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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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54 TITULO DERIVADOS DE BENZOTIAZEPINA Y BENZOTIADIAZEPINA CON ACTIVIDAD
INHIBIDORA DE TRANSPORTE DE ACIDOS BILIARES EN EL ILEON (IBAT)
PARA EL TRATAMIENTO DE HIPERLIPIDEMIA

51 CLASIFICACION INTERNACIONAL A61N31/554

71 SOLICITANTE ASTRAZENECA AB

DOMICILIO SODERTALJE, SUECIA

74 APODERADO RAMIRO CASTRO DUQUE

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1

SOLICITUD DE



Patente de Invención



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Capítulo I



Capítulo II

2

SOLICITANTE
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Otro



Cual

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3

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Otro



Cual

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4

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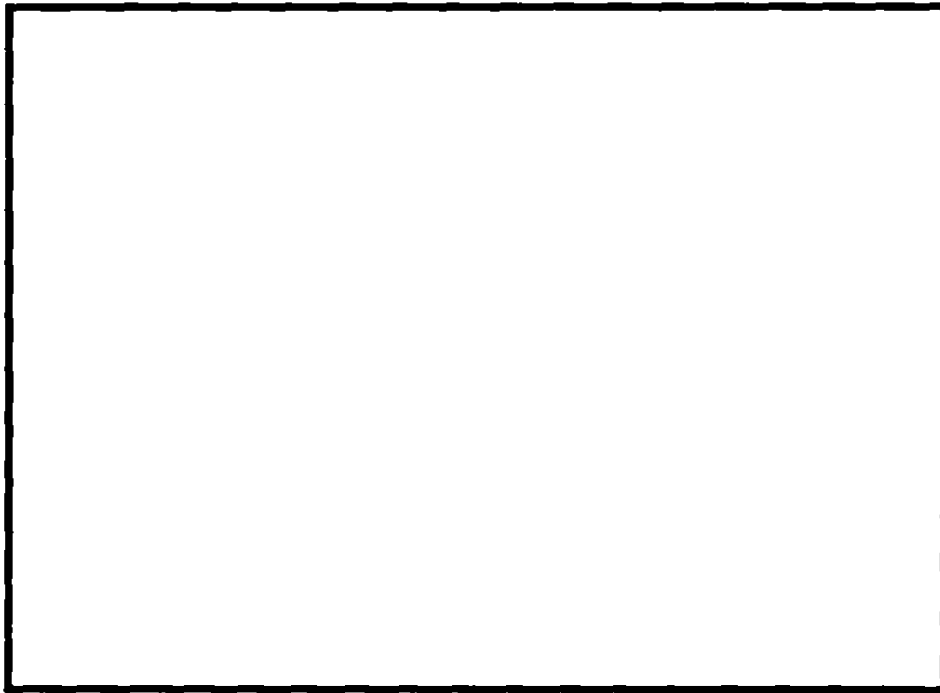
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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

- ☒ Comprobante de pago de la tasa de presentación de la solicitud \$422.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada Anesa
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional (Resumen descripción reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
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- ☐ 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
- ☒ Otros Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA.



12. Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA

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1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL DE PATENTE DE IN TOTAL	422 000 00 \$ 422 000 00

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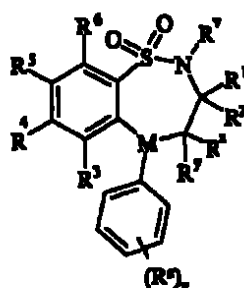
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(54) Title BENZOTHIAZEPINE AND BENZOTHIADIAZEPINE DERIVATIVES WITH IDEAL BILE ACID TRANSPORT
(IBAT) INHIBITORY ACTIVITY FOR THE TREATMENT OF HYPERLIPIDAEMIA



(I)

(57) Abstract: The present invention relates to compounds of formula (I) wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and M are as defined within pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof and their use as ideal bile acid transport (IBAT) inhibitors for the treatment of hyperlipidaemia. Processes for their manufacture and pharmaceutical compositions containing them are also described.

WO 03/022286 A1

BENZOTHIAZEPINE AND BENZOTHIAZADIAZEPINE DERIVATIVES WITH ILEAL BILE ACID TRANSPORT (IBAT) INHIBITORY ACTIVITY FOR THE TREATMENT OF HYPERLIPIDAEMIA

This invention relates to benzothiazepine and benzothiadiazepine derivatives, or pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof. These benzothiazepines and benzothiadiazepines possess ileal bile acid transport (IBAT) inhibitory activity and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions and they are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said benzothiazepine and benzothiadiazepine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit IBAT in a warm-blooded animal, such as man.

It is well-known that hyperlipidaemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein 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). Interfering with the circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous established therapies to reduce the concentration of cholesterol involve, for instance, treatment with HMG-CoA reductase inhibitors, preferably statins such as simvastatin and fluvastatin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and colestipol. One recently proposed therapy ("Bile Acids and Lipoprotein Metabolism: a Renaissance for Bile Acids in the Post Statin Era" Angelin B, Eriksson M, Rudling M, Current Opinion on Lipidology, 1999, 10, 269-74) involved the treatment with substances with an IBAT inhibitory effect.

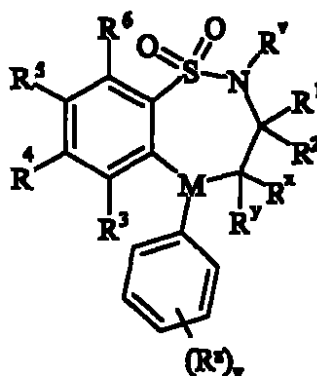
Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process which mainly takes place in the ileum by the IBAT mechanism. Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia (see for instance "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolaemic properties", Biochimica et Biophysica Acta, 1210 (1994) 255-287). Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions. Substituted compounds possessing such IBAT inhibitory activity have been described, see for

instance hypolipidaemic compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/38182, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906 and EP 0 864 582.

A further aspect of this invention relates to the use of the compounds of the invention in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridaemia, hyperbetalipoproteinaemia (high LDL), hyperprebetalipoproteinaemia (high VLDL), hyperchylomicronaemia, hypolipoproteinaemia, hypercholesterolemia, hyperlipoproteinaemia and hypoalphalipoproteinaemia (low HDL). In addition, these compounds are expected to be useful for the prevention and 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.

The present invention is based on the discovery that certain benzothiazepine and benzothiadiazepine compounds surprisingly inhibit IBAT. Such properties are expected to be of value in the treatment of disease states associated with hyperlipidaemic conditions.

Accordingly, the present invention provides a compound of formula (I)



(I)

wherein

R^7 is selected from hydrogen or C_{1-6} alkyl,

One of R^1 and R^2 are selected from hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl and the other is selected from C_{1-6} alkyl or C_{2-6} alkenyl,

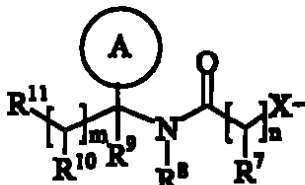
R^3 and R^7 are independently selected from hydrogen, hydroxy, ammo, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkylS(O) $_a$ where a is 0 to 2,

M is selected from -N- or -CH-,

R^4 is selected from halo, nitro, cyano, hydroxy, ammo, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ where a is 0 to 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl,

v is 0-5,

one of R^4 and R^5 is a group of formula (IA)



(IA)

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, ammo, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)ammo, N,N -(C_{1-4} alkyl) $_2$ ammo, C_{1-4} alkanoylammo, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl) $_2$ carbamoyl, C_{1-4} alkylS(O) $_a$ where a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl) $_2$ sulphamoyl, wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{16} ,

X is -O-, -N(R^b)-, -S(O) $_b$ - or -CH(R^b)-, where R^b is hydrogen or C_{1-6} alkyl and b is 0-2,

Ring A is aryl or heteroaryl, wherein Ring A is optionally substituted by one or more substituents selected from R^{17} ,

R^7 is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl, wherein R^7 is optionally substituted by one or more substituents selected from R^{18} ,

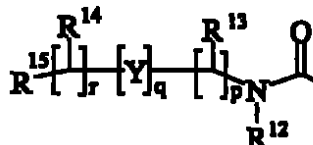
R^8 is hydrogen or C_{1-4} alkyl,

X⁶

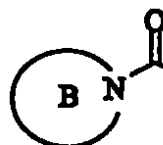
R^9 is hydrogen or C_{1-4} alkyl,

R^{10} is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl, wherein R^{10} is optionally substituted by one or more substituents selected from R^{19} ,

R^{11} is carboxy, sulphy, sulphony, phosphono, $-P(O)(OR^e)(OR^d)$, $-P(O)(OH)(OR^e)$,
 5 $-P(O)(OH)(R^d)$ or $-P(O)(OR^e)(R^d)$ wherein R^e and R^d are independently selected from C_{1-6} alkyl, or R^{11} is a group of formula (IB) or (IC)



(IB)



(IC)

wherein

10 Y is $-N(R^a)-$, $-N(R^a)C(O)-$, $-N(R^a)C(O)(CR^bR^c)-$, $-N(R^a)C(O)-$, $-O-$, and $-S(O)_a-$,
 wherein a is 0-2, v is 1-2, R^a and R^b are independently selected from hydrogen or C_{1-4} alkyl
 optionally substituted by R^{26} and R^c is hydrogen or C_{1-4} alkyl,

R^{12} is hydrogen or C_{1-4} alkyl,

R^{13} and R^{14} are independently selected from hydrogen, C_{1-6} alkyl, carbocyclyl or
 15 heterocyclyl, and when q is 0, R^{14} may additionally be selected from hydroxy, wherein R^{13}
 and R^{14} may be independently optionally substituted by one or more substituents selected
 from R^{20} ,

R^{15} is carboxy, sulphy, sulphony, phosphono, $-P(O)(OR^e)(OR^f)$, $-P(O)(OH)(OR^e)$,
 $-P(O)(OH)(R^f)$ or $-P(O)(OR^e)(R^f)$ wherein R^e and R^f are independently selected from

20 C_{1-6} alkyl,

p is 1-3, wherein the values of R^{13} may be the same or different,

q is 0-1,

r is 0-3, wherein the values of R^{14} may be the same or different,

m is 0-2, wherein the values of R^{10} may be the same or different;

25 n is 1-3, wherein the values of R^7 may be the same or different;

Ring B is a nitrogen linked heterocyclyl substituted on carbon by one group selected
 from R^{23} , and optionally additionally substituted on carbon by one or more R^{24} , and wherein if
 said nitrogen linked heterocyclyl contains an $-NH-$ moiety, that nitrogen may be optionally
 substituted by a group selected from R^{25} ,

R^{16} , R^{17} and R^{18} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a,
 5 where a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl)₂sulphamoyl, wherein R^{16} , R^{17} and R^{18} may be independently optionally substituted on carbon by one or more R^{21} ,

