecutiva o separada con una cantidad eficaz de un compuesto de Grupo X, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un compuesto de Grupo X, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptables.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un compuesto de Grupo X, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en la producción de un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre.

Además de su uso en la medicina terapéutica, los compuestos de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, son también útiles como herramientas farmacológicas en el desarrollo y estandarización de sistemas de análisis *in vitro* e *in vivo* para la evaluación de los efectos de inhibidores de la absorción del colesterol en animales de laboratorio tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la investigación de nuevos agentes terapéuticos.

Muchos de los intermedios descritos aquí son novedosos y, por consiguiente, se proveen como una característica más de la invención. Por ejemplo compuestos de fórmula (VI) muestran actividad inhibidora de absorción de colesterol cuando evalúan en el ensayo de prueba *in vitro* referenciado más arriba y, por lo tanto, se reivindican como una característica adicional de la invención.

Por consiguiente, en una característica más de la invención, se provee un compuesto de fórmula (VI), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona.

Por lo tanto de acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula (VI), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en asociación con un diluyente o vehículo farmacéuticamente aceptable, con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona.

De acuerdo con un aspecto adicional de la presente invención se provee un compuesto de la fórmula (VI), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, para uso en un método de tratamiento profiláctico o terapéutico de un animal de sangre caliente, tal como el hombre, con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-

1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil) carbamoilmetoxi]fenil}azetidin-2-ona.

Así, de acuerdo con este aspecto de la invención se provee un compuesto de la fórmula (VI), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, para uso como un medicamento, con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil) carbamoilmetoxi]fenil}azetidin-2-ona.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (VI), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre, con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi] fenil}azetidin-2-ona.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (VI), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en el tratamiento de enfermedades hiperlipidémicas en un animal de sangre caliente, tal como el hombre, con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para producir un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (VI), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-

fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil) carbamoilmetoxi]fenil}azetidin-2-ona.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método de tratar afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (VI), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona.

En la otra composición farmacéutica ya mencionada, se aplican asimismo las caracterísctcas proceso, método, uso y manufactura de medicamento, las incorporaciones alternativas y preferidas de los compuestos de la invención descritos aquí.

Ejemplos

La invención se ilustrará ahora en los siguientes ejemplos no limitantes, en los cuales pueden utilizarse técnicas estándar conocidas por el químico experto, y técnicas análogas a las descritas en estos ejemplos, donde se consideren apropiadas, y en las cuales, a menos que se afirme lo contrario:

(i) las evaporaciones se llevaron a cabo por evaporación rotatoria *in vacuo* y los procedimientos de preparación se realizaron luego del retiro de los sólidos residuales tales como agentes de secamiento por filtración;

(ii) todas las reacciones se llevaron a cabo bajo una atmósfera inerte a temperatura ambiente, típicamente en el rango de 18-25°C, con solventes de grado HPLC bajo condiciones anhidras, a menos que se indique lo contrario;

(iii) cromatografía de columna (por los procedimientos de destello) se realizó en gel de sílice 40-63 μm (Merck);

(iv) los rendimientos se dan para efectos de ilustración únicamente no son necesariamente el máximo alcanzable;

(v) las estructuras de los productos finales de la fórmula (I) se confirmaron generalmente por resonancia magnética nuclear (generalmente de protones) (NMR) y técnicas de espectros de masa; los valores de cambio químico con resonancia magnética se midieron en $CDCl_3$ deuterado (a menos que se indique lo contrario) en la escala delta (ppm campo abajo de tetrametilsilano); a menos que se indique lo contrario, los datos de protones se citan; los espectros se registran en un espectrómetro Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz o en Varian Inova-500 MHz; a menos que se indique lo contrario, los datos indicados se registraron a 400 MHz; y los múltiplos de picos se muestran como sigue: s, singlete; d, doblete; dd, doble doblete; t, triplete; tt, triple triplete; q, cuartete; tq, triple cuartete; m, multiplete; br, amplio; ABq, AB cuartete; ABd, AB doblete, ABdd, AB doblete de dobletes; dABq, doblete de AB cuartetes;

Los espectros de masas se registraron en uno de los siguientes instrumentos: espectrómetros de masas LCT, QTOF, ZQ, todos de Waters.

LC-MS:

La separación se llevó a cabo usando Módulos Agilent Serie 1100 o bomba Waters 1525 en una columna Synergi MAX-RP (Phenomenex) C12 3x50 mm 4μm con elución de gradiente.

Las muestras se inyectaron usando un Administrador de Muestras (***"Sample Manager"***) de Waters 2700.

Fáses móviles:

Se aplicaron gradientes genéricas de 5% a 95% acetonitrilo.

Se emplearon tampones que contenían 10 mM de acetato de amonio o 5 mM formiato de amoni/5mM ácido fórmico.

Los espectros de masas se registraron con un Waters ZQ2000 o Waters ZMD equipado con una interface de electropulverización, cambiando el modo de ionización positiva y negativa. Se recogieron los espectros UV por un Agilent 1100 PDA o Waters 2996 DAD y la señal de dispersión de

luz con evaporación (*"evaporative light scattering –ELS– signal"*) por un Sedere Sedex 55 o 75.

La recolección de los datos y la evaluación se llevaron a cabo usando el software MassLynx.

Datos de masas exactos se determinaron usando un LCT o QTOF MS (Waters) con leucina encefalina (m/z 556.2771) como sustancia de referencia (*"lockmass"*). A menos que se indique lo contrario el ión de masa citado es (MH+).

A menos que se especifiquen más detalles en el texto, la cromatografía analítica de líquido de alto rendimiento (HPLC) se realizó en Prep LC 2000 (Aguas), Kromasil C_8, 7 µm, (Akzo Nobel); MeCN y agua deionizada 100 mM acetato de amonio como fases móviles, con la composición adecuada;

(vii) en general los intermedios no se caracterizaron plenamente y la pureza se evaluó mediante cromatografía de capa delgada (TLC), HPLC, infra-rojo (IR), MS o análisis NMR;

(viii) donde se secaron las soluciones el agente de secamiento fue sulfato de sodio; y

(ix) las siguientes abreviaturas pueden usarse más arriba o más adelante en el texto:

DCM	diclorometano;
DMF	*N*,*N*-dimetilformamida;
TBTU	o-Benzotriazol-1-il-*N*,*N*,*N'*,*N'*-tetrametiluronio-tetrafluoroborato;
EtOAc	acetato de etilo;
MeCN	acetonitrilo;
TFA	ácido trifluoroacético;
DMAP	4-(dimetilamino)piridina
BSA	*N*,*O*-Bis(trimetilsilil)acetamida; y
TBAF	fluoruro de tetrabutilamonio;
NMM	*N*-metil morfolina;

TEA trietilamina;

DBN 1,5-diazabiciclo-[4,3,0]-non-5-eno.

Ejemplo 1

Ácido (2R)-[(N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil)amino](fenil)acético

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (44 mg, 0.081 mmol), *N*-metilmorfolina (18 ul, 0.16 mmol), *terc*-butil (2*R*)-amino(fenil)acetato (23 mg, 0.11 mmol) y TBTU (36 mg, 0.11 mmol) se agregaron a cloruro de metileno (3ml) y la mezcla de reacción se agitó a temperatura ambiente durante 1.5 hora. La mezcla se purificó por cromatografía de columna en gel de sílice usando cloruro de metileno/acetato de etilo (1/1) como eluyente. El éster intermedio resultante se disolvió en ácido fórmico (2 ml) y la mezcla se agitó de un día para otro a 45°C. El disolvente se evaporó bajo presión reducida y se co-evaporó con tolueno. El residuo se disolvió en metanol (2ml) y se agregó $NaBH_4$ 10 mg, 0.26 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 15 minutos. Una pequeña cantidad de tampón de acetato de amonio se agregó y el metanol se extrajo por evaporación. El residuo se purificó por HPLC preparativa usando tampón acetonitrilo/acetato de amonio (45: 55) como eluyente. Las fracciones recogidas se liofilizaron para obtener 39 mg (71%, 3 pasos) del compuesto del título. (^{1}H-NMR, 400 MHz, CD_3OD): 1.8-2.0 (m, 2H), 3.75 (d, 2H), 4.3 (d, 1H), 4.55 (s, 2H), 4.65-4.80 (m, 2H), 5.05 (d, 1H), 7.0-7.4 (m, 17 H), 7.95 (dd, 1H) 8.25 (t, 1H)

Ejemplo 2

N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-N^6-acetil-D-lisina

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (20 mg, 0.037 mmol), N-metilmorfolina(18 ul, 0.16 mmol) y TBTU (13 mg, 0.041 mol) se agregaron a CH_2Cl_2 (2 ml) y la mezcla de reacción se agitó a 30°C durante 1.5 horas. A la mezcla se agregaron N^6-acetil-D-lisina (14 mg, 0.074 mmol) y DMF (5 gotas) y la mezcla se agitó a temperatura ambiente de un día para otro. El disolvente se evaporó bajo presión reducida y metanol (2 ml) y $NaBH_4$ (30 mg, 0.79 mmol) se agregaron al residuo. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Una pequeña cantidad de tampón de acetato de amonio se agregó, y el metanol se extrajo por evaporación. El residuo se purificó por HPLC preparativa usando tampón acetonitrilo/acetato de amonio (40:60) como eluyente. Las fracciones recogidas se liofilizaron, se disolvieron en *terc*-butanol y se liofilizaron nuevamente para obtener 4 mg (15% 2 pasos) del compuesto del título. (^{1}H-NMR, 400 MHz, DMSO-d_6): 1.2-1.8 (m, 11H), 2.85-2. 95 (m, 2H), 3.7-3.8 (m, 2H), 4.0-4.1 (bs, 1H), 4.25-4.3 (m, 1H), 4.5 (s, 2H), 4.7-4.8 (m, 1H), 5.05 (dd, 1H), 6.95-7.4 (m, 12H), 7.7-7.8 (m, 1H), 7.95-8.05 (m, 1H), 8.25-8.3 (m, 1H)

Ejemplo 3

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-alanil-D-fenilalanina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-alanina (12 mg, 0.022 mmol), *terc*-butil D-fenilalaninato clorhidrato (7 mg, 0.028 mmol) y 4-metilmorfolina (7mg, 0.065 mmol se disolvieron en 0.5 ml DCM. La mezcla se agitó a temperatura de la sala durante 5 minutos. Se agregó TBTU (9 mg,

0.028mmol), y la mezcla de reacción se agitó de un día para otro y luego se purificó en sílice (2g), primero con DCM y luego con DCM: MeOH, 10:1 como eluyente. Las fracciones que contenían el producto se concentraron y se agregó ácido fórmico (1 ml) y la solución se agitó de un día para otro. Se evaporó el ácido fórmico, luego de lo cual el ácido fórmico residual se retiró por la adición de tolueno y mediante evaporación. El residuo se agitó en metanol: trietilamina, 40:1, (2 ml) durante 2.5 días (hidrólisis del éster de ácido fórmico formado), la mezcla se concentró y el residuo se purificó por HPLC preparativa usando una gradiente de 20 % a 100 % CH_3CN en 0.1% tampón de acetato de amonio como eluyente. El secamiento por congelamiento produjo 7.3 mg (48 %) del producto del título. M/z: 702.3 (M-1), NMR (DMSO, 400 MHz): 1.18 (d, 3H), 2.85-2.96 (m, 3H), 3.00-3.07 (m, 1H), 4.05-4.12 (m, 1H), 4.19-4.32 (m, 2H), 4.48 (dd, 2H), 4.68-4.76 (m, 1H), 5.0-5.07 (m, 1H), 6.89-6.95 (m, 2H), 7.05-7.17 (m, 10H), 7.19-7.25 (m, 2H), 7.30-7.36 (m, 4H), 7.65-7.75 (m, 11-1), 8.12-8.18 (m, 1H).

Ejemplo 4

N^2-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]-D-lisina

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (10 mg, 0.016mmol), *terc*-butil N^6-(*terc*-butoxicarbonil)-D-lisinato clorhidrato (7mg, 0.021mmol) y N-metilmorfolina (5mg, 0.048mmol) se disolvieron en DCM (0.5ml). La mezcla se agitó y después de 5 minutos se agregó TBTU (7mg, 0.021) y la mezcla de reacción se agitó durante dos horas. El producto se purificó en una matriz semisólida de sílice (***"on a silica plug"***) con DCM:MeOH, 100:5 como el eluyente. Ácido fórmico (0. 5ml) se agregó al producto purificado y la mezcla se agitó dos horas a 40°C y luego

a temperatura ambiente de un día para otro. El ácido fórmico se retiró bajo presión reducida y se agregó tolueno, tras lo cual el disolvente se retiró. El residuo se disolvió en MeOH y una pequeña cantidad de trietilamina y se agitó de un día para otro a temperatura ambiente. El producto se purificó HPLC preparativa (CH3CN/0.1% acetato de amonio 20:80-100:0). Las fracciones que contenían el producto se liofilizaron y se obtuvieron 4.0mg (33%) del compuesto del título. M/z: 745.4 (M-1). NMR (DMSO, 400 MHz): 1.19-2.30 (m, 2H), 1.30-1.40 (m, 2H), 1.40-1.52 (m, 2H), 1.52-1.68 (m, 2H), 2.63-2.75 (m, 2H), 2.83-2.95 (m, 2H), 3.7-3.8 (m, 1H), 4.28 (dd, 1H), 4.60 (dd, 2H), 4.68-4.76 (m, 1H), 5.04 (dd, 1H), 5.48 (d, 1H), 6.95 (d, 2H), 7.05-7.17 (m, 4H), 7.19-7.28 (m, 5H), 7.30-7.40 (m, 6H), 7.88 (d, 1H), 8.55 (d, 1H).

Ejemplo 5

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-triptofil-D-fenilalanina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tiol-4-oxoazetidin-2-il)fenoxi]acetil}-L-triptófano (0.015 g, 0.022 mmol) se disolvió en CH_2Cl_2 (2 ml). Se agregaron H-D-Phe-OTBU clorhidrato (0.007 g, 0.027 mmol) y N-metilmorfolina (0.007 g, 0.067 mmol). Luego de 10 minutos se agregó TBTU (0.009 g, 0.029 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 2 horas. La mezcla se pasó entonces por una corta almohadilla de gel de sílice y se eluyó con EtOAc/CH_2Cl_2 25/75. Las fracciones puras se recogieron y concentraron. El terc-butil éster resultante se hidrolizó por la adición de ácido fórmico (0.5 ml) seguido por agitación a temperatura de la sala de un día para otro. El producto resultante se concentró y se disolvió en 2ml de MeOH. Se agregó Et_3N (0.1ml) con el fin de hidrolizar el producto tratado con formilo. La mezcla se dejó agitar de un día para otro. El disolvente se evaporó y el residuo se purificó por HPLC preparativa usando una gradiente de 20-60%

CH_3CN en 0.1 M tampón NH_4OAc como fase móvil. El secamiento por congelamiento proporcionó el producto del título (0.004 g, 22%) como un sólido incoloro. M/z: 817.3 (M-1). ^1H NMR (CD_3CN, 400 MHz) δ 2.82-3.20 (m, 6H), 4.07-4.15 (m, 1H), 4.29-4.39 (m, 2H), 4.54-4.89 (m, 4H), 6.74-7.53 (m, 22H), 9.14-9.20 (m, 1H).

Ejemplo 6

***N*-((2*R*)-2-{[(4-{(2*R*,3*R*)-3-[(2-hidroxi-2-feniletil)tio]-4-oxo-1-fenilazetidin-2-il}fenoxi)acetil]amino}-2-fenilacetil)glicina**

Ácido [4-((2*R*,3*R*)-3-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}-4-oxo-1-fenilazetidin-2-il)fenoxi]acético (0.050 g, 0.094 mmol) se disolvió en CH_2Cl_2 (5 ml). Se agregaron *terc*-butil *N*-[(2*R*)-2-amino-2-fenilacetil] glicinato (0.030 g, 0.112 mmol) y *N*-metilmorfolina (0.028 g, 0.281 mmol). Luego de 5 minutos se agregó TBTU (0.039 g, 0.122 mmol). Luego de 1 hora, HPLC mostró una conversión total en el *terc*- butiléster correspondiente. La mezcla de reacción se purificó por cromatografía en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Fracciones puras se recogieron y concentraron. El residuo se disolvió en 3 ml CH_2Cl_2 y se agregó1 ml ácido trifluoroacético. La mezcla de reacción se dejó agitar a temperatura de la sala durante 2 horas, luego de lo cual el ácido resultante se concentró *in vacuo*. El TFA restante se retiró mediante co-evaporación con tolueno (2 ml). El ácido se disolvió en 3 ml de MeOH y se agregó borohidruro de sodio (10 mg, 0.264 mmol). Luego de 5 minutos, HPLC mostró una conversión completa en el alcohol correspondiente. La reacción se extinguió por la adición de 1ml de 0.1M tampón NH_4OAc seguido por concentración de la mezcla. Purificación por HPLC preparativa del residuo usando una gradiente de 20-60% CH_3CN en 0.1M tampón NH_4OAc como fase móvil y liofilización proporcionó el producto del título (0.032 g, 54%) como un sólido incoloro. M/z: 638.5 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.90-2.94 (m, 2H), 3.45-3.65 (m, 2H), 4.25-4.27 (m, 1H), 4.59

(d,1H), 4.64 (d, 1H), 4.68-4.75 (m,1H), 5.02-5.05 (m, 1H), 5.57 (d,1H), 6.94-7.41 (m, 19H), 8.28 (s, br, 1H), 8.55 (d, 1H).

Ejemplo 7

***N*-[(4-{(2*R*,3*R*)-3-[(2-hidroxi-2-feniletil)tio]-4-oxo-1-fenilazetidin-2-il}fenoxi)acetil]glicil-D-fenilalanina**

N-[(4-{(2*R*,3*R*)-4-Oxo-3-[(2-oxo-2-feniletil)tio]-1-fenilazetidin-2-il}fenoxi)acetil]glicina se disolvió en CH_2Cl_2 (3 ml). Se agregaron (R)-fenilalanina *terc*-butil éster clorhidrato (0.012 g, 0.045 mmol) y N-metilmorfolina (0.011 g, 0.113 mmol). Luego de 5 minutos se agregó TBTU (0.016 g, 0.049 mmol). Después de 1 hora, se obtuvo la conversión completa en el *terc*-butil éster correspondiente. La mezcla de reacción se purificó por cromatografía en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 25/75. Fracciones puras se recogieron y se concentraron. El residuo se disolvió en 3 ml CH_2Cl_2 y 0.5 ml ácido trifluoroacético, y la reacción se dejó agitar a temperatura de la sala de un día para otro. El ácido resultante se concentró y se disolvió en 3 ml de MeOH. Se agregó borohidruro de sodio (0.010 g, 0.264 mmol). Se obtuvo conversión completa en el alcohol correspondiente luego de 5 minutos. La reacción se extinguió por la adición de 1 ml de 0.1 M tampón NH_4OAc. Concentración seguida por HPLC preparativa usando una gradiente de 20-60% CH_3CN en 0.1M tampón NH_4OAc como fase móvil proporcionó el producto del título (0.021 g, 84%) como un sólido incoloro luego de secamiento por congelamiento. M/z: 652.3 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.85-3.05 (m, 4H), 3.62-3.80(m, 2H), 4.18-4.35 (m, 2H), 4.48 (d, 1H), 4.51 (d, 1H), 4.68-4.78 (m, 1H), 4.99-5.03(m, 1H), 6.93-7.35 (m, 19H), 7.65-7.80 (m, 1H), 8.23-8.29(m, 1H).

Ejemplo 8

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N-[(2R)-2-({[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]-L-alanina

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.040 g, 0.065 mmol) se disolvió en CH_2Cl_2 (5 ml). Se agregaron *terc*-butil L-alaninato clorhidrato (0.014 g, 0.078 mmol) y *N*-metil-morfilina (0.020 g, 0.195 mmol). Luego de 5 minutos se agregó TBTU (0.027 g, 0.084 mmol). La reacción se dejó agitar durante 1 hora luego de lo cual el *terc*-butil éster resultante se purificó por cromatografía en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 25/75. Fracciones puras se concentraron y disolvieron en CH_2Cl_2 (4ml) y ácido trifluoroacético (0.5 ml). Después de 1.5 horas a temperatura de la sala, se obtuvo conversión completa en el ácido correspondiente. La mezcla de reacción se concentró y el residuo de TFA se retiró por co- evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (3 ml) y se agregó $NaBH_4$ (0.010 g, 0.260 mmol). Se obtuvo conversión completa en el alcohol correspondiente luego de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml). La mezcla se concentró y el residuo se purificó por HPLC preparativa usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como fase móvil. El secamiento por congelamiento proporcionó el compuesto del título (0.020 g, 45%) como un sólido incoloro. M/z: 688.4 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.30-2.35 (m, 3H), 2.86-2.94 (m, 2H), 3.15-3.31 (m,1H), 4.26-4.28 (m, 1H), 4.59 (d, 1H), 4.64 (d, 1H), 4.70-4.76 (m,1H), 5.04-5.07 (m, 1H), 5.46 (d, 1H), 6.94- 7.36 (m, 17H), 8.43-8.55 (m, 2H).

Ejemplo 9

N-[(2R)-2-({[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]-D-alanina

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.040 g, 0.065 mmol) se disolvió en CH_2Cl_2 (5 ml). Se agregaron *terc*-butil D-alaninato clorhidrato (0.014 g, 0.078 mmol) y *N*-metil-morfilina (0.020 g, 0.195 mmol). Luego de 5 minutos se agregó TBTU (0.027 g, 0.084 mmol). La reacción se dejó agitar de un día para otro y el *terc*- butil éster resultante se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Las fracciones puras se concentraron. El residuo se disolvió en CH_2Cl_2 (4 ml) y ácido trifluoroacético (0.5 ml). Luego de 1. 5 horas a temperatura de la sala, se obtuvo conversión completa en el ácido correspondiente. La mezcla de reacción se concentró y el TFA restante se retiró por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (3 ml) y se agregó $NaBH_4$ (0.010 g, 0.260 mmol). Se obtuvo conversión completa en el alcohol correspondiente luego de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml). La mezcla se concentró y el residuo se purificó por HPLC preparativa usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como fase móvil. El secamiento por congelamiento produjo el compuesto del título (0.024 g, 54%) como un sólido incoloro. M/z: 688.6 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.10-1.24 (m, 3H), 2.89-2.94 (m, 2H), 3.99-4.08 (m, 1H), 4.26-4.30 (m, 1H), 4.60 (d, 1H), 4.64 (d,1H), 4.70-4.78 (m, 1H), 5.02-5.08 (m, 1H), 5.53- 5.56 (d, 1H), 6.94-7.40 (m, 17H), 8.39-8.59 (m, 2H).

Ejemplo 10

Ácido (2*R*)-{[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]amino}(fenil)acético

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.040 g, 0.065

mmol) se disolvió en CH_2Cl_2 (5 ml) y se agregaron *terc*-butil (2*R*)-amino(fenil)acetato (0.016 g, 0.078 mmol) y *N*-metil-morfilina (0.020 g, 0.195 mmol). Luego de 5 minutos se agregó TBTU (0.027 g, 0.084 mmol). La reacción se dejó agitar a temperatura de la sala durante 3 horas, luego de lo cual el *terc*-butil éster resultante se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 25/75. Fracciones puras se concentraron. El residuo se disolvió en CH_2Cl_2 (3 ml) y TFA (0.5 ml). La mezcla de reacción se dejó agitar de un día para otro a temperatura de la sala. El ácido resultante se concentró y la traza restante de TFA se retiró por co-evaporación con tolueno (3 ml). El ácido se disolvió en MeOH (3 ml) y se agregó $NaBH_4$ (0.010 g, 0.260 mmol). Luego de 5 minutos, se obtuvo conversión completa en el alcohol correspondiente. La reacción se extinguió por la adición de 1ml de 0.1M tampón NH_4OAc. Concentración seguida por purificación en HPLC preparativa, usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como fase móvil, y el secamiento por congelamiento de las fracciones puras proporcionaron el compuesto del título (0.034 g, 70%) como un sólido incoloro. M/z: 750.4 (M-1). ^1H NMR[$(CD_3)_2SO$), 400 MHz] δ 2.88-2.94 (m, 2H), 4.23-4.29 (m, 1H), 4.56-4.65 (m, 2H), 4.70-4.78 (m, 1H), 4.91-5.06 (m, 2H), 5.65-5.75 (m, 1H), 6.93-7.42 (m, 22H), 8.54-8.69 (m, 2H).

Ejemplo 11

Ácido (2S)-{[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]amino}(fenil)acético

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.040 g, 0.065 mmol) se disolvió en CH_2Cl_2 (5 ml). Se agregaron *terc*-butil (2*S*)-amino(fenil)acetato (0.016 g, 0.078 mmol) y N-metil-morfilina (0.020 g, 0.195 mmol). Luego de 5 minutos, se agregó TBTU (0.027 g, 0.084 mmol).

La mezcla de reacción se agitó a temperatura de la sala durante 3 horas. El *terc*-butil éster resultante se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Las fracciones puras se concentraron. El residuo se disolvió en CH_2Cl_2 (3 ml) y TFA (0.5 ml). La mezcla de reacción se agitó de un día para otro a temperatura de la sala. El ácido resultante se concentró y la traza restante de TFA se retiró por co-evaporación con tolueno (3 ml). El ácido se disolvió en MeOH (3 ml) y se agregó $NaBH_4$ (0.010 g, 0.260 mmol). Luego de 5 minutos, se obtuvo conversión completa en el alcohol correspondiente. La reacción se extinguió por la adición de 1 ml de 0.1 M tampón NH_4OAc. Concentración seguida por purificación en HPLC preparativa, usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como fase móvil, y el secamiento por congelamiento de las fracciones puras proporcionaron el compuesto del título (0.037 g, 76%) como un sólido incoloro. M/z: 750.6 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.87-2.94 (m, 2H), 4.25-4.28 (m, 1H), 4.58-4.78 (m, 3H), 5.01-5.07 (m, 2H), 5.65- 5.74 (m, 1H), 6.94-7.39 (m, 22H), 8.53-8.72 (m, 2H).

Ejemplo 12

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]-D-serina**

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.040 g, 0.065 mmol), *terc*-butil O-(*terc*-butil)-D-serinato clorhidrato (0.020 g, 0.078 mmol) y *N*-metil-morfolina (0.020 g, 0.195 mmol) se disolvieron en CH_2Cl_2 (5 ml) a temperatura de la sala. Después de 5 minutos, se agregó TBTU (0.027 g, 0. 084 mmol). Luego de 1 hora, se obtuvo la conversión completa en el terc-butil éster correspondiente. La mezcla de reacción se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Fracciones puras se

recogieron y se concentraron. El residuo se disolvió en 3 ml CH_2Cl_2 y 1 ml TFA. La mezcla de reacción se agitó durante 1.5 horas y se concentró. La traza restante de TFA se retiró azeotrópicamente por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (3 ml) y se agregó $NaBH_4$ (0.010 g, 0.260 mmol). Se obtuvo conversión completa en el alcohol correspondiente después de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). Purificación en HPLC preparativa usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como fase móvil, seguida por el secamiento por congelamiento de las fracciones puras, proporcionó el compuesto del título (0.032 g, 71%) como un sólido incoloro. M/z: 704.7 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.88-2.94 (m, 2H), 3.42-3.46 (m, 1H), 3.58-3.61 (m, 1H), 3.85-3.90 (m,IM, 4.26- 4.29 (m, 1H), 4.59 (d, 1H), 4.64 (d, 1H), 4.70-4.77 (m, 1H), 5.04-5.07 (m, 1H), 5.57-5.65 (m, 1H), 6.95-7.41 (m, 17H), 8.08-8.20 (m, 1H), 8.53-8.56 (m, 1H).

Ejemplo 13

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]-L-treonina**

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.030 g, 0.049 mmol), *terc*-butil O-(*terc*-butil)-L-treoninato (0.014 g, 0.058 mmol) y N-metil-morfolina (0.015 g, 0.146 mmol) se disolvieron en CH_2Cl_2 (4 ml). Después de 5 minutos, se agregó TBTU (0.020 g, 0.063 mmol). Se obtuvo conversión completa en el *terc*-butil éster correspondiente luego de 1 hora. La mezcla de reacción se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Fracciones puras se recogieron y se concentraron. El residuo se disolvió en 3 ml CH_2Cl_2 y 1 ml TFA, y la mezcla se agitó durante 1.5 horas. El ácido resultante se concentró. La traza restante de

TFA se retiró azeotrópicamente por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (3 ml) y se agregó $NaBH_4$ (0.007 g, 0.195 mmol). Se obtuvo conversión completa en el alcohol correspondiente después de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). Purificación por HPLC preparativa usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como eluyente, seguida por secamiento por congelamiento de las fracciones puras proporcionó el compuesto del título (0.025 g, 71%) como un sólido incoloro. M/z: 721.1. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.69 (d, 3H), 2.88-2.93 (m, 2H), 3.79-3.85 (m, 1H), 3.96-4.01 (m, 1H), 4.27-4.30 (m, 1H), 4.60 (d, 1H), 4.64 (d, 1H), 4.71-4.79 (m, 1H), 5.02-5.08 (m, 1H), 5.65-5.69 (m, 1H), 6.95-7.42 (m, 17H), 8.01-8.09 (m, 1H), 8.51-8.59 (m, 1H).

Ejemplo 14

N^2-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]-L-asparagina

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.030 g, 0.049 mmol), *terc*-butil L-asparaginato clorhidrato (0.013 g, 0.058 mmol) y N-metil-morfolina (0.015 g, 0.146 mmol) se disolvieron en CH_2Cl_2 (4 ml). Después de 5 minutos se agregó TBTU (0.020 g, 0.063 mmol). La conversión completa en el *terc*-butil éster correspondiente se obtuvo luego de 1 hora. La mezcla de reacción se purificó en gel de sílice y se eluyó con EtOAc. Las fracciones puras se recogieron y se concentraron. El residuo se disolvió en 3 ml CH_2Cl_2 y 1 ml TFA, y la mezcla se agitó durante 0.5 hora. El ácido resultante se concentró. La traza restante de TFA se retiró azeotrópicamente por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió MeOH (3 ml) y se agregó $NaBH_4$ (0.007 g, 0.195 mmol). Se obtuvo conversión completa en el alcohol correspondiente luego de 5

minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). Purificación por HPLC preparativa usando una gradiente de 20-40% CH_3CN en 0.1M tampón NH_4OAc como eluyente, seguida por el secamiento por congelamiento de las fracciones puras proporcionó el compuesto del título (0.024 g, 67%) como un sólido incoloro. M/z: 731.6 (M-1). ^1H NMR[$(CD_3)_2SO$), 400MHz] δ 2.16-2.23 (m, 1H), 2.32-2.42 (m, 1H), 2.87-2.95 (m, 2H), 4.20-4.30 (m, 2H), 4.59-4.78 (m, 3H), 5.03-5.07 (m, 1H), 5.54-5.59 (m, 1H), 6.68-6.73 (m, 1H), 6.94-7.38 (m, 17H), 7.78-7.83 (m, 1H), 8.22-8.37 (m, 1H), 8.50-8.58 (m, 1H).

Ejemplo 15

Ácido *N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]-L-aspártico

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.020 g, 0.032 mmol), di-*terc*- butil L-aspartato clorhidrato (0.011 g, 0.039 mmol) y *N*-metil-morfolina (0.010 g, 0.097 mmol) se disolvieron en CH_2Cl_2 (3 ml). Luego de 5 minutos, se agregó TBTU (0.014 g, 0.042 mmol). La conversión completa en el *terc*-butil éster correspondiente se obtuvo después de 1 hora. La mezcla de reacción se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Las fracciones puras se recogieron y se concentraron. El residuo se disolvió en 3 ml de CH_2Cl_2 y 1 ml de TFA. La mezcla de reacción se agitó durante 2 horas y el ácido resultante se concentró. La traza restante de TFA se retiró azeotrópicamente por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (3ml) y se agregó $NaBH_4$ (0.005 g, 0.130 mmol). Se obtuvo conversión completa en el alcohol correspondiente después de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). Purificación por HPLC preparativa usando una gradiente de 10-40% CH_3CN en 0.1M

tampón NH_4OAc como eluyente, seguida por el secamiento por congelamiento de las fracciones puras, proporcionó el compuesto del título (0.018 g,76%) como un sólido incoloro. M/z: 715.7 (M-18). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.00-2.08 (m, 1H), 2.31-2.50 (m, 1H), 2.88-2.94 (m, 2H), 4.18-4.22 (m, 1H), 4.27-4.30 (m, 1H), 4.60-4.78 (m, 3H), 5.03-5.08 (m, 1H), 5.55-5.65 (m, 1H), 6.94-7.40 (m, 17H), 8.22-8.39 (m, 1H), 8.50-8.59 (m, 1H).

Ejemplo 16

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]-D-valina**

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.010 g, 0.016 mmol), *terc*-butil D-valinato clorhidrato (0.004 g, 0.020 mmol) y *N*-metil-morfolina (0.005 g, 0.049 mmol) se disolvieron en CH_2Cl_2 (3 ml). Después de 5 minutos, se agregó TBTU (0.007 g, 0.021 mmol). La conversión completa en el *terc*-butil éster correspondiente se obtuvo luego de 1 hora. La mezcla de reacción se purificó en gel de sílice y se eluyó con $EtOAc/CH_2Cl_2$ (25/75). Las fracciones puras se recogieron y se concentraron. El residuo se disolvió en 3 ml CH_2Cl_2 y 0.5ml TFA. La mezcla de reacción se agitó durante 1.5 horas y se concentró. La traza restante de TFA se retiró azeotrópicamente por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (2 ml) y se agregó $NaBH_4$ (0.002 g, 0.065 mmol). Se obtuvo conversión completa en el alcohol correspondiente después de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). Purificación por HPLC preparativa usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como fase móvil, seguida por el secamiento por congelamiento de las fracciones puras, proporcionó el compuesto del título (0.004 g, 34%)

como un sólido incoloro. M/z: 716.6 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.81-0.85 (m, 6H), 1.98-2.09 (m, 1H), 2.88-2.93 (m, 2H), 3.92-3.98 (m, 1H), 4.22-4.30 (m, 1H), 4.60 (d, 1H), 4.64 (d, 1H), 4.70-4.78 (m, 1H), 5.02-5.07 (m, 1H), 5.62 (d, 1H), 6.94-7.40 (m, 17H), 8.18-8.22 (m, 1H), 8.52 (d, 1H).

Ejemplo 17

***N*-[(2*R*)-2-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)-2-fenilacetil]-L-valina**

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético (0.020 g, 0.032 mmol), *terc*- butil L-valinato clorhidrato (0.008 g, 0.039 mmol) y N-metil-morfolina (0.010 g, 0.097 mmol) se disolvieron en CH_2Cl_2 (4 ml). Después de 5 minutos, se agregó TBTU (0.014 g, 0.042 mmol). La conversión completa en el *terc*-butil éster correspondiente se obtuvo luego de 1 hora. La mezcla de reacción se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Las fracciones puras se recogieron y se concentraron. El residuo se disolvió en 3 ml CH_2Cl_2 y 1 ml TFA. La mezcla de reacción se agitó durante 1.5 horas y se concentró. La traza restante de TFA se retiró azeotrópicamente por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (3 ml) y se agregó $NaBH_4$ (0.005 g, 0.130 mmol). Se obtuvo conversión completa en el alcohol correspondiente luego de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). Purificación por HPLC preparativa usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como eluyente, seguida por el secamiento por congelamiento de las fracciones puras, proporcionó el compuesto del título (0.011 g, 47%) como un sólido incoloro. M/z: 716.5 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.60 (d, 3H), 0.68 (d, 3H), 1.95-2.05 (m, 1H), 2.88-2.94 (m, 2H),

4.00-4.08 (m, 1H), 4.27-4.30 (m, 1H), 4.61 (d, 1H), 4.64 (d, 1H), 4.70-4.78 (m, 1H), 5.02-5.09 (m, 1H), 5.64-5.75 (m, 1H), 6.94-7.44 (m, 17H), 8.39-8. 45 (m, 1H), 8.50-8.58 (m, 1H).

Ejemplo 18

***N*-((2*R*)-2-{[(4-{(2*R*,3*R*)-3-[(2-hidroxi-2-feniletil)tio]-4-oxo-1-fenilazetidin-2-il}fenoxi)acetil]amino}-2-fenilacetil)-L-serina**

Ácido [4-((2*R*,3*R*)-3-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}-4-oxo-1-fenilazetidin-2-il)fenoxi]acético (0.030 g, 0.056 mmol), *terc*-butil *N*-[(2*R*)-2-amino-2-fenilacetil]-O-(*terc*-butil)-L-serinato (0.024 g, 0.068 mmol) y N-metil-morfolina (0.017 g, 0.169 mmol) se disolvieron en CH_2Cl_2 (5 ml). Luego de 5 minutos, se agregó TBTU (0.023 g, 0.073 mmol). La conversión completa en el *terc*-butil éster correspondiente se obtuvo luego de 1 hora. La mezcla de reacción se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Las fracciones puras se recogieron y se concentraron. El residuo se disolvió en 3ml CH_2Cl_2 y 1 ml TFA. La mezcla de reacción se agitó de un día para otro y se concentró. La traza restante de TFA se retiró azeotrópicamente por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (4 ml) y se agregó $NaBH_4$ (0.009 g, 0.225 mmol). Se obtuvo conversión completa en el alcohol correspondiente luego de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). Purificación por HPLC preparativa usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como fase móvil, seguida por el secamiento por congelamiento de las fracciones puras, proporcionó el compuesto del título (0.022 g, 58%) como un sólido incoloro. M/z: 668.5 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.89-2.94 (m, 2H), 3.30-3.35 (m, 1H), 3.46-3.50 (m, 1H), 3.94-4.00 (m, 1H), 4.25-4.27 (m, 1H), 4.60 (d, 1H), 4.65 (d, 1H), 4.69-4.77 (m, 1H), 5.00-5.05 (m, 1H), 5.59-5.66 (m, 1H), 6.94-7.39 (m, 19H), 8.20-8.25 (m, 1H), 8.50-8.58 (m, 1H).

Ejemplo 19

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-alanil-D-valina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-alanina (0.040g, 0.072 mmol) se disolvió en CH_2Cl_2 (5 ml). Se agregaron *terc*-butil D-valinato clorhidrato (0.018 g, 0.087 mmol), N-metilmorfolina (0.022 g, 0.216 mmol) y TBTU (0.030 g, 0.094 mmol). El *terc*-butil éster se obtuvo luego de 1.5 horas. La mezcla de reacción se purificó en gel de sílice y se eluyó con CH_2Cl_2/EtOAc (75/25). Las fracciones puras se recogieron y se concentraron. El residuo se disolvió en CH_2Cl_2 (4 ml) y TFA (1 ml). La mezcla de reacción se agitó durante 3 horas y se concentró. El ácido crudo se disolvió en MeOH (4 ml) y se agregó $NaBH_4$ (0.011 g, 0.289 mmol). Se obtuvo conversión completa en el alcohol correspondiente luego de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml). La mezcla de reacción se concentró y el residuo se purificó por HPLC preparativa usando un eluyente de 20-50% CH_3CN en 0.1M tampón NH_4OAc. Esto produjo el compuesto del título (0.039 g, 82%) como un sólido incoloro. M/z: 654.5 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.79 (d, 6H), 1.21 (d, 3H), 1.96-2.05 (m, 1H), 2.85-2.95 (m, 2H), 3.91-3.97 (m, 1H), 4.22-4.29 (m, 1H), 4.35-4.42 (m, 1H), 4.48 (d, 1H), 4.53 (d, 1H), 4.70-4.78 (m, 1H), 5.02-5.04 (m, 1H), 6.94-7.36 (m, 12H), 7.70- 7.77 (m, 1H), 8.15 (d, 1H).

Ejemplo 20

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-alanil-D-alanina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-alanina (0.040g, 0.072 mmol) se disolvió en CH_2Cl_2 (5ml). Se agregaron *terc*-butil D-alaninato clorhidrato (0.016 g, 0.087 mmol), N-metilmorfolina (0.022 g, 0.216 mmol) y TBTU (0.030 g, 0.094 mmol). La conversión completa del terc-butil éster se obtuvo después de 1.5 h. La mezcla de reacción se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Las fracciones puras se recogieron y se concentraron. El residuo se disolvió en CH_2Cl_2 (3ml) y TFA (1 ml). La conversión completa del ácido se obtuvo después de 2 horas a temperatura de la sala. La mezcla de reacción se concentró y la traza restante de TFA se retiró azeotrópicamente por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (3 ml) y se agregó $NaBH_4$ (0.011 g, 0.289 mmol). Se obtuvo conversión completa en el alcohol correspondiente después de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml). La mezcla de reacción se concentró y el residuo se purificó por HPLC preparativa usando una gradiente de 20-50% CH_3CN en 0.1M tampón NH_4OAc como fase móvil. El secamiento por congelamiento de las fracciones puras produjo el compuesto del título (0.039 g, 86%) como un sólido incoloro. M/z: 626.4 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.17-1.22 (m, 6H), 2.82-2.96 (m, 2H), 3.90-3.98 (m, 1H), 4.25-4.35 (m, 2H), 4.48-4.54 (m, 2H), 4.70- 4.78 (m, 1H), 5.02-5.06 (m, 1H), 6.94-7.37 (m, 12H), 7.85-7.92 (m, 1H), 8.16 (d, 1H).

Ejemplo 21

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-alanil-D-lisina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoacetidin-2-il)fenoxi]acetil}-D-alanina (0.040g, 0.072 mmol) se disolvió en CH_2Cl_2 (5ml). Se agregaron *terc*-butil N^6-(*terc*-butoxicarbonil)-D-lisinato clorhidrato (0.029 g, 0.087 mmol), *N*-metilmorfolina (0.022 g,

0.216 mmol) y TBTU (0.030 g, 0.094 mmol). Después de 1.5 horas se obtuvo la conversión completa del éster. La mezcla de reacción se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Las fracciones puras se recogieron y se concentraron. El residuo se disolvió en CH_2Cl_2 (3 ml) y TFA (1 ml) y se agitó de un día para otro y se formó el ácido correspondiente. La mezcla de reacción se concentró y la traza restante de TFA se retiró azeotrópicamente por co-evaporación con tolueno (3 ml). El ácido crudo se disolvió en MeOH (3 ml) y se agregó $NaBH_4$ (0.011 g, 0.288 mmol). La reducción se completó después de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml). La mezcla se concentró y el residuo se purificó por HPLC preparativa usando una gradiente de 10-50% CH_3CN en 0.1M tampón NH_4OAc como eluyente. El secamiento por congelamiento de las fracciones puras proporcionó el compuesto del título (0.039 g, 79%) como un sólido incoloro. M/z: 685.1. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.21 (d, 3H), 1.22-1.69 (m, 6H), 2.62-2.70 (m, 2H), 2.82-2.93 (m, 2H), 3.78-3.84 (m, 1H), 4.22-4.33 (m, 2H), 4.48 (d, 1H), 4.52 (d, 1H), 4.70-4.78 (m, 1H), 5.01-5.06 (m, 1H), 6.95-7.37 (m, 12H), 7.56-7.63 (m, 1H), 8.27 (d, 1H).

Ejemplo 22

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valil-D-serina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valina (11 mg, 18.9 μmol) se disolvió en DCM (2 ml). Se agregaron *terc*-butil O-(*terc*-butil)-D-serinato clorhidrato (6.3 mg, 24.8 μmol) y *N*-metilmorfolina (10 μl, 91 μmol). Después de 5 minutos, se agregó TBTU (8.2 mg, 25.5 μmol), y la mezcla de reacción, una suspensión blanca, se agitó de un día para otro. Se confirmó la formación del éster. M/z: 780.5 (M-H). El disolvente se retiró bajo presión reducida. El residuo se disolvió en ácido fórmico (1 ml) y se agitó a 50°C durante 5

horas y a temperatura ambiente de un día para otro. El análisis LC-MS mostró la formación del aducto formiato del producto. M/z: 698.2 (M+H) y 696.2 (M-H). El ácido fórmico se retiró bajo presión reducida; se usó tolueno (3x1 ml) para ayudar a este retiro. El residuo aleoso amarillento se disolvió en metanol (1 ml) y se agregó trietilamina (150 μl, 0.12 mmol). La mezcla de reacción se agitó durante 1 hora. El formiato se hidrolizó; M/z: 670.1 (M+1) y 668.0 (M-1). Se agregó borohidruro de sodio (8.4 mg, 0.22 mmol) a la solución de metanol. La mezcla se agitó durante 5 minutos. Se agregó acetato de amonio (7 mg) y el disolvente se retiró bajo presión reducida. El residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20 a 50 % MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de secar por congelamiento, el compuesto del título se obtuvo como un sólido blanco (3.8 mg, 30 %). H-NMR (400 MHz, DMS-d_6): 0.80 (m, 6H), 1.95-2.05 (m, 1H), 2.87-2.93 (m, 2H), 3.46-3.60 (m, 2H), 3.86 (brs, 1H), 4.19-4.32 (m, 2H), 4.59 (br, 2H), 4.69-4.77 (m, 1H), 5.05 (m, 1H), 6.96 (d, 2H), 7.06-7.18 (m, 4H), 7.20-7.26 (m, 2H), 7.30-7.39 (m, 4H), 7.70-7.77 (brs, 1H), 7.96-8.01 (d, 1H). M/z: 670.1 (M-H).

Ejemplo 23

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina (0.022 g, 0.034 mmol) se disolvió en metanol (2 ml). Se agregó $NaBH_4$ (0.0025 g, 0.066 mmol) y cuando la reacción se completó de acuerdo con LC-MS, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.015 g (68 %) del producto

del título. NMR (400 MHz, CD_3COOD) 0.90 (d, 3H), 0.93 (d, 3H), 2.10-2.20 (m, 1H), 2.90-3.06 (m, 2H), 3.99 (s, 2H), 4.03 (d, 0.5H), 4.05 (d, 0.5H), 4.27-4.34 (m, 1H), 4.60 (s, 2H), 4.79-4.84 (m, 1H), 4.89 (d, 0.5H), 4.91 (d, 0.5H), 6.95-7.03 (m, 4H), 7.06 (d, 2H), 7.25-7.30 (m, 2H); 7.30-7.37 (m, 4H).

Ejemplo 24

Ácido (2*R*)-ciclohexil[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil} glicil)amino]acético

Ácido (2*R*)-ciclohexil [(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil)amino] acético (0.0085 g, 0.013 mmol) se disolvió en metanol (2 ml). Se agregó $NaBH_4$ (0.006 g, 0.159 mmol) y cuando la reacción se completó de acuerdo con LC-MS, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando una gradiente gradual de 35%, 40%, luego 50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.007 g (82 %) del producto del título. NMR (500 MHz, CD_3COOD) 1.05-1.33 (m, 5H), 1.60-1.87 (m, 6H), 2.91-3.07 (m, 2H), 3.94-4.06 (m, 3H), 4.32 (d, 1H), 4.60 (s, 2H), 4.79-4.86 (m, 1H), 4.90 (d, 0.5H), 4.92 (d, 0.5H), 6.96-7.03 (m, 4H), 7.03-7.08 (brd, 2H), 7.25-7.31 (m, 2H), 7.31-7.38 (m, 4H)

Ejemplo 25

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-(trimetilsilil)alanina**

Etil 3-(trimetilsilil)alaninato (20mg, 0.106mmol) se disolvió en 1.5 ml Et_3N, 0.2ml MeOH y 0.2ml H_2O y se agitó durante 5 días. El disolvente se evaporó bajo presión reducida a 40°C. Se agregó Et_3N, 1ml, y se evaporó. *N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (20mg, 0.037mmol) se disolvió en 1.5ml DMF seco. Se agregaron N-metilmorfolina (0.010ml, 0.109mmol) y TBTU (15mg, 0.047mmol) y la mezcla se agitó durante 1.5 horas. Se agregó la sal Et_3N del aminoácido hidrolizado de arriba y la mezcla se agitó durante 3 horas. Se agregaron unas cuantas gotas de agua, y la mezcla se agitó durante 15 minutos. Se agregaron MeOH (2ml) y $NaBH_4$ (aprox. 15mg). Luego de 15 minutos se agregaron aprox. 20mg NH_4Ac. La mezcla se dejó de un día para otro y se purificó usando HPLC preparativa en un columna C8. Una gradiente de 20-50% MeCN en 0.1M acetato de amonio se usó como fase móvil. Se recogió una fracción de producto puro y se liofilizó. Masa: 14.5mg. El sólido se puso en el horno de vacío a 40°C durante 5 horas. M/z: 684 (M-1). NMR (400 MHz, DMSO-d_6): 8.23 (t, 1H), 7.88-7.98 (m, 1H), 7.30-7.38 (m, 4H), 7.20-7.25 (m, 2H), 7.05-7.18 (m, 4H), 6.98 (d, 2H), 5.02-5.07 (m, 1H), 4.67-4.76 (m, 1H), 4.51 (s, 2H), 4.24-4.33 (m, 1H), 4.05-4.15 (m, 1H), 3.65-3.80 (m, 2H), 2.82-2.98 (m, 2H), 0.85-1.03 (m, 2H), 0.04 (s, 9H).

Ejemplo 26

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-tirosina**

Una mezcla de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.0227g, 0.042 mmol), (R)-tirosina *terc*-butiléster (0.0144g, 0.061mmol), N-metilmorfolina (0.012 ml, 0.111 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.018 g, 0.056 mmol) y la mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (0.65 ml) y

luego de un par de horas, se completó la hidrólisis. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando una gradiente de 5-100% MeCN en 0.15% de tampón de ácido trifluoroacético como eluyente. Luego de retirar el disolvente bajo presión reducida, el compuesto (M/z 704.1) se disolvió en metanol (2 ml). Se agregó $NaBH_4$ (0.004 g, 0.105 mmol) y cuando la reacción se completó, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo0.021 g (71 %) del producto del título. NMR (400 MHz, CD_3COOD) 2.85-3.10 (m, 4H), 3.90 (ABq, 2H), 4.03 (d, 0.5H), 4.05 (d, 0.5H), 4.51 (dd, 1H), 4.55 (ABq, 2H), 4.79-4.84 (m, 1H), 4.89 (d, 0.5H), 4.90 (d, 0.5H), 6.62-6.67 (m, 2H), 6.95-7.05 (m, 8H), 7.25-7.37 (m, 6H)

Ejemplo 27

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-prolina**

Una mezcla de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.0197g, 0.036 mmol), (R)-prolina *terc*-butiléster (0.0118 g, 0.069 mmol), N-metilmorfolina (0.012 ml, 0.111 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.018 g, 0.056 mmol) y la mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (0.65 ml) y luego de un par de horas se completó la hidrólisis. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando una gradiente de 5-100% MeCN en 0.15% tampón de ácido trifluoroacético como eluyente. Luego de retirar el disolvente bajo presión reducida el compuesto (M/z 638.08) se disolvió en metanol (2 ml). Se agregó $NaBH_4$ (0.004 g, 0.106 mmol) y cuando la

reacción se completó, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.020 g (85 %) del producto del título. NMR (400 MHz, CD_3COOD) 1.80-1.94 (m, 1H), 1.94-2.10 (m, 1.5H), 2.12-2.35 (m, 1.5H), 2.90-3.06 (m, 2H), 3.49-3.67 (m, 2H), 3.85 (d, 0.5H), 4.00-4.07 (m, 1.5H), 4.14-4.24 (m, 1H), 4.35 (dd, 0.5H), 4.41 (brd, 0.5H), 4.57 (s, 1H), 4.59 (s, 1H), 4.78-4.84 (m, 1H), 4.89 (d, 0.5H), 4.91 (d, 0.5H), 6.95-7.08 (m, 6H), 7.25-7.38 (m, 6H).

Ejemplo 28

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-treonina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tiol-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-treonina (0.014 g, 0.022 mmol) se disolvió en metanol (2 ml). Se agregó $NaBH_4$ (0.003 g, 0.079 mmol) y cuando la reacción se completó, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.012 g (85 %) del producto del título. NMR (400 MHz, CD_3COOD) 1.14 (d 3H), 2.91-3.07 (m, 2H), 4.00- 4.08 (m, 3H), 4.21-4.30 (m, 1H), 4.35 (d, 1H), 4.60 (s, 2H), 4.78-4.85 (m, 1H), 4.89 (d, 0.5H), 4.91 (d, 0.5H), 6.96-7.03 (m, 4H), 7.04-7.08 (m, 2H), 7.24-7.38 (m, 6H).

Ejemplo 29

N-{[4-((2R,3R)-1-(4-fluorofenvl)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-lisina

Una mezcla de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.0209g, 0.039 mmol), *terc*-butil N^6-(*terc*-butoxicarbonil)-D-lisinato clorhidrato (0.0205 g, 0.060 mmol), N-metilmorfolina (0.012ml, 0.111 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.018 g, 0.056 mmol) y la mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (0.65 ml) y luego de un par de horas se completó la hidrólisis. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando una gradiente de 5-100% MeCN en 0.15% tampón ácido trifluoroacético como eluyente. Luego de retirar el disolvente bajo presión reducida, el compuesto (M/z 669.13) se disolvió en metanol (2 ml). Se agregó $NaBH_4$ (0.005 g, 0.132 mmol) y cuando la reacción se completó, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, 0.020 g (83%) del producto del título se obtuvo. NMR (400 MHz, CD_3COOD) 1.34-1.47 (m 2H), 1.56-1.74 (m, 3H), 1.84-1.93 (m, 1H), 2.84-3.07 (m, 4H), 3.94 (ABq, 2H), 4.02 (d, 0.5H), 4.05 (d, 0.5H), 4.27 (dd, 1H), 4.61 (s, 2H), 4.79-4.85 (m, 1H), 4.90 (d, 0.5H), 4.91 (d, 0.5H), 6.95-7.08 (m, 6H), 7.24-7.38 (m, 6H).

Ejemplo 30

N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-asparagina

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-asparagina (0.020 g, 0.031 mmol) se

disolvió en metanol (2 ml). Se agregó $NaBH_4$ (0.004 g, 0.106 mmol) y cuando la reacción se completó de acuerdo con LC-MS, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.016 g (80%) del producto del título. NMR (400 MHz, CD_3COOD) 2.62 (dd 1H), 2.73 (dd, 1H), 2.90-3.07 (m, 2H), 3.89-4.08 (m, 3H), 4.55 (dd, 1H), 4.60 (ABq, 2H), 4.78-4.85 (m, 1H), 4.90 (d, 0.5H), 4.92 (d, 0.5H), 6.96-7.09 (m, 6H), 7.24-7.38 (m, 6H).

Ejemplo 31

***N*-[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-metionina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-metionina (0.015 g, 0.022 mmol) se disolvió en metanol (2 ml). Se agregó $NaBH_4$ (0.004 g, 0.106 mmol) y cuando la reacción se completó, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo0.015g (99%) del producto del título. NMR (400 MHz, CD_3COOD) 1.86-2.00 (m, 1H), 2.04 (s, 3H); 2.07- 2.18 (m, 1H), 2.45-2.51 (m, 2H), 2.90-3.08 (m, 2H), 3.97 (s, 2H), 4.04 (d, 0.5H), 4.06 (d, 0.5H), 4.36-4.43 (m, 1H), 4.60 (s, 2H), 4.77-4.85 (m, 1H), 4.90 (d, 0.5H), 4.92 (d, 0.5H), 6.95-7.08 (m, 6H), 7.25-7.38 (m, 6H).

Ejemplo 32

142
189

N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-hidroxi-2-(4-metoxifenil)etil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina

N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina (0.015g, 0.023 mmol) se disolvió en metanol (3 ml). Se agregó $NaBH_4$ (0.006 g, 0.158 mmol) y cuando la reacción se completó, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando25% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.014 g (93%) del producto del título. NMR (500 MHz, CD_3COOD) 0.93 (d, 3H), 0.95 (d, 3H), 2.12-2.22 (m, 1H), 2.91-3.07 (m, 2H), 3.75 (s, 1.5H), 3.76 (s, 1.5H), 3.94-4.06 (m, 3H), 4.33 (d, 1H), 4.60 (s, 2H), 4.72-4.78 (m, 1H), 4.81-4.88 (m, 1H), 6.79-6. 83 (m, 2H), 6.97-7.08 (m, 4H), 7.20-7.36 (m, 6H).

Ejemplo 33

N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-leucina

Una mezcla de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[N-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.015g, 0.028 mmol), *terc*-butil D-leucinato clorhidrato (0.010 g, 0.045 mmol), N-metilmorfolina (0.0092 ml, 0.083 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.012 g, 0.037 mmol) y la mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (1.0ml) y, luego de 2 horas, el disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8, usando una gradiente de 5-100% MeCN en 0.15% de tampón de ácido trifluoroacético como eluyente. Luego de retirar el disolvente bajo presión reducida, el compuesto (M/z 654.25) se disolvió en metanol (2 ml). Se agregó $NaBH_4$

(0.005 g, 0.132 mmol) y la mezcla se agitó durante 5 minutos. Se agregaron unas cuantas gotas de ácido acético, y el disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.014 g (76 %) del producto del título. NMR (400 MHz, CD_3COOD) 0.90-0.94 (m, 6H), 1.52-1.74 (m, 3H), 2.90-3.07 (m, 2H), 3.97 (s 2H), 4.02 (d, 0.5H), 4.04 (d, 0.5H), 4.40 (d, 0.5H), 4.42 (d, 0.5H), 4.59 (s, 2H), 4.78-4.84 (m, 1H), 4.89 (d, 0.5H), 4.91 (d, 0.5H), 6.95-7.08 (m, 6H), 7.24-7.37 (m, 6H).

Ejemplo 34

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-hidroxi-2-(4-metoxifenil)etil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-lisina**

Una mezcla de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.0177g, 0.032 mmol *terc*-butil N^6-(*terc*- butoxicarbonil)-D-lisinato clorhidrato (0.0141 g, 0.042 mmol), N-metilmorfolina (0.0106 ml, 0.096 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.013 g, 0.042 mmol) y la mezcla se agitó durante 2 horas. Se agregó más *terc*-butil N^6-(*terc*-butoxicarbonil)-D-lisinato clorhidrato (0.004 g, 0.012 mmol) y luego de 0.5 hora, se agregó TBTU (0.008g, 0.025 mmol) y la mezcla se agitó durante 10 minutos más. Se agregó ácido trifluoroacético (0.65 ml) y, después de 3 horas, el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando una gradiente de 5-100% MeCN en 0.15% 1M tampón de acetato de amonio como eluyente. Luego de retirar los disolventes bajo presión reducida, el intermedio (M/z 681.4) se disolvió en metanol (3 ml). Se agregó $NaBH_4$ (0.008 g, 0.211mmol) y, cuando la reacción se completó, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida, y el residuo se purificó por HPLC preparativa en una columna

Kromasil C8 usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.020 g (91 %) del producto del título. NMR (500 MHz, CD_3COOD) 1.41-1.52 (m, 2H), 1.58-1.78 (m, 3H), 1.90-2.02 (m 1H), 2.86-3.08 (m, 4H), 3.76 (s, 1.5H), 3.77 (s, 1.5H), 3.90-4.06 (m, 3H), 4.48 (dd, 1H), 4.60-4.62 (m, 2H), 4.73-4.78 (m, 1H), 4.83-4.89 (m, 1H), 6.80-6. 84 (m, 2H), 6.98-7.08 (m, 4H), 7.21-7.31 (m, 4H), 7.31-7.36 (m, 2H), 8.20 (d, NH), 8.54 (t, NH).

Ejemplo 35

***N*²-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tiol-4-oxoazetidin-2-il)fenoxi]acetil}-L-glutaminil-D-fenilalanina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-glutamina (15mg, 0.0244 mmol), *terc*-butil D-fenilalaninato clorhidrato (8 mg, 0.0310 mmol) y N-metilmorfolina (10 mg, 0.099 mmol) se disolvieron en cloruro de metileno (0.5 ml). Se agregó TBTU (10 mg, 0.0313 mmol) y la mezcla se agitó durante 1 hora a temperatura de la sala. El disolvente se evaporó y el residuo se disolvió en ácido fórmico (0.5 ml). La mezcla se calentó a 45-50°C y se agitó a esta temperatura durante 6 horas. La mezcla de reacción se evaporó bajo presión reducida. Se agregó metanol (5 ml) y se evaporó. El residuo se disolvió en metanol (1 ml). Se agregaron dos gotas de TEA y la mezcla se agitó de un día para otro a temperatura de la sala. El disolvente se evaporó y el residuo se purificó por HPLC preparativa usando tampón acetonitrilo/acetato de amonio (40:60) como eluyente. Luego de secar por congelamiento se obtuvieron 12 mg (64%) del compuesto del título. ^{1}H-NMR, 300 MHz, DMSO): 1.55-1.97 (m, 4H), 2.77-3.10 (m, 4H), 4.20-4.38 (m, 3H), 4.49 (s, 2H), 4.66-4.78 (m, 1H), 4.99-5.07 (m, 1H), 6.70 (s, 1H), 6.88-7.40 (m,19H), 8.00-8.20 (m, 2H).

Ejemplo 36

N^2-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-glutaminil-D-tirosina

N^2-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-glutamina (22 mg, 0.0359 mmol), *terc*-butil D-tirosinato clorhidrato (10 mg, 0.0421 mmol) y N-metilmorfolina (14 mg, 0.138 mmol) se disolvieron en cloruro de metileno (0.5 ml). Se agregó TBTU (14 mg, 0.0436 mmol) y la mezcla se agitó de un día para otro a temperatura de la sala. El disolvente se evaporó y el residuo se disolvió en ácido fórmico (1 ml). La mezcla se agitó a 45-50°C durante 4 horas y se evaporó luego bajo presión reducida. Se agregó metanol (10 ml) y se evaporó. El residuo se disolvió en metanol (2 ml). Se agregaron tres gotas de TEA y la mezcla se agitó de un día para otro a temperatura de la sala. El disolvente se evaporó y el residuo se purificó por HPLC preparativa usando tampón acetonitrilo/acetato de amonio (40:60) como eluyente. Luego de secar por congelamiento se obtuvieron 15 mg (54%) del compuesto del título. ^{1}H-NMR, 300 MHz, DMSO): 1.60-2.00 (m, 4H), 2.69-3.0 (m, 4H), 4.09-4.18 (m, 1H), 4.22-4.35 (m, 3H), 4.49 (s, 2H), 4.65-4.78 (m, 1H), 4.97-5.08 (m, 1H), 6.56 (d, 2H), 6.70 (s, 1H), 6.86-7.40 (m, 18H), 7.77-7.91 (m, 1H), 8.12 (d, 1H), 9.10 (bs, 1H).

Ejemplo 37

***N*-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-ciclohexil-D-alanina**

N-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (20mg, 0.0349 mmol) y N-metilmorfolina (20 mg, 0.198 mmol) se disolvieron en cloruro de metileno (0.5 ml). Se agregó TBTU (17 mg, 0.0530 mmol) y la mezcla se agitó durante 15 minutos a temperatura de la sala. Se agregó 3-ciclohexil-D-

alanina (9 mg, 0.0526 mmol) y la agitación se continuó durante 1 hora a temperatura de la sala. El disolvente se evaporó y el residuo se disolvió en metanol (0.5 ml). Se agregó $NaBH_4$ (10 mg, 0.264 mmol) y la mezcla se agitó durante 15 minutos a temperatura de la sala. Se agregaron tres gotas de ácido acético a la mezcla de reacción. El producto se aisló por HPLC preparativa usando tampón acetonitrilo/acetato de amonio (45:55) como eluyente. Luego de secar por congelamiento, se obtuvieron 3 mg (12%) del compuesto del título. El producto se analizó por técnica LC/Micromass Q TOF micro MS. M/z: 728.1973 (masa calculada 728.1964).

Ejemplo 38

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-ciclohexil-D-alanina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (30 mg, 0.0555 mmol) y N-metilmorfolina (30 mg, 0.296 mmol) se disolvieron en DMF (0.5 ml). Se agregó TBTU (23 mg, 0.0717 mmol) y la mezcla se agitó durante 15 minutos a temperatura de la sala. Se agregó 3-ciclohexil-D-alanina (15 mg, 0.0876 mmol) y la agitación se continuó de un día para otro a temperatura de la sala. El disolvente se evaporó bajo presión reducida y el residuo se disolvió en metanol (1 ml). Se agregó NaBH4 (10 mg, 0.264 mmol) y la mezcla se agitó durante 10 minutos a temperatura de la sala. Tres gotas de ácido acético se agregaron a la mezcla de reacción. El producto se aisló por HPLC preparativa usando tampón acetonitrilo/acetato de amonio (40: 60) como eluyente. Luego de secar por congelamiento se obtuvieron 19 mg (49%) del compuesto del título. ^{1}H-NMR, 300 MHz, DMSO): 0.68-0.93 (m, 2H), 1.0-1.75 (m, 11H), 2.78-3.00 (m, 2H), 3.73 (s, 2H), 4.00-4.14 (m, 1H), 4.23-4.35 (m, 1H), 4.51 (s, 2H), 4.65-4.78 (m, 1H), 4.99-5.09 (m, 1H), 6.90-7.44 (m, 12H), 7.72-7.86 (m, 1H), 8.26 (t, 1H).

Ejemplo 39

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-fenilalanina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-fenilalanina (7mg, 0.010mmol) se disolvió en 1.5ml MeOH y se agregó $NaBH_4$ (2mg, 0.053mmol). La mezcla se agitó durante 30 minutos y se extinguió con un exceso de NH_4Ac. LC/MS mostró aprox. 15% del material de partida. La mezcla se diluyó con H_2O y se purificó usando cromatografía preparativa en una columna C8 (25x300mm). Una gradiente de 20% a 40% MeCN en 0.1M acetato de amonio se usó como fase móvil. Se recogió la fracción de producto y se concentró parcialmente. La mezcla se liofilizó para proporcionar 2mg (29%). M/z: 688 (M-1). NMR (400MHz, MeOD): 6.95-7.36 (m, 17H), 4.90 (dd, 1H), 4.53-4.59 (m, 4H), 4.03 (dd, 1H), 3.90 (q, 2H), 3.17 (dd, 1H), 2.90-3.05 (m, 3H).

Ejemplo 40

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-4-metil-leucina**

terc-Butil *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-4-metil-leucinato (aprox. 26mg, 0.036mmol) se disolvió en 1.5 ml ácido fórmico y se calentó a 40°C durante 1.5 horas. El ácido fórmico se evaporó bajo presión reducida. El ácido intermedio se confirmó por análisis LC/MS. M/z: 668. La mezcla cruda se disolvió en 2 ml MeOH. $NaBH_4$ (15mg, 0.40mmol) se agregó y la mezcla se agitó durante 10 min. Se agregó NH_4Ac (30mg). La mezcla cruda se diluyó con 1 ml de agua y se purificó usando HPLC preparativa en una columna C8 (50x300mm). Una gradiente de 20% a 40% MeCN en 0.1M

tampón de acetato de amonio se usó como fase móvil. La liofilización produjo 36mg de sólido blanco. NMR mostró la presencia de agua y HOAc. El producto se secó en el horno de vacío durante 1.5 horas a 40°C. Masa 13mg (52%). M/z: 668 (M-1). NMR (400 MHz, DMSO): 8.22 (t, 1H), 7.53-7.65 (m, 1H), 7.30-7.38 (m, 4H), 7.20-7.25 (m, 2H), 7.05-7.17 (m, 4H), 6.98 (d, 2H), 5.02-5.06 (m, 1H), 4.68-4.76 (m, 1H), 4.51 (s, 2H), 4.24-4.32 (m, 1H), 4.01-4.09 (m, 1H), 3.60-3.77 (m, 2H), 2.82-2.98 (m, 2H), 1.64 (dd, 1H), 1.33 (dd, 1H), 0.83 (s, 9H).

Ejemplo 41

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-seril-D-fenilalanina**

Una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-serina (mezcla diastereomérica) (0.008 g, 0.014 mmol), D-fenilalanina *terc*-butil éster clorhidrato (0.005 g, 0.018 mmol) y *N*-Metilmorfolina (0.006 ml, 0.055 mmol) en DCM (3ml) se agitó a temperatura de la sala durante 5 minutos. Se agregó TBTU (0.008 g, 0.025 mmol). Luego de 3 días la conversión en el éster (M/z: 776.1) se completó y la mezcla se concentró bajo presión reducida. El residuo se disolvió en ácido fórmico (3 ml) y la solución se agitó durante 25 horas. La mezcla se concentró bajo presión reducida y el residuo se disolvió en MeOH (4ml) y TEA (1 ml). La solución se agitó a 40°C durante 6 horas. El disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, 0.005 g (53 % de rendimiento) del producto del título se obtuvo como un sólido blanco. M/z: 720.1. ^{1}H NMR (DMSO, 400 MHz): δ 2.78-2.96 (m, 3H), 3.03-3. 11 (m, 1H), 3.44-3.60 (m, 2H), 4.20-4.36 (m, 3H), 4.51 (s, 2H), 4.67-4.76 (m, 1H), 5.01-5.06 (m, 1H), 5.70 (bs,

1H), 6.90-6.98 (m, 2H), 7.05-7.25 (m, 11H), 7.29-7.37 (m, 4H), 7.84-8.00 (m, 2H).

Ejemplo 42

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-seril-D-serina**

Una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-serina (0.008 g, 0.014 mmol), O-*terc*-butil-D-serina *terc*-butil éster clorhidrato (0.005 g, 0.019 mmol) y N-metilmorfolina (0.006 ml, 0.055 mmol) en DCM (3 ml) se agitó durante 5 minutos. Se agregó TBTU (0.008 g, 0.025 mmol). Luego de 3 días conversión en el éster (M/z: 772.5) se completó y la mezcla se concentró bajo presión reducida. El residuo se disolvió en ácido fórmico (3 ml) y la solución se agitó a temperatura de la sala durante 26 horas. La mezcla se concentró bajo presión reducida y el residuo se disolvió en MeOH (4ml) y TEA (1 ml). La solución se agitó a 40°C durante 6 horas. El disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, 0.005 g (52 % de rendimiento) del compuesto del título se obtuvo como un sólido blanco. M/z: 660.1. ^{1}H NMR (DMSO, 400 MHz): δ 2.83- 2.95 (m, 2H), 3.42-3.66 (m, 4), 3.91-4.01 (m, 1H), 4.25-4.31 (m, 1H), 4.32-4.39 (m, 1H), 4.54 (ABq, 2H), 4.68-4.76 (m, 1H), 5.02-5.06 (m, 1H), 5.68 (bs, 1H), 6.94-7.00 (m, 2H), 7.05-7.18 (m, 4H), 7.19-7.26 (m, 2H), 7.29-7.39 (m, 4H), 7.74-7.81 (m, 1H), 7.99 (d, 1H).

Ejemplo 43

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-2-butilnorleucina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-2-butilnorleucina (0.009 g, 0.012 mmol) se disolvió en MeOH (3 ml). Se agregó $NaBH_4$ (0.007 g, 0.185 mmol) y la mezcla se agitó durante 10 minutos. Se agregó tampón de acetato de amonio (0.1M, 3 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.008 g (94 % de rendimiento) del compuesto del título como un sólido blanco. M/z: 712.1. ^{1}H NMR (DMSO, 400 MHz): δ 0.73-0.83 (m, 6H), 0.89-1.22 (m, 8H), 1.59-1.71 (m, 2H), 1.94-2.06 (m, 2H), 2.83-2.96 (m, 2H), 3.73 (d, 2H), 4.23-4.28 (m, 1H), 4.51 (s, 2H), 4.68-4.76 (m, 1H), 5.02-5.07 (m, 1H), 5.68 (bs, 1H), 6.94-7.00 (m, 2H), 7.05-7.18 (m, 4H), 7.19-7.26 (m, 2H), 7.29-7.39 (m, 4H), 7.53 (s, 1H), 8.30-8.36 (m, 1H).

Ejemplo 44

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-S-metil-L-cisteína**

Una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.015 g, 0.028 mmol), *terc*-butil S-metil-L-cisteinato (0.014 g, 0.073 mmol)) y N-metilmorfolina (0.012 ml, 0.109 mmol) en DCM (5 ml) se agitó durante 5 minutos. Se agregó TBTU (0.013 g, 0.042 mmol). Luego de 20 horas, la conversión en el éster (M/z: 714.1) se completó y la mezcla se concentró bajo presión reducida. El residuo se disolvió en ácido fórmico (3 ml) y la solución se agitó a 40°C durante 22 horas. La mezcla se diluyó con tolueno (2 ml) y el disolvente se retiró nuevamente bajo presión reducida. El residuo se disolvió en MeOH (4 ml) y se agregó $NaBH_4$ en pequeñas porciones a la solución (un total de 0.035 g, 0.925 mmol) hasta que la reducción se completó. Se agregó tampón de acetato de amonio (0.1M, 3 ml) y la mayor

parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.013 g (72 % de rendimiento) del compuesto del título como un sólido blanco.

M/z: 660.3. ^{1}H NMR (DMSO, 400 MHz): δ 2.66-2.74 (m, 1H), 2.82-3.02 (m, 3H), 3.67-3.82 (m, 2H), 4.02-4.12 (m, 1H), 4.24-4.31 (m, 1H), 4.52 (s, 2H), 4.68-4.77 (m, 1H), 5.01-5.07 (m, 1H), 6.95-7.02 (m, 2H), 7.05-7.18 (m, 4H), 7.19-7.26 (m, 2H), 7.29-7.40 (m, 4H), 7.73-7.82 (m, 1H), 8.30-8.37 (m, 1H).

Ejemplo 45

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-isoleucina**

Una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.015 g, 0.028 mmol), L-isoleucina t-butil éster clorhidrato (0.008 g, 0.036 mmol) y N-metilmorfolina (0.012 ml, 0.109 mmol) en DCM (5 ml) se agitó durante 5 minutos. Se agregó TBTU (0.012 g, 0.036 mmol). Después de 22 horas, la conversión en el éster (M/z: 710.2) se completó y la mezcla se concentró bajo presión reducida. El residuo se disolvió en ácido fórmico (3 ml) y la solución se agitó a 40°C durante 20 horas. La mezcla se diluyó con tolueno (2 ml) y el disolvente se retiró bajo presión reducida. El residuo se disolvió en MeOH (4 ml) y se agregó $NaBH_4$ en pequeñas porciones a la solución (un total de 0.060 g, 1.59 mmol) hasta que la reducción se completó. Se agregó tampón de acetato de amonio (0.1M, 3 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.010 g (57 % de rendimiento) del compuesto del

título como un sólido blanco. M/z: 656.2. ^{1}H NMR (DMSO, 400 MHz): δ 0.76-0.84 (m, 6H), 1.05-1.17 (m, 1H), 1.32-1.44 (m, 1H), 1.67- 1.78 (m, 1H), 2.82-2.95 (m, 2H), 3.78 (d, 2H), 4.03-4.11 (m, 1H), 4.23-4.29 (m, 1H), 4.51 (s, 2H), 4.68-4.77 (m, 1H), 5.01-5.07 (m, 1H), 6.94-7.01 (m, 2H), 7.05-7.26 (m, 6H), 7.29-7.39 (m, 4H), 7.79-7.89 (m, 1H), 8.22-8.28 (m, 1H).