R^{19} , R^{20} , R^{24} and R^{26} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a,
 10 where a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl, N,N -(C_{1-4} alkyl)₂sulphamoyl, carbocyclyl, heterocyclyl, benzyloxycarbonylamino, (C_{1-4} alkyl)₃silyl, sulpho, sulphino, amidino, phosphono, $-P(O)(OR^a)(OR^b)$, $-P(O)(OH)(OR^a)$, $-P(O)(OH)(R^a)$ or $-P(O)(OR^a)(R^b)$,
 15 where R^a and R^b are independently selected from C_{1-6} alkyl, wherein R^{19} , R^{20} , R^{24} and R^{26} may be independently optionally substituted on carbon by one or more R^{22} ,

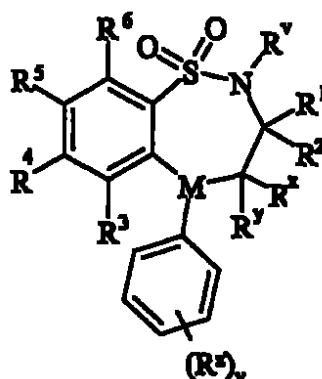
R^{21} and R^{22} are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, methylamino, dimethylamino, N -methylcarbamoyl, N,N -dimethylcarbamoyl, methylthio, methylsulphonyl, mesyl, N -methylsulphamoyl and N,N -dimethylsulphamoyl,

R^{23} is carboxy, sulpho, sulphino, phosphono, $-P(O)(OR^a)(OR^b)$, $-P(O)(OH)(OR^a)$, $-P(O)(OH)(R^a)$ or $-P(O)(OR^a)(R^b)$ wherein R^a and R^b are independently selected from C_{1-6} alkyl,

R^{25} is selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl,

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

30 According to a further aspect of the present invention there is provided a compound of formula (I)



(I)

wherein

R^v is selected from hydrogen or C_{1-6} alkyl,

- 5 One of R^1 and R^2 are selected from hydrogen or C_{1-6} alkyl and the other is selected from C_{1-6} alkyl,

R^3 and R^7 are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, $N-(C_{1-6}alkyl)amino$, $N,N-(C_{1-6}alkyl)_2amino$, $C_{1-6}alkylS(O)_a$ wherein a is 0 to 2,

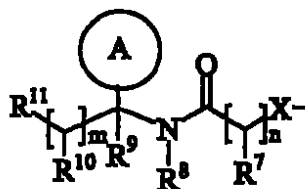
- 10 M is selected from $-N-$ or $-CH-$,

R^2 is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphonamoyl, C_{1-6} alkyl, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkanoyl$, $C_{1-6}alkanoyloxy$, $N-(C_{1-6}alkyl)amino$, $N,N-(C_{1-6}alkyl)_2amino$, $C_{1-6}alkanoylamino$, $N-(C_{1-6}alkyl)carbamoyl$, $N,N-(C_{1-6}alkyl)_2carbamoyl$, $C_{1-6}alkylS(O)_a$ wherein a is 0 to 2, $C_{1-6}alkoxycarbonyl$,

- 15 $N-(C_{1-6}alkyl)sulphonamoyl$ and $N,N-(C_{1-6}alkyl)_2sulphonamoyl$,

v is 0-5,

one of R^4 and R^5 is a group of formula (IA)



(IA)

- 20 R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphonamoyl, C_{1-4} alkyl, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $C_{1-4}alkoxy$, $C_{1-4}alkanoyl$, $C_{1-4}alkanoyloxy$, $N-(C_{1-4}alkyl)amino$, $N,N-(C_{1-4}alkyl)_2amino$, $C_{1-4}alkanoylamino$, $N-(C_{1-4}alkyl)carbamoyl$,

N,N -(C_{1-4} alkyl) $_2$ carbamoyl, C_{1-4} alkylS(O) $_a$ where a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl) $_2$ sulphamoyl, where R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{16} ,

X is -O-, -N(R^a)-, -S(O) $_b$ - or -CH(R^a)-, where R^a is hydrogen or C_{1-6} alkyl and b is 0-

5 2,

Ring A is aryl or heteroaryl, where Ring A is optionally substituted by one or more substituents selected from R^{17} ,

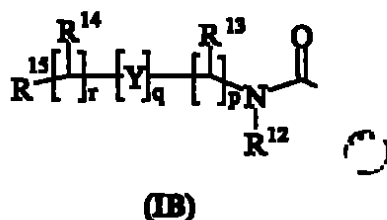
R^7 is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl, where R^7 is optionally substituted by one or more substituents selected from R^{18} ,

10 R^8 is hydrogen or C_{1-4} alkyl,

R^9 is hydrogen or C_{1-4} alkyl,

R^{10} is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl, where R^{10} is optionally substituted by one or more substituents selected from R^{19} ,

15 R^{11} is carboxy, sulphy, sulphony, phosphono, -P(O)(OR ^{e})(OR ^{d}), -P(O)(OH)(OR ^{e}), -P(O)(OH)(R ^{d}) or -P(O)(OR ^{e})(R ^{d}) where R^e and R^d are independently selected from C_{1-6} alkyl, or R^{11} is a group of formula (IB)



wherein

20 Y is -N(R^b)-, -N(R^b)C(O)-, -O-, and -S(O) $_a$ -, where a is 0-2 and R^b is hydrogen or C_{1-4} alkyl,

R^{12} is hydrogen or C_{1-4} alkyl,

R^{13} and R^{14} are independently selected from hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl, where R^{13} and R^{14} may be independently optionally substituted by one or more substituents selected from R^{20} ,

25

R^{15} is carboxy, sulphy, sulphony, phosphono, -P(O)(OR ^{g})(OR ^{f}), -P(O)(OH)(OR ^{g}), -P(O)(OH)(R ^{f}) or -P(O)(OR ^{g})(R ^{f}) where R^g and R^f are independently selected from C_{1-6} alkyl,

p is 1-3, where the values of R^{13} may be the same or different;

30 q is 0-1,

8
X

r is 0-3, wherein the values of R^{14} may be the same or different;

m is 0-2, wherein the values of R^{10} may be the same or different;

n is 1-3, wherein the values of R^7 may be the same or different;

R^{16} , R^{17} and R^{18} are independently selected from halo, nitro, cyano, hydroxy, amino,

- 5 carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl) $_2$ amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl) $_2$ carbamoyl, C_{1-4} alkylS(O) $_a$, wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl) $_2$ sulphamoyl, wherein R^{16} , R^{17} and R^{18} may be independently optionally substituted on carbon by one or more R^{21} ,
- 10

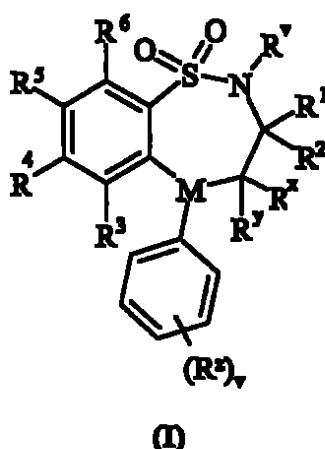
R^{19} and R^{20} are independently selected from halo, nitro, cyano, hydroxy, amino,

- carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl) $_2$ amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl) $_2$ carbamoyl, C_{1-4} alkylS(O) $_a$, wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl, N,N -(C_{1-4} alkyl) $_2$ sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, $-P(O)(OR^a)(OR^b)$, $-P(O)(OH)(OR^a)$, $-P(O)(OH)(R^a)$ or $-P(O)(OR^a)(R^b)$, wherein R^a and R^b are independently selected from C_{1-4} alkyl, wherein R^{19} and R^{20} may be independently optionally substituted on carbon by one or more R^{22} ,
- 15

- R^{21} and R^{22} are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, methylamino, dimethylamino, N -methylcarbamoyl, N,N -dimethylcarbamoyl, methylthio, methylsulphiny, mesyl, N -methylsulphamoyl and
- 20
- 25 N,N -dimethylsulphamoyl,

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 compound of formula (I)



wherein.

R^v is selected from hydrogen or C_{1-6} alkyl,

- 5 One of R^1 and R^2 are selected from hydrogen or C_{1-6} alkyl and the other is selected from C_{1-6} alkyl,

R^7 and R^8 are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, $N-(C_{1-6}alkyl)amino$, $N,N-(C_{1-6}alkyl)_2amino$, $C_{1-6}alkylS(O)_a$ wherein a is 0 to 2,

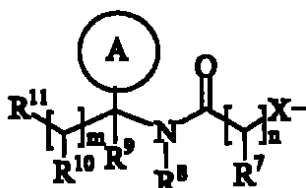
- 10 M is selected from $-N-$ or $-CH-$,

R^7 is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, $C_{1-6}alkanoyl$, $C_{1-6}alkanoyloxy$, $N-(C_{1-6}alkyl)amino$, $N,N-(C_{1-6}alkyl)_2amino$, $C_{1-6}alkanoylamino$, $N-(C_{1-6}alkyl)carbamoyl$, $N,N-(C_{1-6}alkyl)_2carbamoyl$, $C_{1-6}alkylS(O)_a$ wherein a is 0 to 2, $C_{1-6}alkoxycarbonyl$,

- 15 $N-(C_{1-6}alkyl)sulphamoyl$ and $N,N-(C_{1-6}alkyl)_2sulphamoyl$,

v is 0-5,

one of R^4 and R^5 is a group of formula (IA)



(IA)

- 20 R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, $C_{2-4}alkenyl$, $C_{2-4}alkynyl$, $C_{1-4}alkoxy$, $C_{1-4}alkanoyl$, $C_{1-4}alkanoyloxy$, $N-(C_{1-4}alkyl)amino$, $N,N-(C_{1-4}alkyl)_2amino$, $C_{1-4}alkanoylamino$, $N-(C_{1-4}alkyl)carbamoyl$,

N,N-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_a, wherein a is 0 to 2, C₁₋₄alkoxycarbonyl, *N*-(C₁₋₄alkyl)sulphamoyl and *N,N*-(C₁₋₄alkyl)₂sulphamoyl, wherein R³ and R⁶ and the other of R⁴ and R⁵ may be optionally substituted on carbon by one or more R¹⁶,

X is -O-, -N(R^a)-, -S(O)_b- or -CH(R^a)-, wherein R^a is hydrogen or C₁₋₄alkyl and b is 0-2,

Ring A is aryl or heteroaryl, wherein Ring A is optionally substituted by one or more substituents selected from R¹⁷,

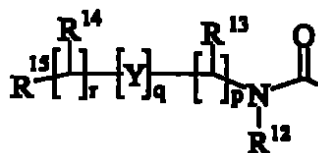
R⁷ is hydrogen, C₁₋₄alkyl, carbocyclyl or heterocyclyl, wherein R⁷ is optionally substituted by one or more substituents selected from R¹⁸,

R⁸ is hydrogen or C₁₋₄alkyl,

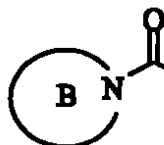
R⁹ is hydrogen or C₁₋₄alkyl,

R¹⁰ is hydrogen, C₁₋₄alkyl, carbocyclyl or heterocyclyl, wherein R¹⁰ is optionally substituted by one or more substituents selected from R¹⁹,

R¹¹ is carboxy, sulphy, sulphony, phosphono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from C₁₋₄alkyl, or R¹¹ is a group of formula (IB) or (IC)