Ejemplo 46

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-alanil-D-valina**

Una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-alanina (0.015 g, 0.027 mmol), D-valina *terc* butil éter clorhidrato (0.008 g, 0.038 mmol) y N-metilmorfolina (0.030 ml, 0.272 mmol) en DCM (4ml) se agitó durante 5 minutos. Se agregó TBTU (0.013 g, 0.041 mmol). Después de 3 horas, la conversión en el éster (M/z: 710.2) se completó y se agregó TFA (3 ml). Transcurridas 4 horas, la mezcla se diluyó con tolueno (2 ml) y el disolvente se retiró bajo presión reducida. El residuo se disolvió en MeOH (4 ml) y se agregó $NaBH_4$ en pequeñas porciones a la solución (un total de 0.065 g, 1.72 mmol) hasta que la reducción se completó. Se agregó tampón de acetato de amonio (0.1M, 3 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20- 50% MeCN en a 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.014 g (77 % de rendimiento) del compuesto del título como un sólido blanco. M/z: 656.1. ^{1}H NMR (DMSO, 400 MHz): δ 0.75-0.83 (m, 6H), 1.22 (d, 3H), 1.95-2.07 (m, 1H), 3.83-3.96 (m, 2H), 3-98-4.06 (m, 1H), 4-24-4.31 (m, 1H), 4.40-4.54 (m, 3H), 4.67-4.76 (m, 1H), 5.01-5.07 (m, 1H), 6.91- 7.98 (m, 2H), 7.05-7.17 (m, 4H), 7.19-7.25 (m, 2H), 7.29-7.39 (m, 4H), 7.84-7.95 (m, 1H), 8.07 (d, 1H).

Ejemplo 47

Ácido 1-[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil)amino] ciclopentanocarboxílico

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.015 g, 0.028 mmol), NMM (0.012 ml, 0.109 mmol) y TBTU (0.011 g, 0.034 mmol) se disolvieron en DMF (2 ml) a 30°C. Luego de 30 minutos, se agregó ácido 1-amino-1-ciclopentanocarboxílico (0.004 g, 0.030 mmol, 97 %) y la mezcla se agitó a 30°C durante 1 hora. La reacción se extinguió con agua (0.2 ml) y la mezcla se diluyó con MeOH (2 ml). Se agregó NaBH4 (0.015 g, 0.397 mmol) y la mezcla se agitó durante 10 minutos. Se agregó tampón de acetato de amonio (0.1M, 3 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, el compuesto del título (0.009 g, 49 % de rendimiento) se obtuvo como un sólido blanco. M/z: 654.0. ^{1}H NMR (DMSO, 400 MHz): δ 1.56-1.66 (m, 4H), 1.78-1.87 (m, 2H), 1.97-2.07 (m, 2H), 2.84-2.94 (m, 2H), 3.74 (d, 2H), 4.24-4.29 (m, 1H), 4.51 (s, 2H), 4.68-4.76 (m, 1H), 5.02-5.07 (m, 1H), 6.92-7.00 (m, 2H), 7.05-7.26 (m, 6H), 7.29-7.39 (m, 4H), 8.09-8.15 (m, 2H).

Ejemplo 48

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*N*-bencilglicina**

TBTU (0.011 g, 0.034 mmol) se agregó a una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-

il)fenoxi]acetil}glicina (0.015 g, 0.028 mmol) y NMM (0.020 ml, 0.182 mmol) en DMF (2 ml) a 30°C. Luego de 30 minutos, se agregó *N*-bencilglicina (0.005 g, 0.030 mmol, 98 %) y la mezcla se agitó a 30°C durante 1 hora. La reacción se extinguió con agua (0.2 ml) y la mezcla se diluyó con MeOH (2 ml). Se agregó $NaBH_4$ (0.015 g, 0.397 mmol) y la mezcla se agitó durante 10 minutos. Se agregó tampón de acetato de amonio (0.1M, 3 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, el compuesto del título (0.010 g, 53 % de rendimiento) se obtuvo como un sólido blanco. M/z: 690.0. ^{1}H NMR (DMSO, 400 MHz): δ 2.83-2.94 (m, 2H), 3.91 (s, 1H), 3.98-4.09 (m, 3H), 4.25-4.29 (m, 1H), 4.50 (s, 2H), 4.54 (s, 1H), 4.62 (s, 1H), 4.68-4.76 (m, 1H), 5.02-5.07 (m, 1H), 6.92-7.02 (m, 2H), 7.05-7.40 (m, 15H), 8.14-8.21 (m, 1H).

Ejemplo 49

Ácido [3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-xoazetidin-2-il)fenoxi]acetil}glicil)amino](difenil)acético

TBTU (0.016 g, 0.050 mmol) se agregó a una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.020 g, 0.037 mmol) y NMM (0.012ml, 0.109 mmol) en DMF (2 ml) a 30°C. Después de 30 minutos, se agregó 2,2-difenilglicina (0.009 g, 0.037 mmol, 98 %) y la mezcla se agitó a 30°C durante 2.5 horas. La reacción se extinguió con agua (0.2 ml) y la mezcla se diluyó con MeOH (2 ml). Se agregó $NaBH_4$ (0.020 g, 0.529 mmol) y la mezcla se agitó durante 10 minutos. Se agregó tampón de acetato de amonio (0. 1M, 3 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio

como eluyente. Luego de secar por congelamiento, el compuesto del título (0.012 g, 44 % de rendimiento) se obtuvo como un sólido blanco. M/z: 752.0. ^{1}H NMR (DMSO, 400 MHz): δ 2.83-2.95 (m, 2H), 3.75 (d, 2H), 4.24-4.28 (m, 1H), 4.54 (s, 1H), 4.68-4.75 (m, 1H), 5.02-5.06 (m, 1H), 6.95-7.03 (m, 2H), 7.04-7.38 (m, 20H), 8.43-8.51 (m, 1H), 8.90 (s, 1H).

Ejemplo 50

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicilglicina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicilglicina (0.011 g, 0.018 mmol) se disolvió en MeOH (3 ml). Se agregó $NaBH_4$ (0.013 g, 0.344 mmol) y la mezcla se agitó durante 10 minutos. Se agregó tampón de acetato de amonio (0.1M, 3 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, el compuesto del título (0.011 g, 97 % de rendimiento) se obtuvo como un sólido blanco. M/z: 600.0. ^{1}H NMR (DMSO, 400 MHz): 2.97-2.84 (m, 2H), 3.44-3.50 (m, 2H), 3.74 (d, 2H), 4.26-4.32 (m, 1H), 4.46-4.54 (m, 2H), 4.67-4.76 (m, 1H), 5.02-5.07 (m, 1H), 6.95-7.01 (m, 2H), 7.05-7.26 (m, 6H), 7.30- 7.40 (m, 4H), 7.60-7.80 (m, 1H), 8.32-8.38 (m, 1H).

Ejemplo 51

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valil-L-serina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valina (6.9 mg, 11.8 μmol) se disolvió en

DCM (3 ml). Se agregaron *terc*-butil O-(*terc*-butil)-L-serinato clorhidrato (3.7 mg, 14.2 μmol) y *N*-metilmorfolina (5.5 μl, 50 μmol). Después de 5 minutos, se agregó TBTU (4.6 mg, 14.3 mol) y la mezcla de reacción se agitó de un día para otro. Se confirmó la formación del éster. M/z: 780.57 (M-1). La mezcla se extrajo entre DCM (5ml) y $KHSO_4$ acuoso (5 ml pH de 2). La fase orgánica se lavó con $NaHCO_3$ acuoso (5 ml, pH de 9). La fase acuosa se extrajo con DCM (2x5 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. Se agregó ácido fórmico (1.5ml) y la mezcla de reacción se agitó de un día para otro. Se obtuvo el formiato del ácido intermedio. El disolvente se retiró bajo presión reducida, se agregó tolueno (3x1 ml) y se evaporó. El residuo se disolvió en MeOH (1.5 ml) y se agregó trietilamina (90 μl, 0.65 mmol) y la mezcla de reacción se agitó durante 1 hora. Se agregó borohidruro de sodio (4.0 mg, 0.11 mmol) y la mezcla de reacción se agitó durante 1 hora. Se agregó acetato de amonio (15 mg). El disolvente se retiró bajo presión reducida y el residuo se purificó en HPLC preparativa usando una columna C8. Una gradiente de 20% a 50 % MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, el compuesto del título se obtuvo como un sólido blanco (5.3 mg, 67 %). HRMS calculada para $C_{33}H_{35}F_2N_3O_8S$ 671.2113, hallada 672.2192 $[M+H]^+$.

Ejemplo 52

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valilglicina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valina (11.8 mg, 0.02 mmol), *terc*-butil glicinato clorhidrato (4.6 mg, 0.03 mmol) y *N*-metilmorfolina (10 μl, 0.09 mmol) se disolvieron en DCM (1.5 ml). Después de 5 minutos, TBTU se agregó y la mezcla de reacción se agitó durante 3.5 horas. Se confirmó la formación del éster. M/z: 694.0 (M-H). La mezcla se extrajo entre DCM

(3 ml) y $KHSO_4$ acuoso (5 mol, pH de 3). La fase acuosa se extrajo con DCM (2x5 ml). Las fases orgánicas combinadas se lavaron con agua (2x5 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron. Se agregó ácido fórmico (3 ml) y la solución se calentó a 40°C de un día para otro. El disolvente se retiró bajo presión reducida, se agregó tolueno y se evaporó. El residuo se disolvió en metanol (3ml) y se agregó borohidruro de sodio (8.5 mg, 0.23 mmol). La mezcla de reacción se agitó durante 15 minutos. El disolvente se retiró bajo presión reducida. El residuo se purificó en HPLC preparativa en una columna C8. Una gradiente de 20% a 50 % MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, el compuesto del título se obtuvo como un sólido blanco (6.2 mg, 48 %). HRMS calculada para $C_{32}H_{33}F_2N_3O_7S$ 641.2007, hallada 642.2086 $[M+H]^+$.

Ejemplo 53

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valil-L-valina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valina (11.5, 0.02 mmol), *terc*-butil L-valinato clorhidrato (5.3 mg, 0.025 mmol) y *N*-metilmorfolina (10 µl, 0.091 mmol) se disolvieron en DCM (1.5 ml). Después de 5 minutos, TBTU (7.8 mg, 0.024 mmol) se agregó y la mezcla de reacción se agitó de un día para otro. Se agregaron más *terc*-butil L-valinato clorhidrato (1.5 mg, 7.2 µmol), *N*-metilmorfolina (6.5 µl, 58 µmol) y TBTU (2.0 mg, 6.2 µmol, 0.31 eq) y la mezcla se agitó durante 2.5 horas. Se confirmó la formación del éster. M/z: 736.1 (M-H). La mezcla de reacción se extrajo entre $KHSO_4$ acuoso (5 ml, pH de 3) y DCM (5 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se disolvió en ácido fórmico (2ml) y se calentó a 40°C de un día para otro. El disolvente se retiró bajo presión reducida. Se agregó tolueno y se retiró bajo presión reducida. El residuo se

disolvió en MeOH (2 ml) y se agregó borohidruro de sodio (8.1 mg, 0.21 mmol). La mezcla se agitó durante 30 minutos. Se agregó acetato de amonio (16 mg) y el disolvente se retiró bajo presión reducida. El residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 50 % MeCN en 0.1 M tampón NH_4OAc se usó como eluyente. Luego de la liofilización, el compuesto del título se obtuvo como un sólido blanco (7.3 mg, 54 %) H-NMR (400MHz, DMSO-d_6): 0.70 (d, 3H), 0.79 (d, 3H), 0.83 (d, 6H), 2.00 (m, 2H), 2.86-2.92 (m, 2H), 4.07 (brs, 1H), 4.25-4.29 (m, 1H), 4.40 (m, 1H), 4.59 (brs, 2H), 4.72 (m, 1H) 5.03 (d, 0.5H), 5.05 (d, 0.5H), 5.68 (brs, 1H), 6.95 (d, 2H), 7.06-7.16 (m, 4H), 7.19-7.24 (m, 2H), 7.29-7.37 (m, 4H), 7.80 (d, 1H), 8.05-8.15 (brs, 1H). M/z: 682.1 (M-H).

Ejemplo 54

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valil-D-valina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-Fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valina (11.9 mg, 0.02 mmol), *terc*-butil D-valinato clorhidrato (5.6 mg, 0.027 mmol) y *N*-metilmorfolina (10 μl, 0.092 mmol) se disolvieron en DCM (1.5 ml). Transcurridos 5 minutos, se agregó TBTU (8.2 mg, 0.0255 mmol) y la mezcla de reacción se agitó de un día para otro. Se agregaron más *terc*-butil D-valinato clorhidrato (1.7 mg, 8.1 μmol), *N*- metilmorfolina (6.5 μl, 58 μmol), TBTU (2 mg, 6.2 μmol), y la mezcla se agitó durante 3 horas. Se confirmó la formación del éster. M/z: 736.2 (M-H). El disolvente se retiró bajo presión reducida y el residuo se purificó en gel de sílice (1 g) usando DCM: MeOH (8:2) como eluyente. Las fracciones se recogieron y se concentraron. El residuo se disolvió en ácido fórmico (1 ml) y la solución resultante se agitó a 25-30°C de un día para otro. El disolvente se evaporó y se agregó tolueno y se retiró bajo presión reducida. El residuo se disolvió en metanol (1 ml) y se agregó

borohidruro de sodio (8.8 mg, 0.23 mmol). La mezcla se agitó durante 30 minutos. Se agregó acetato de amonio (18 mg) y el disolvente se retiró bajo presión reducida. El residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 50 % MeCN en 0.1 M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, el compuesto del título se obtuvo como un sólido blanco (2.5 mg, 18%). H-NMR (400 MHz, DMSO-d_6): 0.75 (d, 3H), 0-79-0.87 (m, 9H), 1.92-2.06 (m, 2H), 2.86-2.92 (m, 2H), 4.01 (brs, 1H), 4.25 (d, 0.5H), 4.28 (d, 0.5H), 4.32 (t, 1H), 4.57 (d, 2H), 4.67-4.76 (m, 1H), 5.03 (d, 0.5H), 5.05 (d, 0.5H), 5.69 (brs, 1H), 6.93 (d, 2H), 7.04-7.17 (m, 4H), 7.18-7.25 (m, 2H), 7.29-7.38 (m, 4H), 7.85 (d, 1H), 7.96 (brs, 1H). M/z: 682.1 (M-H).

Ejemplo 55

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valil-L-metionina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valina (13.3 mg, 0.023 mmol), *terc*-butil L-metioninato clorhidrato (7.4 mg, 0.031 mmol) y *N*-metilmorfolina (10 μl, 0.091 mmol) se disolvieron en 1 ml. Después de 5 minutos, se agregó TBTU (8.9 mg, 0.028 mmol) y la suspensión resultante se agitó de un día para otro. Se agregaron más *terc*-butil L-metioninato clorhidrato (2.1 mg, 0087 mmol), *N*-metilmorfolina (5 μl, 45 μmol) y TBTU (2.1 mg, 6.54 μmol) y la mezcla se agitó durante 2 horas. Se confirmó la formación del éster. M/z 768.1 (M-H) y 770.0 (M+H). La suspensión amarilla se purificó en gel de sílice (1g) y se eluyó con EtOAc: DCM (15:85). Las fracciones puras se concentraron y se agregó ácido fórmico (1.5ml). La solución se agitó a 50°C de un día para otro. El disolvente se retiró bajo presión reducida. Se agregó tolueno y se retiró bajo presión reducida. El residuo se disolvió en metanol (1ml) y se agregó borohidruro de sodio (9.9 mg, 0.26 mmol). La mezcla de reacción resultante se agitó durante 10 minutos. Se agregó

acetato de amonio (18.9 mg) y el disolvente se retiró bajo presión reducida. El residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 40 % MeCN en 0.1 M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (4.6 mg, 28%). ^{1}H-NMR (400 MHz, DMSO-d_6): 0.75 (d, 3H), 0.79 (d, 3H), 1.79-1.97 (m, 3H), 1.99 (s, 3H), 2.36-2.44 (m, 2H), 2.86-2.92 (m, 2H), 2.24-4.35 (m, 3H), 4.58 (d, 2H), 4.67-4.76 (m, 1H), 5.03 (d, 0.5H), 5.5 (d, 0.5H), 5.63 (t, 1H), 6.95 (d, 2H), 7.05-7.16 (m, 4H), 7.18-7.24 (m, 2H), 7.30-7.38 (m, 2H), 7.82 (d, 1H), 7.37 (d, 1H). M/z: 714.0 (M-1) y 716.1 (M+H).

Ejemplo 56

***N*-[(4-{(2*R*,3*R*)-1-(4-fluorofenil)-3-[(2-hidroxi-2-feniletil)tio]-4-oxoazetidin-2-il}fenoxi)acetil]glicil-D-valina**

Ácido (4-{(2*R*,3*R*)-1-(4-fluorofenil)-4-oxo-3-[(2-oxo-2-feniletil)tio]azetidin-2-il}fenoxi)acético (15 mg, 0.043 mmol), *terc*-butil glicil-D-valinato clorhidrato, (14.3 mg, 0.054 mmol) y *N*-metilmorfolina (14 μl, 0.13 mmol) se disolvieron en DCM (2 ml). Después de 5 minutos, se agregó TBTU (16.9 mg, 0.053 mmol) y la mezcla de reacción se agitó durante 2.5 horas. Se confirmó la formación del éster. M/z: 678.35 (M+H). El disolvente se retiró bajo presión reducida. El residuo se disolvió en EtOAc:DCM (1:3) y se purificó en gel de sílice (1 g) usando EtOAc:DCM (1:3) como eluyente. Las fracciones se recogieron y se concentraron. El residuo (0.029 g) se disolvió en DCM (3 ml) y se agregó TFA (0.5 ml). La mezcla de reacción se agitó de un día para otro. El disolvente se retiró bajo presión reducida y se agregó tolueno y se retiró bajo presión reducida. El residuo amarillento se disolvió en MeOH (2 ml) y se agregó borohidruro de sodio (16.2 mg, 0.43 mmol). La mezcla de reacción se agitó durante 10 minutos. Se agregó acetato de amonio (31.4 mg) y el disolvente se retiró bajo presión reducida. El residuo se purificó con HPLC preparativa en una

columna C8. Una gradiente de 20% a 50 % MeCN en 0.1 M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (7.6 mg, 28 %). H-NMR (400 MHz,DMSO-d_6): 0.79 (d, 3H), 0.81 (d, 3H) 1.95- 2.05 (m, 1H), 2.84-2.96 (m, 2H), 3.79 (d, 2H), 3.98-4.04 (m, 1H), 4.27 (d, 0.5H), 4.30 (d, 0.5H), 4.51 (s, 2H), 4.66-4.75 (m, 1H), 5.02 (d, 0.5H), 5.04 (d, 0.5H), 6.98 (d, 2H), 7.10-7.17 (m, 2H), 7.19-7.32 (m,7H), 7.36 (d, 2H), 7.77 (t, 1H), 8.26 (t, 1H). M/z: 622.1 (M-H) y 624.2(M+H).

Ejemplo 57

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-hidroxi-2-(4-metilfenil) etil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina**

Ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metilfenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (15.0 mg, 0.043 mmol), *terc*-butil glicil-D-valinato clorhidrato (10.8 mg, 0.04 mmol), *N*-metilmorfolina (10 μl, 0.09mmol) se disolvieron en DCM (2 ml). Luego de 5 minutos, se agregó TBTU (12.1 mg, 0.04 mmol) y la mezcla de reacción se agitó de un día para otro. Se confirmó la formación del éster. M/z: 690.13 (M-H) y 692.15 (M+H). La mezcla de reacción se purificó en gel de sílice (1 g) y se eluyó con EtOAc: DCM (1: 4). Las fracciones recogidas se concentraron. El residuo oleoso se disolvió en DCM (1.5 ml) y se agregó TFA (1 ml). La mezcla de reacción se agitó durante 2.5 horas. El disolvente se evaporó. Se agregó tolueno y se evaporó para contribuir al retiro de TFA. El residuo se disolvió en metanol (1.5ml) y se agregó borohidruro de sodio (12.2 mg, 0.32 mmol). Se agregó más borohidruro de sodio (4.2 mg, 0.11 mmol) y la mezcla se agitó durante 15 minutos. El disolvente se retiró bajo presión reducida y el residuo se purificó en HPLC preparativa en una columna C8. Una gradiente de 20% a 50 % MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (10.4 mg, 52%). H-NMR (400MHz, DMSO-

d_6): 0.80 (d,6H), 1.95- 2.05 (m, 1H), 2.24 (brs, 3H), 2.80-2.94 (m, 2H), 3.78 (d, 2H), 4.00 (brs, 1H), 4.23 (d, 0.5H), 4.27 (brs, 0.5H) 4.51 (s, 2H), 4.61-4.70 (m, 1H), 5.00 (m, 1H), 6.97 (d, 2H) 7.06 (d, 2H), 7.10-7.18 (m, 4H), 7.19-7.25 (m, 2H), 7.34 (d, 2H), 7.76 (brs, 1H), 8.26 (t, 1H). M/z: 636.1 (M-H) y 638.1 (M+H).

Ejemplo 58

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valil-D-tirosina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valina (14.7 mg, 0.025 mmol), *terc*-butil D-tirosinato clorhidrato (10.5 mg, 0.038 mmol) y *N*-metilmorfolina (10 μl, 91 mol) se disolvieron en DCM (1.5 ml). Después de 5 minutos, se agregó TBTU (9.9 mg, 0.031 mmol) y la mezcla de reacción se agitó de un día para otro. Se agregaron más *terc*-butil D-tirosinato clorhidrato (3.6 mg, 0.013 mmol), N-metilmorfolina (10 μl, 91 mol) y TBTU (3.1 mg, 9.7 μmol). La mezcla se agitó durante 3 horas. Se confirmó la formación del éster. M/z. 800.07 (M-H) y 802.08 (M+H). Se agregó $KHSO_4$ acuoso (3 ml) y la mezcla (pH de 2) se extrajo con DCM (3x5 ml). Las fases orgánicas combinadas se lavaron con agua (2x10 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo oleoso (22.4 mg) se disolvió en DCM (1.5 ml) y se agregó TFA (1.0 ml). La mezcla se agitó de un día para otro. El disolvente se evaporó. Se agregó tolueno y se retiró bajo presión reducida. El residuo se disolvió en metanol (2ml) y se agregó borohidruro de sodio (14 mg). La solución se agitó durante 10 minutos. Se agregó acetato de amonio (15 mg) y el disolvente se retiró bajo presión reducida. El residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 50 % MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (8.4 mg, 45 %). ^{1}H-NMR (400 MHz, DMSO-

d_6): 0.70 (d, 3H), 0.76 (d, 3H), 1.90-1.99 (m, 1H), 2.73-2.80 (m, 1H), 2.86-2.95 (m, 3H), 3.96-4.04 (m, 1H), 4.06-4.12 (m, 1H), 4.27 (d, 0.5H), 4.29 (d, 0.5H), 4.50-4.61 (m, 2H), 4.67-4.76 (m, 1H), 5.02 (d, 0.5H), 5.04 (d, 0.5H), 6.53 (d, 2H), 6.91 (q, 4H), 7.04-7.15 (m, 4H), 7.18-7.25 (m, 2H), 7.30-7.38 (m, 4H), 7.58-7.65 (brs, 1H), 7.91 (d, 1H). M/z: 746.0 (M-H).

Ejemplo 59

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valil-D-lisina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-valina (14.7, 0.025 mmol), *terc*-butil N^6-(*terc*-butoxicarbonil)-D-lisinato clorhidrato (10.3, 0.03 mmol) y *N*-metilmorfolina (10 μl, 91 μmol) se disolvieron en DCM (1.5 ml). Luego de 5 min, se agregó TBTU (9.8 mg, 0.03 mmol) y la mezcla de reacción se agitó de un día para otro. Se agregaron más N^6-(*terc*-butoxicarbonil)-D-lisinato clorhidrato (3.4 mg, 0.01 mmol), N-metilmorfolina (5 μl, 45 μmol) y TBTU (3.3 mg, 0.01 mmol) y la mezcla se agitó durante 2 horas. Se agregó $KHSO_4$ acuoso (3 ml) y la mezcla (pH de 3) se extrajo con DCM (3x5 ml). Las fases orgánicas combinadas se lavaron con agua (2x5 ml) y se secaron sobre Na_2SO_4. El disolvente se retiró bajo presión reducida. El residuo crudo (17.1 mg) se disolvió en DCM (1.5 ml) y TFA (1ml). La solución se agitó durante 1.5 horas. El disolvente se retiró bajo presión reducida. Se agregó tolueno y se evaporó para contribuir al retiro de TFA. El residuo se disolvió en metanol (2 ml) y se agregó borohidruro de sodio (11.5 mg, 0.30 mmol). La mezcla se agitó durante aprox. 15 minutos. Luego del retiro del disolvente bajo presión reducida, el residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 50% MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco. (7.8 mg, 43 %). ^{1}H-NMR (400 MHz, DMSO-d_6): 0.75 (d, 3H), 0.79 (d, 3H),

1.17-1.63 (m, 4H), 1.96-2.06 (m, 1H), 2.61-2.69 (m, 2H), 2.85-2.93 (m, 2H), 3.72-3.80 (m, 1H), 4.12 (t, 1H), 4.27 (s, 0.5H), 4.30 (s, 0.5H), 4.53-5.64 (m, 2H), 4.67-4.76 (m, 1H), 5.01-5.05 (m, 1H), 6.94 (d, 2H), 7.03-7.16 (m, 4H), 7.29-7.39 (m, 4H), 7.50-7.57 (brs, 1H), 8.05 (d, 1H). M/z:713. 1.

Ejemplo 60

***N*-[(4-{(2*R*,3*R*)-3-[(2-hidroxi-2-feniletil)tio]-4-oxo-1-fenilazetidin-2-il} fenoxi)acetil]glicil-D-valina**

Ácido [4-((2*R*,3*R*)-3-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}-4-oxo-1-fenilazetidin-2-il)fenoxi]acético (12.6 mg, 0.024 mmol) y *N*-metilmorfolina (15 μl, 0.14 mmol) se disolvieron en DCM (2 ml). Se agregaron más DCM (2 ml), N-metilmorfolina (20 μl, 0.18 mmol) y *terc*-butil glicil-D-valinato clorhidrato (9.0 mg, 0.034 mmol) después de 0.5 hora y la mezcla se agitó durante 10 minutos. Se agregó TBTU (10.5 mg, 0.033 mmol) y la mezcla se agitó de un día para otro. Se confirmó la formación del éster. M/z: 746.1. El disolvente se retiró bajo presión reducida y el residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 50% MeCN en 0.1 M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, el compuesto obtenido se disolvió en DCM (2ml) y se agregó TFA (1 ml). La mezcla de reacción se agitó durante 2.5 horas. Se confirmó la hidrólisis del éster. M/z: 604.2. El disolvente se retiró bajo presión reducida. Se efectuó co-evaporación con tolueno para contribuir al retiro de TFA. El residuo se disolvió en metanol (2 ml) y se agregó borohidruro de sodio (9.2 mg, 0.24 mmol). Luego de 15 minutos, el disolvente se extrajo por evaporación y el residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 50 % MeCN en 0.1 M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (4.0 mg, 28%). H-NMR (400 MHz, DMSO-d_6): 0.78 (d,6H), 1.95-2.04 (m, 1H), 2.83-2.97 (m, 2H), 3.76 (d, 2H), 3.89-3.95 (m, 1H), 4.26 (d,

0.5H), 4.30 (d, 0.5H), 4.51 (s, 2H), 4.67-4.75 (m, 1H), 5.01 (d, 0.5H), 5.03 (d, 0.5H), 6.98 (d, 2H), 7.03 (t, 1H), 7.17-7.22 (m, 3H), 7.23-7.32 (m, 6H), 7.36 (d, 2H), 7.55-7.65 (m, 1H), 8.29 (t, 1H). M/z: 603.96 (M-H).

Ejemplo 61

***N*-{[4-((2*R*,3*R*)-1-(4-Clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina**

Ácido [4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (15.3 mg, 0.03 mmol), *N*-metilmorfolina (10 µl, 0.091 mmol) y *terc*-butil glicil-D-valinato clorhidrato (10.4 mg, 0.039 mmol) se disolvieron en DCM (2 ml). Después de 10 minutos, se agregó TBTU (11.9 mg, 0.037 mmol) y la mezcla se agitó de un día para otro. Se confirmó el intermedio *terc*-butiléster. M/z: 727.8 (M-H). La mezcla de reacción se extrajo entre agua (10 ml, acidificada a pH de 3 con $KHSO_4$ (2M)) y DCM (3x10 ml). Las fases orgánicas combinadas se lavaron con agua (2x20 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo oleoso se disolvió en DCM (2 ml) y se agregó TFA (1.3 ml). La mezcla se agitó de un día para otro. El disolvente se evaporó y se realizó co-evaporación con tolueno para contribuir al retiro de TFA. El residuo se disolvió en metanol (2 ml) y se agregó borohidruro de sodio (12.3 mg, 0.33 mmol). Luego de 15 minutos, se agregó acetato de amonio (17mg) y el disolvente se retiró bajo presión reducida. El residuo se purificó en HPLC preparativa en columna C8. Una gradiente de 20% a 50% MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (15.1 mg, 77%). H-NMR (400MHz, DMSO-d_6): 0.78 (d, 3H), 0.80 (d, 3H), 0.95-1.03 (m, 1H), 2.83-3.00 (m, 2H), 3.75-3.80 (m, 2H), 3.93-4-00 (t, 1H), 4.30 (d, 0.5H), 4.36-4.38 (brs, 0.5H), 4.52 (s, 2H), 4.69- 4.77 (m, 1H), 5.02 (d, 0.5H), 5.06 (d, 0.5H), 6.96-7.00 (m 2H), 7.18-7.22 (m, 2H),7.31-7.38 (m, 8H), 7.60-7.74 (m, 1H), 8.28 (t, 1H). M/z: 671.9 (M+H).

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Ejemplo 62

***N*-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-lisina**

N-{[4-((2*R*,3*R*)-1-(4-Clorofenil)-3-{[2-(4-clorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (14.6 mg, 0.026 mmol) y N-metilmorfolina (20 µl, 0.18 mmol) se disolvieron en DCM (2 ml). Se agregó *terc*-butil N^6-(*terc*-butoxicarbonil)-D-lisinato clorhidrato (11.1 mg, 0.033 mmol) y luego de 5 minutos se agregó TBTU (9.8 mg, 0.031 mmol) a la suspensión. La mezcla se agitó de un día para otro. Se agregaron más *terc*-butil N^6-(*terc*-butoxicarbonil)-D-lisinato (4.8 mg, 0.014 mmol), *N*-metilmorfolina (10 µl, 91 µmol) y TBTU (4.6 mg, 0.014 mmol) y la mezcla se agitó durante 2.5 horas. Se confirmó la formación del éster. M/z: 855.4 (M-H). Se agregaron DCM (3 ml) y agua (5ml) y la solución se acidificó a pH 3 con $KHSO_4$ (2M). La fase orgánica se lavó con agua (2x5 ml). Las fases acuosas combinadas se extrajeron con DCM (2x5 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida. El residuo oleoso se disolvió en DCM (1.5ml) y se agregó TFA (1 ml). La mezcla se agitó durante 2.5 horas. La mezcla se concentró y se realizó co-evaporación con tolueno para contribuir al retiro de TFA. El residuo se disolvió en metanol (2ml) y se agregó borohidruro de sodio (10.4 mg, 0.027 mmol). Después de 15 minutos, se agregó tampón de acetato de amonio (0.1M, 1.5ml) y el disolvente se retiró bajo presión reducida. El residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 50 % MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, el compuesto del título se obtuvo como un sólido blanco (10.8 mg, 59 %). H-NMR (400 MHz, DMSO-d_6): 1.18-1.36 (m, 2H), 1.41-1.70 (m, 4H), 2.71 (t, 2H), 2.84-2.97 (m, 2H), 3.72-3.75 (brd, 2H), 3.93 (m, 1H), 4.30 (d, 0.5H), 4.34 (d, 0.5H), 4.52 (s, 2H), 4.68-4.77(m, 1H), 5.03 (d, 0.5H), 5.07 (d, 0.5H), 6.98 (d, 2H),

7.20 (d, 2H), 7.31-7.38 (m, 8H), 7.63-7.72 (m, 1H), 8.34 (t, 1H). M/z: 705.1.

Ejemplo 63

Ácido (2*R*)-2-[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil)amino]-4-fenilbutanoico

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (14.4 mg, 0.027 mmol) y *N*-metilmorfolina (15 μl, 0.14 mmol) se disolvieron en DMF (3 ml). Después de 5 minutos, se agregó TBTU (10.3 mg, 0.032 mmol) y la mezcla se agitó a 30°C durante 20 minutos. Se agregó ácido (2*R*)-2-amino-4-fenilbutanoico (5.7 mg, 0.032 mmol) y la mezcla se agitó a temperatura ambiente durante 1.5 horas. Se confirmó la formación del intermedio ácido. M/z: 702.0. Se agregaron MeOH (2.5ml) y borohidruro de sodio, y la mezcla se agitó durante 20 minutos. Se agregó acetato de amonio (31 mg). La mezcla se concentró y se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 45% MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, el compuesto del título se obtuvo como un sólido blanco (9.4 mg, 50 %). H-NMR (400MHz, DMSO-d_6): 1.74-1.87 (m, 1H), 1.89-1.99 (m, 1H), 2.49-2.53 (m, 2H), 2.82-2.98 (m, 2H), 3.77 (d, 2H), 3.94-4.01 (m, 1H), 4.27 (d, 0.5H), 4.31 (d, 0.5H), 4.53 (s, 2H), 4.68-4.77 (m, 1H), 5.02 (d, 0.5H), 5.05 (d, 0.5H), 6.99 (d, 2H), 7.05-7.16 (m, 7H), 7.19-7.26 (m, 4H), 7.30-7.38 (m, 4H), 7.78-7.88 (dd, 1H), 8.35 (t, 1H). M/z: 702.0 (M-H).

Ejemplo 64

Ácido (2*R*)-2-[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-flu rofenil)-2-hidroxietil]tiol-4-oxoazetidin-2-il)fenoxi]acetil}glicil)amino]-4-(4-hidroxifenil)butanoico

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (15.2 mg, 0.028 mmol) y *N*-metilmorfolina (15 μl, 0.14 mmol) se disolvieron en DMF (2 ml). Se agregó TBTU (10.5 mg, 0.033 mmol) y, luego de 20 minutos, se agregó hidrobromuro de ácido (2*R*)-2-amino-4-(4-hidroxifenil)butanoico (9.2 mg, 0.033 mmol). La mezcla de reacción se agitó durante 1.5 horas. Se confirmó la formación del intermedio ácido. M/z: 718.3. Se agregaron MeOH (2 ml) y borohidruro de sodio (10.7 mg, 0.28 mmol), y la mezcla se agitó durante 20 minutos. Se agregó acetato de amonio (34 mg) y el metanol se retiró bajo presión reducida. El residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 45% MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, el compuesto del título se obtuvo como un sólido blanco (9.6 mg, 47%). H-NMR (400MHz, DMSO-d_6): 1.75-1.86 (m, 1H), 1.89-1.98 (m, 1H), 2.41 (t, 2H), 2.81-2.98 (m, 2H), 3.78 (d, 2H), 3.97-4.05 (m, 1H), 4.27 (d, 0.5H), 4.31 (d, 0.5H), 4.53 (s, 2H), 4.67-4.76 (m, 1H), 5.02 (d, 0.5H), 5.05 (d, 0.5H), 6.62 (d, 2H), 6.91 (d, 2H), 6.98 (d, 2H), 7.05-7.16 (m, 4H), 7.20-7.25 (m, 2H), 7.30-7.39 (m, 4H), 7.87-7.97 (m, 1H), 8.30 (t, 1H), 8.91-9.30 (br, 1H). M/z: 718.0 (M-H).

Ejemplo 65

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-hidroxi-2-(4-metoxifenil) etil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-alanina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.04 g, 0.072 mmol) y N-metilmorfolina (0.022 g, 0.217 mmol) se disolvieron en CH_2Cl_2 (4 ml). Se

agregaron *terc*-butil D-alaninato clorhidrato (0.016 g, 0.087 mmol) y TBTU (0.030 g, 0.094 mmol). Después de 2 horas, la mezcla de reacción se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Fracciones puras se recogieron y se concentraron. El residuo se disolvió en CH_2Cl_2 (3 ml) y TFA (2 ml). Se completó la hidrólisis después de 2 horas. La mezcla de reacción se concentró y se agregaron MeOH (3 ml) y $NaBH_4$ (0.011 g, 0.290 mmol). La mezcla se agitó durante 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml) y el disolvente se evaporó. El residuo se purificó por HPLC preparativa usando un eluyente de 0-50% CH_3CN en 0.1M tampón NH_4OAc. El secamiento por congelamiento de las fracciones puras proporcionó el compuesto del título (0.030 g, 66%) como un sólido incoloro. M/z: 624.2, (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.16 (d, 3H), 2.83-2.93 (m, 2H), 3.68-3.74 (m,SH), 3.88-3.95 (m, 1H), 4.23-4.26 (m, 1H), 4.51 (s, 2H), 4.60-4.70 (m, 1H), 5.00-5.03 (m, 1H), 6.81-7.37 (m, 12H), 7.74-7.79 (m, 1H), 8.29-8.34 (m, 1H).