(IB)



(IC)

wherein

Y is -N(R^b)-, -N(R^b)C(O)-, -N(R^b)C(O)(CR^bR^b)-N(R^b)C(O)-, -O-, and -S(O)_a-, wherein a is 0-2, v is 1-2, R^d and R^f are independently selected from hydrogen or C₁₋₄alkyl optionally substituted by R²⁶ and R^a is hydrogen or C₁₋₄alkyl,

R¹² is hydrogen or C₁₋₄alkyl,

R¹³ and R¹⁴ are independently selected from hydrogen, C₁₋₄alkyl, carbocyclyl or heterocyclyl, and when q is 0, R¹⁴ may additionally be selected from hydroxy; wherein R¹³ and R¹⁴ may be independently optionally substituted by one or more substituents selected from R²⁰,

R¹⁵ is carboxy, sulphy, sulphony, phosphono, -P(O)(OR^g)(OR^h), -P(O)(OH)(OR^g), -P(O)(OH)(R^g) or -P(O)(OR^g)(R^h) wherein R^g and R^h are independently selected from C₁₋₄alkyl,

p is 1-3, wherein the values of R^{13} may be the same or different;

q is 0-1,

r is 0-3, wherein the values of R^{14} may be the same or different;

m is 0-2, wherein the values of R^{10} may be the same or different;

5 n is 1-3, wherein the values of R^7 may be the same or different;

Ring B is a nitrogen linked heterocyclyl substituted on carbon by one group selected from R^{23} , and optionally additionally substituted on carbon by one or more R^{24} , and wherein if said nitrogen linked heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by a group selected from R^{25} ,

10 R^{16} , R^{17} and R^{18} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a, wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and
15 N,N -(C_{1-4} alkyl)₂sulphamoyl, wherein R^{16} , R^{17} and R^{18} may be independently optionally substituted on carbon by one or more R^{21} ,

R^{19} , R^{20} , R^{24} and R^{26} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a,
20 wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl, N,N -(C_{1-4} alkyl)₂sulphamoyl, carbocyclyl, heterocyclyl, benzyloxycarbonylamino, sulpho, sulphino, amidino, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^b), wherein R^a and R^b are independently selected from C_{1-4} alkyl, wherein R^{19} , R^{20} , R^{24} and R^{26} may be independently
25 optionally substituted on carbon by one or more R^{22} ,

R^{21} and R^{22} are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, N -methylcarbamoyl,
30 N,N -dimethylcarbamoyl, methylthio, methylsulphonyl, mesyl, N -methylsulphamoyl and N,N -dimethylsulphamoyl,

R²³ is carboxy, sulphy, sulphony, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^b) wherein R^a and R^b are independently selected from C₁₋₆alkyl,

R²⁵ is selected from C₁₋₆alkyl, C₁₋₆alkanoyl, C₁₋₆alkylsulphonyl, C₁₋₆alkoxycarbonyl, carbamoyl, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl,

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

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, "C₁₋₆alkyl" includes C₁₋₆alkyl, C₁₋₃alkyl, 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 "phenylC₁₋₆alkyl" would include phenylC₁₋₆alkyl, 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.

"Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Preferably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "heteroaryl" are thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridyl and quinolyl. Preferably the term "heteroaryl" refers to thienyl or indolyl.

"Aryl" is a totally unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms. Preferably "aryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "aryl" include phenyl or naphthyl. Particularly "aryl" is phenyl.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a $-C(O)-$ or a ring sulphur atom may be optionally oxidised to form the S-oxides. Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a $-C(O)-$ or a ring sulphur atom may be optionally oxidised to form S-oxide(s). Examples and suitable values of the term "heterocyclyl" are thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidinonyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolmonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouacalyl, 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-azabicyclo[2.2.1]heptyl, 4-thiazolidonyl, morpholino, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, 2,3-dihydrobenzofuranyl, benzothienyl, tetrahydropyranyl, piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholino, 1,1-dioxothiomorpholino, tetrahydropyranyl, 1,3-dioxolanyl, homopiperazinyl, thienyl, isoxazolyl, imidazolyl, pyrrolyl, triadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, pyranyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl and 1-isoquinolonyl.

A "nitrogen linked heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is nitrogen and the heterocyclyl is linked to the carbonyl group of formula (IC) via this nitrogen, which may additionally contain further heteroatoms chosen from nitrogen, sulphur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a $-C(O)-$ or a ring sulphur atom may be optionally oxidised to form the S-oxides. Preferably a "nitrogen linked heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is nitrogen and the heterocyclyl is linked to the carbonyl group of formula (IC) via this nitrogen, which may additionally contain further heteroatoms chosen from nitrogen, sulphur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a $-C(O)-$ or a ring sulphur atom may be optionally oxidised to form the S-oxides. Examples and suitable values of the term "nitrogen linked heterocyclyl" are morpholino, pyrrolidin-1-yl, imidazol-1-yl, pyrazolidin-1-yl, piperidin-1-yl and piperazin-1-yl. Particularly a "nitrogen linked heterocyclyl" is pyrrolidin-1-yl.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms, wherein a $-\text{CH}_2-$ group can optionally be replaced by a $-\text{C}(\text{O})-$. Preferably "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. Particularly "carbocyclyl" is cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl or 1-oxoindanyl

An example of " C_{1-6} alkanoyloxy" and " C_{1-4} alkanoyloxy" is acetoxy. Examples of " C_{1-6} alkoxycarbonyl" and " C_{1-4} alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of " C_{1-6} alkoxy" and " C_{1-4} alkoxy" include methoxy, ethoxy and propoxy. Examples of " C_{1-6} alkanoylamino" and " C_{1-4} alkanoylamino" include formamido, acetamido and propionylamino. Examples of " C_{1-6} alkylS(O)_{*a*}" wherein *a* is 0 to 2" and " C_{1-4} alkylS(O)_{*a*}" wherein *a* is 0 to 2" include methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, mesyl and ethylsulphonyl. Examples of " C_{1-6} alkanoyl" and " C_{1-4} alkanoyl" include propionyl and acetyl. Examples of " $N-(\text{C}_{1-6}$ alkyl)amino" and " $N-(\text{C}_{1-4}$ alkyl)amino" include methylamino and ethylamino. Examples of " $N,N-(\text{C}_{1-6}$ alkyl)₂amino" and " $N,N-(\text{C}_{1-4}$ alkyl)₂amino" include di-*N*-methylamino, di-*N*-ethylamino and *N*-ethyl-*N*-methylamino. Examples of " C_{2-6} alkenyl" and " C_{2-4} alkenyl" are vinyl, allyl and 1-propenyl. Examples of " C_{2-6} alkynyl" and " C_{2-4} alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of " $N-(\text{C}_{1-6}$ alkyl)sulphamoyl" and " $N-(\text{C}_{1-4}$ alkyl)sulphamoyl" are *N*-(C_{1-3} alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of " $N-(\text{C}_{1-6}$ alkyl)₂sulphamoyl" " $N-(\text{C}_{1-4}$ alkyl)₂sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of " $N-(\text{C}_{1-6}$ alkyl)carbamoyl" and " $N-(\text{C}_{1-4}$ alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of " $N,N-(\text{C}_{1-6}$ alkyl)₂carbamoyl" and " $N,N-(\text{C}_{1-4}$ alkyl)₂carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Example of " C_{1-6} alkylsulphonyl" are mesyl and ethylsulphonyl. Examples of " $(\text{C}_{1-4}$ alkyl)₃silyl," include trimethylsilyl and methyldiethylsilyl

A suitable pharmaceutically acceptable salt of a compound of the invention 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

5 tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) 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)

10 An *in vivo* hydrolysable ester of a compound of the formula (I) 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 C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters,
15 C₂₋₆cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl, 1,3-dioxolan-2-onylmethyl esters for example 5-methyl-1,3-dioxolan-2-onylmethyl, and C₁₋₆alkoxycarbonyloxyethyl 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) containing a hydroxy
20 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,
25 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)
30 containing a carboxy group is, for example, a *N*-C₁₋₆alkyl or *N,N*-di-C₁₋₆alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

12
M

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 IBAT inhibitory activity

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

Particular values are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined herebefore or hereinafter

R^v is hydrogen.

R¹ and R² are C₁₋₄alkyl

R¹ and R² are both butyl

One of R¹ and R² is ethyl and the other is butyl

One of R² and R^v is hydrogen and the other is hydroxy

R² and R^v are both hydrogen.

M is -N-

M is -CH-

v is 0 or 1

v is 0

R² is C₁₋₄alkyl.

R³ and R⁶ are hydrogen.

R⁴ is methylthio or bromo

R⁴ is methylthio

R⁴ is halo, C₁₋₄alkyl or C₁₋₄alkylS(O)_a where a is 0

R⁴ is bromo, methyl or methylthio

R⁵ is a group of formula (IA) (as depicted above) where

X is -O-,

Ring A is phenyl optionally substituted by one or more substituents selected from R¹⁷,

n is 1,

R⁷ is hydrogen,

R^8 is hydrogen,

R^9 is hydrogen,

m is 0,

R^{11} is a group of formula (IB) (as depicted above) wherein.

5 R^{12} is hydrogen,

p is 1 or 2,

R^{13} is hydrogen,

q is 0;

r is 0,

10 R^{15} is carboxy or sulpho, and

R^{17} is hydroxy

R^5 is N -{(R)- α -[N -(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy, N -{(R)- α -[N -(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy or N -{(R)- α -[N -(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy

15 R^5 is a group of formula (IA) (as depicted above) wherein.

X is -O-,

Ring A is phenyl optionally substituted by one or more substituents selected from R^{17} ,

n is 1,

R^7 is hydrogen,

20 R^8 is hydrogen,

R^9 is hydrogen,

m is 0,

R^{11} is carboxy, a group of formula (IB) (as depicted above) or a group of formula (IC) (as depicted above) wherein

25 R^{12} is hydrogen or C_{1-4} alkyl,

p is 1 or 2,

R^{13} is hydrogen or C_{1-4} alkyl optionally substituted by R^{20} wherein R^{20} is hydroxy, carbamoyl, amino, benzyloxycarbonylamino or C_{1-4} alkylS(O)_{*a*} wherein *a* is 0,

R^{14} is hydrogen or hydroxy,

30 q is 0,

r is 0 or 1,

R^{15} is carboxy or sulpho,

R^{17} is hydroxy; and

Ring B is pyrrolidin-1-yl substituted on carbon by one group selected from R^{23} ,
wherein R^{23} is carboxy

- R^5 is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -
- 5 [*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(R)-1-carboxy-2-methylthio-ethyl]carbamoyl]
- 10 benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-carbamoyl-ethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]-
- 15 4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(S)-1-carboxy-2-(S)-2-methylbutyl)carbamoyl]benzyl}
- 20 carbamoylmethoxy, *N*-{(R)- α -carboxy-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-aminobutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-(benzyloxycarbonylamino)butyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-2-carboxypyrrolidin-1-ylcarbonyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)-*N*-methylcarbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(R)-2-(R)-
- 25 1-carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(sulphomethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -carboxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxybutyl)carbamoyl]-4-
- 30 hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-

hydroxybenzyl} carbamoylmethoxy or *N*-{(R)- α -[*N*-(R)-1-carboxy-2-methylthioethyl]carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy

R^5 is a group of formula (IA) (as depicted above) wherein.

X is -O-,

5 Ring A is phenyl optionally substituted by one or more substituents selected from R^{17} ,

n is 1,

R^7 is hydrogen,

R^8 is hydrogen,

R^9 is hydrogen,

10 m is 0,

R^{11} is carboxy, a group of formula (IB) (as depicted above) or a group of formula (IC) (as depicted above) wherein.

R^{12} is hydrogen or C_{1-4} alkyl,

p is 1 or 2,

15 R^{13} is hydrogen or C_{1-4} alkyl optionally substituted by R^{20} wherein R^{20} is hydroxy, carbamoyl, ammo, benzyloxycarbonylammo, C_{1-4} alkylS(O)_a wherein a is 0 or (C_{1-4} alkyl)₃silyl,

R^{14} is hydrogen or hydroxy or C_{1-4} alkyl, wherein R^{14} may be optionally substituted by one or more substituents selected from R^{20} ,

Y is -N(R^a)C(O)- wherein R^a is hydrogen,

20 q is 0 or 1,

r is 0 or 1,

R^{15} is carboxy or sulpho,

R^{17} is hydroxy; and

R^{20} is selected from hydroxy;

25 Ring B is pyrrolidin-1-yl or azetidinyl substituted on carbon by one group selected from R^{23} , and optionally additionally substituted on carbon by one or more R^{24} , wherein R^{23} is carboxy and R^{24} is hydroxy

R^5 is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]

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- benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(R)-1-carboxy-2-methylthio-ethyl}carbamoyl]
benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxy-2-carbamoyl-
ethyl}carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-
hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]-4-
5 hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxyethyl}carbamoyl]-4-
hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxy-2-hydroxyethyl} carbamoyl]-
4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]
benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxy-2-(R)-hydroxypropyl}carbamoyl]
benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxy-2-methylpropyl}carbamoyl]benzyl}
10 carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxy-3-methylbutyl}carbamoyl]benzyl}
carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(S)-1-carboxy-2-(S)-2-methylbutyl)carbamoyl]benzyl}
carbamoylmethoxy, *N*-{(R)- α -carboxy-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-
{(S)-1-carboxy-4-aminobutyl}carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-
carboxy-4-(benzyloxycarbonylamino)butyl}carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -
15 {(S)-2-carboxypyrrolidin-1-ylcarbonyl}benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-
(carboxymethyl)-*N*-methylcarbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(R)-2-(R)-
1-carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-
(sulphomethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -carboxybenzyl}
carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxy-2-(R)-hydroxypropyl}carbamoyl]-4-
20 hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxy-2-methylpropyl}carbamoyl]-
4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxybutyl}carbamoyl]-4-
hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-carboxypropyl}carbamoyl]-4-
hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(R)-1-carboxy-2-methylthio-
ethyl}carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-
25 carboxypropyl}carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-[*N*-
{(S)-2-hydroxy-1-carboxyethyl}carbamoyl]propyl} carbamoyl]benzyl} carbamoylmethoxy, *N*-
{(R)- α -[2-(S)-2-(carboxy)-4-(R)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]benzyl}
carbamoylmethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)azetidin-1-ylcarbonyl]benzyl}
carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-[*N*-{(S)-1-
30 carboxyethyl}carbamoyl]ethyl} carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(R)-1-
carboxy-3,3-dimethylbutyl}carbamoyl] benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-

carboxy-3,3-dimethylbutyl)carbamoyl] benzyl} carbamoylmethoxy, *N*-{(R)- α -{*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-((R)- α -{*N*-[(S)-1-carboxy-2-(trimethylsilyl)ethyl] carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy or *N*-((R)- α -{*N*-[(R)-1-carboxy-2-(trimethylsilyl)ethyl]carbamoyl}-4-

5 hydroxybenzyl)carbamoylmethoxy

R^3 is hydrogen.

R^4 is a group of formula (IA)

R^5 is a group of formula (IA)

Therefore in an further aspect of the invention, there is provided a compound of

10 formula (I) (as depicted above) wherein.

R^y is hydrogen,

R^1 and R^2 are C_{1-4} alkyl,

R^x and R^y are both hydrogen,

M is -N-,

15 v is 0,

R^3 and R^6 are hydrogen,

R^4 is halo, C_{1-4} alkyl or C_{1-4} alkylS(O)_a wherein a is 0;

R^5 is a group of formula (IA) (as depicted above) wherein

X is -O-,

20 Ring A is phenyl optionally substituted by one or more substituents selected from R^{17} ,

n is 1,

R^7 is hydrogen,

R^8 is hydrogen,

R^9 is hydrogen,

25 m is 0,

R^{11} is carboxy, a group of formula (IB) (as depicted above) or a group of formula (IC)

(as depicted above) wherein.

R^{12} is hydrogen or C_{1-4} alkyl,

p is 1 or 2,

30 R^{13} is hydrogen or C_{1-4} alkyl optionally substituted by R^{20} wherein R^{20} is hydroxy, carbamoyl, amino, benzyloxycarbonylamino, C_{1-4} alkylS(O)_a wherein a is 0 or $(C_{1-4}$ alkyl)₃silyl,

R^{14} is hydrogen or hydroxy or C_{1-6} alkyl, wherein R^{14} may be optionally substituted by one or more substituents selected from R^{20} ,

Y is $-N(R^q)C(O)-$ wherein R^q is hydrogen,

q is 0 or 1,

5 r is 0 or 1,

R^{15} is carboxy or sulphy,

R^{17} is hydroxy; and

R^{20} is selected from hydroxy; and

10 Ring B is pyrrolidin-1-yl or azetidinyl substituted on carbon by one group selected from R^{23} , and optionally additionally substituted on carbon by one or more R^{24} , wherein R^{23} is carboxy and R^{24} is hydroxy;

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

Therefore in an additional aspect of the invention, there is provided a compound of formula (I) (as depicted above) wherein

15 R^v is hydrogen,

R^1 and R^2 are both butyl,

R^x and R^y are both hydrogen,

M is $-N-$,

v is 0,

20 R^3 and R^6 are hydrogen,

R^4 is bromo, methyl or methylthio, and

R^5 is $N-((R)-\alpha-[N-(\text{carboxymethyl})\text{carbamoyl}]\text{benzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-(\text{carboxymethyl})\text{carbamoyl}]\text{benzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-(2-\text{sulphoethyl})\text{carbamoyl}]-4\text{-hydroxybenzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-((S)-1\text{-carboxy-2-hydroxyethyl})\text{carbamoyl}]\text{benzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-((S)-1\text{-carboxyethyl})\text{carbamoyl}]\text{benzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-((S)-1\text{-carboxypropyl})\text{carbamoyl}]\text{benzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-((R)-1\text{-carboxy-2-methylthio-ethyl})\text{carbamoyl}]\text{benzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-((S)-1\text{-carboxy-2-carbamoyl-ethyl})\text{carbamoyl}]\text{benzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-(2\text{-sulphoethyl})\text{carbamoyl}]-4\text{-hydroxybenzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-(\text{carboxymethyl})\text{carbamoyl}]-4\text{-hydroxybenzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-((S)-1\text{-carboxyethyl})\text{carbamoyl}]-4\text{-hydroxybenzyl})\text{carbamoylmethoxy}$, $N-((R)-\alpha-[N-((S)-1\text{-carboxy-2-hydroxyethyl})\text{carbamoyl}]-$

- 4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl] benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl] benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3-methylbutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(S)-1-carboxy-2-(S)-2-methylbutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -carboxy-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-aminobutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(S)-1-carboxy-4-(benzyloxycarbonylamino)butyl]carbamoyl} benzyl} carbamoylmethoxy, *N*-{(R)- α -((S)-2-carboxypyrrolidin-1-ylcarbonyl)benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)-*N*-methylcarbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(R)-2-(R)-1-carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(sulphomethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -carboxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl} carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)-4-(R)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)azetidin-1-ylcarbonyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-1-carboxyethyl)carbamoyl]ethyl} carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyl] benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3,3-dimethylbutyl)carbamoyl] benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-[(S)-1-carboxy-2-(trimethylsilyl)ethyl] carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy or *N*-{(R)- α -[*N*-((R)-1-carboxy-2-(trimethylsilyl)ethyl]carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy;
- or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

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X

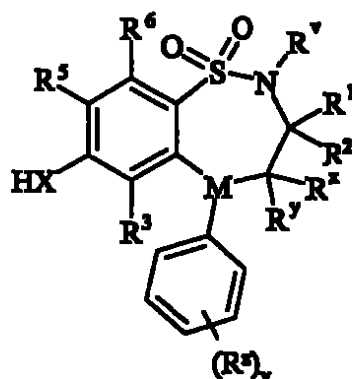
In another aspect of the invention, preferred compounds of the invention are any one of examples 5, 6, 7, 9, 11, 14, 15, 26, 27, 28, 30 or 33 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In another aspect of the invention, preferred compounds of the invention are any one of the examples or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

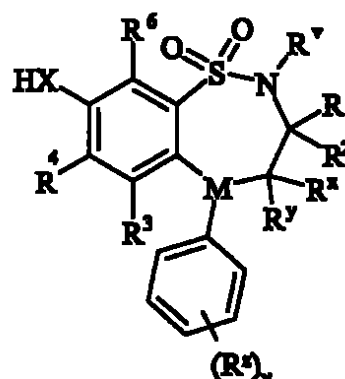
Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof

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) for compounds of formula (I) wherein X is -O-, -NR^a or -S-, reacting a compound of formula (IIa) or (IIb)

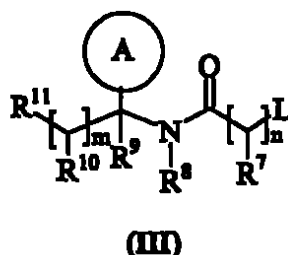


(IIa)



(IIb)

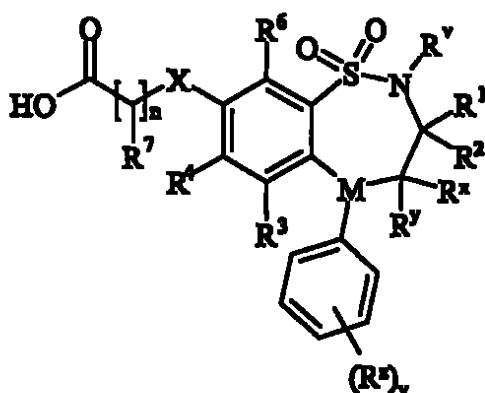
with a compound of formula (III)