Ejemplo 66

Ácido 1-[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil)amino] ciclopropanocarboxílico

N-Metil morfolina (0.037 g, 0.370 mmol) y TBTU (0.039 g, 0.120 mmol) se agregaron a una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.025 g, 0.046 mmol) en DMF (2 ml) a 30°C. Después de 1 hora, se agregó ácido 1-aminociclopropanocarboxílico (0.019 g, 0.185 mmol). Luego de 1 hora, la reacción se extinguió por la adición de agua (1 ml). Después de 10 minutos, se agregaron MeOH (2 ml) y $NaBH_4$ (0.035 g, 0.925 mmol). Se obtuvo conversión completa en el alcohol correspondiente luego de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc

(2 ml). El producto se purificó por HPLC preparativa (eluyente 0-50% CH_3CN en 0.1M tampón NH_4OAc). El secamiento por congelamiento de las fracciones puras proporcionó el compuesto del título (0.045 g, 78%) como un sólido incoloro. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.78-0.88 (m, 2H), 1.08-1.22 (m, 2H), 2.84-2.94 (m, 2H), 3.63-3.72 (m, 2H), 4.24-4.29 (m, 1H), 4.48-4.52 (m, 2H), 4.68-4.75 (m, 1H), 5.03-5.06 (m, 1H), 6.96-7.37 (m, 12H), 7.78-8.36 (m, 2H).

Ejemplo 67

***N*-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-metil-D-valina**

TBTU (0.020 g, 0.063 mmol) se agregó a una solución de *N*-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.030 g, 0.052 mmol) y N-metilmorfolina (0.016 g, 0.157 mmol) en CH_2Cl_2 (5 ml) a 30°C. Luego de 30 minutos, se agregó D-*terc*-leucina (0.008 g, 0.063 mmol), y la mezcla se agitó durante 30 minutos. La mezcla de reacción se concentró. Se agregó tolueno (2 ml) y se evaporó. Se agregaron MeOH (3 ml) y borohidruro de sodio (0.020 g, 0.523 mmol). Se obtuvo conversión completa en el alcohol correspondiente luego de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml) y la mezcla se concentró. El residuo se purificó por HPLC preparativa usando un eluyente de 0-50% CH_3CN en 0.1M tampón NH_4OAc. El secamiento por congelamiento de las fracciones puras proporcionó el compuesto del título (0.021 g, 58%) como un sólido incoloro. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.85 (s, 9H), 2.82-2.98 (m, 2H), 3.75-3.81 (m, 2H), 3.91-3.96 (m, 1H), 4.29-4.37 (m, 1H), 4.52 (s, 2H), 4.70-4.78 (m, 1H), 5.01-5.06 (m, 1H), 6.97-6.99 (m, 2H), 7.19-7.21 (m, 2H),7.32-7.36 (m, 8H), 7.52-7.63 (m, 1H), 8.27-8.32 (m, 1H).

Ejemplo 68

_N_-{[4-((2_R_,3_R_)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-triptófano

TBTU (0.016 g, 0.051 mmol) se agregó a una solución de _N_-{[4-((2_R_,3_R_)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.025 g, 0.046 mmol) y N-metilmorfolina (0.014 g, 0.139 mmol) en DMF (2 ml) a 30°C. Trascurrida 1 hora, se agregaron DMSO (1 ml) y D-triptófano (0.019 g, 0.092 mmol). Luego de 10 minutos, la reacción se extinguió por la adición de agua (1ml). La mezcla se agitó durante 10 minutos y se agregaron MeOH (1ml) y $NaBH_4$ (0.035 g, 0.925 mmol). Después de 5 minutos, se obtuvo conversión completa en el alcohol correspondiente. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1ml). La mezcla de reacción se concentró y el residuo se purificó por HPLC preparativa usando un eluyente de 0-50% CH_3CN en 0.1M tampón NH_4OAc. Esto produjo el compuesto del título (0.028 g, 83%) como un sólido incoloro. M/z: 727.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.79-3.18 (m, 4H), 3.61-3.80 (m, 2H), 4.26-4.34 (m, 2H), 4.43-4.54 (m, 2H), 4.68-4.78 (m, 1H), 4.97-5.04 (m, 1H), 6.84-7.55 (m, 17H), 7.65-7.82 (m, 1H), 8.22-8.25 (m, 1H), 10.73 (s, 1H).

Ejemplo 69

_N_-{[4-((2_R_,3_R_)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-histidina

TBTU (0.016 g, 0.051 mmol) se agregó a una solución de _N_-{[4-((2_R_,3_R_)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.025 g, 0.046 mmol) y N-metilmorfolina (0.014 g, 0.139 mmol) en DMF (2 ml) a 30°C. Transcurrida 1 hora, se agregaron D-histidina (0.014 g, 0.092 mmol) y bromuro de tetrabutilamonio (0.003 g, 0.009 mmol). La mezcla de reacción se agitó de un día para otro (30% de

conversión) y la reacción se extinguió por la adición de agua (2 ml). Purificación por HPLC preparativa usando un eluyente de 0-50% CH_3CN en 0.1M tampón NH_4OAc proporcionó el intermedio acetona, la cual se redujo por la adición de MeOH (3 ml) y $NaBH_4$ (0.005 g, 0.139 mmol). Se obtuvo conversión completa en el alcohol correspondiente después de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml) y la mezcla se concentró. Purificación por HPLC preparativa usando un eluyente de 0-40% CH_3CN en 0.1M tampón NH_4OAc proporcionó el compuesto del título (0.001 g, 4.5%) como un sólido incoloro. M/z: 680.0. ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.82-2.93 (m, 4H), 3.71-3.80 (m, 2H), 4.11-4.30 (m, 2H), 4.52 (s, 2H), 4.68-4.73 (m, 1H), 5.04-5.07 (m, 1H), 6.68-7.50 (m, 14H), 7.90-7.96 (m, 1H), 8.27-8.33 (m, 1H).

Ejemplo 70

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-(2-naftil)-D-alanina**

TBTU (0.019 g, 0.060 mmol) se agregó a una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.025 g, 0.046 mmol) y N-metilmorfolina (0.014 g, 0.139 mmol) en CH_2Cl_2 (5 ml) a 30°C. Luego de 1 hora, se agregaron DMF (3 ml), DMSO (1ml) y D-(2-naftil)alanina (0.011 g, 0.051 mmol). La reacción se extinguió por la adición de agua (1 ml) después de 1 hora. Se agregó $NaBH_4$ (0.035 g, 0.925 mmol). Luego de 5 minutos, se obtuvo conversión completa en el alcohol correspondiente. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml) y la mezcla se concentró. Purificación por HPLC preparativa usando un eluyente de 0-55% CH_3CN en 0.1M tampón NH_4OAc proporcionó el compuesto del título (0.017 g, 48%) como un sólido incoloro. M/z: 738.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.75-3.27 (m, 4H), 3.55-3.83 (m, 2H), 4.25-4.55

(m, 4H), 4.68-4.79 (m, 1H), 4.92-5.02 (m, 1H), 6.72-7.80 (m, 20H), 8.26-8.30 (m, 1H).

Ejemplo 71

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-metil-D-valina**

TBTU (0.021 g, 0.067 mraol) se agregó a una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.030 g, 0.056 mmol) y N-metil morfolina (0.017 g, 0.166 mmol) en CH_2Cl_2 (5 ml) a 30 °C. Después de 1.5 horas, se agregó D-*terc*-leucina (0.011 g, 0.083 mmol). Se obtuvo la completa conversión en la amida correspondiente luego de 30 minutos. La reacción se extinguió por la adición de agua (1 ml). Pasados 10 minutos, se agregaron MeOH (3 ml) y $NaBH_4$ (0.042 g, 1.11 mmol). Después de 5 minutos, la reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml). La mezcla de reacción se concentró y se purificó por HPLC preparativa usando un eluyente de 0-50% CH_3CN en 0.1M tampón NH_4OAc. El compuesto del título (0.025 g, 69%) se obtuvo como un sólido incoloro. M/z: 654.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.86 (s, 9H), 2.82-2.98 (m, 2H), 3.76-3.81 (m, 2H), 3.92-3.96 (m, 1H), 4.26-4.33 (m, 1H), 4.52 (s, 2H), 4.68-4.76 (m, 1H), 5.02-5.07 (m, 1H), 6.97-7.37 (m, 12H), 7.58-7.63 (m, 1H), 8.29-8.34 (m, 1H).

Ejemplo 72

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-(3*R*,4*S*,5*R*)-3,4,5,6-tetrahidroxi-D-norleucina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.025 g, 0.046 mmol) se disolvió en DMSO (2 ml) a 30°C. Se agregaron N-Metilmorfolina (0.014 g, 0.139 mmol) y TBTU (0.018 g, 0.056 mmol). Luego de 1 hora, se agregaron ácido D-glucosamínico (0.018 g, 0.092 mmol) y bromuro de tetrabutilamonio (0.001 g, 0.005 mmol). La mezcla se agitó durante 15 minutos. Se agregó más TBTU (18 mg, 0.056 mmol). Pasados 30 minutos, había ocurrido aproximadamente 30% de formación de la amida. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). El intermedio acetona se purificó por HPLC preparativa usando un eluyente de 0-50% CH_3CN en 0.1M tampón NH_4OAc y se secó por congelamiento. Se agregaron MeOH (3 ml) y $NaBH_4$ (0.005 g, 0.139 mmol). Pasados 5 minutos, la reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml). La concentración de la mezcla y la purificación por HPLC preparativa usando un eluyente de 0-50% CH_3CN en 0.1M tampón NH_4OAc produjo el compuesto del título (0.005 g, 16%) como un sólido incoloro. M/z: 718.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.82-2.94 (m, 2H), 3.34-3.56 (m, 4H), 3.76-3.80 (m, 2H), 3.87-3.90 (m, 1H), 4.07-4.11 (m, 1H), 4.27-4.32 (m, 1H), 4.52 (s, 2H), 4.68-4.76 (m, 1H), 5.02-5.05 (m, 1H), 6.97-7.39 (m, 12H), 7.63-7.70 (m, 1H), 8.28-8.35 (m, 1H).

Ejemplo 73

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-β-fenil-D-fenilalanina**

TBTU (0.018 g, 0.056 mmol) se agregó a una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.025 g, 0.046 mmol) y N-metilmorfolina (0.023 g, 0.231 mmol) en CH_2Cl_2 (5 ml) a 30°C. Pasadas 1.5 horas, se agregó sal de ácido β-fenil-D-fenilalanina trifluoroacético (0.033 g, 0.092 mmol). La mezcla se agitó durante 5 minutos. Se agregó agua (1 ml) y la mezcla se

concentró. Se agregaron MeOH (3 ml) y $NaBH_4$ (0.017 g, 0.462 mmol). Después de 5 minutos, la reacción se extinguió por la adición de 0.1M tampón NH_4OAc (1 ml) seguida por concentración de la mezcla. Purificación por HPLC preparativa usando un eluyente de 0-45% CH_3CN en 0.1M tampón NH_4OAc y liofilización produjo el compuesto del título (0.021 g, 59%) como un sólido incoloro. M/z: 764.1 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 2.82-2.95 (m, 2H), 3.42-3.49 (m, 1H), 3.66-3.74 (m, 1H), 4.25-4.33 (m, 2H), 4.42 (d, 1H), 4.47 (d, 1H), 4.69- 4.76 (m, 1H), 5.03-5.12 (m, 2H), 6.94-7.38 (m, 22H), 8.10-8.14 (m, 1H), 8.18-8.24 (m, 1H).

Ejemplo 74

Ácido (2*R*)-4-ciclohexil-2-[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil} glicil)amino]butanoico

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.025 g, 0.046 mmol) se disolvió en DMF (2 ml) a 30°C. Se agregaron *N*-metilmorfolina (0.034 g, 0.333 mmol) y TBTU (0.043 g, 0.133 mmol). Pasada 1 hora, se agregaron (2*R*)-2-amino-4-ciclohexilbutanoato de sodio (0.039 g, 0.189 mmol), DMSO (2 ml) y bromuro de tetrabutilamonio (0.004 g, 0.011 mmol). La mezcla se agitó durante 1 hora y se agregó agua (1ml). Luego de 1 hora, se agregaron MeOH (2 ml) y $NaBH_4$ (0.084 g, 2.220 mmol). Se obtuvo conversión completa en el alcohol correspondiente después de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). La mezcla se purificó por HPLC preparativa (eluyente 0-50% CH_3CN en 0.1M tampón NH_4OAc). El secamiento por congelamiento de las fracciones puras produjo el compuesto del título (0.034 g, 43%) como un sólido incoloro. M/z: 708.1 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.75-1.62 (m, 15H), 2.82-2.99 (m, 2H), 3.68-3.78 (m, 2H), 3.90-3.96 (m, 1H), 4.23-4.35 (m,

1H), 4.50 (s, 2H), 4.69-4.75 (m, 1H),5.01-5.07 (m, 1H), 6.95-7.39 (m, 12H), 7.68-7.80 (m, 1H), 8.20-8.34 (m, 1H).

Ejemplo 75

Ácido (2*R*)-ciclopentil[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil} glicil)amino]acético

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.035 g, 0.065 mmol) se disolvió en DMF (2 ml) a 30°C. Se agregaron N-metilmorfolina (0.026 g, 0.259 mmol) y TBTU (0.027 g, 0.084 mmol). Pasada 1 hora, se agregó ácido (2*R*)-amino(ciclopentil)acético (0.014 g, 0.097 mmol). La mezcla se agitó durante 1 hora y se agregó agua (1 ml). Luego de 10 minutos, se agregaron MeOH (2ml) y $NaBH_4$ (0.037 g, 0.971 mmol). Se obtuvo conversión completa en el alcohol correspondiente después de 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml). La mezcla se purificó por HPLC preparativa (eluyente 0-50% CH_3CN en 0.1M tampón NH_4OAc). El secamiento por congelamiento de las fracciones puras produjo el compuesto del título (0.018 g, 42%) como un sólido incoloro. M/z: 666.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 1.19-1.62 (m, 8H), 2.09-2.19 (m, 1H), 2.83-2.95 (m, 2H), 3.78 (d, 2H), 4.06-4.10 (m, 1H), 4.25-4.30 (m, 1H), 4.51 (s, 2H), 4.68-4.75 (m, 1H), 5.03-5.06 (m, 1H), 6.97-7.37 (m, 12H), 7.95-8.00 (m, 1H), 8.22 (t, 1H).

Ejemplo 76

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-metil-D-isovalina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.035 g, 0.065 mmol) se disolvió en DMF (2 ml) a 30°C. Se agregaron N-metilmorfolina (0.026 g, 0.259 mmol) y TBTU (0.027 g, 0.084 mmol). Transcurrida 1 hora, se agregó 3-metil-D-isovalina (0.013 g, 0.097 mmol). La mezcla se agitó durante 2 horas y se agregó agua (1 ml). Luego de 10 minutos, se agregaron MeOH (2 ml) y $NaBH_4$ (0.037 g, 0.971 mmol). Se obtuvo conversión completa en el alcohol correspondiente después de 5 minutos y se agregó 0.1M tampón NH_4OAc (2 ml). La mezcla se purificó por HPLC preparativa (eluyente 0-50% CH_3CN en 0.1M tampón NH_4OAc). El secamiento por congelamiento de las fracciones puras proporcionó el compuesto del título (0.020g, 47%) como un sólido incoloro. M/z: 654.0 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.79 (d, 3H), 0.87 (d, 3H), 1.29 (s, 3H), 2.00-2.07 (m, 1H), 2.84-2.94 (m, 2H), 3.73 (d, 2H), 4.25-4.28 (m, 1H), 4.51 (s, 2H), 4.69-4.75 (m, 1H), 5.03-5.06 (m, 1H), 6.97-7.37 (m, 12H), 7.82 (s, 1H), 8.24 (t, 1H).

Ejemplo 77

_N_-{[4-((2_R_,3_R_)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-S-(*terc*-butil)-D-cisteína

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}4-oxoazetidin-2-il)fenoxi]acetil}glicina (20 mg, 0.037 mmol) y N-metilmorfolina (20 μl, 0.18 mmol) se disolvieron en DMF (3 ml). Se agregó TBTU (14.6mg, 0.046mmol) y la mezcla se agitó a 30°C durante 45 minutos. Se agregó *S*-(*terc*-butil)-D-cisteína clorhidrato (9.7 mg, 0.045 mmol) y la mezcla de reacción se agitó durante 1.5 horas. Se confirmó la formación de la acetona del compuesto del título. M/z: 700.0. Se agregaron metanol (2 ml) y borohidruro de sodio (14.3 mg, 0.38 mmol) y la mezcla se agitó durante 30 minutos. Se agregó tampón de acetato de amonio (0.1M, 2ml) y la mezcla se concentró. El residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20% a 45 %

MeCN en 0.1M tampón NH_4OAc se usó como eluyente. El MeCN se retiró de la fracción recogida bajo presión reducida. La solución acuosa restante se acidificó a pH 1 con HCl (1M) y se extrajo con DCM. La fase orgánica se concentró bajo presión reducida y el residuo se disolvió en MeCN y agua. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (16.5 mg, 65%). H-NMR (400 MHz, DMSO-d_6): 1.21 (s, 9H), 2.71-2.78 (m, 1H), 2.82-2.86 (m, 3H), 2.74-2.80 (m, 2H), 2.18-2.26 (m, 1H), 4.27 (d, 0.5H), 4.30 (d, 0.5H), 4.51 (s, 2H), 2.67-2.76 (m, 1H), 5.03 (d, 0.5H), 5.05 (d, 0.5), 6.98 (d, 2H), 7.05-7.17 (m, 4H), 7.20-7.25 (m, 2H), 7.30-7.39 (m, 4H), 7.94-8.06 (b, 1H), 8.26 (t, 1H). M/z: 700.0 (M-H) y 702.1 (M+H).

Ejemplo 78

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*N*,2-dimetilalanina**

A una mezcla de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.020g, 0.037 mmol) y NMM (0.012ml, 0.109mmol) en DMF (3 ml) a 30°C se agregó TBTU (0.018 g, 0.056 mmol). La mezcla de reacción se agitó durante 20 minutos, luego de los cuales se agregó ácido 2-(metilamino)isobutírico (0.005 g, 0.038 mmol). La mezcla se agitó a 30°C durante 20 horas antes de extinguir la reacción por la adición de agua (1 ml). La mezcla se diluyó con MeOH (2ml) y se agregó $NaBH_4$ (0.018 g, 0.486 mmol). Después de 10 minutos la reacción se extinguió por la adición de 0.1M tampón de acetato de amonio (2 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. El secamiento por congelamiento de las fracciones puras proporcionó el producto deseado como un sólido blanco (0.012 g, 50 % de rendimiento).

Masa exacta: 642.211 $(M+1)^+$

Ejemplo 79

Ácido (2*R*)-3-(4-cianofenil)-2-{[({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil} amino)acetil]amino}propanoico

Ácido (2*R*)-3-(4-cianofenil)-2-{[({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino) acetil]amino}propanoico (0.006 g, 0.0084 mmoles) se disolvió en metanol (1.5 ml). Se agregó $NaBH_4$ (0.0035 g, 0.092 mmoles) y cuando la reacción se completó, de acuerdo con LC-MS, se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando una gradiente gradual de 33.5%, 43% y luego 55.5% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.005 g (83 %) del producto deseado.
NMR (500 MHz, CD_3COOD) 2.91-3.12 (m, 3H), 3.26-3.32 (m, 1H), 3.91 (ABq, 2H), 4.03-4.07 (m, 1H), 4.57 (s, 2H), 4.65 (brt, 1H), 4.80-4.85 (m, 1H), 4.90-4.93 (m, 1H), 6.97-7.08 (m, 6H), 7.26-7.32 (m, 2H), 7.32-7.41 (m, 6H), 7.60 (d, 2H)

Ejemplo 80

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-hidroxi-2-(4-pentilfenil)etil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-ciclohexil-D-alanina**

A una solución de ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-4-oxo-3-{[2-oxo-2-(4-pentilfenil)etil]tio}azetidin-2-il)fenoxi]acético (0.020 g, 0.037 mmol) y NMM (0.012 ml, 0.109 mmol) en DMF (2 ml) a 30°C se agregó TBTU (0.019 g, 0.059 mmol). Pasados 15 minutos, se agregó glicil-3-ciclohexil-

D-alanina (0.009 g, 0.039 mmol) y la mezcla se agitó a 30°C durante 22 horas. La reacción se extinguió por la adición de agua (1 ml) antes de diluir la mezcla con MeOH (2 ml). A esta solución se agregó $NaBH_4$ (0.020 g, 0.529 mmol) y la mezcla se agitó durante 10 minutos. Esta reacción se extinguió por la adición de 0.1M tampón de acetato de amonio (3 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa usando una gradiente de 20-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. El secamiento por congelamiento de las fracciones puras proporcionó el producto deseado como un sólido blanco (0.009 g, 32 % de rendimiento).

^{1}H NMR (CD_3OD, 400 MHz) δ: 0.82-1.03 (m,5H), 1.10-1.45 (m, 8H), 1.48-1.74 (m, 8H), 1.75-1.85 (m, 1H), 2.51-2.60 (m, 2H), 2.89-3.08 (m, 2H), 3.91-4.04 (m, 3H), 4.42-4.49 (m, 1H), 4.56-4.60 (m, 2H), 4.71-4.87 (m, 2H), 6.95-7.10 (m, 6H), 7.18-7.35 (m, 6H).

Ejemplo 81

***N*-({4-[(2*R*,3*R*)-1-(4-Fluorofenil)-3-({2-hidroxi-2-[4-(metiltio)fenil]etil}tio)-4-oxoazetidin-2-il]fenoxi}acetil)glicil-3-ciclohexil-D-alanina**

A una solución de ácido {4-[(2*R*,3*R*)-1-(4-fluorofenil)-3-({2-hidroxi-2-[4-(metiltio)fenil]etil}tio)-4-oxoazetidin-2-il]fenoxi}acético (0.020 g, 0.039 mmol) y NMM (0.025 ml, 0.227 mmol) en DMF (3 ml) a temperatura de la sala se agregó TBTU (0.025 g, 0.078 mmol). La mezcla de reacción se agitó durante 90 minutos, tras los cuales se agregó glicil-3-ciclohexil-D-alanina (0.010 g, 0.044 mmol). La mezcla se agitó durante 22 horas entes de extinguir la reacción por la adición de agua (1 ml). La mezcla se diluyó con MeOH (1 ml) y luego se agregó $NaBH_4$ (0.016 g, 0.423 mmol). Luego de 10 minutos, la reacción se extinguió por la adición de 0.1M tampón de acetato de amonio (2 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa usando

una gradiente de 20-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. El secamiento por congelamiento de las fracciones puras proporcionó el producto deseado como un sólido blanco (0.009 g, 32% de rendimiento).

ES- m/z: 723.1 (M-1)-. ^{1}H NMR (DMSO, 500 MHz) δ: 0.75-0.95 (m, 2H), 1.05-1.35 (m, 4H), 1.42-1.72 (m, 7H), 2.43-2.47 (m, 3H), 2.85-2.97 (m, 2H), 4.15-4.23 (m, 1H), 4.26-4.32 (m, 1H), 4.53 (s, 2H), 4.65-4.74 (m, 1H), 5.01-5.07 (m, 1H), 5.66 (bs, 1H), 6.97-7.03 (m, 2H), 7.13-7.29 (m, 8H), 7.35-7.41 (m, 2H), 7.96-8.06 (m, 1H), 8.22-8.29 (m, 1H).

Ejemplo 82

***N*-({4-[(2*R*,3*R*)-1-(4-Fluorofenil)-3-({2-hidroxi-2-[4-(metiltio) fenil]etil]tio)-4-oxoazetidin-2-il]fenoxi}acetil)glicil-D-valina**

Una solución de ácido {4-[(2*R*,3*R*)-1-(4-fluorofenil)-3-({2-hidroxi-2-[4-(metiltio) fenil]etil}tio)-4-oxoazetidin-2-il]fenoxi}acético (0.015g, 0.029 mmol), *terc*-butil glicil-D-valinato clorhidrato (0.009g, 0.034 mmol) y N-metilmorfolina (0.013ml, 0.118mmol) en DCM (3 ml) se agitó a temperatura de la sala durante 10 minutos, tras los cuales se agregó TBTU (0.014g, 0.044 mmol). Luego de 17 horas, se completó la conversión en el intermedio (m/z: 724.7, M+1). La solución se diluyó con TFA (2 ml) y la mezcla se dejó agitar durante 2 horas. El ácido resultante (m/z: 668.6, M+1) se concentró y el residuo se disolvió en MeOH (3 ml). A esta solución se agregó $NaBH_4$ (80 mg, 2.11 mmol) en porciones hasta que la reducción de la acetona se completó (LC/MS). La reacción se extinguió por la adición de 0.1M tampón de acetato de amonio (3 ml) antes de retirar la mayor parte del metanol bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. El secamiento por

congelamiento de las fracciones puras proporcionó el producto deseado (0.014g, 70%) como un sólido blanco.

ES-m/z: 669.0 $(M-1)^-$. ^1H NMR (CD_3OD, 400 MHz) δ: 0.88-0.98 (m, 6H), 2.10-2.23 (m, 1H), 2.40-2.47 (m, 3H), 2.89-3.08 (m, 2H), 3.93-4.06 (m, 3H), 4.31 (d, 1H), 4.59 (s, 2H), 4.73-4.84 (m, 2H), 6.95-7.07 (m,4H), 7.13-7.18 (m, 2H), 7.21-7.34 (m, 6H).

Ejemplo 83

***N*-({4-[(2*R*,3*R*)-1-(4-Fluorofenil)-3-({2-hidroxi-2-[4-(metiltio) fenil]etil]tio)-4-oxoazetidin-2-il]fenoxi}acetil)glicil-3-metil-D-valina**

A una solución de ácido {4-[(2*R*,3*R*)-1-(4-fluorofenil)-3-({2-hidroxi-2-[4-(metiltio)fenil]etil}tio)-4-oxoazetidin-2-il]fenoxi}acético (0.020 g, 0.039 mmol) y NMM (0.020 ml, 0.182 mmol) en DMF (3 ml) a temperatura de la sala se agregó TBTU (0.020 g, 0.062 mmol). La mezcla de reacción se agitó durante 60 minutos, tras los cuales se agregó glicil-3-metil-D-valina (0.008 g, 0.043 mmol). La mezcla se agitó durante 18 horas antes de extinguir la reacción por la adición de agua (1 ml). La mezcla se diluyó con MeOH (1 ml) y se agregó $NaBH_4$ (0.040 g, 1.06 mmol). Pasados 10 minutos, la reacción se extinguió por la adición de 0.1M tampón de acetato de amonio (2 ml) y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa usando una gradiente de 20-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. El secamiento por congelamiento de las fracciones puras proporcionó el producto deseado como un sólido blanco (0.006 g, 22 % de rendimiento).

ES-m/z: 683.0 $(M-1)^-$. ^1H NMR (DMSO, 500 MHz) δ: 0.88-0.94 (m, 9H), 2.44-2.46 (m, 3H), 2.85-2.98 (m, 2H), 3.80-3.87 (m, 2H), 4.01-4.07 (m, 1H), 4.27-4.35 (m, 1H), 4.55 (s, 2H), 4.66-4.75 (m, 1H), 5.01-5.07 (m, 1H),

6.97-7.03 (m, 2H), 7.14-7.29 (m, 8H), 7.36-7.41 (m, 2H), 7.70-7.85 (m, 1H), 8.28-8.33 (m, 1H).

Ejemplo 84

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxilacetil}glicil-4-metil-D-leucina**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (20mg, 0.037mmol) se disolvió en 1.5ml DMF. Se agregaron *N*-metilmorfolina (13μl, 118mmol) y TBTU (15mg, 0.047mmol) y la mezcla se agitó durante 1 hora. Se agregó *β-terc*-butil-D-alanina (11 mg, 0.076mmol) y la mezcla se agitó durante 3 horas. Se agregó agua (0. 2ml) y la mezcla se agitó durante 15 minutos. Se agregaron MeOH (2ml) y $NaBH_4$ (15mg). Se agregó NH_4AC (aprox. 20mg) después de 15 minutos. Se realizó la purificación usando HPLC preparativa en una columna C8. Una gradiente de 20-50% MeCN en 0.1M NH_4Ac se usó como fase móvil. La liofilización produjo 17.5mg (70%) del compuesto del título. M/z: 668 (M-1). NMR (400 MHz, DMSO): 8.24 (t, 1H), 7.77-7.87 (m, 1H), 7.32-7.40 (m, 4H), 7.22-7.27(m, 2H), 7.07-7.19 (m, 4H), 6.99 (d, 2H), 5.06 (dd, 1H), 4.70-4.78 (m, 1H), 4.53 (s, 2H), 4.31 (dd, 1H), 4.09-4.17 (m, 1H), 3.65-3.81 (m, 2H), 2.84-3.00 (m, 2H), 1.65 (dd, 1H), 1.42 (dd, 1H), 0.86 (s, 9H).

Ejemplo 85

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-ciclopentil-D-alanina**

A una solución de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.05 g, 0.092 mmol) y N-metilmorfolina (0.037 g, 0.37 mmol) en DMF (2 ml), bajo una atmósfera

de nitrógeno, se agregó TBTU (0.039 g, 0.12 mmol). Transcurridas 1.5 horas, se agregó3-ciclopentil-D-alanina (0.022 g, 0.139 mmol). La reacción se dejó agitar durante 1 hora, luego de lo cual se agregó agua (1 ml). Después de 10 minutos, se agregaron MeOH (2 ml) y $NaBH_4$ (0.035 g, 0.925 mmol). La conversión completa en el alcohol correspondiente se logró en 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml) y el producto se aisló por HPLC preparativa de la mezcla (eluyente 0-50% CH_3CN en 0.1M tampón NH_4OAc). El secamiento por congelamiento de las fracciones puras proporcionó el compuesto deseado (0.031 g, 49%) como un sólido incoloro. M/z: 680.7 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.97-1.10 (m, 2H), 1.38-1.81 (m, 9H), 2.84-2.94 (m, 2H), 3.77 (d, 2H), 4.11-4.16 (m, 1H), 4.25-4.28 (m, 1H), 4.51 (s, 2H), 4.69-4.75 (m, 1H), 5.03-5.06 (m, 1H), 6.97-7.37 (m, 12H), 8.02-8. 06 (m, 1H), 8.22 (t, 1H).

Ejemplo 86

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-hidroxi-2-(4-metoxifenil) etil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-metil-D-valina**

A una solución de ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (0.04 g, 0.081 mmol) y N-metilmorfolina (0.033 g, 0.323 mmol) en DMF (2 ml), bajo una atmósfera de nitrógeno, se agregó TBTU (0.034 g, 0.105mmol). Luego de 1.5 horas, se agregó glicil-3-metil-D-valina sal trifluoroacetato (0.037 g, 0.121 mmol). La mezcla se dejó agitar durante 1 hora, luego de la cual se agregó agua (1 ml). Transcurridos 10 minutos, se agregaron MeOH (2 ml) y $NaBH_4$ (0.031 g, 0.807 mmol). La conversión completa en el alcohol correspondiente se logró en 5 minutos. La reacción se extinguió por la adición de 0.1M tampón NH_4OAc (2 ml) y el producto se aisló por HPLC preparativa de la mezcla (eluyente 0-50% CH_3CN en 0.1M tampón NH_4OAc). El secamiento por congelamiento de las fracciones puras

proporcionó el compuesto deseado (0.027 g, 50%) como un sólido incoloro. m/z: 666.7 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.88 (s,9H), 2.81-2.93 (m, 2H), 3.69- 3.70 (m, 3H), 3.82 (d, 2H), 4.03-4.07 (m, 1H), 4.22-4.25 (m, 1H), 4.51 (s, 2H), 4.61-4.68 (m, 1H), 5.01-5.03 (m, 1H), 6.81-7.36 (m, 12H), 7.81-7.86 (m, 1H), 8.25 (t, 1H).

Ejemplo 87

***N*-({4-[(2*R*,3*R*)-3-{[2-(4-etoxifenil)-2-hidroxietil]tio}-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acetil)glicil-3-metil-D-valina**

A una solución de ácido {4-[(2*R*,3*R*)-3-{[2-(4-etoxifenil)-2-oxoetil]tio}-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acético (0.04 g, 0.078 mmol) y N-metilmorfolina (0.032 g, 0.314 mmol) en DMF (2 ml) bajo una atmósfera de nitrógeno se agregó TBTU (0.033 g, 0.102 mmol). Luego de 45 minutos, se agregó sal trifluoroacetato de glicil-3-metil-D-valina (0.031 g, 0.102 mmol). La mezcla se dejó agitar durante 15 minutos, tras los cuales se agregó agua (1 ml). Pasados 10 minutos, se agregaron MeOH (2 ml) y $NaBH_4$ (0.030 g, 0.785 mmol). La conversión completa en el alcohol correspondiente se logró en 5 minutos. La reacción se extinguió por la adición de 0. 1M tampón NH_4OAc (2 ml) y el producto se aisló por HPLC preparativa de la mezcla (eluyente 0-50% CH_3CN en 0.1M tampón NH_4OAc). El secamiento por congelamiento de las fracciones puras proporcionó el compuesto deseado (0.027 g, 50%) como un sólido incoloro. m/z: 680.8 (M-1). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.89 (s, 9H), 1.26-1.30 (m, 3H), 2.81-2.92 (m, 2H), 3.82 (d, 2H), 3.93-3.99 (m, 2H), 4.05-4.08 (m, 1H), 4.22-4.25 (m, 1H), 4.51 (s, 2H), 4.60-4.67 (m, 1H), 5.01-5.03 (m, 1H), 6.79-7.36 (m,12H), 7.82-7.87 (m, 1H), 8.25 (t, 1H).

Ejemplo 88

N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-S-(4-metoxibencil)-D-cisteína

A una solución agitada de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (21.3 mg, 0.039 mmol) in DMF (3ml) se agregó *N*-metilmorfolina (20 μl, 0.18 mmol). Se agregó TBTU (15.1 mg, 0.047 mmol) y la mezcla se agitó a 30°C durante 35 minutos. Se agregó *S*-(4-metoxibencil)-D-cisteína (12.8 mg, 0.053 mmol) y la mezcla se agitó 1 hora a 30°C y 1.5 horas a temperatura ambiente. Se confirmó la formación de la acetona del compuesto del título. M/z: 764.11 (M+1) y 762.06 (M-1). Se agregaron metanol (3 ml) y borohidruro de sodio (15 mg, 0.40 mmol) y la mezcla se agitó durante 20 minutos. Se agregó acetato de amonio (25 mg) y el metanol se retiró bajo presión reducida. La solución DMF restante se purificó con HPLC preparativa en una columna C8, UV 240/260 nm. Una gradiente de 20 a 47% MeCN en 0.1M NH_4OAc se usó como eluyente. El MeCN se retiró de las fracciones recogidas bajo presión reducida. La solución acuosa restante se acidificó a pH 1 con $KHSO_4$ (2M) y se extrajo con DCM. La fase orgánica se concentró bajo presión reducida y el residuo se disolvió en MeCN y agua. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (10.7 mg, 36 %). H-NMR (400 MHz, DMSO-d_6): 2-60-2.80 (m, 2H), 2.83-2.97 (m, 2H), 3.63-3.66 (bd, 2H), 3.69 (s, 3H), 3.77-3.81 (bd, 2H), 4.24-4.33 (m, 2H), 4.52 (s, 2H), 4.67-4.76 (m, 1H), 5.03 (d, 0.5H), 5.06 (d, 0.5H), 5.60-5.90 (b, 1H), 6.82 (d, 2H), 6.98 (d, 2H), 7.05-7.25 (m, 8H), 7.30-7.38 (m,4H), 8.00-8.10 (b, 1H), 8.30 (t, 1H). M/z: 764.07 (M-1).

Ejemplo 89

N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-O-bencil-L-serina

A una solución agitada de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (20.3 mg, 0.038 mmol) en DMF (2 ml) se agregó *N*-metilmorfolina (15 μl, 0.14 mmol). Se agregó TBTU (14.8 mg, 0.046 mmol) y la mezcla se agitó a 30°C durante 1.5 horas. Se agregó *O*-bencil-L-serina (8.8 mg, 0.045 mmol) y la mezcla se agitó de un día para otro. Se confirmó la formación de la acetona del compuesto del título. M/z: 718.04 (M+1) y 716.02 (M-1). Se agregaron metanol (3 ml) y borohidruro de sodio (10.3 mg, 0.27 mmol) y la mezcla se agitó durante 1.5 horas. Se agregó acetato de amonio (20 mg) y el metanol se retiró bajo presión reducida. La solución DMF restante se purificó por HPLC preparativa en una columna C8, UV 240/260 nm. Una gradiente de 20 a 45 % MeCN en 0.1M tampón NH_4OAc se usó como eluyente. Las fracciones puras se recogieron y el MeCN se retiró bajo presión reducida. La solución acuosa restante se acidificó a pH 1 con HCl (1M) y se extrajo con DCM. Las fases orgánicas combinadas se concentraron y el residuo se disolvió en MeCN y agua. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (2.3 mg, 8.5 %). H-NMR (400 MHz, DMSO-d_6): 2.85-2.94 (m, 2H), 3.58-3.63 (m, 1H), 3.69-3.75 (m, 1H), 3.83 (d, 2H), 4.25 (d, 0.5H), 4.27 (d, 0.5H), 4.39-4.44 (m, 1H), 4.46 (d, 2H), 4.51 (s, 2H), 4.68-4.75 (m, 1H), 5.03 (d, 0.5H), 5.06 (d, 0.5), 6.98 (d, 2H), 7.05-7.17 (m, 4H), 7.20-7.26 (m, 3H), 7.28-7.39 (m, 8H), 8.20 (d, 1H), 8.25 (t, 1H). M/z: 718.10 (M-1).