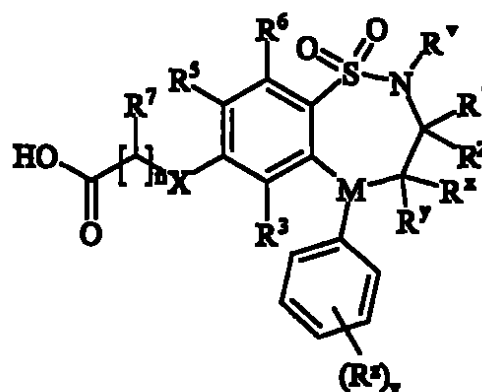
(III)

wherein L is a displaceable group,

Process 2) reacting an acid of formula (IVa) or (IVb)

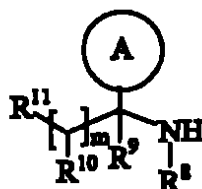


(IVa)



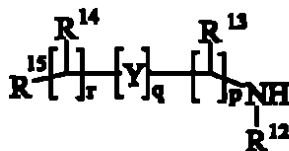
(IVb)

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



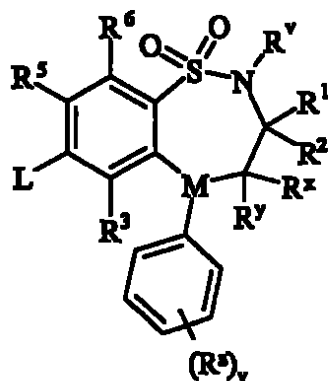
(V)

Process 3) for compounds of formula (I) wherein R^{11} is a group of formula (IB), reacting a compound of formula (I) wherein R^{11} is carboxy with an amine of formula (VI)

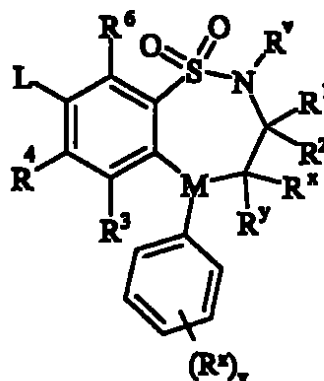


(VI)

- 10 *Process 4)* for compounds of formula (I) wherein one of R^4 and R^5 are independently selected from C_1 -alkylthio optionally substituted on carbon by one or more R^{17} , reacting a compound of formula (VIIa) or (VIIb)



(VIIa)



(VIIb)

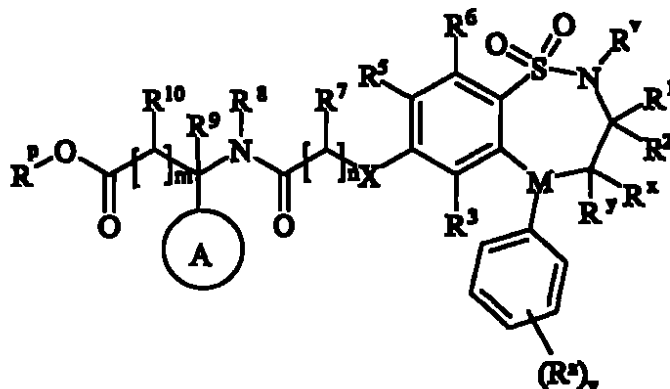
wherein L is a displaceable group, with a thiol of formula (VIII)



(VIII)

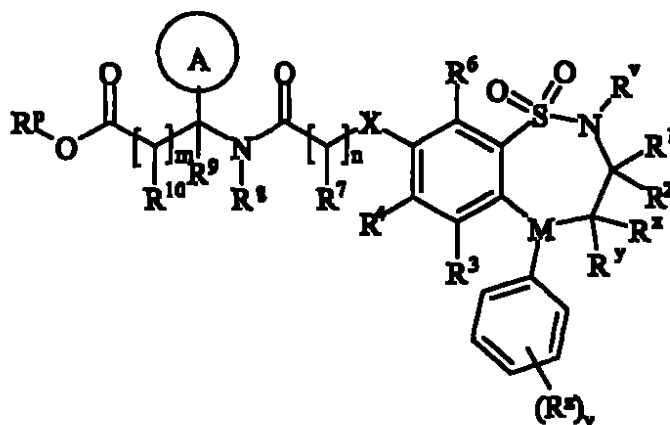
wherein R^m is C_{1-6} alkylthio optionally substituted on carbon by one or more R^{16} ,

- 5 *Process 5)* for compounds of formula (I) wherein R^{11} is carboxy, deprotecting a compound of formula (IXa)



(IXa)

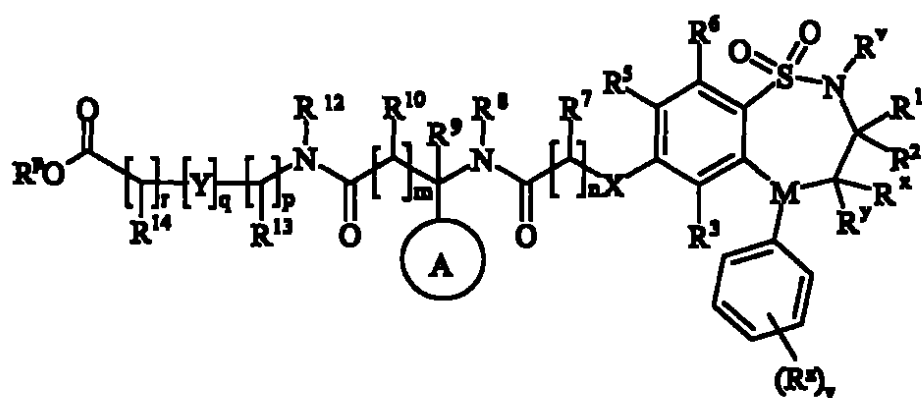
or (IXb)



(IXb)

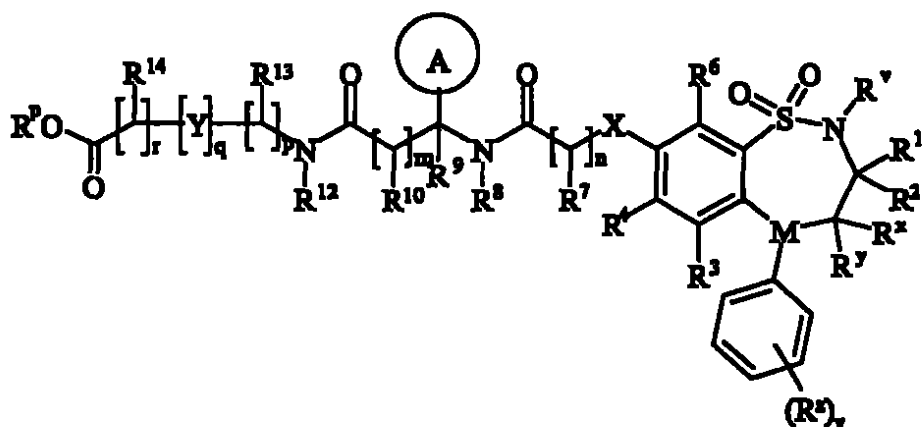
wherein R^p together with the $-OC(O)-$ group to which it is attached forms an ester,

- Process 6)* for compounds of formula (I) wherein R^{11} is a group of formula (IB) and R^{15} is carboxy, deprotecting a compound of formula (Xa)



(Xa)

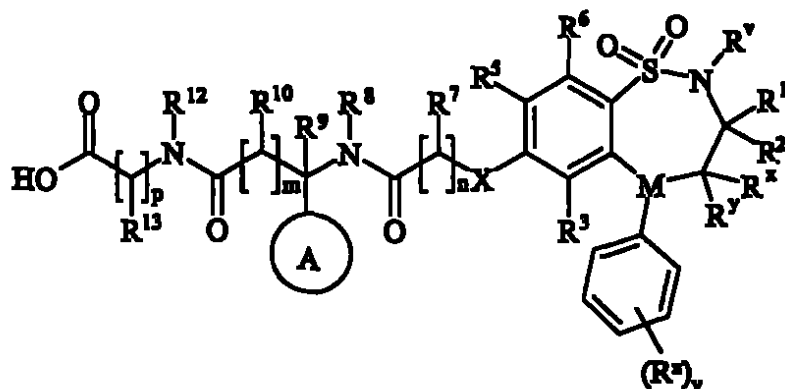
or (Xb)



(Xb)

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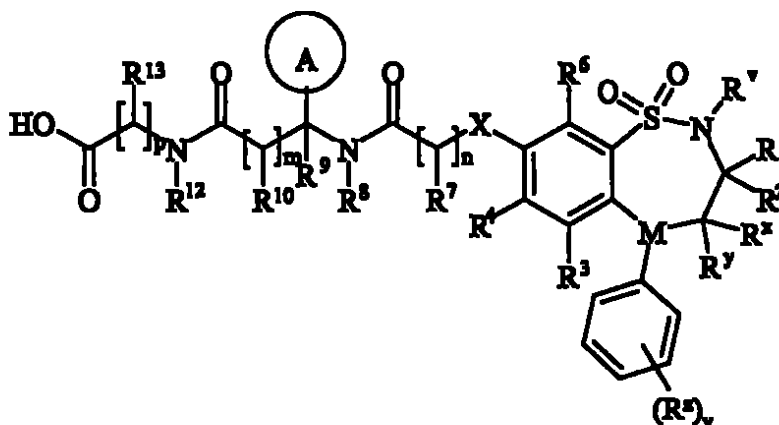
wherein R^p together with the -OC(O)- group to which it is attached forms an ester;
Process 7) for compounds of formula (I) wherein R¹¹ is a group of formula (IB) and
 N(Rⁿ)C(O)-, reacting an acid of formula (XIa)



(XIa)

10

or (XIb)



(XIIb)

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



(XII)

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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.

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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

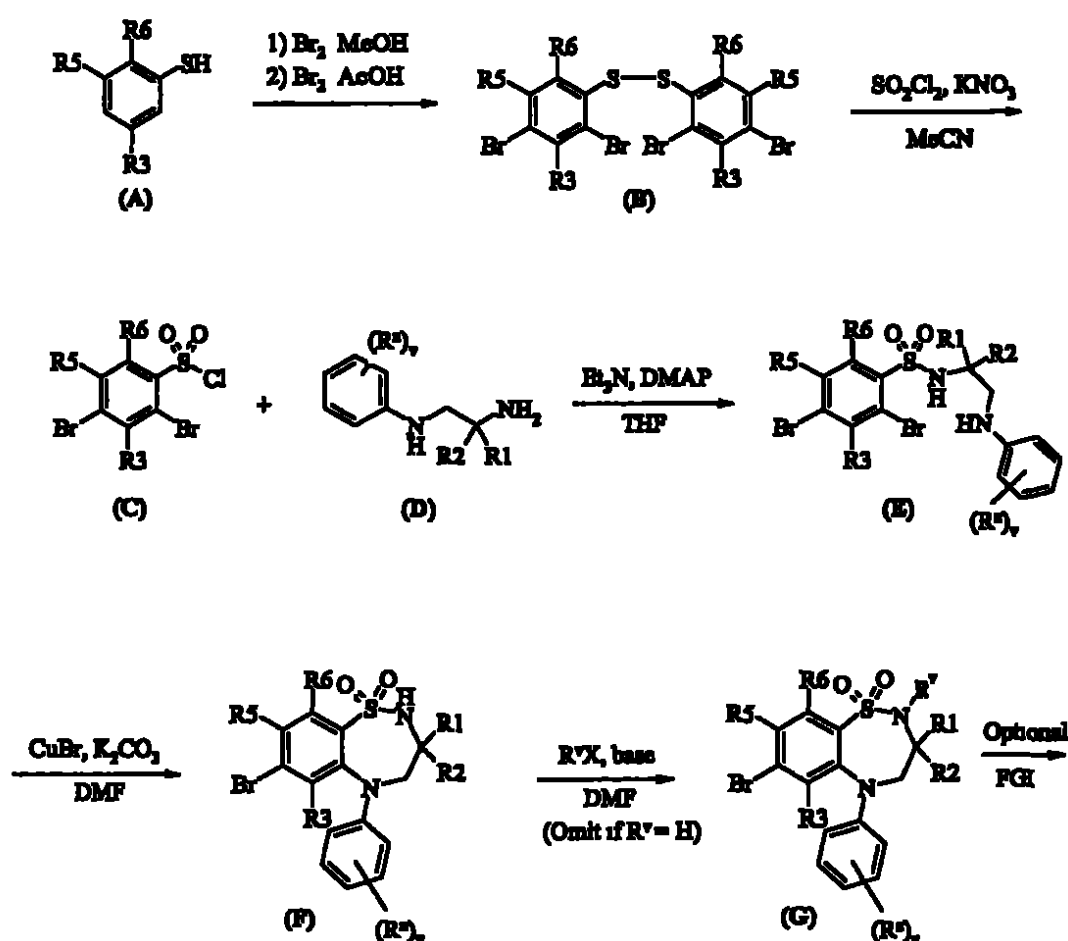
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R^p together with the -OC(O)- group to which it is attached forms an ester. Preferably R^p is methyl or ethyl. More preferably R^p is methyl. In another aspect of the invention R^p is C₁₋₆alkyl or phenylC₁₋₆alkyl, preferably C₁₋₄alkyl or benzyl, more preferably *t*-butyl, methyl, ethyl or benzyl.

Specific reaction conditions for the above reactions are as follows

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The bicyclic ring systems of the present invention may be assembled according to Scheme Ia or Scheme Ib. The skilled person will appreciate to make any of the above identified intermediates the value of R⁴ or R⁵ in the following schemes would be replaced with the appropriate group. For example, to synthesize a compound of formula (IIa) R⁴ would be HX in the following scheme

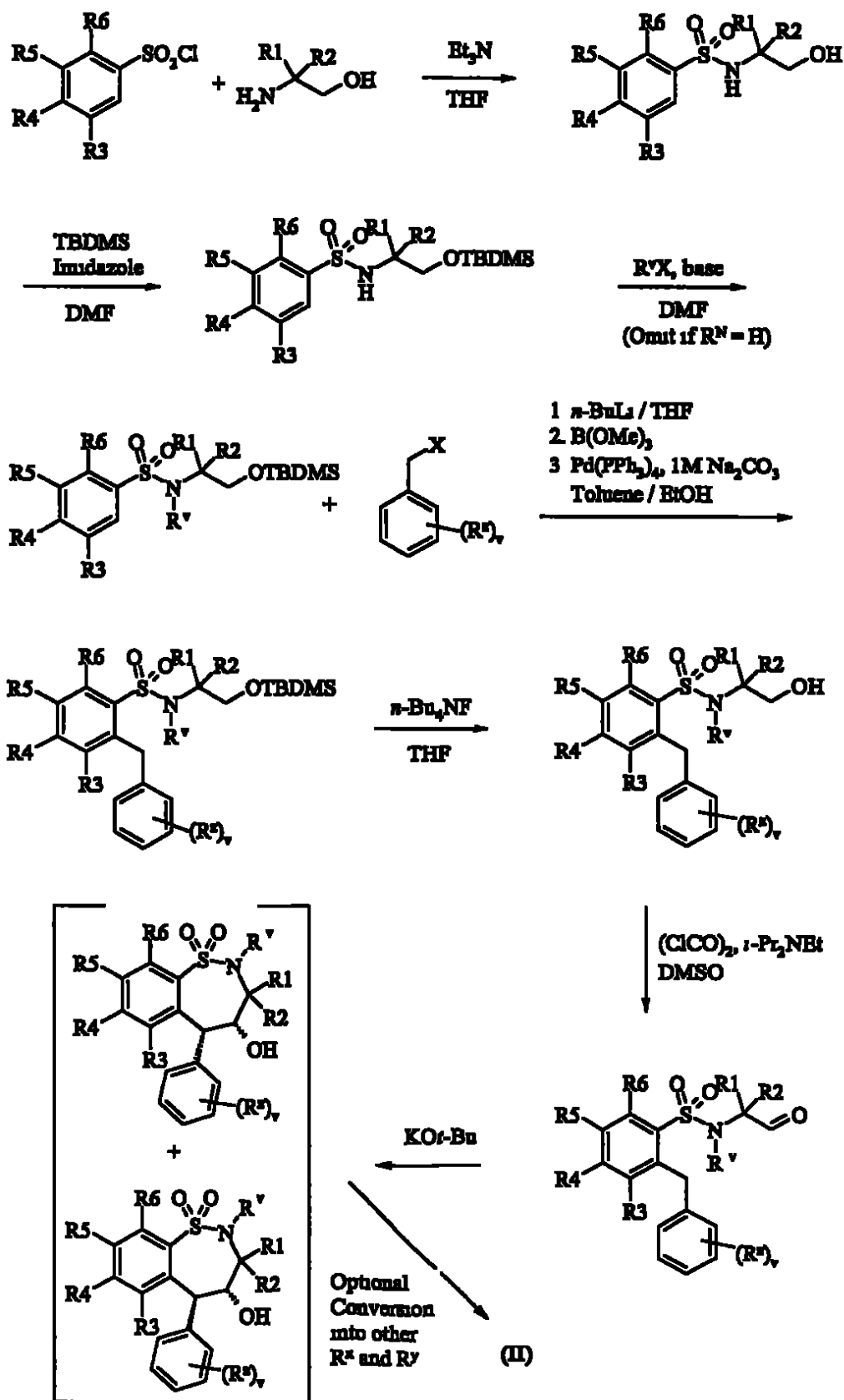


Scheme 1a

Wherein FGI is functional interconversion of the Br into other values of R^4 using procedures known to the skilled person.

- 5 Compounds of formula (A) and (D) are commercially available, or they are known in the literature, or they may be prepared by standard processes known in the art.

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Scheme 1b

Process 1) Compounds of formula (IIa) or (IIb) 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 (III) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 2) and Process 3) and Process 7) 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, or 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

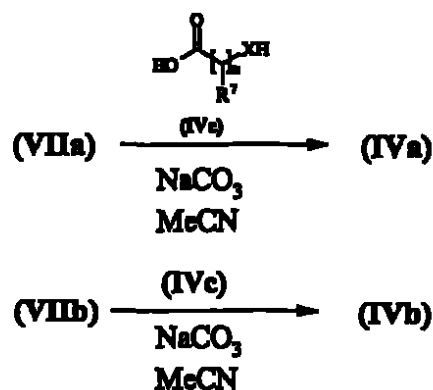
2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane,

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

Compounds of formula (IVa) or (IVb) wherein X=O, -NRⁿ, -S- may be prepared according to Scheme 2

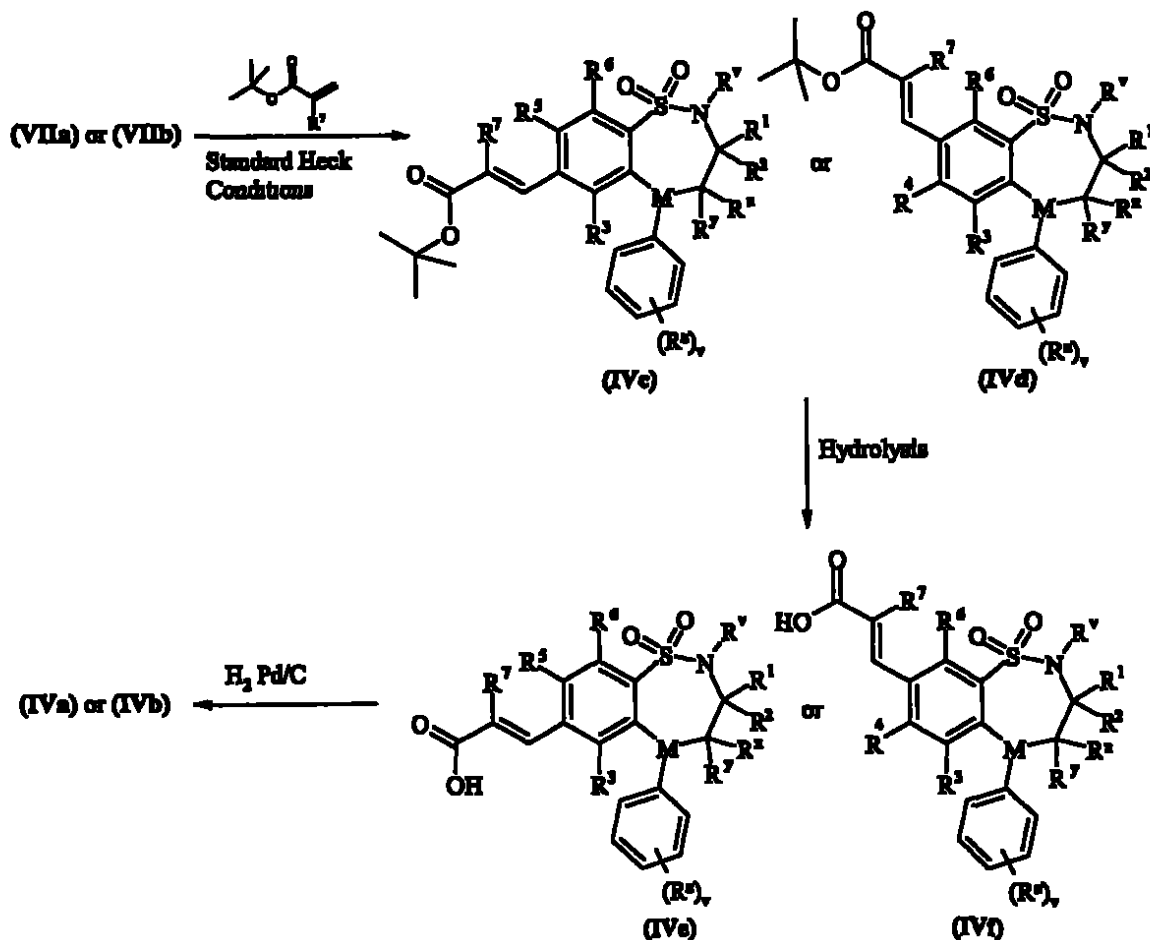


Scheme 2

Wherein L in (VIIa) and (VIIb) is a displaceable group e.g. bromo, chloro, fluoro, mesyl or tosyl and wherein X is -O-, -S-, NR^a (optionally for -SO- and -SO₂- followed by the oxidation step of Process 1)

Compounds of formula (IVa) and (IVb) where X is -SO- or -SO₂- may be prepared by oxidising the resulting compounds of formula (IVa) and (IVb) from Schemes 2 where X is -S-

Compounds of formula (Va) or (Vb) wherein X is -CH₂- and n is 1 may be prepared according to Scheme 3



Scheme 3

The skilled person will appreciate that the above reaction scheme may be manipulated to prepare compounds of formula (Va) or (Vb) where n is 2 or 3

Compounds of formula (XIa) and (XIb) may be prepared by manipulations known to the skilled person of the processes described herein.