Ejemplo 90

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-5-(4-metilbencil)-D-cisteína**

A una solución agitada de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (19.9 mg, 0.037 mmol) en DMF (2.0 ml) se agregó *N*-metilmorfolina (15 μl, 0.14mmol). Se agregó TBTU (14.4 mg, 0.045 mmol) y la mezcla se agitó a

30°C durante 45 minutos. Se agregó *S*-(4-metilbencil)-D-cisteína (10.5 mg, 0.047 mmol) y la mezcla se agitó a 30°C durante 1 hora. Se confirmó la formación de la acetona del compuesto del título. M/z: 748.02 (M+1). Se agregaron metanol (2 ml) y borohidruro de sodio (14.7 mg, 0.39 mmol) y la mezcla se agitó durante 30 minutos. Se agregó acetato de amonio (20 mg), y el metanol se retiró bajo presión reducida. La solución DMF restante se purificó con HPLC preparativa en una columna C8, detección UV 240/260 nm. Una gradiente de 20 a 50% MeCN en 0.1M tampón NH_4OAc se usó como eluyente. Las fracciones puras se recogieron y el MeCN se retiró bajo presión reducida. La solución acuosa restante se acidificó a pH 1 con HCl (1M) y se extrajo con DCM. Las fases orgánicas combinadas se concentraron y el residuo se disolvió en MeCN y agua. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (8.7 mg, 31.5 %). H-NMR (400 MHz, DMSO-d_6): 2.24 (s, 3H), 2.60-2.68 (m, 1H), 2.72-2.79 (m, 1H), 2.86-2.94 (m, 2H), 3.68 (s, 2H), 3.82 (d, 2H), 4.25 (d, 0.5H), 4.27 (d, 0.5H), 4.39-4.46 (m, 1H), 4.52 (s, 2H), 4.67-4.77 (m, 1H), 5.03 (d, 0.5H), 5.06 (d, 0.5H), 5.60-5.67 (bs, 1H), 6.98 (d, 2H), 7.05-7.18 (m, 8H), 7.20-7.25 (m, 2H), 4.30-4.39 (m, 4H), 8.23-8.32 (m, 2H), 12.80-12.95 (bs, 1H). M/z: 748.04 (M-1).

Ejemplo 91

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-ornitina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-ornitina (0.021 g, 0.032 mmoles) se disolvió en metanol (1.5 mL). Se agregó $NaBH_4$ (0.0032 g, 0.085 mmoles) y después de alrededor de 15 minutos la reacción se completó de acuerdo con LC-MS. Se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 37% MeCN en 0.1M

tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.018 g (85%) del producto deseado.

NMR (500 MHz, CD_3COOD) 1.62-1.80 (m, 3H), 1.91-2.00 (m, 1H), 2.92-3. 10 (m, 4H), 3.98 (ABq, 2H), 4.05 (d, 0.5H), 4.08 (d, 0.5H), 4.27-4.32 (m, 1H), 4.64 (s, 2H), 4.82-4.87 (m, 1H), 4.93 (d, 0.5H), 4.94 (d, 0.5H), 6.99-7.06 (m, 4H), 7.09 (d, 2H), 7.28-7.33 (m, 2H), 7.33-7.41 (m, 4H)

Ejemplo 92

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-N^6,N^6- dimetil-L-lisina acetato**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-N^6,N^6-dimetil-L-lisina (0.05 g, 0.007 mmoles) se disolvió en metanol (1.5 mL). Se agregó $NaBH_4$ (0.0065 g, 0.0172 mmoles) y luego de alrededor de 15 minutos la reacción se completó de acuerdo con LC-MS. Se agregaron unas cuantas gotas de ácido acético. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando 33.5% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.004g (73%) del producto deseado como la sal de acetato.

NMR (500 MHz, CD_3COOD) 1.33-1.43 (m, 2H), 1.62-1.78 (m, 3H), 1.85-1.98 (m, 4H), 2.83 (s, 6H), 2.91-3.08 (m, 4H), 3.94 (s, 2H), 4.02 (d, 0.5H), 4.05 (d, 0.5H), 4.25-4.30 (m, 1H), 4.61 (s, 2H), 4.79-4.85 (m, 1H), 4.90 (d, 0.5H), 4.92 (d, 0.5H), 6.96-7.08 (m, 6H), 7.25-7.30 (m, 2H),7.30-7.38 (m, 4H)

Ejemplo 93

N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-b,b- dimetil-D-fenilalanina

A una solución agitada de *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (25.2 mg, 0.047 mmol) en DMF (2ml) se agregó *N*-metilmorfolina (30 μl, 0.027 mmol). Se agregó TBTU (18.0 mg, 0.056 mmol) y la mezcla se agitó a 30°C durante 1 hora. Se agregó trifluoroacetato de β,β-dimetil-D-fenilalanina y la mezcla se agitó a 30°C durante 1.25 horas. Se confirmó la formación de la acetona del compuesto del título. M/z: 716.07 (M+1) y 714.05 (M-1). Se agregó agua (0.5 ml). Se agregaron metanol (2 ml) y borohidruro de sodio (18.2 mg, 0.48 mmol), y la mezcla se agitó durante 25 minutos. Se agregó acetato de amonio (30 mg), y el metanol se retiró bajo presión reducida. La solución DMF restante se purificó con HPLC preparativa. Una gradiente de 20 a 48 % MeCN en 0.1M tampón NH_4OAc se usó como eluyente. El MeCN se retiró bajo presión reducida, y la solución acuosa restante se acidificó a pH 1 con HCl (1M) y se extrajo con DCM. La fase orgánica se concentró bajo presión reducida y el residuo se disolvió en MeCN y agua. Luego de la liofilización, el compuesto del título se obtuvo como un sólido blanco (20.5 mg, 62 %). H-NMR (400 MHz, DMSO-d_6): 1.27-1.32 (m, 6H), 2.75-3.05 (m, 2H), 3.55-3.67 (m, 1H), 3.79 (dd, 1H), 4.25-4.30 (m, 0.5H), 4.40 (s, 0.5H), 4.45-4.53 (m, 3H), 4.68-4.78 (m, 1H), 4.99 (d, 0.5H), 4.05 (d, 0.5H), 6.88-6.98 (m, 2H), 7.05-7.17 (m, 5H), 7.20-7.40 (m, 10H) 7.45-7.75 (m, 1H) 8.22 (t, 1H). M/z: 718.09 (M+1) y 716.07 (M-1).

Ejemplo 94

1-(4-Fluorofenil)-3-(R)-[2-(4-fluorofenil)-2-hidroxietiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(hidroxi)-1-(S)-(carboxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona

A una solución de 1-(4-fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(hidroxi)-1-(S)-(carboxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona (0.039 g, 0.055 mmol) en MeOH (3ml) se agregó $NaBH_4$ (0.005 g, 0.135 mmol). Pasados 10 minutos, se agregaron agua (2 ml) y ácido acético (2 gotas) antes de retirar la mayor parte del disolvente bajo presión reducida. El residuo se purificó por HPLC preparativa usando una gradiente de 20-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento se obtuvo el producto deseado en 0.038 g (96%) como un sólido blanco. NMR (DMSO, 500 MHz): 2.90-3.00 (m, 2H), 3.50 (dd, 1H), 3.60 (dd, 1H), 4.15-4.30 (m, 2H), 4.60 (ABq, 2H), 4.70-4.80 (m, 1H), 5.00-5.05 (m, 1H), 5.65 (d, 1H), 6.95-7.45 (m, 17H), 8.30-8.45 (m, 2H); m/z: 706.4.

Ejemplo 95

1-(4-Fluorofenil)-3-(R)-[2-(4-fluorofenil)-2-hidroxietiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxi)-1-(S)-(carboxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona

A una solución de 1-(4-fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(t-butoxi)-1-(S)-(carboxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona (0.002 g, 0.003 mmol) en MeOH (3 ml) se agregó $NaBH_4$ (0.004 g, 0.108 mmol). Transcurridos 10 minutos, a la solución se agregó agua (1 ml) y ácido acético (2 gotas) antes de retirar la mayor parte del disolvente bajo presión reducida. El residuo se purificó por HPLC preparativa usando una gradiente de 20-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento el producto deseado se obtuvo in 0.002 g (~ rendimiento cuantitativo) como un sólido blanco. NMR (DMSO, 500 MHz): 1.00 (s, 9H), 2.90-3.00 (m, 2H), 3.40-3.55 (m, 2H), 4.20-4.30 (m, 2H), 4.60 (ABq, 2H), 4.70-4.80 (m, 1H), 5.00-5.05 (m, 1H), 5.70 (d, 1H), 6.95-7.45 (m, 17H), 8.20 (bs, 1H), 8.35 (d, 1H); m/z: 762.5.

Ejemplo 96

1-(4-Fluorofenil)-3-(R)-[2-(4-fluorofenil)-2-hidroxietiltio]-4-(R)-{4-[*N*-{*N*-[2-(hidroxi)-1-(R)-(carboxi)etil]carbamoilmetil}carbamoilmetoxi] fenil} azetidin- 2-ona

A una solución de 1-(4-fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-{*N*-[2-(hidroxi)-1-(R)-(carboxi)etil]carbamoilmetil} carbamoilmetoxi]fenil}azetidin-2-ona (0.028 g, 0.045 mmol) en MeOH (3 ml) se agregó $NaBH_4$ (0.010 g, 0.264 mmol). Luego de 10 minutos, el disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento se obtuvo el producto deseado en 0.014 g (50%) como un sólido blanco. NMR (CD_3COOD, 400 MHz): 3.00-3.20 (m, 2H), 3.95 (dd, 1H), 4.00-4.15 (m, 2H), 4.25 (ABq, 2H), 4.70 (s, 2H), 4.70-4.80 (m, 1H), 4.85-5.00 (m, 2H), 6.95-7.10 (m, 6H), 7.25-7.45 (m, 6H); m/z: 630.1.

Ejemplo 97

1-(4-Fluorofenil)-3-(R)-[2-(4-fluorofenil)-2-hidroxietiltio]-4-(R)-{4-[*N*-{*N*-[2-(fenil)-1-(R)-(carboxi)etil]carbamoilmetil}carbamoilmetoxi] fenil}azetidin-2-ona

1-(4-Fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-{*N*-[2-(fenil)-1-(R)-(carboxi)etil]carbamoilmetil}carbamoilmetoxi]fenil} azetidin-2-ona (15mg, 0.022mmol) se disolvió en metanol (1 ml), y se agregó borohidruro de sodio (4 mg). El disolvente se evaporó y el residuo se purificó por HPLC preparativa usando una gradiente de 10% a 100 % MeCN en 0.1 M tampón de acetato de amonio como fase móvil.

Liofilización de la fracción del producto produjo 8 mg (53 %) del producto deseado. NMR (400 MHz, CD_3COOD): 3.02-3.17 (m, 3H), 3.19-3.25 (m, 1H), 4.06-4.17 (m, 3H), 4.66 (s, 2H), 4.87-4.96 (m, 3H), 6.97-7.05 (m, 6H), 7.10-7.40 (m, 12H); m/z 688.3 (m-H).

Ejemplos 98-136

Los siguientes compuestos pudieron prepararse por el procedimiento de Ejemplo 97, pero en ellos es posible emplear grupos protectores diferentes.

Ej.	R^1	R^2	R^3	R^4
98	H	Me	F	H
99	Ph	Me	F	H
100	H	Me	F	F
101	H	Me	H	H
102	Ph	Me	H	H
103	H	-$CH(Me)_2$	F	H
104	Ph	-$CH(Me)_2$	F	H
105	Ph	-$CH(Me)_2$	H	H
106	H	-$CH_2CH(Me)_2$	F	H
107	Ph	-$CH_2CH(Me)_2$	F	H
108	Ph	$CH_2CH(Me)_2$	F	F
109	H	$CH_2CH(Me)_2$	H	H
110	Ph	$CH_2CH(Me)_2$	H	H
111	H	Ph	F	H
112	Ph	Ph	F	H
113	H	Ph	H	H
114	Ph	Ph	H	
115	H	-CH_2Ph	F	H
116	Ph	-CH_2Ph	F	H
117	Ph	-CH_2Ph	F	F
118	Ph	-CH_2Ph	H	H

Ej.	R^1	R^2	R^3	R^4
119	H	-CH_2(4-HOPh)	F	H
120	Ph	-CH_2(4-HOPh)	F	H
121	Ph	-CH_2(4-HOPh)	F	F
122	H	-CH_2(4-HOPh)	H	H
123	Ph	-CH_2(4-HOPh)	H	H
124	H	-CH_2OH	H	H
125	H	-CH_2COOH	F	F
126	H	-CH_2CH_2COOH	F	F
127	H	-$H_2CH_2CH_2CH_2NHC(=NH)NH_2$	F	F
128	H	4-HOPh	F	F
129	Ph	-CH_2CH_2COOH	F	F
130	Ph	-$CH_2CH_2CH_2CH_2NHC(=NH)NH_2$	F	F
131	Ph	4-HOPh	F	F
132	Ph	-CH_2indol-3-ilo	F	F
133	Ph	-CH_2imidazol-4-ilo	F	F
134	Ph	-CH_2CH_2SMe	F	F
135	Ph	Ciclohexilo	F	F
136	Ph	-Ch_2ciclohexilo	F	F

Preparación de materiales de partida para los Ejemplos anteriores

Métodos

Método 1

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-alanina**

Ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (50 mg, 0.1mmol), *terc*-butil D-alaninato (23 mg, 0.12mmol) y 4-metilmorfolina (31 mg, 0. 31 mmol) se disolvieron en DCM (1.5 ml) y se agitaron a temperatura de la sala durante 5 minutos.

Se agregó TBTU (40 mg, 0.12 mmol), y la mezcla de reacción se agitó durante 2 horas. Se agregó TFA (0.7 ml) y la solución se agitó durante 90 minutos. Se retiraron TFA y DCM bajo presión reducida, y el residuo se disolvió en DCM y se lavó con agua. La capa orgánica se secó sobre sulfato de sodio y el disolvente se retiró bajo presión reducida produciendo 55 mg (95 %) del producto del título. M/z: 553.0 (M-1).

Método 2

Ácido [4-((2*R*,3*R*)-3-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}-4-xo-1-fenilazetidin-2-il)fenoxi]acético

A una solución de etil [4-((2*R*,3*R*)-3-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}-4-oxo-1-fenilazetidin-2-il)fenoxi]acetato (0.86 g, 1.53 mmol) en MeOH (25 ml) se agregaron agua (2.5ml) y trietilamina (1.55 g). La reacción se agitó durante 48 horas a 50°C. El disolvente se evaporó y el residuo se purificó por HPLC preparativa usando una gradiente de 20-70% CH_3CN en 0.1M tampón NH_4OAc. El secamiento por congelamiento de las fracciones puras produjo el compuesto del título como un sólido incoloro. ^1H NMR [$(CD_3)_2SO$), 400 MHz] □ 0.50 (s, 3H), 1.15 (s, 3H), 2.93 (d, 1H), 2.96 (d, 1H), 3.21-3.37 (m, 4H), 4.13 (d, 1H), 4.28 (s, 2H), 4.97 (d, 1H), 6.83-7.41 (m, 14H).

Método 3

***N*-[(4-{(2*R*,3*R*)-4-oxo-3-[(2-oxo-2-feniletil)tio]-1-fenilazetidin-2-il} fenoxi)acetil]glicina**

Glicina *terc*-butil éster (0.015 g, 0.112 mmol) y N-metilmorfolina (0.028 g, 0.281 mmol) se agregaron a una solución de ácido [4-((2*R*,3*R*)-3-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}-4-oxo-1-fenilazetidin-2-il)fenoxi]acético (0.050 g, 0.094 mmol) en CH_2Cl_2 (5 ml). Pasados 10

minutos, se agregó TBTU (0.039 g, 0.122 mmol). La reacción se agitó de un día para otro. El *terc*-butil éster resultante se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2 (25/75). Las fracciones puras se recogieron y se concentraron. Se agregaron CH_2Cl_2 (4 ml) y TFA (1 ml). El disolvente se evaporó luego de 2 horas, y el residuo se purificó por HPLC preparativa usando un eluyente de 20-70% CH_3CN en 0.1M tampón NH_4OAc. El secamiento por congelamiento de las fracciones puras proporcionó el producto del título como un sólido incoloro. M/z: 503.5 (M-1). ^1H NMR (CD_3CN), 400 MHz] δ 3.84 (d, 2H), 4.18 (d, 1H), 4.24 (s, 2H), 4.50 (s, 2H), 5.04 (d, 1H), 6.99-7.12 (m, 3H), 7.25-7.66 (m, 9H), 7.94-7.96 (m, 2H).

Método 4

Ácido (2*R*)-({[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}amino)(fenil)acético

Ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio]-4-oxoazetidin-2-il)fenoxi]acético (0.40 g, 0.827 mmol) se disolvió en CH_2Cl_2 (40 ml), y se agregaron *terc*-butil (2*R*)-amino(fenil)acetato (0.206 g, 0.993 mmol) y N-metilmorfolina (0.251 g, 2.48 mmol). Pasados 10 minutos, se agregó TBTU (0.345 g, 1.076 mmol). La reacción se agitó de un día para otro. El *terc*-butil éster resultante se concentró y se purificó en gel de sílice (eluido con EtOAc/CH_2Cl_2 25/75). Las fracciones puras se recogieron y se concentraron. Se agregaron CH_2Cl_2 (25 ml) y TFA (3 ml). La mezcla se agitó durante 5 días y el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa usando una gradiente de 20-70% CH_3CN en 0.1M tampón NH_4OAc. El secamiento por congelamiento de las fracciones puras produjo el compuesto del título como un sólido incoloro. M/z: 615.50 (M-1). ^1H NMR [$(CD_3)_2SO$), 400 MHz] δ 4.35 (d, 1H), 4.36 (d, 1H), 4.40 (d, 1H), 4.53 (d, 1H), 4.58 (d, 1H), 4.94 (d, 1H), 5.19 (d, 1H), 6.97-7.40 (m, 15H), 8.02-8.06 (m, 2H), 8.26-8.32 (m, 1H).

Método 5

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin- 2-il)fenoxi]acetil}-D-valina**

Ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (50.0 mg, 0.10 mmol) se disolvió en DCM (2 ml). Se agregaron *terc*-butil D-valinato clorhidrato (28.4 mg, 0.14 mmol) y *N*-metilmorfolina (3.0 µl, 0.31 mmol). Transcurridos 5 minutos, se agregó TBTU (43.7 mg, 0.14 mmol) y la mezcla se agitó de un día para otro. Se confirmó el intermedio *terc*-butil éster del compuesto del título. M/z: 637.1 (M-H). El disolvente se retiró bajo presión reducida. El residuo amarillo se disolvió en ácido fórmico (1.5 ml) y se calentó a 50°C durante 5 horas. El disolvente se evaporó y el residuo se purificó por HPLC preparativa en una columna C8. Una gradiente de 20 a 50% MeCN en 0.1 M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (30.5 mg, 51 %). ^{1}H-NMR (400 MHz, DMS-d_6): 0.74 (t, 6H), 1.98-2.07 (m, 1H), 3.84 (brs, 1H), 4.32 (d, 1H), 4.35 (s, 1H), 4.36 (s, 1H), 4.50 (brs, 2H), 5.16 (d, 1H), 6.96 (d, 2H), 7.10-7.17 (m, 2H), 7.19-7.24 (m, 2H), 7.31-7.38 (m, 4H), 7.66 (brs, 1H), 7.99-8. 04 (m, 2H). M/z: 583.0 (M+H) y 581.0 (M-H).

Método 6

(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina

Una mezcla de 3-(R)-4-(R)-1-(4-Fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.0229g, 0.042 mmol), (R)-valina *terc*-butil éster clorhidrato (0.0121 g, 0.058 mmol) y N-metilmorfolina (0.012ml, 0.111 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.018 g, 0.056 mmol), y la

mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (0.65 ml) y, luego de un par de horas, se completó la hidrólisis de acuerdo con LC-MS. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando una gradiente de 5-100% MeCN en 0.15% tampón de ácido trifluoroacético como eluyente. El disolvente se retiró bajo presión reducida y se obtuvo 0.022 g (81 %) del producto del título. M/z 640.06.

Método 7

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin- 2-il)fenoxi]acetil}glicil-L-treonina**

Una mezcla de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.0188g, 0.035 mmol), *terc*-butil *O*-(*terc*-butil)-L-treoninato (0.0151 g, 0.065 mmol) y N-metilmorfolina (0.012ml, 0.111 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.018 g, 0.056 mmol), y la mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (0.65 ml) y, luego de un par de horas, se completó la hidrólisis de acuerdo con LC-MS. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando una gradiente de 5-100% MeCN en 0.15% tampón de ácido trifluoroacético como eluyente. El disolvente se retiró bajo presión reducida y se obtuvo 0.014 g (63%) del producto del título. M/z 641.92.

Método 8

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tiol-4-oxoazetidin- 2-il)fenoxi]acetil}glicil-L-asparagina**

Una mezcla de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.0213g, 0.039 mmol), *terc*-butil L-asparaginato clorhidrato (0.0141 g, 0.063 mmol) y N-metilmorfolina (0.012ml, 0.111 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.018 g, 0.056 mmol), y la mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (0.65ml) y, luego de un par de horas, se completó la hidrólisis de acuerdo con LC-MS. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8 usando una gradiente de 5-100% MeCN en 0.15% tampón de ácido trifluoroacético como eluyente. El disolvente se retiró bajo presión reducida y se obtuvo 0.020 g (77%) del producto del título. M/z 655.11.

Método 9

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-metionina**

Una mezcla de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil) metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.0197g, 0.036 mmol), *terc*-butil L-metioninato clorhidrato (0.0144 g, 0.060 mmol) y N-metilmorfolina (0.012 ml, 0.111 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.018 g, 0.056 mmol) y la mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (0.65 ml) y, luego de un par de horas, se completó la hidrólisis de acuerdo con LC-MS. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8, usando una gradiente de 5-100% MeCN en 0.15% tampón de ácido trifluoroacético como eluyente. El disolvente se retiró bajo presión reducida y se obtuvo 0.015 g (61 %) del producto del título. M/z 672.10.

Método 10

***terc*-Butil *N*-[(benciloxi)carbonil]glicil-D-valinato**

Una mezcla de *N*-[(benciloxi)carbonil]glicina (2.4g, 11.5 mmol), *terc*-butil D-valinato clorhidrato (2.4 g, 11.4 mmol) y N-metilmorfolina (2.53ml, 22.9 mmol) en DCM (20ml) se agitó a temperatura de la sala. Se agregó TBTU (4.79 g, 14.9 mmol), y la mezcla se agitó durante tres días. El disolvente se retiró bajo presión reducida. Se agregó agua y la mezcla se extrajo dos veces con tolueno. La capa orgánica se lavó con salmuera, se secó (Na_2SO_4), se filtró y se concentró. El producto crudo se purificó por cromatografía de destello usando DCM: EtOAc: acetona 4:1:1 como eluyente para producir 3.92 g (94%) del compuesto del título. NMR (500 MHz, CD_3COOD) 0.88-0.99 (m, 6H), 1.48 (s, 9H), 2.08-2.19 (m, 1H), 3.85 (ABq, 2H), 4.24 (d, 1H), 5.12 (ABq, 2H), 7.28-7.41 (m, 5H).

Método 11

***terc*-Butil glicil-D-valinato clorhidrato**

terc-Butil *N*-[(benciloxi)carbonil]glicil-D-valinato (3.89g, 10.7 mmol) y Pd sobre carbón vegetal (95%, 0.3g) se mezclaron en EtOH (95%, 80 ml) y se agitaron bajo una atmósfera de H_2 durante 2 horas. La mezcla se filtró a través de Celita 521, y el disolvente se evaporó bajo presión reducida. Se agregaron MeCN (25 ml) y clorhidrato de piridina (1.25g, 10.8 mmol). El disolvente se evaporó bajo presión reducida para producir 2.3g (81%) del producto del título. NMR (500 MHz, CD_3COOD) 0.96-1.01 (m, 6H), 1.49 (s, 9H), 2.13-2.23 (m 1H), 3:76 (AB, 2H), 4.28-4.33 (m, 1H).

Método 12

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina**

Una mezcla de ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (0.0153g, 0.031 mmol), *terc*-butil glicil-D-valinato clorhidrato (0.0099 g, 0.037 mmol) y N-metilmorfolina (0.010ml, 0.091 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.016 g, 0.050 mmol), y la mezcla se agitó durante 3.5 horas. Se agregó ácido trifluoroacético (0.5 ml) y, luego de 3.5 horas, el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa en una columna Kromasil C8, usando una gradiente de 5-100% MeCN en 0.15% tampón de ácido trifluoroacético como eluyente. El disolvente se retiró bajo presión reducida y se obtuvo0.015 g (74 %) del producto del título. M/z 652.20.

Método 13

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina**

Una mezcla de ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (0.150g, 0.30 mmol), *terc*-butil glicinato clorhidrato (0.0635 g, 0.38 mmol) y N-metilmorfolina (0.10ml, 0.91 mmol) in DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.128 g, 0.40 mmol), y la mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (4.0ml) y, después de 2 horas, el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa en una columna Kromasil C8, usando 35% MeCN en 0.1M tampón de acetato de amonio como eluyente. El disolvente se retiró bajo presión reducida y se obtuvo 0.159 g (95 %) del producto del título. M/z 553.02.

Método 14

_N_-{[4-((2_R_,3_R_)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil] tio}-4-xoazetidin-2-il)fenoxi]acetil} glicil-2-butilnorleucina

_N_-{[4-((2_R_,3_R_)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (0.020 g, 0.037 mmol) y NMM (0.040ml, 0.363 mmol) se disolvieron en DCM (5 ml) a 30°C. Se agregó en porciones TBTU (un total de 0.016 g, 0.050 mmol), y la mezcla se agitó durante 1 hora. Se agregó 2-butilnorleucina (0.007 g, 0.037 mmol) y la mezcla se agitó a 30°C durante 18 horas. La mezcla de reacción se concentró bajo presión reducida y el residuo se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.009 g (34 % de rendimiento) del producto del título como un sólido blanco. M/z: 710.1. ^{1}H NMR (DMSO, 400 MHz): δ 0.73-0.82 (m, 6H), 0.88-1.22 (m, 8H), 1.56-1.69 (m, 2H), 1.96-2.07 (m, 2H), 3.71 (d, 2H), 4.32 (d, 1H), 4.36 (ABq, 2H), 4.52 (s, 2H), 5.16 (d, 1H), 6.95-7.01 (m, 2H), 7.11-7.26 (m,4H), 7.30-7.40 (m, 4H), 7.61 (s, 1H), 7.98-8.06 (m, 2H), 8.25-8. 42 (m, 1H).

Método 15

_N_-{[4-((2_R_,3_R_)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-alanina

Una solución de ácido [4-((2_R_,3_R_)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (0.020 g, 0.041 mmol), L-alanina *terc*-butil éster clorhidrato (0.009 g, 0.050 mmol) y _N_-metilmorfolina (0.018 ml, 0.163 mmol) en DCM (4ml) se agitó durante 5 minutos. Se agregó TBTU (0.017 g, 0.053 mmol). Se confirmó la formación del éster luego de 3 horas. M/z: 611.1. Se agregó TFA (3 ml). Pasadas 2 horas, la mezcla se diluyó con tolueno (2 ml), y el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa,

usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.023 g (> 98%) del producto del título como un sólido blanco. M/z: 555.1.1H NMR (DMSO, 400 MHz): δ 1.17 (d, 3H), 3.73- 3.82 (m, 1H), 4.33 (d, 1H), 4.35 (ABq, 2H), 4.43 (s, 2H), 5.15 (d, 1H), 6.92-7.98 (m, 2H), 7.10-7.24 (m, 4H), 7.29-7.39 (m, 4H), 7.84 (d, 1H), 7.97-8.04 (m, 2H).

Método 16

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-fenilalanina**

Metil *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-fenilalaninato (20 mg, 0.029 mmol) se disolvió en 1.6 ml MeOH y 0.2 ml H_2O. Se agregó Et_3N (0.2 ml, 1.44 mmol), y la mezcla se agitó de un día para otro. La mezcla se calentó a 80°C durante 7 horas. La mezcla se purificó por HPLC preparativa usando una columna C8 (25x300mm). Una gradiente de 20% a 40% MeCN en 0.1 M acetato de amonio se usó como fase móvil. La fracción del producto se concentró y se liofilizó para proporcionar 7 mg (36%). M/z: 688.

Método 17

Metil *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-L-fenilalaninato

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (66 mg, 0.12 mmol) se disolvió en 2 ml DCM. Se agregaron *N*-metilmorfolina (40 ul, 0.36 mmol), L-(S)-fenilalanina metil éster clorhidrato (33 mg, 0.15 mmol) y, finalmente, TBTU (45 mg, 0.14 mmol). La mezcla se agitó de un día para otro. La

mezcla cruda se purificó por cromatografía de destello en 5g SiO_2. EtOAc:Hex (1:1), DCM y, finalmente, DCM: Acetona (4:1) se usaron como eluyentes. La fracción recogida se concentró para proporcionar 67mg (78%) del compuesto del título. M/z: 702 (M+1).

Método 18

***terc*-Butil *N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-4-metil-leucinato**

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina (20 mg, 0.037 mmol) se disolvió en 3 ml DCM. Se agregaron N-metilmorfolina (9 µl, 0.082 mmol) y TBTU (14 mg, 0.044 mmol). Pasados 5 minutos, se agregó *terc*-butil 4-metil-leucinato (9 mg, 0.045 mmol) y la mezcla se agitó durante 2 horas. Se agregó más *terc*-butil 4-metil-leucinato (aprox. 3 mg, 0.015 mmol). Después de 15 minutos, se agregó agua (2 ml), y la mezcla se acidificó a un pH de 2 usando 2M $KHSO_4$. La fase acuosa se extrajo con 2ml DCM, y las fases orgánicas combinadas se lavaron con 3 ml de agua, se secaron sobre Na_2SO_4 y se filtraron. El retiro del disolvente bajo presión reducida produjo el compuesto del título. M/z: 724.

Método 19

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicilglicina**

Una solución de ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (0.200 g, 0.414 mmol), glicilglicina metil éster clorhidrato (0.090 g, 0.493 mmol) y N-metilmorfolina (0.150 ml) en DCM (5ml) se agitó durante 10 minutos. Se agregó TBTU (0.170 g) y la mezcla se agitó durante 20 horas. Se confirmó

la formación del éster. M/z: 612.0. El disolvente se retiró bajo presión reducida. El residuo se disolvió en una mezcla de MeOH (5 ml), agua (1 ml) y Et_3N (0.5 ml). La solución se agitó a 50°C durante 18 horas. Se agregó DBN (0.050 ml, 0.405 mmol), y la mezcla se agitó durante 2 horas a 50°C. Se agregó tampón de acetato de amonio (0.1 M, 3ml) y la mezcla se concentró. El residuo se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo el producto del título (0.094 g, 38 % de rendimiento) como un sólido blanco. M/z: 598.2. ^{1}H NMR (DMSO, 400 MHz): 3.50 (d, 2H), 3.75 (d, 2H), 4.32 (d, 1H), 4.35 (ABq, 2H), 4.46-4.53 (m, 2H), 5.15 (d, 1H), 6.94-7.00 (m, 2H), 7.10-7.25 (m, 4H), 7.29-7.39 (m,4H), 7.68-7.81 (m, 1H), 7.98-8.04 (m, 2H), 8.30-8.36 (m, 1H).

Método 20

Etil {[(5, 5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}acetato

Etil [(2-oxo-2-feniletil)tio]acetato (10.8 g, 45.3 mmol) se disolvió en tolueno (250 ml). Se agregaron 2,2-dimetil-1,3-propanodiol (37.6 g, 0.36 mol) y ácido p-toluensulfónico (cat., 500 mg). La mezcla se agitó a reflujo en un aparato Dean-Stark durante dos horas y a temperatura de la sala de un día para otro. La mezcla se concentró bajo presión reducida.

El aceite crudo se purificó por cromatografía de destello (hexano: EtOAc-7:1) para producir 11.2 g (70 %) del compuesto del título como un aceite incoloro. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2- 1.3 (t, 3H), 1.4 (s, 3H), 3.0 (s, 2H), 3.2 (s, 2H), 3.5 (s, 4H), 4.1-4.2 (q, 2H), 7.3-7.6 (m, 5H).

Método 21

Ácido {[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}acético

Etil{[(5, 5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}acetato (11.2 g, 34.3 mmol) se disolvió en THF (150 ml) y se enfrió a 0°C. Se agregó LiOH (2.88 g, 68.7 mmol) en agua (40 ml), y la mezcla se agitó durante 19 horas. Los disolventes se evaporaron. El producto crudo se extrajo entre agua y éter dietílico. La capa acuosa se acidificó a un pH de 6 usando 2M HCl, y se extrajo dos veces con CH_2Cl_2. Las capas CH_2Cl_2 combinadas se secaron (Na_2SO_4) y se concentraron bajo presión reducida para producir 9.8 g (96 %) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.4 (s, 3H), 3.0 (s, 2H), 3.3 (s, 2H), 3.5 (s,4H), 7.3-7.6 (m,5H).

Método 22

(4*S*)-3-({[(5,5-Dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}acetil)-4-fenil-1,3-oxazolidin-2-ona

Ácido {[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}acético (9.9 g, 33.0 mmol) se disolvió en CH_2Cl_2 seco (250 ml) y se enfrió a 0°C. Se agregaron N,N'-diciclohexilcarbodiimida (DCC, 7.63 g, 37.0 mmol) y 4-(dimetilamino)piridine (DMAP, 8.57 g, 70.0 mmol), y la mezcla se agitó a 0°C durante 20 minutos. Se agregó (S)-(+)-4-Fenil-2-oxazolidinona (5.38 g, 33.0 mmol), y la mezcla se agitó a temperatura de la sala durante 70 horas. La mezcla se filtró, se concentró bajo presión reducida y se purificó por cromatografía de destello (hexano: EtOAc-7:3). Esto proporcionó 10.2 g (70 %) del compuesto del título como un sólido blanco. ^{1}H- NMR ($CDCl_3$, 200 MHz): 0.6 (s, 3H), 1.3 (s, 3H), 2.8 (s, 2H), 3.4 (s, 4H), 3.8 (s, 2H), 4.1-4.15 (dd, 1H), 4.6-4.8 (t, 1H), 5.35-5.45 (dd, 1H), 7.25-7.45 (m, 9H).

Método 23

Etil (4-{(1*S*,2*R*)-1-anilino-2-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil] tio}-3-oxo-3-[(4*S*)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil} fenoxi)acetato

Tetraisopropil ortotitanato (0.5 ml, 1.7 mmol) se agregó a una solución de $TiCl_4$ (1M in CH_2Cl_2, 5.1 ml, 5.1 mmol) en CH_2Cl_2 (50 ml) a 0°C bajo una atmósfera inerte. La mezcla se agitó durante 10 minutos. (4*S*)-3-({[(5,5-Dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}acetil)-4-fenil-1,3-oxazolidin-2-ona (3.0 g, 6.8 mmol) en CH_2Cl_2 seco (60 ml) se agregó gota a gota durante 20 minutos, y la mezcla se agitó durante 10 minutos. Se agregó gota a gota etil {4-[(fenilimino)metil]fenoxi}acetato (3.8 g, 13.6 mmol) en CH_2Cl_2 seco (60 ml) durante 30 minutos, y la mezcla se enfrió a -40°C y se agitó durante 20 minutos. Se agregó gota a gota etil diisopropil amina (2.3 ml, 13.6 mmol) durante diez minutos y la mezcla se agitó a -40°C durante seis horas. La mezcla se enfrió a -78°C y se agregó isopropanol (90ml). La mezcla se calentó lentamente a temperatura de la sala de un día para otro. Se agregó H_2O (100 ml), y la mezcla se agitó durante 35 minutos a temperatura de la sala. Se agregó NH_4Cl (10%) y la mezcla se extrajo dos veces con éter dietílico.

Las capas orgánicas combinadas se lavaron con agua, se secaron ($MgSO_4$) y se concentraron bajo presión reducida. Purificación por cromatografía de destello (hexano:EtOAc 5:1, luego 7:3, luego 6:4) produjo 2.13 g (43 %) del compuesto del título como un sólido amarillo. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2-1.4 (m, 6H), 2.8-3.0 (m, 2H), 3.3-3.5 (m, 4H), 4.5-4.7 (m, 3H), 5.3-5.5 (m, 1H), 5.7-5.8 (d, 1H), 6.4-6.5 (d, 2H), 6.6-6.9 (m, 4H), 6.9-7.0 (d, 2H), 7.0-7.5 (m, 7H). M/z: 747.3 (M^+ + Na)

Método 24

Etil [4-((2*R*,3*R*)-3-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil] tio}-4-oxo-1-fenilazetidin-2-il)fenoxi]acetato

Etil (4-{(1*S*,2*R*)-1-anilino-2-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil] tio}-3-oxo-3-[(4*S*)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil} fenoxi)acetato (2.1 g, 2.9 mmol) se disolvió en tolueno seco (200ml) y se calentó a 90°C bajo una atmósfera inerte. Se agregó N,O-bis(trimetilsilil) acetamida (BSA, 2.1 ml, 8.7 mmol), y la mezcla se agitó a 90°C durante 1 horas. A 45°C se agregó fluoruro de tetrabutilamonio (TBAF, cat., 0.1 g), y la mezcla se agitó a 45°C durante 18 horas. La mezcla se concentró bajo presión reducida. El residuo se purificó por cromatografía de destello (hexano: EtOAc 5:1). Esto proporcionó 0.98 g (60 %) del compuesto del título como un aceite amarillo. ^{1}H-NMR ($CDCl_3$, 200 MHz): 0.6 (s, 3H), 1.2-1.4 (m, 6H), 3.0-3.2 (t, amplio, 2H), 3.3-3.5 (m, 4H), 3.95 (d, 1H), 4.2-4.4 (q, 2H), 4.6 (s, 2H), 4.8 (d, 1H), 6.9-7.1 (m, 3H), 7.2-7.6 (m, 11H). MS (CI) M/z: 584.2 (M^+ + Na).