Compounds of formula (IVc), (V), (VI), (XII) 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) Compounds of formula (VIIa) and (VIIb) may be reacted with thiols of formula (VIII) in the presence of 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 DMF or THF at a temperature in the range of 0°C to reflux

- 5 Compounds of formula (VIIa) and (VIIb) may be prepared by any of the procedures above for the preparation of compounds of formula (I), but wherein one of R^4 and R^5 is L.

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

- Process 5) and Process 6)* Esters of formula (IXa), (IXb), (Xa) and (Xb) may be deprotected
10 under standard conditions such as those described below, for Example they may be deprotected with sodium hydroxide in methanol at room temperature.

Esters of formula (IXa), (IXb), (Xa) and (Xb) may be prepared by any of the procedures above for the preparation of compounds of formula (I), but wherein R^{11} or R^{15} is C_{1-4} alkoxycarbonyl.

- 15 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
20 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
25 aluminum trichloride) under Friedel Crafts conditions, the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminum 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
30 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

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protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. A particular instance where a protecting group may be used is in protecting the nitrogen in the 2-position of the benzothiadiazepine ring during the synthesis of certain intermediates.

5 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.

10 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
15 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
20 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.

25 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.
30 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.

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

As stated hereinbefore the compounds defined in the present invention possess IBAT inhibitory activity. These properties may be assessed, for example, using an *in vitro* test assay for studying the effect on bile acid uptake in IBAT-transfected cells (Smith L., Price-Jones M. J., Hughes K. T. and Jones N. R. A., J Biomolecular Screening, 3, 227-230) or *in vivo* by
10 studying the effect on radiolabelled bile acid absorption in mice/rats (Lewis M. C., Brieddy L. E. and Root C., J, J Lip Res 1995, 36, 1098-1105)

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
15 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
20 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
25 unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.02-100 mg/kg, preferably 0.02-50 mg/kg, and thus 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 range
30 of 0.02-20 mg/kg is employed. 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.

5 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 IBAT 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 an IBAT 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 manufacture of a medicament for use in the treatment of hyperlipidaemic conditions 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 manufacture of a medicament for use in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridaemia, hyperbetaipoproteinaemia (high LDL), hyperprebetaipoproteinaemia (high VLDL), hyperchylomicronaemia, hypolipoproteinaemia, hypercholesterolaemia, hyperlipoproteinaemia and hypoalphalipoproteinaemia (low HDL) 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 manufacture of a medicament for use in 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
5 thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks 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 manufacture of a medicament for use in the
10 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.

According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in
15 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.

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
20 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.

According to a further feature of this aspect of the invention there is provided a method of treating dyslipidemic conditions and disorders such as hyperlipidaemia,
25 hypertriglyceridaemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL) 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,
30 solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating different clinical conditions such as atherosclerosis, arteriosclerosis,

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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, aneurysms, 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 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

10 According to a further feature of this aspect of the invention there is provided a method of treating atherosclerosis, coronary heart diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks 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

15 There is evidence that an IBAT inhibitor might potentially be useful in the treatment and/or prevention of gallstones. According to a further feature of this aspect of the invention there is provided a method of treating and / or preventing gallstones 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

20 The size of the dose required for the therapeutic or prophylactic treatment will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 0.1-50mg/kg preferably 0.1-10 mg/kg is envisaged.

25 The IBAT 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 IBAT 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 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

(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R, 5S)-3,5-dihydroxyhept-6-enoic acid (rosuvastatin), 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 (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid (rosuvastatin), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A preferable particular statin is rosuvastatin calcium salt.

In an additional 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 a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and/or a bile acid binder thereby avoiding a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such as diarrhoea in patients during therapy comprising the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

An HMG CoA-reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof will by its action decrease the endogenous cholesterol available for the bile acid synthesis and have an additive effect in combination with the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof on lipid lowering

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Suitable bile acid binders for such a combination therapy are resins, such as cholestyramme and cholestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutic dose for treatment of cholesteraemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT 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 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.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT 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 in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT 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 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, in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature 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 (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.

Therefore in an additional feature 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 (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 binder

Therefore in an additional feature 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 (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, in simultaneous, sequential or separate administration with a bile acid binder

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 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 binder, in association with a pharmaceutically acceptable diluent or carrier

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, and a bile acid binder 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

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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 compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder

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 and a bile acid binder

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, in a first unit dosage form,

b) a bile acid binder, 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, 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,

c) a bile acid binder, in a third unit dosage form, and

d) container means for containing said first, second and third 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 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 bile acid binder, 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) a bile acid binder, in a third unit dosage form, and
- d) container means for containing said first, second and third 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 an IBAT 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

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prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the production of an IBAT 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, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the production of an IBAT 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, 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 treatment of hyperlipidaemic conditions 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, a bile acid binder, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions 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, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions 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 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 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 bile acid binder, 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 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 excipient, with the simultaneous, sequential or separate administration of an effective amount of a bile acid binder, 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 one or more of the following agents selected from

- a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;
- a cholesterol absorption antagonist for example ezetimones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference,
- a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;
- a fibric acid derivative, for example clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate;

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- a nicotinic acid derivative, for example, nicotinic acid (niacin), acipimox and nicentrol,
- a phytosterol compound for example stanols,
- probucol,
- 5 ➤ an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629),
- an antihypertensive compound for example an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic
- 10 blocker, an adrenergic stimulant, calcium channel blocker, a diuretic or a vasodilator;
- insulin,
- sulphonylureas including glibenclamide, tolbutamide;
- metformin, and/or
- acarbose,
- 15 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.

- Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in
- 20 combination with a compound of formula (I) include but are not limited to, the following compounds: alacepril, alatriopril, altopril calcium, ancovenm, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, 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, hemorphan-4,
- 25 idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracem A, muracem B, muracem C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril,
- 30 spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide,trandolapril,trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and

enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula (I) include, but are not limited to, compounds candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil

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, 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, 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. Additional suitable PPAR alpha and/or gamma agonists are NN622/Ragaglitazar and BMS 298585

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT 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 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

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Therefore in an additional feature 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 (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 the production of an IBAT 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, 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 the treatment of hyperlipidaemic conditions 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 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 IBAT 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 (IXa), (IXb), (Xa) and (Xb) show IBAT 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 (IXa), (IXb), (Xa) or (Xb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (IXa), (IXb), (Xa) or

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(Xb), 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

According to an additional aspect of the present invention there is provided a compound of the formula (IXa), (IXb), (Xa) or (Xb), 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.

Thus according to this aspect of the invention there is provided a compound of the formula (IXa), (IXb), (Xa) and (Xb), 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 (IXa), (IXb), (Xa) or (Xb), 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 an IBAT 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 (IXa), (IXb), (Xa) or (Xb), 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 treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an IBAT 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 (IXa), (IXb), (Xa) or (Xb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

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 (IXa), (IXb), (Xa) or (Xb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

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.

- 5 (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,
- 10 (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
- 15 resonance chemical shift values were measured in deuterated CD₃OD (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, and peak multiplicities are shown as follows s, singlet; d, doublet; dd, double doublet, t, triplet; tt,
- 20 triple triplet, q, quartet; tq, triple quartet, m, multiplet; br, broad, LCMS were recorded on a Waters ZMD, LC column xTerra MS C₈(Waters), detection with a HP 1100 MS-detector diode array equipped, mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-detector diode array equipped, unless otherwise stated the mass ion quoted is (MH⁺),
- 25 (vi) unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Kromasil C₈, 7µm, (Akzo Nobel), MeCN and de-ionised water 100 mM ammonium acetate as mobile phases, with suitable composition,
- (vii) intermediates were not generally fully characterised and purity was assessed by thin layer
- 30 chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis,
- (viii) where solutions were dried sodium sulphate was the drying agent,

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(ix) where an "ISOLUTE" column is referred to, this means a column containing 2g of silica, the silica being contained in a 6ml disposable syringe and supported by a porous disc of 54Å pore size, obtained from International Sorbent Technology under the name "ISOLUTE", "ISOLUTE" is a registered trade mark;

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

DCM	dichloromethane,
DMF	N,N-dimethylformamide;
TFA	trifluoroacetic acid,
TBTU	o-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate,
10 EtOAc	ethyl acetate, and
MeCN	acetonitrile

Example 1

15 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzotriadiazepine

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzotriadiazepine (Method 2, 0.020 g, 3.71×10^{-5} mol) in DCM (4 ml) was added (R)-α-[N-(t-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 5, 0.013 g, 4.82×10^{-5} mol) and N-methylmorpholine (0.015 ml, 1.48×10^{-4} mol). The mixture was stirred for 5 min and then TBTU (0.015 g, 4.82×10^{-5} mol) was added. The reaction mixture was stirred overnight and then TFA (1.5 ml) was added. After 1 hour, the solution was diluted with toluene, before the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent, and freeze-dried, to give the title compound in 0.026 g (96 %) as a white solid. NMR (400 MHz, DMSO-d₆) 0.60-0.80 (m, 6H), 0.80-1.60 (m, 12H), 3.30 (dd (AB), 1H), 3.45 (dd (AB), 1H), 3.85 (brs, 2H), 4.70 (d (AB), 1H), 4.75 (d (AB), 1H), 5.60 (d, 1H), 6.90-7.50 (m, 12H), 8.00-8.10 (m, 1H), 8.55 (d, 1H).