Método 25

***terc*-Butil (4-{(1*S*,2*R*)-2-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil] tio}-1-[(4-fluorofenil)amino]-3-oxo-3-[(4*S*)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil}fenoxi)acetato**

Tetraisopropil ortotitanato (0.51 ml, 1.8 mmol) se agregó a una solución de $TiCl_4$ (1M in CH_2Cl_2, 5.1 ml, 5.1 mmol) en CH_2Cl_2 (50 ml) a 0°C bajo una atmósfera inerte. La mezcla se agitó durante 10 minutos. (4S)-3-({[(5,5-Dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}acetil)-4-fenil-1,3-oxazolidin-2-ona (3.0 g, 6.8 mmol) en CH_2Cl_2 seco (50 ml) se agregó gota a gota durante 20 minutos. Luego de 10 minutos, se agregó gota a gota *terc*-butil (4-{[(4-fluorofenil)imino]metil}fenoxi)acetato (4.5 g, 13.6 mmol) en CH_2Cl_2 seco (50ml) durante 30 minutos. La mezcla se enfrió a -30°C y se agitó durante 20 minutos. Se agregó gota a gota etil diisopropil amina (2.3 ml, 13.4 mmol) en 20 ml CH_2Cl_2 seco durante diez minutos, y la mezcla se agitó a -30°C durante 6 horas. La mezcla se enfrió a -78°C. Se agregó isopropanol

(60 ml) y se aumentó la temperatura de un día para otro. Se agregó H_2O (100 ml), y la mezcla se agitó durante 35 minutos a temperatura de la sala. La mezcla se extrajo dos veces con éter dietílico. Las capas orgánicas combinadas se lavaron con agua, se secaron ($MgSO_4$) y se concentraron bajo presión reducida. Purificación por cromatografía de destello (hexano:EtOAc 5:1) proporcionó 2.95 g (56%) del compuesto del título como un sólido amarillo. M/z: 793.3 (M^+ + Na).

Método 26

***terc*-Butil {4-[(2*R*,3*R*)-3-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acetato**

terc-Butil (4-{(1*S*,2*R*)-2-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}-1-[(4-fluorofenil)amino]-3-oxo-3-[(4S)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil}fenoxi)acetato (2.6 g, 3.4 mmol) se disolvió en tolueno seco (250 ml) y se calentó a 90°C bajo una atmósfera inerte. Se agregó N,O-Bis (trimetilsilil)acetamida (BSA, 2.5 ml, 10.3 mmol), y la mezcla se agitó a 90°C durante 1 hora. La mezcla se enfrió a 45°C, y se agregó fluoruro de tetrabutilamonio (TBAF, cat., 0.5 g). La mezcla se agitó a 45°C durante 2 horas. La mezcla se concentró bajo presión reducida y se purificó por cromatografía de destello (hexano: EtOAc 7:1). Esto proporcionó 0.65 g (31 %) del compuesto del título como un sólido amarillo. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2 (s, 3H), 1.5 (s, 9H), 2.9-3.1 (q, amplio, 2H), 3.4 (q, 4H), 4.0 (s, 1H), 4.5 (s, 2H), 4.8 (s, 1H), 6.9-7.0 (m, 4H), 7.2-7.3 (m, 5H), 4.3-4.4 (m, 4H).

Método 27

Ácido (4-{(2*R*,3*R*)-1-(4-fluorofenil)-4-oxo-3-[(2-oxo-2-feniletil)tio] azetidin-2-il}fenoxi)acético

terc-Butil{4-[(2*R*,3*R*)-3-{[(5,5-dimetil-2-fenil-1,3-dioxan-2-il)metil]tio}-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acetato (1.34 g, 2.21 mmol) se disolvió en ácido fórmico (20 ml) y se agitó durante 90 minutos. La mezcla se concentró bajo presión reducida (temperatura <30°C). El aceite crudo se purificó por cromatografía de destello (hexano:acetona:ácido fórmico 60:40:0.1) para proporcionar 0.7 g (68 %) del compuesto del título como un sólido amarillo pálido. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 4.15 (d, 1H), 4.22 (d, 2H), 4.71 (s, 2H), 4.91 (d, 1H), 6.92-7.00 (m, 4H), 7.24-7.30 (m, 4H), 7.46-7.63 (m, 3H), 7.94-7.99 (d, 2H). MS (CI) M/z: 464.2 (M-1).

Método 28

Etil ({[2-(4-metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acetato

Etil {[2-(4-metoxifenil)-2-oxoetil]tio}acetato (9.57 g, 35.7 mmol) se disolvió en benceno (250 ml). Se agregaron 2,2-dimetil-1,3-propanodiol (29.7 g, 0.29 mol) y ácido *p-toluen*sulfónico (500 mg). La mezcla se agitó a reflujo en un aparato Dean-Stark durante 3 horas y a temperatura de la sala de un día para otro. La mezcla se concentró bajo presión reducida. Se agregó CH_2Cl_2 y la solución se lavó dos veces con H_2O y con salmuera. La fase orgánica se secó ($MgSO_4$) y se filtró. Concentración bajo presión reducida proporcionó un aceite crudo, el cual se purificó por cromatografía de destello (hexano:EtOAc 7:1) para proporcionar 5.95 g (47 %) del compuesto del título como un aceite incoloro. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2-1.4 (m, 6H), 3.0 (s, 2H), 3.2 (s, 2H), 3.4 (s, 4H), 3.8 (s, 3H), 4.2 (q, 2H), 6.9 (d, 2H), 7.4 (d, 2H).

Método 29

Ácido ({[2-(4-metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acético

Etil ({[2-(4-metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acetato (5.95 g, 16.8 mmol) se disolvió en THF (75 ml) y se enfrió a 0°C. Se agregó LiOH (2.11 g, 50.4 mmol) en agua (40 ml), y la mezcla se agitó durante 90 minutos. Se agregó agua, y la mezcla se extrajo dos veces con éter dietílico. La capa acuosa se acidificó usando 2M HCl hasta logra un pH=4 y se extrajo dos veces con CH_2Cl_2. Las capas CH_2Cl_2 combinadas se secaron (Na_2SO_4) y se concentraron bajo presión reducida para proporcionar 5.4 g (>98%) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.4 (s, 3H), 3.0 (s, 2H), 3.4 (s, 2H), 3.5 (s, 4H), 3.9 (s, 3H), 6.9 (d, 2H), 7.4 (d, 2H).

Método 30

(4*S*)-3-[({[2-(4-Metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio) acetil]-4-fenil-1,3-oxazolidin-2-ona

Ácido ({[2-(4-metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acético (5.4 g, 16.5 mmol) se disolvió en CH_2Cl_2 seco (80 ml) y se enfrió a 0°C. Se agregaron N,N'-diciclohexilcarbodiimida (DCC, 3.76 g, 18.2 mmol) en 20 ml de CH_2Cl_2 y 4-(dimetilamino)piridina (DMAP, 4.04 g, 33.1 mmol), y la mezcla se agitó a 0°C durante 30 minutos. Se agregó (S)-(+)-4-fenil-2-oxazolidinona (2.69 g, 16.5 mmol), y la mezcla se agitó a temperatura de la sala durante 17 horas. La mezcla se filtró, se concentró bajo presión reducida y se purificó por cromatografía de destello (hexano: EtOAc 4:1 luego 2:1). Esto proporcionó 5.69 g (73 %) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 2.8 (s, 2H), 3.4 (s, 4H), 3.8 (s, 2H), 3.8 (s, 3H), 4.3 (dd, 1H), 4.7 (t, 1H), 5.4 (dd, 1H), 6.9 (d, 2H), 7.3 (m, 7H).

Método 31

***terc*-Butil (4-{(1*S*,2*R*)-1-[(4-fluorofenil)amin]-2-({[2-(4-metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)-3-oxo-3-[(4S)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil}fenoxi)acetato**

Tetraisopropil ortotitanato (0.31 ml, 1.06 mmol) se agregó a una solución de $TiCl_4$ (1M in CH_2Cl_2, 3.18 ml, 3.18 mmol) en CH_2Cl_2 (50ml) a 0°C bajo una atmósfera inerte. La mezcla se agitó durante 10 minutos. Se agregó gota a gota (4*S*)-3-[({[2-(4-metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acetil]-4-fenil-1,3-oxazolidin-2-ona (2.00 g, 4.24 mmol) en CH_2Cl_2 seco (50 ml) durante 20 minutos. La mezcla se agitó durante 10 minutos. Se agregó gota a gota *terc*-butil (4-{[(4-fluorofenil)imino]metil}fenoxi)acetato (2.79 g, 8. 48 mmol) en CH_2Cl_2 seco (50 ml) durante 30 minutos. La mezcla se enfrió a -30°C y se agitó durante 20 minutos. Se agregó gota a gota durante diez minutos etil diisopropil amina (1.45ml, 8.48 mmol) en 10 ml CH_2Cl_2 seco, y la mezcla se agitó a -30°C durante 5 horas. La mezcla se enfrió a -78°C. Se agregó isopropanol (60 ml), y se dejó aumentar la temperatura de un día para otro. Se agregó H_2O (100 ml), y la mezcla se agitó durante 20 minutos y se extrajo dos veces con éter dietílico. Las capas orgánicas combinadas se lavaron con agua, se secaron ($MgSO_4$) y se concentraron bajo presión reducida. Purificación por cromatografía de destello (hexano: EtOAc 3:1) proporcionó 2.00 g (59 %) del compuesto del título como un sólido amarillo. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 1.5 (s, 9H), 2.6-2.9 (m, 2H), 3.3-3.5 (m, 4H), 3.8 (s, 3H), 4.1-4.3 (m, 2H), 4.5 (s, 2H), 4.6-4.8 (m, 2H), 5.0-5.4 (s, amplio, 1H), 5.4 (m, 1H), 5.7 (d, 1H), 6.4 (m, 2H), 6.6-6.8 (m, 4H), 6.8-7.0 (m, 4H), 7.1-7.4 (m, 7H).

Método 32

***terc*-Butil {4-[(2*R*,3*R*)-1-(4-fluorofenil)-3-({[2-(4-metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)-4-oxoazetidin-2-il]fenoxi}acetato**

terc-Butil (4-{(1*S*,2*R*)-1-[(4-fluorofenil)amino]-2-({[2-(4-metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)-3-oxo-3-[(4*S*)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil}fenoxi)acetato (2.0 g, 2.5 mmol) se disolvió en tolueno seco (200ml) y se calentó a 90°C bajo una atmósfera inerte. Se agregó N,O-Bis(trimetilsilil)acetamida (BSA, 1.8 ml, 7.5 mmol), y la mezcla se agitó a 90°C durante 1 hora. La mezcla se enfrió a 45°C, y se agregó fluoruro de tetrabutilamonio (TBAF, 150 mg) y la mezcla se agitó a 45°C durante 2 horas. La mezcla se concentró bajo presión reducida y se filtró a través de una corta columna de sílice (hexano:EtOAc 4:1). Purificación del aceite crudo por cromatografía de destello (hexano: EtOAc 5:1) produjo 0.65 g (41%) del compuesto del título como un sólido amarillo. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 1.5 (s, 9H), 3.0-3.2 (m, 2H), 3.3-3.5 (m, 4H), 3.8 (s, 3H), 4.0 (d, 1H), 4.5 (s, 2H), 4.8 (d, 1H), 6.8-7.0 (m, 6H), 7.2-7.4 (m, 6H).

Método 33

Ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético

terc-Butil{4-[(2*R*,3*R*)-1-(4-fluorofenil)-3-({[2-(4-metoxifenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)-4-oxoazetidin-2-il]fenoxi}acetato (0. 65 g, 1.02 mmol) se disolvió en ácido fórmico (10 ml) y se agitó durante 90 minutos. La mezcla se concentró bajo presión reducida (temperatura < 30°C), y el aceite crudo se purificó por cromatografía de destello (hexano:acetona:ácido fórmico 60:40:0.1) para proporcionar 0.45 g (88 %) del compuesto del título como un sólido amarillo pálido. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 3.9 (s, 3H), 4.1 (d, 1H), 4.1 (s, 2H), 4.7 (s, 2H), 4.9 (d, 1H), 6.9-7.1 (m, 6H), 7.2-7.4 (m, 4H), 7.9-8.0 (d, 2H). MS (CI) M/z: 494.1 (M^+-1), 495.1 (M^+)

Método 34

Etil ({[5,5-dimetil-2-(4-metilfenil)-1,3-dioxan-2-il]metil}tio)acetato

Etil {[2-(4-metilfenil)-2-oxoetil]tio}acetato (12.2 g, 48.4 mmol) se disolvió en benceno (350 ml). Se agregaron 2,2-dimetil-1,3-propanodiol (40.3 g, 0.387 mol) y ácido *p-toluen* sulfónico (1g). La mezcla se agitó a reflujo en un aparato Dean-Stark durante 2 horas, se enfrió y se concentró bajo presión reducida. Se agregó CH_2Cl_2 y la fase orgánica se lavó dos veces con salmuera y se secó ($MgSO_4$). Filtración y concentración bajo presión reducida proporcionaron un aceite crudo, el cual se purificó por cromatografía de destello (hexano:EtOAc 8:1) para proporcionar 10.0 g (61%) del compuesto del título como un aceite claro.
^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2-1.4 (m, 6H), 2.4 (s, 3H), 3.0 (s, 2H), 3.2 (s, 2H), 3.4-3.5 (m, 4H), 4.2 (q, 2H), 7.2-7.4 (m, 4H).

Método 35

Ácido ({[5,5-dimetil-2-(4-metilfenil)-1,3-dioxan-2-il]metil}tio)acético

Etil ({[5,5-dimetil-2-(4-metilfenil)-1,3-dioxan-2-il]metil}tio)acetato (10.1 g, 29.8 mmol) se disolvió en THF (150ml) y se enfrió a 0°C. Se agregó LiOH (3.76 g, 89.5 mmol) en agua (50 ml), y la mezcla se agitó durante 2 horas a temperatura de la sala. La mezcla se concentró bajo presión reducida. Se agregó agua y la mezcla se extrajo con éter dietílico. La capa acuosa se acidificó usando 2M HCl a pH 3 y se extrajo dos veces con CH_2Cl_2. Las capas CH_2Cl_2 combinadas se secaron (Na_2SO_4) y se concentraron bajo presión reducida para proporcionar 8.7 g (94 %) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2 (s, 3H), 2.4 (s, 3H), 3.0 (s, 2H), 3.4 (s, 2H), 3.4 (s, 4H), 7.2-7.4 (m. 4H).

Método 36

(4*S*)-3-[({[5,5-Dimetil-2-(4-metilfenil)-1,3-dioxan-2-illmetil]tio)acetil]-4-fenil-1,3-oxazolidin-2-ona

Ácido ({[5,5-dimetil-2-(4-metilfenil)-1,3-dioxan-2-il]metil}tio)acético (8.7 g, 28.0 mmol) se disolvió en CH_2Cl_2 seco (120 ml) y se enfrió a 0°C. Se agregaron N,N'-diciclohexilcarbodiimida (DCC, 6.35 g, 30.8 mmol) en 30 ml de CH_2Cl_2 y 4-(dimetilamino)piridina (DMAP, 6.85 g, 56.1 mmol). La mezcla se agitó a 0°C durante 30 minutos. Se agregó (S)-(+)-4-fenil-2-oxazolidinona (4.57 g, 28.0 mmol), y la mezcla se agitó a temperatura de la sala durante 19 horas. La mezcla se filtró, se concentró bajo presión reducida y se purificó por cromatografía de destello (hexano: EtOAc 5:1 luego 4:1). Esto proporcionó 7.07 g (55 %) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2 (s, 3H), 2.4 (s, 3H), 2.8 (s, 2H), 3.4 (s,4H), 3.8 (s, 2H), 4.3 (dd, 1H), 4.7 (t, 1H), 5.4 (dd, 1H), 7.2-7.5 (m, 9H).

Método 37

***terc*-Butil (4-{(1*S*,2*R*)-2-({[5,5-dimetil-2-(4-metilfenil)-1,3-dioxan-2-il] metil}tio)-1-[(4-fluorofenil)amino]-3-oxo-3-[(4*S*)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil}fenoxi)acetato**

Tetraisopropil ortotitanato (0.37 ml, 1.23 mmol) se agregó a una solución de $TiCl_4$ (1M in CH_2Cl_2, 3.3ml, 3.3 mmol) en CH_2Cl_2 (50ml) a 0°C bajo una atmósfera inerte. La mezcla se agitó durante 10 minutos. Se agregó gota a gota durante 20 minutos (4*S*)-3-[({[5,5-dimetil-2-(4-metilfenil)-1,3-dioxan-2-il]metil}tio)acetil]-4-fenil-1,3-oxazolidin-2-ona (2.0 g, 4.4 mmol) en CH_2Cl_2 seco (50 ml), y la mezcla se agitó durante 10 minutos. Se agregó gota a gota durante 30 minutos *terc*-butil (4-{[(4-fluorofenil)imino]metil}fenoxi)acetato (2.9 g, 8.8 mmol) en CH_2Cl_2 seco (50 ml). La mezcla se enfrió a -30°C y se agitó durante 20 minutos. Se

agregó gota a gota durante diez minutos etil diisopropil amina (1.5 ml, 8.8 mmol) en 10 ml CH_2Cl_2 seco. La mezcla se agitó a -30°C durante 4 horas. La mezcla se enfrió a -78°C, y se agregó isopropanol (60 ml). La temperatura se dejó alcanzar la temperatura de la sala durante dos horas. Se agregó H_2O (100 ml), y la mezcla se agitó durante 20 minutos y se extrajo dos veces con éter dietílico. Las capas orgánicas combinadas se lavaron con agua, se secaron ($MgSO_4$) y se concentraron bajo presión reducida. Purificación por cromatografía de destello (hexano: EtOAc 5:1 luego 4:1) proporcionó 2.55 g (74 %) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 1.5 (s, 9H), 2.4 (s, 3H), 2.6-2.9 (m, 2H), 3.3-3.5 (m, 4H), 4.1-4.3 (m, 1H), 4.5 (s, 2H), 4.6-4.8 (m, 2H), 5.0-5.3 (s, amplio, 1H), 5.2 (m, 1H), 5.7 (d, 1H), 6.4 (m, 2H), 6.6-6.8 (m, 4H), 6.9 (m, 2H), 7.1-7.4 (m, 9H).

Método 38

***terc*-butil {4-[(2*R*,3*R*)-3-({[5,5-dimetil-2-(4-metilfenil)-1,3-dioxan-2-il] metil}tio)-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi} acetato**

terc-butil (4-{(1*S*,2*R*)-2-({[5,5-dimetil-2-(4-metilfenil)-1,3-dioxan-2-il]metil}tio)-1-[(4-fluorofenil)amino]-3-oxo-3-[(4*S*)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil}fenoxi)acetato (2.55 g, 3.25 mmol) se disolvió en tolueno seco (250 ml) y se calentó a 90°C bajo una atmósfera inerte. Se agregó N,O-Bis (trimetilsilil)acetamida (BSA, 2.38 ml, 9.75 mmol), y la mezcla se agitó a 90°C durante 1 hora. La mezcla se enfrió a 45°C, y se agregó fluoruro de tetrabutilamonio (TBAF, 0.25 g), y la mezcla se agitó a 45°C durante 1 hora. La mezcla se concentró bajo presión reducida y se purificó por cromatografía de destello (hexano: EtOAc 6:1). Esto proporcionó 1.06 g (52 %) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.3 (s, 3H), 1.5 (s,9H), 2.4 (s, 3H), 3.0-3.2 (m, 2H), 3.3-3.5 (m, 4H), 3.9 (d, 1H), 4.5 (s, 2H), 4.8 (d, 1H), 6.8-7.0 (m, 6H), 7.1-7.4 (m, 6H).

Método 39

Ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metilfenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético

terc-Butil {4-[(2*R*,3*R*)-3-({[5,5-dimetil-2-(4-metilfenil)-1,3-dioxan-2-il]metil}tio)-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acetato (1.04 g, 1.67 mmol) se disolvió en ácido fórmico (20 ml) y se agitó durante 60 minutos. La mezcla se concentró bajo presión reducida (temperatura <30°C), y el aceite crudo se purificó por cromatografía de destello (hexano: acetona: ácido fórmico 60:40:0.1) para proporcionar 0.72 g (90%) del compuesto del título como un sólido amarillo pálido. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.4 (s, 3H), 4.1 (d, 1H), 4.2 (s, 2H), 4.7 (s, 2H), 4.9 (d, 1H), 6.9 (m, 6H), 7.2-7.4 (m, 4H), 7.8 (d, 2H). MS (CI) M/z: 478.1 (M+-1).

Método 40

***terc*-Butil (4-{(*E*)-[(4-clorofenil)imino]metil}fenoxi)acetato**

Una suspensión de NaH (60 % en aceite mineral, 3.69 g, 92.2 mmol) en DMF seco (70 ml) se enfrió a 0°C. Una solución de 4-hidroxibenzaldehído (10.0 g, 82.0 mmol) en DMF seco (35 ml) se agregó gota a gota. La mezcla se agitó a 0°C durante 40 minutos. Se agregó *terc*-butil bromoacetato (12.1ml, 82.5 mmol), y la mezcla se agitó a temperatura de la sala durante 17 horas. La mezcla se concentró bajo presión reducida. Se agregó éter dietílico y la mezcla se lavó con 10% NH_4Cl, agua y salmuera. La fase orgánica se secó ($MgSO_4$), se concentró bajo presión reducida y se purificó por cromatografía de destello (10%-20% EtOAc en hexano). Esto produjo *terc*-butil (4-formilfenoxi)acetato (17.4 g, 73.4 mmol, 90% de rendimiento) como un aceite incoloro. Este intermedio se disolvió en tolueno seco (120 ml), y se agregó 4-cloroanilina (9.37 g, 73.4 mmol). La mezcla se hizo

refluir en un aparato Dean-Stark durante 20 horas, se enfrió y se concentró bajo presión reducida. Se agregó hexano y el precipitado formado se filtró, se lavó dos veces con hexano frío y se secó. Esto proporcionó 20.0 g (79%) del compuesto del título como un sólido amarillo. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.5 (s, 9H), 4.6 (s, 2H), 7.0 (d, 2H), 7.2 (d, 2H), 7.4 (d, 2H), 7.8 (d, 2H), 8.4 (s, 1H). MS (CI) M/z: 368.0 (M^++Na, 100), 369.0 (20), 370.0 (30), 371.0 (10).

Método 41

Etil ({[2-(4-clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio) acetato

Etil {[2-(4-clorofenil)-2-oxoetil]tio}acetato (8.15 g, 29.9 mmol) se disolvió en tolueno (165 ml). Se agregaron 2,2-dimetil-1,3-propanodiol (24.8 g, 238 mmol) y ácido *p-toluen*sulfónico (300 mg). La mezcla se agitó a reflujo en un aparato Dean-Stark durante 2.5 horas y se concentró bajo presión reducida. El producto crudo se disolvió en CH_2Cl_2. La mezcla se lavó con H_2O (3x), salmuera, se secó (Na_2SO_4) y se concentró bajo presión reducida. El residuo se purificó por cromatografía de destello (Hexano:EtOAc 9:1) para producir 3.36 g (31 %) del compuesto del título como un aceite amarillo. MS (CI) M/z: 381.0 (M^+ + Na, 100), 382.0 (15), 383.0 (30), 384 (5)

Método 42

Ácido ({[2-(4-clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acético

Etil ({[2-(4-clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acetato (3.36 g, 9.36 mmol) se disolvió en THF (45ml) y se enfrió a 0°C. Se agregó LiOH (0.79 g, 18.8 mmol) en agua (12 ml), y la mezcla se agitó durante 18 horas a temperatura de la sala. Los disolventes se evaporaron. El producto crudo se extrajo entre agua y éter dietílico. La capa acuosa se acidificó

usando 2M HCl a pH 6 y se extrajo dos veces con CH_2Cl_2. Las capas CH_2Cl_2 combinadas se secaron (Na_2SO_4) y se concentraron bajo presión reducida para proporcionar 2.98 g (96 %) del compuesto del título como un aceite amarillo. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.62 (s, 3H), 1.34 (s, 3H), 2.95 (s, 2H), 3.34 (s, 2H), 3.45 (s, 4H), 7.4 (m, 4H)

Método 43

(4*S*)-3-[({[2-(4-Clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acetil]-4-fenil-1,3-oxazolidin-2-ona

Ácido ({[2-(4-clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acético (2.00 g, 6.05 mmol) se disolvió en CH_2Cl_2 seco (45 ml) y se enfrió a 0°C. Se agregaron N,N'-diciclohexilcarbodiimida (DCC, 1.43 g, 6.93 mmol) y 4-(dimetilamino)piridina (DMAP, 1.70 g, 10.4 mmol), y la mezcla se agitó a 0°C durante 20 minutos. Se agregó (S)-(+)-4-Fenil-2-oxazolidinona (1.40 g, 11.5 mmol), y la mezcla se agitó a temperatura de la sala durante 70 horas. La mezcla se filtró, se concentró bajo presión reducida y se purificó por cromatografía de destello (20%-30% EtOAc en hexano). Esto proporcionó 1.27 g (44 %) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.62 (s, 3H), 1.34 (s, 3H), 2.78 (s, 2H), 3.42 (s, 4H), 3.85 (s, 2H), 4.27-4.33 (dd, 1H), 4.69-4.78 (t, 1H), 5.34-5.42 (dd, 1H), 7.29-7.38 (m, 9H).

Método 44

***terc*-Butil(4-{(1*S*,2*R*)-1-[(4-clorofenil)amino]-2-({[2-(4-clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)-3-oxo-3-[(4S)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil}fenoxi)acetato**

Tetraisopropil ortotitanato (0.23 ml, 0.77 mmol) se agregó a una solución de $TiCl_4$ (1M en CH_2Cl_2, 2.25ml, 2.25 mmol) en CH_2Cl_2 (22 ml) a 0°C bajo

una atmósfera inerte. La mezcla se agitó durante 10 minutos. Se agregó gota a gota durante 45 minutos (4*S*)-3-[({[2-(4-clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)acetil]-4-fenil-1,3-oxazolidin-2-ona (1.44 g, 3.03 mmol) en CH_2Cl_2 seco (25 ml), y la mezcla se agitó durante 10 minutos. Se agregó gota a gota durante 80 minutos *terc*-butil (4-{(*E*)-[(4-clorofenil)imino]metil}fenoxi)acetato (2.09 g, 6.04 mmol) en CH_2Cl_2 seco (25 ml). La mezcla se enfrió a -40°C y se agitó durante 20 minutos. Se agregó gota a gota durante 40 minutos etil diisopropil amina (1.03 ml, 6.02 mmol), y la mezcla se agitó a -40°C durante 10 minutos. La mezcla se enfrió a -78°C, y se agregó isopropanol (80 ml). Se dejó que la temperatura alcanzara la temperatura de la sala durante 3 horas. Se agregó NH_4Cl (10%, 80 ml), y la mezcla se agitó durante 35 minutos. Se agregó salmuera (200 ml), y la mezcla se extrajo dos veces con 400 ml éter dietílico. Las capas orgánicas combinadas se secaron ($MgSO_4$) y se concentraron bajo presión reducida. Purificación por cromatografía de destello (10%-20% EtOAc en hexano) proporcionó 1.69 g (65 %) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.65 (s, 3H), 1.3 (s, 3H), 1.5 (s, 9H), 2.6-2.9 (m, 2H), 3.4 (m, 4H), 4.2 (m, 1H), 4.5 (s, 2H), 4.6-4-8 (m, 2H), 5.3 (m, 1H), 5.7 (d, 1H), 6.4 (m, 2H), 6.7-7.4 (m, 15H).

Método 45

***terc*-Butil {4-[(2*R*,3*R*)-1-(4-clorofenil)-3-({[2-(4-clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)-4-oxoazetidin-2-il]fenoxi}acetato**

terc-Butil (4-{(1S,2R)-1-[(4-clorofenil)amino]-2-({[2-(4-clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metiltio)-3-oxo-3-[(4*S*)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil}fenoxi)acetato (1.69 g, 2.06 mmol) se disolvió en tolueno seco (140ml) y se calentó a 90°C bajo una atmósfera inerte. Se agregó N,O-Bis (trimetilsilil) acetamida (BSA, 1.48 ml, 6.05 mmol), y la mezcla se agitó a 90°C durante 1 hora. La mezcla se enfrió a 45°C, y se agregó fluoruro de tetrabutilamonio (TBAF, 0.1 g) y la mezcla se agitó a

45°C durante 1 hora y a temperatura de la sala de un día para otro. La mezcla se concentró bajo presión reducida y se purificó por cromatografía de destello (10%-20% EtOAc en hexano). Esto proporcionó 0.84 g (61 %) del compuesto del título como un sólido blanco. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.6 (s, 3H), 1.2 (s, 3H), 1.5 (s, 9H), 2.9-3.1 (t, amplio, 2H), 3.4 (s, 4H), 4.0 (s, 1H), 4.5 (s, 2H), 4.8 (s, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 10H).

Método 46

Ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-4-oxo-3-{[2-oxo-2-(4-pentilfenil)etil] tio}azetidin-2-il)fenoxi]acético

terc-Butil (4-{(2*R*,3*R*)-1-(4-fluorofenil)-3-[(3-nitropiridin-2-il)ditio]-4-oxoazetidin-2-il}fenoxi)acetato (0.20 g, 0.36 mmol) se disolvió en acetona (10 ml) a temperatura de la sala. Se agregaron agua (2.5 ml) y trifenil fosfina (0.094 g, 0.36 mmol). La mezcla se agitó a temperatura de la sala durante 30 minutos y luego se concentró bajo presión reducida para proporcionar el tiol crudo como un aceite marrón. Este tiol crudo se disolvió inmediatamente en CH_2Cl_2 (10 ml), y se agregó 2-bromo-1-(4'-pentil fenil)etan-1-ona (0.19 g, 0.72 mmol), seguida por Et_3N (0.10 ml, 0.72 mmol). La mezcla se agitó a temperatura de la sala durante 20 horas, se concentró bajo presión reducida y se purificó por cromatografía de destello (Hex:EtOAc 4:1). Esto proporcionó 0.21 g de una mezcla de *terc*-butil[4-((2*R*,3*R*)-1-(4-fluorofenil)-4-oxo-3-{[2-oxo-2-(4-pentilfenil)etil]tio} azetidin-2-il)fenoxi]acetato y 2-[(3-nitropiridin-2-il)tio]-1-(4-pentilfenil) etanona. Esta mezcla se disolvió en HCOOH (10 ml) y se agitó a temperatura de la sala durante 18 horas. Concentración bajo presión reducida y purificación por cromatografía de destello (hex:acetona: HCOOH 60:40:0.1) proporcionaron 0.11 g (61 %) del compuesto deseado como un sólido amarillo pálido.

^{1}H-NMR (CD_3Cl, 300 MHz): δ 0.8-1.0 (m, 3H), 1.2-1.5 (m, 4H), 1.6-1.8 (m, 2H), 2.7 (t, 2H), 4.1 (d, 1H), 4.2 (s, 2H), 4.7 (s, 2H), 4.9 (d, 1H) 6.9-7.1 (m, 4H), 7.2-7.4 (m, 6H), 7.9 (d, 2H).

Método 47

(2*R*)-2-Amino-4-ciclohexilbutanoato de sodio

Etil (2*R*)-2-amino-4-ciclohexilbutanoato clorhidrato (4.00 g, 18.75 mmol) se disolvió en MeOH/agua (10/5 ml). Se agregó hidróxido de sodio (1.50 g, 37.50 mmol). La mezcla de reacción se agitó durante 1 hora y se concentró para producir el compuesto del título como un sólido incoloro (que contenía 100 mol% de cloruro de sodio). ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] δ 0.83-0.97 (m, 2H), 1.10-1.33 (m, 6H), 1.48-1.78 (m,7H), 3.15 (dd, 1H).

Método 48

***N*-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina**

Ácido [4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético, 302.1 mg, 0.585 mmol) se disolvió en DCM (6 ml). Se agregaron *N*-metilmorfolina (190 μl, 1.728 mmol) y *terc*-butil glicinato clorhidrato (133.4 mg, 0.80 mmol). Pasados 10 minutos, se agregó TBTU (224.3 mg, 0.67 mmol), y la mezcla de reacción se agitó durante 60 horas. Se confirmó el intermedio *terc*-butiléster del compuesto del título. M/z: 626.88 (M-H). Se agregaron DCM (10 ml) y agua (15 ml), y la mezcla se acidificó a un pH de 3 usando $KHSO_4$ (2M). La fase orgánica se lavó con agua (2x15 ml). Las fases acuosas combinadas se extrajeron con DCM (10 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron. Una solución del residuo (500 mg) en DCM (10 ml) y TFA (4 ml) se agitó de un día para otro. El disolvente se retiró bajo presión

reducida. Se agregó tolueno y se evaporó para contribuir al retiro de TFA. El residuo se purificó con HPLC preparativa en una columna C8. Una gradiente de 20 a 50 % MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Luego de la liofilización, se obtuvo el compuesto del título como un sólido blanco (166.9 mg, 50 %). H-NMR (400 MHz, DMS-d_6): 3.51 (d, 2H), 4.33 (d, 1H), 4.34 (s, 1H), 4.36 (s, 1H), 4.47 (s, 2H), 5.17 (d, 1H), 6.96 (d, 2H), 7.16-7.21 (m, 2H), 7.35 (d, 4H), 7.54-7.59 (m, 2H), 7.83-7.90 (brs, 1H), 7.91-7.95 (m, 2H). M/z: 571.04 (M-H) y 572.88 (M+H).

Método 49

Ácido (2*R*)-ciclohexil[(*N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil)amino] acético

TBTU (0.0092 g, 0.029 mmol) se agregó a una mezcla de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[*N*-(carboximetil) carbamoilmetoxi]fenil}azetidin-2-ona (0.016g, 0.030 mmol) y N-metilmorfolina (0.101ml, 0.98 mmol) en DMF (2ml). La mezcla se agitó de un día para otro bajo una atmósfera de N_2. Se agregó más TBTU (0.0092 g, 0.029 mmol), y la mezcla se agitó a 35°C durante 2 horas. Se agregó ácido (2*R*)-amino(ciclohexil)acético clorhidrato (0.0068 g, 0.035 mmol). La mezcla se agitó a 35°C durante 2 horas y a temperatura de la sala de un día para otro. El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa en una columna Kromasil C8, usando una gradiente de 5-100% MeCN en 0.15% tampón de ácido trifluoroacético como eluyente. El disolvente se retiró bajo presión reducida y se obtuvo 0.009 g (47 %) del producto del título.
M/z 680.01

Método 50

terc-butil N^2-[(benciloxi)carbonil]-N^5-(terc-butoxicarbonil)-D-ornitinato

N^2-[(benciloxi)carbonil]-N^5-(*terc*-butoxicarbonil)-D-ornitina (1g, 2.73 mmoles) se disolvió en tolueno (5mL) y se mantuvo a 100°C. Se agregó *N,N*-dimetilformamida di-*terc*-butil acetal (1.5mL, 6.25 mmole) gota a gota. Pasados 40 minutos, la mezcla se dejó enfriar a temperatura de la sala y se mantuvo allí durante 3 días. La capa orgánica se lavó con solución de $NaHCO_3$ y salmuera, se secó (Na_2SO_4), se filtró y el disolvente se retiró bajo presión reducida. Se obtuvo 0.67 g (58%) del producto deseado.

NMR (500 MHz, CD_3COOD) 1.35-1.71 (m, 21H), 1.72-1.85 (m, 1H), 3.06 (t, 2H), 4.05 (dd, 1H), 5.11 (ABq, 2H), 7.29-7.40 (m,5H)

Método 51

terc-Butil N^5-(terc-butoxicarbonil)-D-ornitinato

terc-Butil N^2-[(benciloxi)carbonil]-N^5-(*terc*-butoxicarbonil)-D-ornitinato (0.67g, 1.83 mmoles) y Pd en carbón vegetal (95%, 0.115g) se mezclaron en EtOH (95%, 20 mL) y se agitaron bajo una atmósfera de H_2 durante 5 horas y 15 minutos. La mezcla se filtró a través de Celita 521, y el disolvente se evaporó bajo presión reducida para producir 0.45g (85%) del producto deseado.

NMR (500 MHz, CD_3COOD) 1.41-1.76 (m22H), 3.07 (t, 2H), 3.32-3.36 (m 1H)

Método 52

Glicil-3-ciclohexil-D-alanina

N-(*terc*-butoxicarbonil)glicina (2.0 g, 11.4 mmol) y DIPEA (4.0 g, 31 mmol) se disolvieron en cloruro de metileno (25 ml). Se agregó TBTU (4.1 g, 12.8 mmol), y la mezcla se agitó durante 15 minutos a temperatura de la sala. Se agregó 3-ciclohexil-D-alanina (2.1 g, 12.2 mmol), y la mezcla de reacción se agitó de un día para otro a temperatura de la sala. La mezcla de reacción se transfirió a un embudo de separación y se extrajo luego con una solución de agua/ácido acético (100 ml 5% ácido acético). La capa orgánica se separó y se evaporó bajo presión reducida. El residuo se disolvió en ácido fórmico (20ml), y la mezcla se agitó de un día para otro a 40°C. El ácido fórmico se retiró bajo presión reducida. El residuo se lavó con agua (50 ml) y luego se agitó en acetona (25 ml) durante 1 hora a temperatura de la sala. El material sólido se extrajo por filtración y se lavó con acetona (20 ml). Se obtuvieron 530 mg (20%) del compuesto del título.

^{1}H-NMR, 300 MHz, CD_3COOD): 0.8-1.9 (m, 13H), 3.9-4.1 (m, 2H), 4.55-4.65 (m, 1H).

Método 53

β,β-Dimetil-D-fenilalanina trifluoroacetato

N-(*terc*-butoxicarbonil)-b,b-dimetil-D-fenilalanina sal de *terc*-butil amonio (51.2 mg, 0.14 mmol) se disolvió en DCM (15 ml). Se agregó agua (10 ml), y la mezcla se acidificó a pH 1 con HCl (1M). La fase orgánica se lavó con agua (3x10 ml), y la fase acuosa se extrajo con DCM (3x10 ml). El disolvente se retiró bajo presión reducida. El residuo se disolvió en DCM (4 ml), y se agregó TFA (2.5 ml) y la mezcla se agitó durante 2 horas. El disolvente se retiró bajo presión reducida, y el residuo se secó bajo vacío de un día para otro. El compuesto del título se obtuvo como un sólido blanco (36.1 mg, 85 %). M/z: 194.18 (M+1).

Método 54

Glicil-3-metil-D-valina trifluoroacetato

A una solución a 30°C de *N*-(*terc*-butoxicarbonil)glicina (0.450 g, 2.569 mmol) y N-metilmorfolina (1.30 g, 12.84 mmol) en CH_2Cl_2 (50 ml) se agregó TBTU (0.99 g, 3.08 mmol). Pasadas 1.5 horas, se agregó D-*terc*-leucina (0.303 g, 2.31 mmol). Después de 30 minutos, la reacción se extinguió por la adición de agua (1 ml). La mezcla se concentró y el residuo se purificó a través de HPLC preparativa, usando un eluyente de 0-40% CH_3CN en 0.1M tampón NH_4OAc. Fracciones puras se recogieron y se concentraron. Al residuo se agregaron CH_2Cl_2 (10 ml) y TFA (3 ml). La conversión completa en el correspondiente aminoácido se obtuvo después de 30 minutos. La mezcla de reacción se concentró para producir el compuesto deseado (0.359 g, 46%) como un sólido incoloro. ^{1}H NMR [$(CD_3)_2SO$), 400 MHz] □0.94 (s, 9H), 3.60-3.67 (m, 2H), 4.16 (d, 1H), 7.90-8.00 (m, 3H), 8.47 (d, 1H).

Método 55

Ácido {4-[(2*R*,3*R*)-3-{[2-(4-*terc*-butilfenil)-2-oxoetil]tio}-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acético

terc-Butil(4-{(2*R*,3*R*)-1-(4-fluorofenil)-3-[(3-nitropiridin-2-il)ditio]-4-oxoazetidin-2-il}fenoxi)acetato (0.20 g, 0.36 mmol) se disolvió en acetona (10ml) a temperatura de la sala, luego se agregaron agua (2.5 ml) y trifenil fosfina (0.094 g, 0.36 mmol). La mezcla se agitó a temperatura de la sala durante 15 minutos y luego se concentró bajo presión reducida para proporcionar el tiol crudo como un aceite marrón. Este tiol crudo se disolvió inmediatamente en CH_2Cl_2 (8 ml), y se agregó 2-bromo-1-(4'-*terc*-butil-fenil)-etan-1-ona (0.15 g, 0.72 mmol), seguida por Et_3N (0.10 ml, 0.72mmol). La mezcla se agitó a temperatura de la sala durante 1.5 horas, se concentró bajo presión reducida y se purificó por cromatografía de

destello (Hex: EtOAc 4.1). Esto proporcionó 0.26 g de una mezcla de *terc*-butil {4-[(2*R*,3*R*)-3-{[2-(4-*terc*-butilfenil)-2-oxoetil]tio}-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acetato y 1-(4-*terc*-butilfenil)-2-[(3-nitropiridin-2-il)tio]etanona. Esta mezcla se disolvió en ácido fórmico (10 ml) y se agitó a temperatura de la sala durante 17 horas. Concentración bajo presión reducida y purificación por cromatografía de destello (hex:acetona:ácido fórmico 70: 30: 0.1) proporcionó 0.08 g (43 %) del producto deseado como un sólido blanco.

^{1}H-NMR (CD_3Cl, 200 MHz): δ 1.30 (s, 9H), 4.10 (s, 1H), 4.15 (s, 2H), 4.60 (s, 2H), 4.85 (s, 1H), 6.80-7.00 (m, 4H), 7.15-7.30 (m, 4H), 7.60-7.70 (m, 2H), 7.80-7.90 (m, 2H).

Método 56

***N*-({4-[(2*R*,3*R*)-3-{[2-(4-*terc*-Butilfenil)-2-hidroxietil]tiol-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acetil)glicil-3-ciclohexil-D-alanina**

A una solución de ácido {4-[(2*R*,3*R*)-3-{[2-(4-*terc*-butilfenil)-2-oxoetil]tio}-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acético (0.020 g, 0.038 mmol) y NMM (0.013ml, 0.118 mmol) en DMF (3ml) a temperatura ambiente se agregó TBTU (0.019 g, 0.059mmol). Pasados 90 minutos, se agregó glicil-3-ciclohexil-D-alanina (0.009 g, 0.039 mmol), y la mezcla se agitó durante 18 horas antes de extinguir la reacción por la adición de agua (1 ml). La mezcla se diluyó con MeOH (1 ml), se agregó y $NaBH_4$ (0.025 g, 0.661 mmol). Luego de 10 minutos, la reacción se extinguió por la adición de 0.1M tampón de acetato de amonio (2ml), y la mayor parte del metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa usando una gradiente de 20-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. El secamiento por congelamiento de las fracciones puras proporcionó el producto deseado como un sólido blanco (0.010 g, 36 % de rendimiento).

ES- m/z: 733.2 $(M-1)^-$. ^{1}H NMR (DMSO, 500 MHz) δ: 0.70-0.93 (m, 2H), 1.00-1.35 (m, 13H), 1.35-1.71 (m, 7H), 2.84-2.96 (m, 2H), 3.72-3.80 (m, 2H), 4.12-4.22 (m, 1H), 4.22-4.28 (m, 1H), 4.50 (s, 2H), 4.60-4.72 (m, 1H), 4.98-5.03 (m, 1H), 6.94-7.01 (m, 2H), 7.09-7.39 (m, 10H), 7.94-8.03 (m, 1H), 8.19-8.27 (m, 1H).

Método 57

Ácido {4-[(2*R*,3*R*)-3-{[2-(4-etoxifenil)-2-oxoetil]tio}-1-(4-fluorofenil)-4-oxoazetidin-2-il]fenoxi}acético

terc-Butil(4-{(2*R*,3*R*)-1-(4-fluorofenil)-3-[(3-nitropiridin-2-il)ditio]-4-oxoazetidin-2-il}fenoxi)acetato (0.25 g, 0.45 mmol) se disolvió en acetona (10 ml) a temperatura de la sala. Se agregaron agua (2.5 ml) y trifenil fosfina (0.12 g, 0.45 mmol). La mezcla se agitó a temperatura de la sala durante 15 minutos y luego se concentró bajo presión reducida para proporcionar el tiol crudo como un aceite marrón. Este tiol crudo se disolvió inmediatamente en CH_2Cl_2 (10 ml), y se agregó (2-bromo-3'-etoxi acetofenona (0.22 g, 0.90 mmol), seguida por Et_3N (0.13 ml, 0.90 mmol). La mezcla se agitó a temperatura de la sala durante 19 horas, se concentró bajo presión reducida y se purificó por cromatografía de destello (Hex: EtOAc 3:1). Esto proporcionó un aceite incoloro, que se disolvió en ácido fórmico (10 ml) y se agitó a temperatura ambiente durante 18 horas. Concentración bajo presión reducida y purificación por cromatografía de destello (hex: acetona: ácido fórmico 60: 40: 0.1) proporcionó 0.13 g (57%) del producto deseado como un sólido amarillo pálido.

^{1}H-NMR (CD_3Cl, 200 MHz): δ 1.4 (t, 3H), 4.0-4.1 (m, 5H), 4.5 (s, 2H), 4.8 (d, 2H), 6.8-7.0 (m, 6H), 7.1-7.3 (m, 4H), 7.9 (d, 2H).

Método 58

terc-Butil (4-{[(4-fluorofenil)imino]metil}fenoxi)acetato

terc-Butil (4-formilfenoxi)acetato (21.6 g, 0.09 mol) se disolvió en tolueno seco (150 ml), y se agregó4-fluoroanilina (8.8 ml, 0.091 mol). La mezcla se hizo refluir en un aparato Dean-Stark durante 23 horas, se enfrió y se concentró bajo presión reducida. La adición de hexano y la concentración bajo presión reducida proporcionaron 30.0 g (rendimiento cuantitativo) del compuesto del título como un sólido blancuzco. NMR (200 MHz): 1.5 (s, 9H), 4.6 (s, 2H), 7.0-7.2 (m, 6H), 7.8 (d, 2H), 8.4 (s, 1H).

Método 59

(4_S_)-3-{[(4-Metoxibencil)tio]acetil}-4-fenil-1,3-oxazolidin-2-ona

Ácido (4-metoxi-bencilsulfanil)-acético (1.3 g, 6.1 mmol) se disolvió en DCM seco (40 ml) y se enfrió a 0°C. Se agregaron N,N'-diciclohexilcarbodiimida (6.1 g, 6.1 mmol) y DMAP (1.6 g, 12.9 mmol), y la mezcla se agitó durante 30 minutos. Se agregó (S)-(+)-4-fenil-2-oxazolidinona (1,0 g, 6.1 mol), y la mezcla se agitó a temperatura de la sala durante 24 horas. La mezcla se filtró, se concentró bajo presión reducida y se purificó por cromatografía de destello (Hex: EtOAc 8:2, luego 1:1). Esto proporcionó 1.7 g (77 %) del compuesto del título como un sólido blanco. NMR (200 MHz): 3.46-3.59 (m, 3H), 3.74-3.76 (m, 4H), 4.23- 4.28 (m, 1H), 4.68 (t, 1H), 5.38-5-42 (m, 1H), 6.78 (d, 2H), 7.14 (d, 2H), 7.32-7.40 (m, 5H).

Método 60

terc-Butil (4-{(1_R_)-1-(4-fluoroanilino)-2-[(4-metoxibencil)tio]-3-oxo-3-[(4_S_)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil} fenoxi)acetato

$TiCl_4$ (1M in DCM, 7.2 ml, 7.2 mmol) se agregó a una solución de tetraisopropil ortotitanato (0.71 ml, 2.4 mmol) en DCM (40 ml) mantenida a 0°C bajo una atmósfera inerte. La mezcla se agitó durante 15 minutos, luego se agregó (4S)-3-{[(4-metoxibencil)tio]acetil}-4-fenil-1,3-oxazolidin-2-ona (3.4 g, 9.6 mmol) en DCM seco (20 ml), y la mezcla se agitó durante 5 minutos. Luego se agregó *terc*-butil(4-{[(4-fluorofenil)imino] metil}fenoxi)acetato (6.3 g, 19.0 mmol) en DCM seco (30 ml), y la mezcla enfriada a -40°C y se agitó durante 20 minutos. Se agregó etil diisopropil amina (3.3ml, 19.0 mmol), y la mezcla se agitó a -40°C durante 19 horas. La mezcla se enfrió entonces a -78°C, se agregó isopropanol (50ml) y lentamente se enfrió a temperatura de la sala de un día para otro. Se agregó agua (100 ml), y la mezcla se agitó durante 35 minutos a temperatura de la sala y luego se extrajo dos veces con éter dietílico. La capa orgánica combinada se lavó con agua, se secó ($MgSO_4$) y se concentró bajo presión reducida. El producto crudo se disolvió en metanol, y se formó un precipitado blancuzco. Filtración y secamiento proporcionó 1.7 g (26 %) del compuesto del título como un sólido blancuzco. NMR (200 MHz): 1.5 (s, 9H), 3.65 (s, 1H), 3.8 (s, 3H), 4.1 (m, 1H), 4.4-4.6 (m, 4H), 5.0-5.2 (m, 2H), 5.4 (m, 1H), 6.4-6.6 (m, 2H), 6.7-7-4 (m, 15H).

Método 61

3-(R)-4-(R)-1-(4-Fluorofenil)-3-(4-metoxibencilsulfanil)-4-[4-(*t*-butoxicarbonil metoxi)fenil]azetidin-2-ona

terc-Butil (4-{(1R)-1-(4-fluoroanilino)-2-[(4-metoxibencil)tio]-3-oxo-3-[(4S)-2-oxo-4-fenil-1,3-oxazolidin-3-il]propil}fenoxi)acetato (1.3 g, 1.9 mmol) se disolvió en tolueno seco (140 ml) y se calentó a 90°C bajo una atmósfera inerte. Se agregó BSA (1.4 ml, 5.7 mmol), y la mezcla se agitó a 90°C durante 1 hora. La mezcla se enfrió entonces a 45°C, y se agregó TBAF (seco, 0.1 g). Pasadas 18 horas, se agregó más BSA (0.5 ml, 2.0 mmol), y la temperatura se mantuvo a 45°C durante otras seis horas. Luego

de enfriar, la mezcla se concentró bajo presión reducida y se purificó por cromatografía de destello (Hex: EtOAc 5:1). Esto proporcionó 0.55 g (55 %) del compuesto del título como un sólido blanco. MR (200 MHz): 1.5 (s, 9H), 3.7 (s, 3H), 3.9 (m, 3H), 4.5 (m, 3H), 6.7 (d, 2H), 6.8-7.0 (m, 4H), 7.0-7.2 (m, 6H).

Método 62

3-(R)-4-(R)-1-(4-Fluorofenil)-3-[(3-nitropiridin-2-il)ditio]-4-[4-(*t*-butoxicarbonil metoxi)fenil]azetidin-2-ona

3-(R)-4-(R)-1-(4-Fluorofenil)-3-(4-metoxibencilsulfanil)-4-[4-(*t*-butoxicarbonil metoxi)fenil]azetidin-2-ona (0.65 g, 1.24 mmol) se disolvió en DCM (50 ml) y se enfrió a 0°C bajo una atmósfera inerte. Se agregó 3-nitro-2-piridinsulfenil cloruro (0.28 g, 1.49 mmol), y la mezcla se agitó durante 75 minutos a 0°C. Luego se agregó más 3-nitro-2-piridinsulfenil cloruro (0.05 g, 0.27 mmol), y la mezcla se agitó durante 45 minutos más a 0°C. Concentración bajo presión reducida y purificación por cromatografía de destello (Hex: EtOAc 4:1, luego 2: 1) proporcionaron 0.67 g (97 %) del producto deseado como un aceite amarillo. NMR (200 MHz): 1.6 (s, 9H), 4.3 (d, 1H), 4.5 (s, 2H), 5.2 (d, 1H), 6.8-7.0 (m, 4H), 7.1-7.3 (m, 4H), 7.4 (m, 1H) 8.5 (d, 1H), 8.9 (d, 1H).

Método 63

3-(R)-4-(R)-1-(4-Fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-[4-(*t*-butoxicarbonil metoxi)fenil]azetidin-2-ona

3-(R)-4-(R)-1-(4-Fluorofenil)-3-[(3-nitropiridin-2-il)ditio]-4-[4-(t-butoxicarbonil metoxi)fenil]azetidin-2-ona (0.67 g, 1.2 mmol) se disolvió en acetona (50 ml) a temperatura de la sala, luego se agregaron agua (10 ml) y tributil fosfina (0.30 ml, 1.2 mmol). La mezcla se agitó a temperatura

de la sala durante 30 minutos y luego se concentró bajo presión reducida para proporcionar el tiol crudo como un aceite marrón. Este tiol crudo se disolvió inmediatamente en DCM (40 ml), y se agregó2-bromo-4'-fluoroacetofenona (0.29 g, 1.3 mmol), seguida por Et_3N (0.20 ml, 1.4 mmol). La mezcla se agitó a temperatura de la sala durante 90 minutos, se concentró bajo presión reducida y se purificó por cromatografía de destello (Hex: EtOAc 4:1). Esto proporcionó 0.42 g (65 % total en dos pasos) del compuesto del título como un sólido blanco. NMR (200 MHz) 1.44 (s, 9H), 4.06 (d, J = 2.4 Hz, 1H), 4.13 (d, J = 3.8 Hz, 2H), 4.48 (s, 2H), 4.81 (d, J = 2.2 Hz, 1H), 6.83-6.93 (m, 4H), 7.05-7.21 (m, 6H), 7.90-7.97 (m, 2H).

Método 64

3-(R)-4-(R)-1-(4-Fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-[4-(carboximetoxi)fenil] azetidin-2-ona

3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-[4-(t-butoxicarbonilmetoxi)fenil]azetidin-2-ona (0.42 g, 0.78 mmol) se disolvió en DCM (30 ml) a 0°C, y TFA (7.5ml) se agregó gota a gota. La mezcla se enfrió lentamente a temperatura de la sala durante varias horas y luego se agitó a temperatura de la sala de un día para otro. Concentración bajo presión reducida y purificación por cromatografía de destello (EtOAc, luego 5% MeOH en EtOAc) proporcionaron 0.32 g (85 %) del compuesto del título como un sólido blanco. NMR (CD_3OD, 300 MHz): 4.1 (d, 1H), 4.2 (s, 2H), 4.5 (s, 2H),5.0 (d, 1H), 6.9-7.0 (m, 4H), 7.1-7.3 (m, 6H), 8.0 (m, 2H).

Método 65

***terc*-Butil *N*-[(2*R*)-2-amino-2-fenilacetil]-*O*-(*terct*-butil)-L-serinato**

terc-Butil *N*-((2*R*)-2-{[(benciloxi)carbonil]amino}-2-feniletanoil)-*O*-(*terc*-butil)-L-serinato (Método 15; 3.3 g, 6.8 mmol) se disolvió en EtOH (95%, 30ml), y se agregó una cantidad catalizadora (***"a cat. amount"***) de Pd/C (5%)(50% en agua), y se realizó hidrogenación a presión atmosférica durante 3 horas a temperatura de la sala. La mezcla de reacción se filtró a través de tierras de diatomeas, y el disolvente se evaporó para producir el compuesto del título (2.35 g, 98 %). NMR (500 MHz, CD_3OD): 1.1 (s, 9H), 1.45 (s, 9H), 3.45-3.8 (m, 2H), 4.5 (t, 1H), 4.55 (s, 1H), 4.85 (s, 2H), 7.3-7.5 (m, 5H).

Método 66

1-(4-Fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxi)-1-(S)-(*t*-butoxicarbonil)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona

Una solución de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil) metiltio]-4-[4-(carboximetoxi)fenil]azetidin-2-ona (0.090 g, 0.186 mmol), *terc*-butil *N*-[(2*R*)-2-amino-2-fenilacetil]-*O*-(*terc*-butil)-L-serinato (Método 8; 0.098 g, 0.280 mmol) y N-metilmorfolina (0.062 ml, 0.563 mmol) en DMF (6 ml) se agitó a temperatura de la sala durante 10 minutos, tras los cuales se agregó TBTU (0.096 g, 0.299 mmol). Pasadas 22 horas, a la mezcla de reacción se agregó agua (15ml), y se extrajo tres veces con éter (3x10 ml). Las capas orgánicas combinadas se lavaron con salmuera (10 ml), se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía de destello en gel de sílice, usando Hept: EtOAc (6:4) como eluyente. El producto deseado se obtuvo en 0.053 g (35%) como un sólido blanco. NMR (400 MHz): 0.90 (s, 9H), 1.45 (s, 9H), 3.35 (dd, 1H), 3.65 (dd, 1H), 4.10 (d, 1H), 4.15 (ABq, 2H), 4.50 (ABq, 2H), 4.50-4.60 (m, 1H), 4.85 (d, 1H), 5.55 (d, 1H), 6.40 (d, 1H), 6.90-7.00 (m, 4H), 7.10-7.40 (m,11H), 7.90-8.00 (m, 3H); m/z: 816.7.

Método 67

1-(4-Fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(hidroxi)-1-(S)-(carboxi)etil]carbamoil}bencil)carbamoilmetoxi] fenil}azetidin-2-ona

y

Método 68

1-(4-Fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxi)-1-(S)-(carboxi)etil]carbamoil}bencil) carbamoilmetoxi] fenil}azetidin-2-ona

TFA (2 ml) se agregó a una solución de 1-(4-fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxi)-1-(S)-(*t*-butoxicarbonil)etil]carbamoil}bencil)carbamoilmetoxi]fenil} azetidin-2-ona (0.050 g, 0.061 mmol) en DCM (5 ml) a temperatura de la sala. Pasadas 2.5 horas, el disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa usando una gradiente de 20-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 1-(4-fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(hidroxi)-1-(S)-(carboxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona en 0.039g (90%). NMR (DMSO, 400 MHz): 3.35 (dd, 1H), 3.50 (dd, 1H), 3,95-4.05 (m, 1H), 4.30 (d, 1H), 4.35 (ABq, 2H), 4.60 (ABq, 2H), 5.15 (d, 1H), 5.65 (d, 1H), 6.90-7.00 (m, 2H), 7.10-7.40 (m, 13H), 7.95-8. 05 (m, 2H), 8.25 (d, 1H), 8.55 (d, 1H); m/z: 704.5. Se obtuvo 1-(4-fluorofenil)-3-(R)-[(4- fluorobenzoil)metiltio]-4-(R)-{4-[*N*-(α-(R)-{*N*-[2-(*t*-butoxi)-1-(S)-(carboxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona en 0.002g (4%). NMR (CD_3COOD, 400 MHz): 1.00 (s, 9H), 3.50 (dd, 1H), 3.80 (dd, 1H), 4.20-4.30 (m, 3H), 4.70 (s, 2H), 4.80-4.85 (m, 1H), 5.00-5.05

(m, 1H), 5.90-6.00 (m, 1H), 6.95-7.05 (m, 4H), 7.15-7.50 (m, 11H), 8.00-8.10 (m, 2H); m/z: 760.5. Los dos eran sólidos blancos.

Método 69

3-(R)-4-(R)-1-(4-Fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona

Una solución de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil) metiltio]-4-[4-(carboximetoxi)fenil]azetidin-2-ona (0.200 g, 0.414 mmol), glicina *terc*-butil éster clorhidrato (0.113 g, 0.674 mmol) y N-metilmorfolina (0.180 ml, 1.63 mmol) en DCM (5 ml) se agitó a temperatura de la sala durante 10 minutos, tras los cuales se agregó TBTU (0.193 g, 0.601 mmol). Pasadas 25 horas, la conversión en el éster (m/z: 597.43 $(M+1)^+$) se completó, y se agregó TFA (2 ml) a la solución. Luego de 1 hora, el disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, el producto deseado se obtuvo en 0.093 g (41 %) como un sólido blanco. NMR (DMSO, 500 MHz): 3.65 (d, 2H), 4.35 (d, 1H), 4.40 (ABq, 2H), 4.50 (s, 2H), 5.20 (d, 1H), 6.95-7.05 (m, 2H), 7.15-7.40 (m, 8H), 8.00-8.15 (m, 3H); m/z: 541.3.

Método 70

1-(4-Fluorofenil)-3-(R)-[(4-fluorobenzoil)metiltio]-4-(R)-{4-[*N*-{*N*-[2-(hidroxi)-1-(R)-(carboxi)etil]carbamoilmetil}carbamoilmetoxi]fenil} azetidin-2-ona

Una solución de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil) metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.030 g, 0.056 mmol), D-serine *terc*-butil éster clorhidrato (0.017 g, 0.067 mmol) y N-metilmorfolina (0.019 ml, 0.172 mmol) in DCM (4 ml) se agitó

a temperatura de la sala durante 10 minutos, tras los cuales se agregó TBTU (0.023 g, 0.072 mmol). Luego de 22 horas, la conversión en el éster (m/z: 740.58 (M+1)+) se completó. Se agregó TFA (1.5 ml) a la solución y, después de 2 horas, el disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, el producto deseado se obtuvo en 0.035 g (~ rendimiento cuantitativo) como un sólido blanco. NMR (CD_3COOD, 400 MHz): 3.95 (dd, 1H), 4.10 (dd, 1H), 4.20-4.30 (m,5H), 4.65 (s, 2H), 4.70-4.80 (m, 1H), 5.00 (d, 1H), 6.95-7.10 (m, 4H), 7.15-7.45 (m, 6H), 8.00-8.10 (m, 2H); m/z: 628.4.

Método 71

1-(4-Fluorofenil)-3-(R)-[(4-lluorobenzoil)metiltio]-4-(R)-{4-[*N*-{*N*-[2-(fenil)-1-(R)-(carboxi)etil]carbamoilmetil}carbamoilmetoxi]fenil} azetidin-2-ona

3-(R)-4-(R)-1-(4-Fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[N (carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (21 mg, 0.039 mmol), *terc*-butil D-fenilalaninato HCl (12 mg, 0.047 mmol) y 4-metilmorfolina (12 mg, 0.12 mmol) se mezclaron en DCM (1 ml). Se agregó TBTU (15 mg, 0.046 mmol) después de 5 minutos, y la mezcla se agitó durante 20 horas. El disolvente se retiró bajo presión reducida y el residuo se purificó por cromatografía en sílice con hexano: EtOAc 1:1 como el eluyente. El producto se disolvió en ácido fórmico y se agitó durante 20 horas. El ácido fórmico se retiró bajo presión reducida, tras lo cual se agregó tolueno y se evaporó dando (21 mg 64%). M/z 686.3 (M-H)-.

Método 72

Ácido {4-[(2*R*,3*R*)-1-(4-fluorofenil)-3-({2-hidroxi-2-[4-(metiltio)fenil] etil}tio)-4-oxoazetidin-2-il]fenoxi}acético

terc-Butil(4-{(2*R*,3*R*)-1-(4-fluorofenil)-3-[(3-nitropiridin-2-il)ditio]-4-oxoazetidin-2-il}fenoxi)acetato (0.25 g, 0.45 mmol) se disolvió en acetona (10 ml) a temperatura de la sala, luego se agregaron agua (2.5ml) y trifenil fosfina (0.12 g, 0.45 mmol). La mezcla se agitó a temperatura de la sala durante 15 minutos y luego se concentró bajo presión reducida para proporcionar el tiol crudo como un aceite marrón. Este tiol crudo se disolvió inmediatamente en CH_2Cl_2 (10 ml), y se agregó (2-bromo-3'-tiometil acetofenona (0.22 g, 0.90 mmol), seguida por Et_3N (0.13 ml, 0.90 mmol). La mezcla se agitó a temperatura de la sala durante 19 horas, se concentró bajo presión reducida y se purificó por cromatografía de destello (Hex: EtOAc 4:1, luego 3:1). Esto proporcionó 0.4 g de una mezcla de *terc*-butil {4-[(2*R*,3*R*)-1-(4-fluorofenil)-3-({2-[4-(metiltio)fenil]-2-oxoetil}tio)-4-oxoazetidin-2-il]fenoxi}acetato y 1-[4-(metiltio)fenil]-2-[(3-nitropiridin-2-il)tio]etanona. Esta mezcla se disolvió en HCOOH (15 ml) y se agitó a temperatura de la sala durante 19 horas. Concentración bajo presión reducida y purificación por cromatografía de destello (hex: acetona: HCOOH 60: 40: 0.1) proporcionaron 0.16 g (70 %) del compuesto deseado como un sólido amarillo pálido.

^{1}H-NMR (CD_3Cl, 200 MHz): δ 2.5 (s, 3H), 4.0 (d, 1H), 4.1 (s, 2H), 4.6 (s, 2H), 4.8 (d, 1H), 6.8-7.0 (m, 4H), 7.1-7.3 (m, 6H), 7.8 (d, 2H).

Método 73

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil} glicil-D-ornitina**

Una mezcla de 3-(R)-4-(R)-1-(4-fluorofenil)-3-[(4-fluorobenzoil) metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.020g, 0.037

mmole) *terc*-butil N^5-(*terc*-butoxicarbonil)-D-ornitinato (0.012 g, 0.042 mmoles), y N-metilmorfolina (0.012mL, 0.111 mmoles) en DCM (3mL) se agitó a temperatura de la sala. Se agregó TBTU (0.018 g, 0.056 mmoles), y la mezcla se agitó de un día para otro. Se agregó ácido trifluoroacético (1.0 mL) y, luego de 6 horas, el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa en una columna Kromasil C8, usando una gradiente de 5-100% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de retirar el disolvente bajo presión reducida, se obtuvo0.021 g (87 %) del producto deseado. M/z 655.21

Método 74

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-N^6,N^6-dimetil-L-lisina**

3-(R)-4-(R)-1-(4-Fluorofenil)-3-[(4-fluorobenzoil)metiltio]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona (0.010g, 0.018 mmoles) y N-metilmorfolina (0.006mL, 0.055 mmoles) se disolvieron en DMF (0.5mL). Se agregó TBTU (0.0099 g, 0.031 mmoles). La mezcla se agitó a 30-40°C durante 30 minutos bajo una presión de N_2. Se agregó N^6,N^6- dimetil-L-lisina clorhidrato (0.0045 g, 0.021 mmoles), y la mezcla se agitó a 30-40°C durante algunas horas, luego a temperatura de la sala de un día para otro. Se agregaron unas cuantas gotas de agua, y el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa en una columna Kromasil C8, usando una gradiente de 5-100% MeCN en 0.1M tampón de acetato de amonio como eluyente. Después de retirar el disolvente bajo presión reducida, se obtuvo0.005 g (39 %) del producto deseado.
M/z 697.31

Método 75

N-{[4-((2R,3R)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicina

Una mezcla de ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-metoxifenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (0.0153g, 0.031 mmol), *terc*-butil glicil-D-valinato clorhidrato (0.0099 g, 0.037 mmol) y N-metilmorfolina (0.010ml, 0.091 mmol) en DCM (2ml) se agitó a temperatura de la sala. Se agregó TBTU (0.016 g, 0.050 mmol), y la mezcla se agitó durante 3.5 horas. Se agregó ácido trifluoroacético (0.5ml) y, luego de 3.5 horas, el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa en una columna Kromasil C8, usando una gradiente de 5-100% MeCN en 0.15% tampón de ácido trifluoroacético como eluyente. El disolvente se retiró bajo presión reducida, y se obtuvo 0.015 g (74 %) del producto del título. M/z 652.20.

Método 76

Ácido [4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético

terc-Butil{4-[(2*R*,3*R*)-1-(4-clorofenil)-3-({[2-(4-clorofenil)-5,5-dimetil-1,3-dioxan-2-il]metil}tio)-4-oxoazetidin-2-il]fenoxi}acetato (1.69 g, 2.57 mmol) se disolvió en ácido fórmico (25 ml) y se agitó durante 2 horas. La mezcla se concentró bajo presión reducida (temperatura <30°C), y el aceite crudo se purificó por cromatografía de destello (hexano: acetona: ácido fórmico 60:40:0.1) para proporcionar 1.08 g (81 %) del compuesto del título como un sólido amarillo pálido. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 4.0-4.2 (m, 3H), 4.7 (s, 2H), 4.9 (d, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 6H), 7.5 (d, 2H), 7.9 (d, 2H). MS (CI) M/z: 514.2 (M^+), 515.2 (30), 516.1 (70), 517.2 (20).

Ejemplos de intermedios de fórmula (VI) y XV

Método 77

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]alanina**

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-alanina se disolvió en metanol (1.5 ml). Se agregó borohidruro de sodio, y la mezcla se agitó durante 30 minutos. Se agregó una solución de acetato de amonio/H_2O (2 ml), y se evaporó el metanol. El producto se purificó por HPLC preparativa (CH_3CN/0.1 % tampón de acetato de amonio 20:80-100: 0). Las fracciones que contenían el producto se liofilizaron, y se obtuvieron 27 mg (48%) del producto del título. M/z: 555.0 (M-1).

Método 78

***N*-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-triptófano**

Ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (0.050 g, 0.103 mmol) se disolvió en CH_2Cl_2 (5 ml). Se agregaron triptófano *terc*-butil éster clorhidrato (0.037g, 0.12 mmol) y N-metilmorfolina (31 mg, 0.31 mmol). Pasados 10 minutos, se agregó TBTU (43 mg, 0.13 mmol), y la mezcla se agitó durante 4 horas. El éster crudo se purificó en gel de sílice y se eluyó con EtOAc/CH_2Cl_2, 25/75. Las fracciones que contenían el éster puro se concentraron. Se agregaron CH_2Cl_2 (5 ml) y TFA (1 ml), y la reacción se agitó durante 4 horas. La mezcla se concentró y la traza restante de TFA se retiró azeotrópicamente por co-evaporación con tolueno (2 X 5 ml). El residuo se disolvió en 5 ml de MeOH, y se agregó borohidruro de sodio (0.016 g, 0.414 mmol). La reacción se extinguió por la adición de 0. 1M tampón

NH_4OAc (1 ml) después de 5 minutos. La mezcla se concentró y se purificó por HPLC preparativa (gradiente 20-50% CH_3CN en 0.1M tampón de acetato de amonio). El secamiento por congelamiento de las fracciones puras produjo el compuesto del título como un sólido incoloro (0.040 g, 58%). M/z: 670.3(M-1). ^1H NMR[$(CD_3)_2SO$), 400 MHz] δ 2.85-2.95 (m, 2H), 3.07-3.12 (m, 1H), 3.22-3.27 (m, 1H), 4.24-4.27 (m, 1H), 4.34-4.38 (m, 1H), 4.41 (s, 2H), 4.70-4.76 (m, 1H), 5.01-5.04 (m, 1H), 6.80-7.35 (m, 16H), 7.50-7.53 (m, 1H), 7.85-7.92 (m, 1H), 10.76 (s, 1H).

Método 79

N^2-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-glutamina

Ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (50 mg, 0.103 mmol), *terc*-butil L-glutaminato clorhidrato (30 mg, 0.124 mmol) y N-metilmorfolina (40 mg, 0.396 mmol) se disolvieron en cloruro de metileno (1 ml). Se agregó TBTU (40 mg, 0.125 mmol), y la mezcla se agitó durante 90 minutos. El disolvente se evaporó, y el residuo se disolvió en ácido fórmico (1 ml). La mezcla se calentó a 45-50°C durante 4 horas. La mezcla de reacción se evaporó bajo presión reducida. Se agregó tolueno (5 ml) y se evaporó. El residuo se disolvió en metanol (1 ml). Se agregó $NaBH_4$ (30 mg, 0.793 mmol), y la mezcla se agitó durante 15 minutos. Se agregó ácido acético (50 mg, 0.83mmol), y la mezcla de reacción se evaporó bajo presión reducida. El residuo se purificó por HPLC preparativa, usando tampón acetonitrilo/acetato de amonio (35: 65) como eluyente. Luego de secar por congelamiento, se obtuvieron 47 mg (74%) del compuesto del título. ^1H-NMR, 300 MHz, DMSO): 1.72-2.16 (m, 4H), 2.81-2.95 (m, 2H), 4.08-4.20 (m, 1H), 4.26-4.31 (m, 1H), 4.50 (s, 2H), 4.65-4.78 (m, 1H), 5.03-5.08 (m, 1H), 6.68 (s, 1H), 6.89-7.44 (m, 14H), 8.29 (d, 1H).

Método 80

***N*-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}-D-serina**

Una solución de ácido [4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-oxoetil]tio}-4-oxoazetidin-2-il)fenoxi]acético (0.050 g, 0.103 mmol), *O*-(*terc*-butil)-D-serina *terc*-butil éster clorhidrato (0.032 g, 0.147 mmol) y N-metilmorfolina (0.035 ml, 0.318 mmol) en DCM (4 ml) se agitó durante 5 minutos. Se agregó TBTU (0.044 g, 0.137 mmol). Se confirmó la formación del éster luego de 3 horas. M/z: 683.1. Se agregó TFA (2 ml), y la mezcla se agitó durante 22 horas. El disolvente se retiró bajo presión reducida. El residuo se disolvió en MeOH (4 ml), y se agregó $NaBH_4$ (en total 0.130 g, 3.44 mmol) en pequeñas porciones. La reacción se extinguió por la adición de 0.1M tampón de acetato de amonio (3 ml). El metanol se retiró bajo presión reducida. La solución restante se purificó por HPLC preparativa, usando una gradiente de 20-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. Luego de secar por congelamiento, se obtuvo 0.021 g (36 % de rendimiento) del producto del título como un sólido blanco. M/z: 573.1. ^{1}H NMR (DMSO, 400 MHz): δ 2.84-2.96 (m, 2H), 3.47 (dd, 1H), 3.69 (dd, 1H), 3.97-4.06 (m, 1H), 4.27-4.32 (m, 1H), 4.52 (ABq, 2H), 4.68-4.77 (m, 1H), 5.04-5.09 (m, 1H), 5.65 (bs, 1H), 6.99 (d, 2H), 7.07-7.41 (m,10H), 7.89 (d, 1H).

Se observará por los expertos en el arte que los ejemplos pueden modificarse en las esferas de la invención, por lo cual la invención no se limita a incorporaciones particulares.

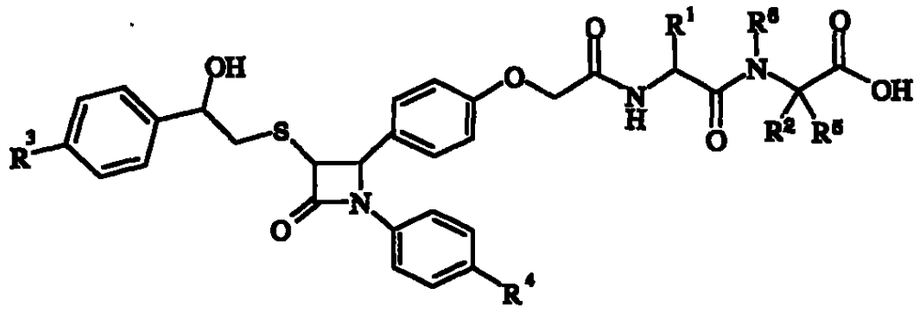
Absorpción

La absorción de los compuestos de fórmula (I) se probó en un modelo de células Caco-2 (Gastroenterology 1989, 96, 736):

Compuesto (I)	Valor Caco (10^{-6} cm/s)
N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina	0.06
N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-tirosina	0.07
N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-lisina	0.2
1-(4-Fluorofenil)-3-(R)-[2-(4-fluorofenil)-2-hidroxietiltio]-4-(R)-{4-[*N*-{*N*-[2-(fenil)-1-(R)-(carboxi) etil]carbamoilmetil}carbamoilmetoxi]fenil}azetidin-2-ona	0.09

Reivindicaciones

1. Un compuesto de fórmula (I)



(I)

en donde:

R^1 es hidrógeno, C_{1-6}alquilo, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, guanidino, carbamoilo, carboxi, C_{1-6}alcoxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_1-C_6 alquilcarbonilamino C_{1-6}alquil$S(O)_a$ en donde a es 0-2, C_{3-6}cicloalquilo o arilo; y en donde cualquier grupo arilo puede sustituirse en forma opcional por uno o dos sustituyentes seleccionados de halo, hidroxi, C_{1-6}alquilo o C_{1-6}alcoxi ;

R^2 y R^5 son independientemente hidrógeno, un C_{1-6}alquilo ramificado o no ramificado, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, guanidino, ciano, carbamoilo, carboxi, C_{1-6}alcoxi, arilC_{1-6}alcoxi, $(C_1$-$C_4)_3Si$, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquil$S(O)_a$, C_{3-6}cicloalquilo, arilo o arilC_{1-6}alquil$S(O)_a$, en donde a es 0-2; y en donde cualquier grupo arilo puede sustituirse en forma opcional por uno o dos sustituyentes seleccionados de halo, hidroxi, C_{1-6}alquilo o C_{1-6}alcoxi;

R^3 es hidrógeno, alquilo, halo, C_{1-6}alcoxi o C_{1-6} alquilS-;

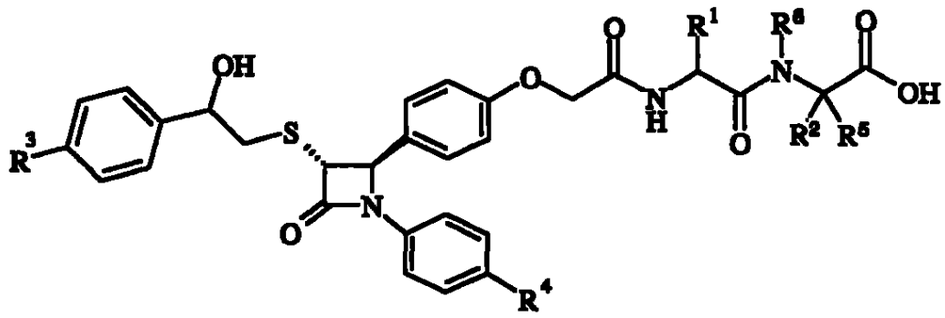
R^4 es hidrógeno, C_{1-6} alquilo, halo o C_{1-6}alcoxi;

R^6 es hidrógeno, C_{1-6} alquilo, o arilC_{1-6} alquilo;

en donde R^5 y R^6 pueden formar un anillo con 2-7 átomos de carbono y en donde R^6 y R^2 pueden formar un anillo con 3-6 átomos de carbono;

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco; con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-[4-(*N*-{*N*-[(R)-1-(carboxi)-2-(hidroxi)etil]carbamoilmetil}carbamoilmetoxi)fenil]azetidin-2-ona; o 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi) etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona.

2. Un compuesto de fórmula (I2):



I2

en donde:

R^1 es hidrógeno, C_{1-6}alquilo, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, guanidino, carbamoilo, carboxi, C_{1-6}alcoxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_1-C_6 alquilcarbonilaminoC$_{1-6}$alquilS(O)$_a$ en donde a es 0-2, C_{3-6}cicloalquilo o arilo; y en donde cualquier grupo arilo puede sustituirse en forma opcional por uno o dos sustituyentes seleccionados de halo, hidroxi, C_{1-6}alquilo o C_{1-6}alcoxi;

R^2 y R^5 son independientemente hidrógeno, C_{1-6}alquilo ramificado o no ramificado, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, guanidino, ciano, carbamoilo, carboxi, C_{1-6}alcoxi, arilC$_{1-6}$alcoxi, $(C_1$-$C_4)_3$Si, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquilS(O)$_a$, C_{3-6}cicloalquilo, arilo o arilC$_{1-6}$alquilS(O)$_a$, en donde a es 0-2; y en donde cualquier grupo

arilo puede sustituirse en forma opcional por uno o dos sustituyentes seleccionados de halo, hidroxi, C_{1-6}alquilo o C_{1-6}alcoxi;

R^3 es hidrógeno, alquilo, halo, C_{1-6}alcoxi o C_{1-6}alquilS-;

R^4 es hidrógeno, C_{1-6} alquilo, halo o C_{1-6}alcoxi;

R^6 es hidrógeno, C_{1-6}alquilo, o arilC_{1-6} alquilo;

en donde R^5 y R^2 pueden formar un anillo con 2-7 átomos de carbono y en donde R^6 y R^2 pueden formar un anillo con 3-6 átomos de carbono;

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco;

con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-[4-(*N*-{*N*-[(R)-1-(carboxi)-2-(hidroxi)etil]carbamoilmetil}carbamoilmetoxi)fenil]azetidin-2-ona; o 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi) etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona.

3. Un compuesto de acuerdo con la reivindicación 1 ó 2, en donde:

R^1 es hidrógeno o fenilo.

4. Un compuesto de acuerdo con una de las reivindicaciones precedentes, en donde:

R^2 es hidrógeno, un C_{1-6}alquilo ramificado o no ramificado, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, acilamino, C_{1-6}alquilS(O)$_a$ en donde a es 0-2, C_{3-6}cicloalquilo o arilo; y en donde cualquier grupo arilo puede sustituirse en forma opcional por hidroxi, alquilo, alcoxi o ciano.

5. Un compuesto de acuerdo con una de las reivindicaciones precedentes, en donde:

R^3 es hidrógeno, C_1-C_2alquilo, halo o metoxi.

6. Un compuesto de acuerdo con una de las reivindicaciones precedentes, en donde:
R^3 es hidrógeno, metilo, cloro, flúor, C_{1-6} alquilS-, o metoxi.

7. Un compuesto de acuerdo con una de las reivindicaciones precedentes, en donde:
R^4 es hidrógeno o halo.

8. Un compuesto de acuerdo con una de las reivindicaciones precedentes, en donde:
R^4 es cloro o flúor.

9. Un compuesto de acuerdo con una de las reivindicaciones precedentes, en donde:
R^6 es hidrógeno, C_{1-6} alquilo, arilC_{1-6}alquilo o R^6 y R^2 forman un anillo con 3-6 átomos de carbono.

10. Un compuesto de acuerdo con la reivindicación 1, en donde:
R^1 es hidrógeno;
R^2 es un C_{1-4}alquilo ramificado o no ramificado, sustituido de manera opcional por un C_{3-6}cicloalquilo, alquilS-, arilo sustituido de manera opcional por hidroxi o ciano, amino, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino o arilC_{1-6} alquil$S(O)_a$, en donde a es 0-2

R^3 y R^4 son halo;
R^5 es hidrógeno o C_{1-6} alquilo; y
R^6 es hidrógeno.

11. Uno o más compuestos seleccionados de:
N-{[4-((2R,3R)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}6-acetil}glicil-N^6-acetil-D-lisina;

1-(4-fluorofenil)-3-(R)-[2-(4-fluorofenil)-2-hidroxietiltio]-4-(R)-{4-[*N*-{*N*-[2-(fenil)-1-(R)-(carboxi)etil]carbamoilmetil} carbamoilmetoxi]fenil}azetidin-2-ona;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-tirosina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-prolina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-lisina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-hidroxi-2-(4-metoxifenil)etil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-2-butilnorleucina;

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*S*-metil-L-cisteína;

N-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-ciclohexil-D-alanina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-ciclohexil-D-alanina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-4-metil-leucina;

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}-L-alanil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-hidroxi-2-(4-metilfenil) etil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-clorofenil)-3-{[2-(4-clorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-metil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-(2-naftil)-D-alanina;

N-{[4-(2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-3-metil-D-valina;

N-{[4-(2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-(3*R*,4*S*,S*R*)-3,4,5,6-tetrahidroxi-D-norleucina;

N-{[4-((2*R*,3*R*)-1-(4-Fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil] tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*N*,2-dimetilalanina;

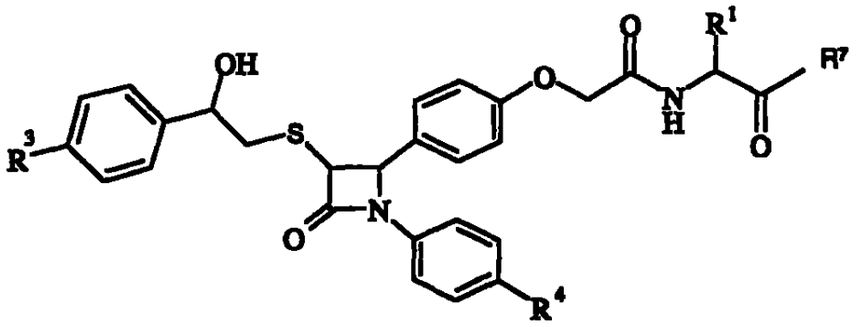
N-({4-[(2*R*,3*R*)-1-(4-Fluorofenil)-3-({2-hidroxi-2-[4-(metiltio)fenil] etil}tio)-4-oxoazetidin-2-il]fenoxi}acetil)glicil-3-metil-D-valina;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*S*-(4-metilbencil)-D-cisteína;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-*S*-(*terc*-butil)-D-cisteína;

N-{[4-((2*R*,3*R*)-1-(4-fluorofenil)-3-{[2-(4-fluorofenil)-2-hidroxietil]tio}-4-oxoazetidin-2-il)fenoxi]acetil}glicil-b,b-dimetil-D-fenilalanina.

12. Un compuesto de la fórmula (XV) o sus ésteres hidrolizables o amidas:



(XV)

en donde:

R^1 es hidrógeno, C_{1-6}alquilo, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, guanidino, carbamoilo, carboxi, C_{1-6}alcoxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_1-C_6 alquilcarbonilaminoC_{1-6}alquil$S(O)_a$ en donde a es 0-2, C_{3-6}cicloalquilo o arilo; y en donde cualquier grupo arilo puede sustituirse en forma opcional por uno o dos sustituyentes seleccionados de halo, hidroxi, C_{1-6}alquilo o C_{1-6}alcoxi;

R^2 y R^5 son independientemente hidrógeno, un C1$_{-6}$alquilo ramificado o no ramificado, C_{3-6}cicloalquilo o arilo; en donde dicho C_{1-6}alquilo puede sustituirse de manera opcional por uno o más hidroxi, amino, guanidino, carbamoilo, carboxi, C_{1-6}alcoxi, arilC_{1-6}alcoxi, $(C_1$-$C_4)_3$Si, *N*-(C_1-

$_6$alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquilS(O)$_a$, arilC_{1-6} alquilS(O)$_a$, en donde a es 0-2, C_{3-6}cicloalquilo o arilo; y en donde cualquier grupo arilo puede sustituirse en forma opcional por uno o dos sustituyentes seleccionados de halo, hidroxi, C_{1-6}alquilo o C_{1-6}alcoxi;

R^3 es hidrógeno, alquilo, halo, C_{1-6}alcoxi o C_{1-6} alquilS-;

R^4 es hidrógeno, C_{1-6} alquilo, halo o C_{1-6}alcoxi;

R^6 es hidrógeno, C_{1-6} alquil, o arilC_{1-6} alquil;

R^7 es un grupo hidroxi o un grupo C_{1-3} alcoxi;

en donde R^5 y R^2 pueden formar un anillo con 2-7 átomos de carbono y en donde R^6 y R^2 pueden formar un anillo con 3-6 átomos de carbono;

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco;

con la salvedad que dicho compuesto no sea 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-[4-(*N*-{*N*-[(R)-1-(carboxi)-2-(hidroxi)etil]carbamoilmetil}carbamoilmetoxi)fenil]azetidin-2-ona; o 3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-{(S)-1-(carboxi)-2-(hidroxi) etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona.

13. Un método de tratar o prevenir enfermedades hiperlipidémicas, que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 a un mamífero necesitado de ello.

14. Un método de tratar o prevenir arterioesclerosis, que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 a un mamífero necesitado de ello.

15. Un método para tratar o prevenir enfermedad de Alzheimer, que comprende la administración de una cantidad efectiva de un compuesto de

acuerdo con una cualquiera de las reivindicaciones 1 a 12 a un mamífero necesitado de ello.

16. Un método para tratar o prevenir tumores asociados con colesterol, que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 a un mamífero necesitado de ello.

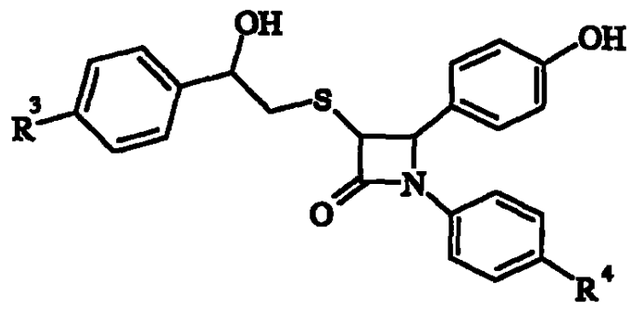
17. Una formulación farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 en mezcla con coadyuvantes, diluyentes y/o vehículos farmacéuticamente aceptables.

18. Una combinación de un compuesto de acuerdo con formula (I) o (I2) con un agonista PPAR alfa y/o gamma.

19. Una combinación de un compuesto de acuerdo con formula (I) o (I2) con un inhibidor de HMG Co-A reductasa.

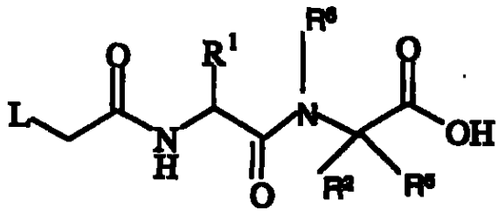
20. Un proceso para preparar un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, proceso que (en donde grupos variables, a menos que se especifique otra cosa, son como se define en fórmula (I)) consta de:

Proceso 1) hacer reaccionar un compuesto de fórmula (II):



(II)

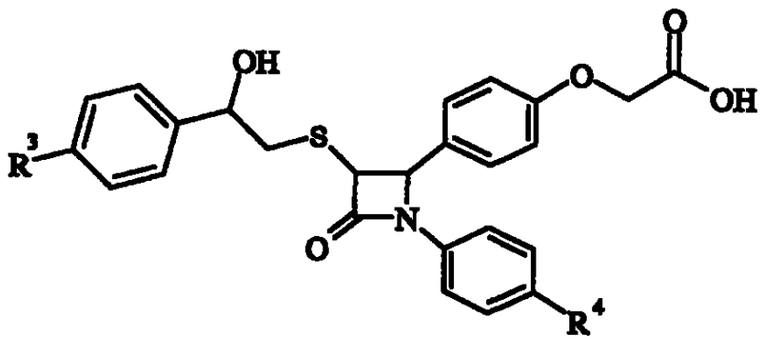
con un compuesto de fórmula (III):



(III)

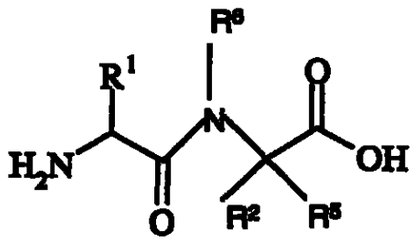
en donde L es un grupo desplazable;

Proceso 2) hacer reaccionar un ácido de fórmula (IV):



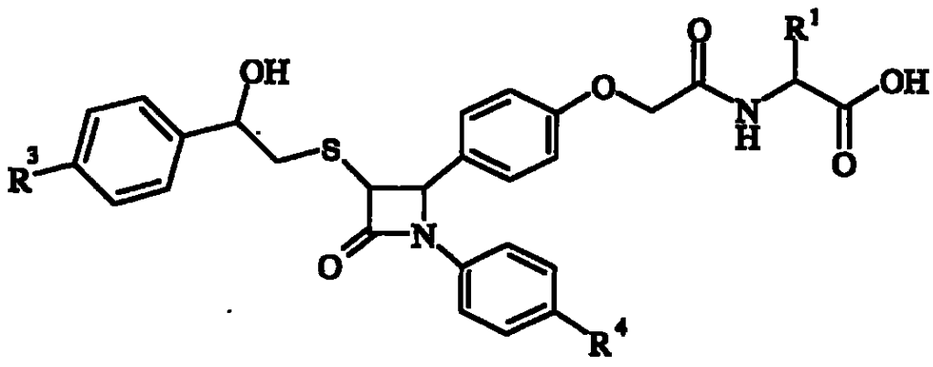
(IV)

o su derivado activado; con una amina de fórmula (V):



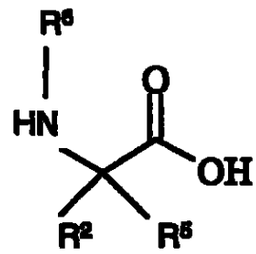
(V)

Proceso 3) hacer reaccionar un ácido de fórmula (VI):



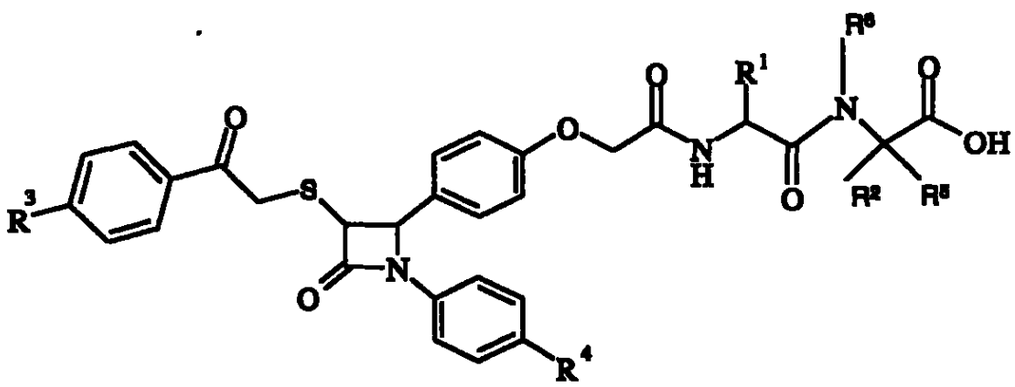
(VI)

o su derivado activado; con una amina de fórmula (VII):



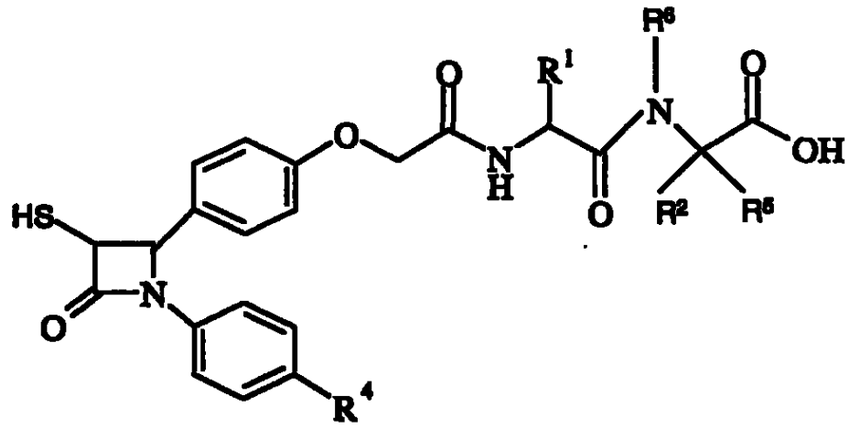
(VII)

Proceso 4): reducir un compuesto de fórmula (VIII):



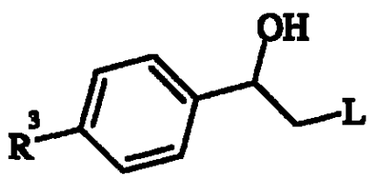
(VIII)

Proceso 5): hacer reaccionar un compuesto de fórmula (IX):



(IX)

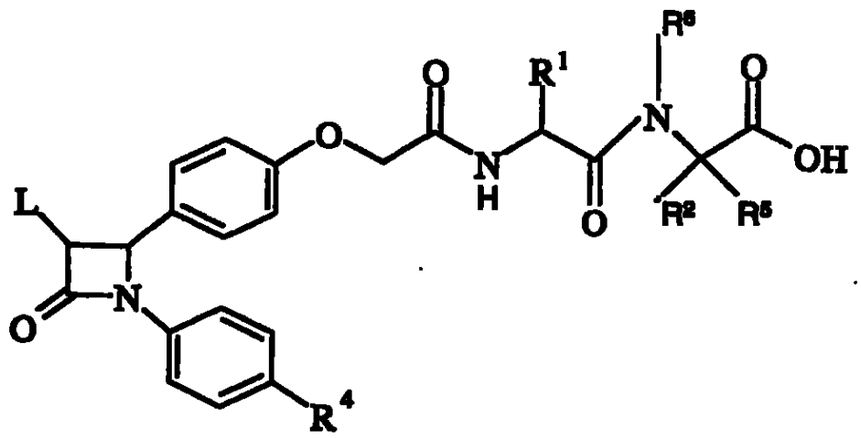
con un compuesto de fórmula (X):



(X)

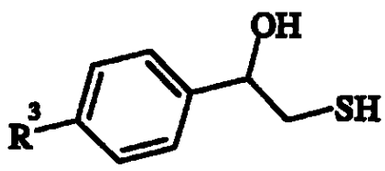
en donde L es un grupo desplazable;

Proceso 6): hacer reaccionar un compuesto de fórmula (XI):



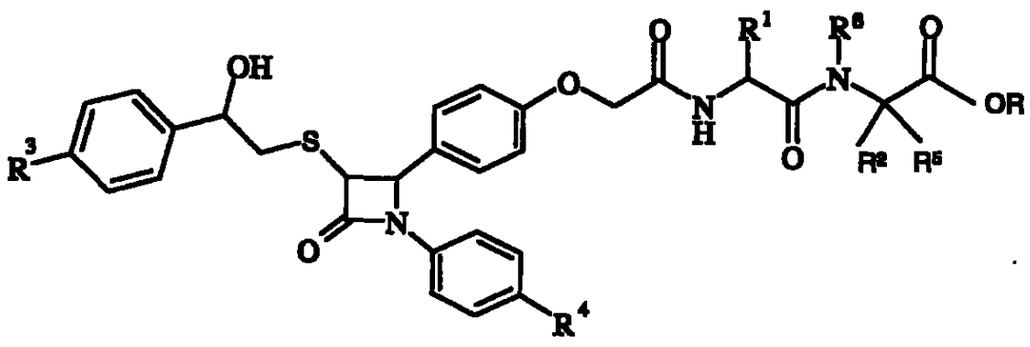
(XI)

en donde L es un grupo desplazable; con un compuesto de fórmula (XII):



(XII)

Proceso 7): des-esterificar un compuesto de fórmula (XIII)



(XIII)

en donde el grupo C(O)OR es un grupo éster;

y posteriormente, si es necesario o deseable:

i) convertir un compuesto de la fórmula (I) en otro compuesto de la fórmula (I);

ii) retirar cualesquiera grupos protectores;

iii) formar una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco; o

iv) separar dos o más enantiómeros.

L es un grupo desplazable; valores apropiados para L son por ejemplo, un halógeno o grupo sulfoniloxi, por ejemplo un grupo cloro, bromo, metanosulfoniloxi o tolueno-4-sulfoniloxi.

C(O)OR es un grupo éster; valores apropiados para C(O)OR son metoxicarbonilo, etoxicarbonilo, *t*-butoxicarbonilo y benciloxicarbonilo.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001960

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 205/08, A61K 31/397, A61P 3/06, A61P 9/10, A61P 25/28
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)

IPC7: C07D, A61K, A61P

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0250060 A1 (AVANTIS PHARMA DEUTSCHLAND GMBH), 27 June 2002 (27.06.2002), examples; claims, especially examples 17 and 19; claim 1	1-20
A	US 5633246 A (BRIAN A. MCKITTRICK ET AL), 27 May 1997 (27.05.1997), claims; examples; especially example 6	1-20
P,X	WO 2004005247 A1 (ASTRAZENECA AB), 15 January 2004 (15.01.2004), claims; examples	1-20

[X] Further documents are listed in the continuation of Box C. [X] 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 but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2005	13 -04- 2005
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	**Authorized officer** Eva Johansson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001960

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	McKittrick, Brian A. et al, "Synthesis of C3 Heteroatom-Substituted Azetidinones That Display Potent Cholesterol Absorption Inhibitory Activity", J. Med. Chem., 1998, vol. 41, page 752 - page 759 ---	1-20
A	US 5744467 A (BRIAN A. MCKITTRICK ET AL), 28 April 1998 (28.04.1998), examples, claims --- --------	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2004/001960

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-16
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 13-16 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

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				CN	1481381	T	10/03/2004
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				CZ	20031733	A	17/09/2003
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				EE	200300238	A	15/08/2003
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				EP	1345932	A	24/09/2003
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				HU	0401073	A	28/09/2004
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				MX	PA03005019	A	25/09/2003
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				ES	2169162	T	01/07/2002
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				SK	283860	B	02/03/2004
				US	5744467	A	28/04/1998
				WO	9616037	A	30/05/1996
				US	5624920	A	29/04/1997
WO	2004005247	A1	15/01/2004	GB	0215579	D	00/00/0000

US	5744467	A	28/04/1998	AT	213726	T	15/03/2002
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				WO	9616037	A	30/05/1996
				US	5624920	A	29/04/1997

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.163)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	Swedish Patent Office (RO/SE)
0-7	Applicant's or agent's file reference	101340-1 WO
I	Title of invention	DIPHENYLAZETIDINONE DERIVATES I
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	ASTRAZENECA AB
II-5	Address	151 85 Södertälje Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No.	+46 8 553 260 00
II-9	Facsimile No.	+46 8 553 288 20
III-1	Applicant and/or inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	ALENFALK, Susanne
III-1-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-1-6	State of nationality	SE
III-1-7	State of residence	SE

III-2	Applicant and/or inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	DAHLSTRÖM, Mikael
III-2-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-2-6	State of nationality	FI
III-2-7	State of residence	SE
III-3	Applicant and/or inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	HUNEGNAW, Fana
III-3-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-3-6	State of nationality	SE
III-3-7	State of residence	SE
III-4	Applicant and/or inventor	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	KARLSSON, Staffan
III-4-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-4-6	State of nationality	SE
III-4-7	State of residence	SE
III-5	Applicant and/or inventor	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	LEMURELL, Malin
III-5-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-5-6	State of nationality	SE
III-5-7	State of residence	SE

III-6	Applicant and/or inventor	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	LINDQVIST, Ann-Margret
III-6-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-6-6	State of nationality	SE
III-6-7	State of residence	SE
III-7	Applicant and/or inventor	
III-7-1	This person is	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	SKJÄRET, Tore
III-7-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-7-6	State of nationality	NO
III-7-7	State of residence	SE
III-8	Applicant and/or inventor	
III-8-1	This person is	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	STARKE, Ingemar
III-8-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-8-6	State of nationality	SE
III-8-7	State of residence	SE
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	ASTRAZENECA
IV-1-2	Address	Global Intellectual Property 151 85 Södertälje Sweden
IV-1-3	Telephone No.	+46 8 553 260 00
IV-1-4	Facsimile No.	+46 8 553 288 20

V	DESIGNATIONS		
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.		
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	23 December 2003 (23.12.2003)	
VI-1-2	Number	0329780.1	
VI-1-3	Country	GB	
VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	21 July 2004 (21.07.2004)	
VI-2-2	Number	0401907-1	
VI-2-3	Country	SE	
VI-3	Priority claim of earlier national application		
VI-3-1	Filing date	15 November 2004 (15.11.2004)	
VI-3-2	Number	0402785-0	
VI-3-3	Country	SE	
VII-1	International Searching Authority Chosen	Swedish Patent Office (ISA/SE)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

364 311

PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	171	-
IX-3	Claims	11	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	189	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-11	Copy of general power of attorney	reference no. GF 5069/04	-
IX-13	Priority document(s)	Item(s) VI-1 VI-2 VI-3	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	Christer Wahlström	
X-1-1	Name	ASTRAZENECA	
X-1-2	Name of signatory	Christer Wahlström	
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/SE
10-6	Transmittal of search copy delayed until search fee is paid	

PCT REQUEST

Original (for SUBMISSION)

3/11 3/12

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

AS: 101303

3/6

3B

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Pais: Suecia**

   El presente documento oficial

2. **ha sido firmado por** Anne-Marie Bonde
3. **en su calidad de** Notario Público
4. **y lleva el timbre/sello de** Notario Público

   en Estocolmo

Lo cual se certifica

5. **en** Estocolmo **6. el** 10.5.2006
7. **por** Björn Sandin

   Notario Público
8. **No** 1833
9. **Timbre/Sello:** **10. Firma:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

101340
Colombia

ASSIGNMENT

TRASPASO

The undersigned,

abajo firmado

Susanne ALENFALK, Mikael DAHLSTRÖM, Fana HUNEGNAW, Staffan KARLSSON, Malin LEMURELL, Ann-Margret LINDQVIST, Tore SKJÄRET, Ingemar STARKE

domiciled in

domiciliado en

AstraZeneca R&D Mölndal, SE-431 83 Mölndal, Sweden
(same address for all inventors)

hereby state under oath to be the sole and true inventor of

declara bajo juramento ser único y verdadero inventor de.

DIPHENYLAZETIDINONE DERIVATES PROCESSING CHOLESTEROL ABSORPTION INHIBITORY ACTIVITY

We state as well that we assign, without reservations or limitation, in favor of

Declaramos asimismo que cedemos y transferimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

a corporation organized and existing under the laws of

organizada y existente de conformidad con la leyes de

Sweden

domiciled in

domiciliada en

SE-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Susanne ALENFALK

Mikael DAHLSTRÖM

Fana HUNEGNAW

Staffan KARLSSON

Malin LEMURELL

Ann-Margret LINDQVIST

Tore SKJÄRET

Ingemar STARKE

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

Yo, la suscrita, Anne-Marie Bonde, Notario Publico en Estocolmo, Suecia, certifica que

SUSANNE ALENFALK, FANA HUNEGNAW, MALIN LEMURELL,
TORE SKJÄRET, MIKAEL DAHLSTRÖM, STAFFAN KARLSSON,
ANN-MARGRET LINDQVIST y INGEMAR STARKE

han ortogado y firmado el documento que antecede.

Derechos 550:- **Estocolmo,** 2006-05-10

Coronas **De oficio:**

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

TRADUCCION DEL SELLO QUE SE ENCUENTRA EN LA APOSTILLA DEL DOCUMENTO DE CESIÓN DE DERECHOS SOBRE LA INVENCIÓN, OTORGADO POR LOS INVENTORES: SUSANNE ALENFALK, MIKAEL DAHLSTRÖM, FANA HUNEGNAW, STAFFAN KARLSSON, MALIN LEMURELL, ANN-MARGRET LINDQVIST, TORE SKJÄRET, INGEMAR STARKE, A LA SOCIEDAD **ASTRAZENECA AB**, DOMICILIADA EN S-151 85 SÖDERTÄLJE, SUECIA, DEL SUECO AL CASTELLANO.

BJÖRN SANDIN
NOTARIO PÚBLICO DE ESTOCOLMO

TRADUCCION DEL SELLO QUE SE ENCUENTRA EN EL DOCUMENTO DE CESIÓN DE DERECHOS SOBRE LA INVENCIÓN, OTORGADO POR LOS INVENTORES: SUSANNE ALENFALK, MIKAEL DAHLSTRÖM, FANA HUNEGNAW, STAFFAN KARLSSON, MALIN LEMURELL, ANN-MARGRET LINDQVIST, TORE SKJÄRET, INGEMAR STARKE A LA SOCIEDAD **ASTRAZENECA AB**, DOMICILIADA EN S-151 85 SÖDERTÄLJE, SUECIA, DEL SUECO AL CASTELLANO.

ANNE-MARIE BONDE
NOTARIO PÚBLICO DE ESTOCOLMO

Brigard & Castro

BOGOTA - COLOMBIA

PODER / POWER OF ATTORNEY

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
domiciliado(s) en la Carrera 7 No. 16-66 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

I (We) ASTRAZENECA AB

domiciled in SE-151 Sodertalje, Sweden

Hereby appoint **RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.**
of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.**
domiciled in Carrera 7 No. 16-66, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in Macclesfield, Cheshire, England

this 16th day of July 2003

Name: [illegible] BILL
Director, IP Services

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia con el original que se ha tenido a la vista.
02 FEB. 2006
NOTARIO CUARENTA (E)
Henry Fernando Mora Sánchez
Bogotá, D.C. Colombia

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of
personally appeared before me
KEVIN BILL
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
ATTORNEY
of
ASTRAZENECA AB

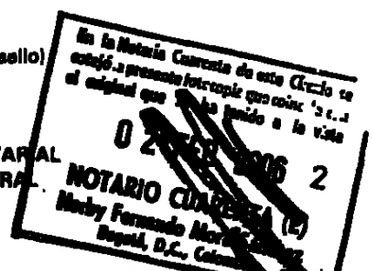
Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer -this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that purpose for which this instrument is granted included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Sweden
under date of 1st January 2003

and that he (she) who grants the present power of attorney is its Representative.

Notary Public (Seal)



CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Notary Public (Seal)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

320 317

2

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: J B Hodgson

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 17 February 2004

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.

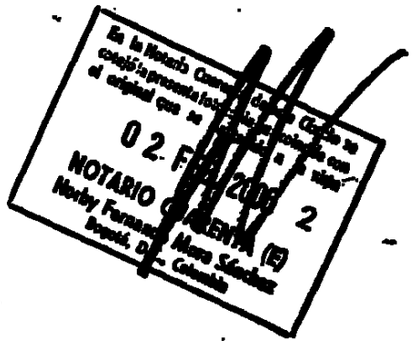
8. Number/sous No: G348987

9. Stamp: / timbre:

10. Signature: J. Ireland

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.



318

TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el Poder concedido por ASTRAZENECA AB, domiciliada en SE - 151 Sodertalje, Suecia a Ramiro Castro Duque y/o Juan Pablo Cadena Sarmiento y/o Beatriz Jaramillo S, domiciliados en la Carrera 7 #16-56, P. 9, Bogotá D.C., Colombia.

AUTENTICACIÓN

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

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

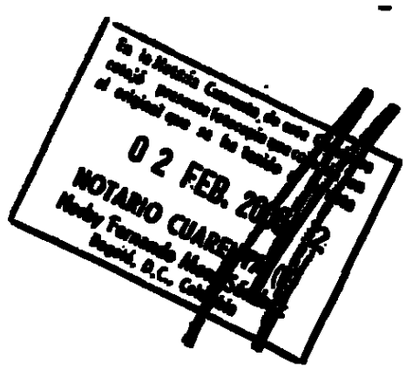
1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
2. Este documento público
   ha sido firmado por **J. B. Hodgson**
3. actuando en capacidad de **Notario Público**
4. lleva el sello de: **Dicho Notario Público**

CERTIFICADO

5. en Londres **6. el 17 de Febrero de 2004**
7. por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad
8. No. **G348987**
9. Sello 10. Firma

J. Ireland (Firma)

Si este documento va a ser utilizado en un país que no es parte de la Convención de La Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión que representa a ese país.



REPÚBLICA DE COLOMBIA

GAVIRIA

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

Datos de la oficina de registro

Clase de oficina: Registraduría		Notaría	X	Consulado		Corregimiento		Insp. de Policía		Código	9995

País - Departamento - Municipio - Corregimiento o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C NOTARIA 32.

Datos del inscrito

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción

Lugar de la Defunción País - Departamento - Municipio - Corregimiento o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción										Hora	Número de certificado de defunción
Año 2004				Mes 10		Día 30				04:10 PM	A- 2094375.

Presunción de muerte

Juzgado que profirió la sentencia	Fecha de la sentencia		
	Año	Mes	Día

Documento presentado			Nombre y cargo del funcionario
Autorización judicial		Certificado Médico	X	ANDRES DIAZ CAMPOS.- R. M. No. 79982662

Datos del denunciante

Apellidos y nombres completos

EDGAR DAVID REGINO II.

Documentos de Identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA CORDOBA	

Primer testigo

Apellidos y nombres completos

Documentos de Identificación (Clase y número)	Firma

Segundo testigo

Apellidos y nombres completos

Documentos de Identificación (Clase y número)	Firma

Fecha de inscripción										Nombre y firma del funcionario que autoriza
Año 2004				Mes 11		Día 02				BLANCA LUCIA GALEANO RESTREPO NOTARIA 32

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

CERTIFICO : QUE:

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número: ST 62204.....
que expido en la ciudad de Bogotá D.C., hoy: 05 NOV. 2004.....

NOTARIA 32 DEL C...
...D.C. BOGOTA D.C.
SECRETARIO DELEGADO

NELSON FLOREZ R.
SECRETARIO DELEGADO PARA COPIAS
DECRETO 1134 DE 1989

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-060219- -00000-0000
Fec: 2006-06-21 16:38:35 Dep: 2020 NUECREACIONE
Tra: 11 PATENTESYII
Cve: 379 FASENACIONALII
Act 411 PRESENTACION Folios: 322

Industria y Comercio
SUPERINTENDENCIA.

323
320

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] 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 se 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 trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Fernando B
Firma Responsable

Fecha 21-JUN-6

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Folio 324

2020
Bogotá D.C.,

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No.	06 60219
	Solicitud internacional	PCT/SE2004/001960
	Fecha inicio fase nacional	23/07/2006
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	1719
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 02 NOV. 2006

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11

Industria y Comercio
SUPERINTENDENCIA

322

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-060219

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **573**

DE FECHA **28 DE FEBRERO** DEL **2007**, EL TERMINO HABIL SEÑALADO

POR LA LEY EXPIRA EL **30** DE **MAYO** DEL **2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _X_ NO__ _ _ __

Bogotá D.C., Junio de 2007