Example 2**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[N-(carboxymethyl)carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine**

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-
 5 2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3, 0.016 g, 3.16×10^{-5} mol) in DCM (4 ml) was added (R)- α -[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 5, 0.012 g, 4.54×10^{-5} mol) and *N*-methylmorpholine (0.015 ml, 1.48×10^{-4} mol). The mixture was stirred for 5 min and then TBTU (0.015 g, 4.82×10^{-5} mol) was added. The reaction mixture was stirred overnight and then TFA (1.5 ml) was added. After 1 hour, the solution was diluted
 10 with toluene, before the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent and freeze-dried, to give the title compound in 0.018 g (82 %) as a white solid. NMR (400 MHz, DMSO-*d*₆) 0.65-0.80 (m, 6H), 0.85-1.60 (m, 12H), 2.10 (s, 3H), 3.65 (dd (AB), 1H), 3.75 (dd (AB), 1H), 3.85 (bra, 2H), 4.65 (d (AB), 1H), 4.75 (d (AB), 1H), 5.60 (d, 1H), 6.55 (s, 1H),
 15 6.90-7.50 (m, 11H), 8.45 (d, 1H), 8.50-8.60 (m, 1H)

Example 3**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-(N-((R)- α -[N-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine**

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-
 20 tetrahydro-1,2,5-benzothiadiazepine (Method 2, 0.050 g, 9.27×10^{-5} mol) in DMF (6 ml) was added 2-[[[(2*R*)-2-amino-2-(4-hydroxyphenyl)ethanoyl]amino]ethanesulphonic acid (Method 6, 0.033 g, 1.20×10^{-4} mol) and *N*-methylmorpholine (0.041 ml, 3.72×10^{-4} mol). The mixture was stirred for 10 min and then TBTU (0.039 g, 1.21×10^{-4} mol) was added. The reaction
 25 mixture was stirred overnight and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent and freeze-dried, to give the title compound in 0.039 g (53 %) as a white solid. NMR (400 MHz, DMSO-*d*₆) 0.60-0.80 (m, 6H), 0.80-1.60 (m, 12H), 2.40-2.60 (m, 2H), 3.10-3.50 (m, 2H), 3.85 (bra, 2H), 4.70 (d (AB), 1H), 4.75 (d (AB), 1H), 5.25 (d, 1H), 6.70 (s, 1H), 6.75 (s, 1H), 6.85-7.80 (m, 10H), 8.15-8.25 (m, 1H), 8.45 (d, 1H), 9.40 (bra, 1H)
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22**Example 4****1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[N-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine**

- 5 A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3, 0.050 g, 0.099 mmol), *t*-butyl *N*-[(2*R*)-amino-2-phenylethanoyl]-*o*-(*t*-butyl)-*L*-serinate (Method 14, 0.042 g, 0.120 mmol) and *N*-methylmorpholine (0.033 ml, 0.299 mmol) in DCM (4 ml) was stirred at RT for 10 min, after which TBTU (0.041 g, 0.128 mmol) was added. After 8h, the conversion was completed,
- 10 *m/z*. 839.7 TFA (2 ml) was added and the reaction mixture was stirred for 12 hours. The solution was transferred to a separating funnel and washed twice with water and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.045 g (63 %) as a white solid. NMR (400 MHz, DMSO-*d*₆) 0.60-0.80 (6H, m), 0.85-1.60 (12H, m), 2.10 (3H, s), 3.40-3.65 (2H, m), 3.85 (2H, brs), 4.10-4.20 (1H, m), 4.70 (1H, d(AB)), 4.75 (1H, d(AB)), 5.70 (1H, d), 6.60 (1H, s), 6.85-7.50 (12H, m), 8.50 (1H, d), 8.60 (1H, d), *m/z*. 839.7
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Example 5

- 20 **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**

- A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((*R*)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 0.055 g, 0.086 mmol), *L*-alanine, 1,1-dimethylethyl ester, hydrochloride (0.017 g, 0.098 mmol) and *N*-methylmorpholine (0.028 ml, 0.254 mmol) in DCM (5 ml) was stirred at RT for 10 min, after which TBTU (0.033 g, 0.103 mmol) was added. After 16h the conversion was complete; *m/z*. 767.4 TFA (2.5 ml) was added and the reaction mixture was stirred for 2 hours. The solution was diluted with toluene and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as
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- 30 eluent. The title compound was obtained in 0.044 g (72 %) as a white solid. NMR (400 MHz) 0.70-0.85 (6H, m), 0.90-1.70 (12H, m), 1.30 (3H, d), 2.10 (3H, s), 3.95 (2H, brs), 4.25-4.40

(1H, m), 4.60 (1H, d(AB)), 4.65 (1H, d(AB)), 5.60 (1H, s), 6.60 (1H, s), 6.95-7.50 (11H, m),
m/z 767.4.

Example 6

5 **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**

A solution of 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 0.055 g, 0.086 mmol), butanoic acid, 2-amino-, 1,1-dimethylethyl ester, hydrochloride, (2S)- (0.020 g, 0.102 mmol) and N-methylmorpholine (0.035 ml, 0.316 mmol) in DCM (5 ml)
10 was stirred at RT for 10 min, after which TBTU (0.036 g, 0.112 mmol) was added. After 19h additional butanoic acid, 2-amino-, 1,1-dimethylethyl ester, hydrochloride, (2S)- (0.020 g, 0.102 mmol), N-methylmorpholine (0.035 ml, 0.316 mmol) and TBTU (0.036 g, 0.112 mmol) were added. After 68h, the conversion was completed, m/z 781.5. TFA (2 ml) was added and
15 the reaction mixture was stirred for 7h and then additional TFA (2 ml) was added. After 18h the reaction was completed. The solution was transferred to a separating funnel and washed twice with water and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.026 g (41 %) as a white solid. NMR (400 MHz, DMSO-d₆) 0.65 (3H, t),
20 0.65-0.80 (6H, m), 0.85-1.75 (14H, m), 2.10 (3H, s), 3.80 (2H, brs), 3.95-4.10 (1H, m), 4.65 (1H, d(AB)), 4.75 (1H, d(AB)), 5.65 (1H, d), 6.55 (1H, s), 6.85-7.50 (12H, m), 8.50 (1H, d), 8.60 (1H, d), m/z 781.5

Example 7

25 **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**

A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 0.055 g, 0.086 mmol), S-methyl-L-cysteine tert-butyl ester (Pestic. Sci., EN, 45, 4, 1995, 357-362, 0.020 g, 0.105 mmol) and N-methylmorpholine (0.035 ml, 0.317 mmol) in DCM (5 ml)
30 was stirred at RT for 10 min, after which TBTU (0.036 g, 0.112 mmol) was added. After 19h

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additional S-methyl-L-cysteine tert-butyl ester (0 020 g, 0 105 mmol), N-methylmorpholine (0 035 ml, 0 317 mmol) and TBTU (0 036 g, 0 112 mmol) were added. After 68 h the conversion was complete, m/z 811 6 (M-1) TFA (1 5 ml) was added and the reaction mixture was stirred for 7h and additional TFA (1 5 ml) was added. After 18 h the reaction was complete. The solution was transferred to a separating funnel and washed twice with water and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0 1M ammonium acetate buffer as eluent. The title compound was obtained in 0 042 g (65 %) as a white solid. NMR (400 MHz, DMSO-d₆) 0 65-0 80 (6H, m), 0 85-1 60 (12H, m), 1 85 (3H, s), 2 10 (3H, s), 2 60-2 80 (2H, m), 3 80 (2H, brs), 4 20-4 35 (1H, m), 4 65 (1H, d(AB)), 4 75 (1H, d(AB)), 5 65 (1H, d), 6 55 (1H, s), 6 85-7 50 (12H, m), 8 45 (1H, d), 8 65 (1H, d)

Example 8

1.1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-[N-((S)-1-carboxy-2-carbamoyl-ethyl)carbamoyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

N-Methylmorpholine (0 034 ml, 0 314 mmol), TBTU (0 033 g, 0 103 mmol) and L-asparagine, 1,1-dimethylethyl ester, monohydrochloride (0 021 g, 0 093 mmol) was successively added to a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 0 050 g, 0 078 mmol) in DCM (5 ml). After 2h there were still starting material left and additional N-methylmorpholine (0 035 ml, 0 314 mmol) and TBTU (0 033 g, 0 103 mmol) were added. After 12h the conversion was complete, m/z 810 5. The solution was diluted with water (~5 ml) and then extracted three times with ether. The combined organic phases was dried over magnesium sulphate and concentrated. The residue was dissolved in a mixture of DCM (5 ml) and TFA (2 5 ml) and the solution was stirred for 21 hours. The solution was transferred to a separating funnel and washed with water and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0 1M ammonium acetate buffer as eluent. The title compound was obtained in 0 022 g (37 %) as a white solid. NMR (400 MHz, DMSO-d₆) 0 60-0 80 (6H, m), 0 80-1 60 (12H, m), 2 10 (3H, s), 2 25-2 70 (2H, m), 3 80 (2H, brs), 4 35-4 45 (1H, m), 4 65 (1H, d(AB)), 4 75 (1H, d(AB)), 5 60 (1H, d), 6 55 (1H, s), 6 70-7 60 (14H, m), 8 45 (1H, d), 8 55-8 70 (1H, m), m/z 810 5

Example 9

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 ammonium salt

5 The title compound was synthesized using the procedure of Example 3 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3, 43mg, 0.085mmol). The solvent was evaporated after 3 hours and the crude product was purified by preparative HPLC (C8 column, 50x250mm) using a gradient (40/60 to 60/40) of MeCN/0.1M ammonium acetate buffer as eluent. Lyophilization
 10 yielded 38mg (57% yield) of the title compound. NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 2.8-3.0 (m, 2H), 3.55-3.7 (m, 2H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.35 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H), 7.15-7.4 (m, 7H), 8.15 (t, 1H), m/z 763

Example 10

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-1,2,5-benzothiadiazepine

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 (Example 18, 50mg,
 20 0.076mmol) was dissolved in DCM (4ml). Glycine *tert*-butyl ester (12mg, 0.091mmol), 2,6-lutidine (20 μ l, 0.15mmol) and TBTU (30mg, 0.091mmol) were added successively. After 3h DMF (2ml) was added and a clear solution was obtained. Glycine *tert*-butyl ester (0.04mmol), 2,6-lutidine (0.15mmol) and TBTU (2x0.03mmol) were added and the mixture was stirred for an additional 3h. The reaction mixture was concentrated and then extracted between aqueous
 25 KHSO₄ (0.05M, pH=1) and EtOAc (2x20ml). The organic phase was washed with brine, dried and concentrated to yield an oil containing the *tert*-butyl ester of the title compound. M/z 769 and 786 (M+18 (NH₄⁺)). DCM (4ml) and TFA (1.5ml) were added. The mixture was stirred for 2 hours and was then concentrated and purified by preparative HPLC on a C8 column
 (50x250mm) using a gradient (20/80 to 50/50) of MeCN/0.1M ammonium acetate buffer as
 30 eluent. Lyophilization yielded the title compound in 52% (28mg). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.9

(ABq, 2H), 3 95 (brs, 2H), 4 6 (ABq, 2H), 5 45 (s, 1H), 6 6 (s, 1H), 6 75 (d, 2H), 7 05 (t, 1H)
7 15-7 4 (m, 7H), m/z 730 (M+18 (NH₄⁺))

Example 11

5 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

The title compound was synthesized by the procedure described in Example 10 starting from 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 (Example 10
18, 50mg, 0 076mmol) and *tert*-butyl L-alaninate hydrochloride. The intermediate *tert*-butyl ester of the title compound was confirmed. M/z 783 and 800 (M+18 (NH₄⁺)) Hydrolysis and purification by preparative HPLC yielded the title compound in 20 mg (37% yield) NMR (400MHz) 0 8 (t, 6H), 1 0-1.2 (m, 6H), 1 25-1 4 (m, 2H), 1 3 (d, 3H), 1 4-1 5 (m, 2H), 1 55-
15 1 7 (m, 2H), 2 1 (s, 3H), 3 95 (brs, 2H), 4 35 (q, 1H), 4 6 (ABq, 2H), 5 45 (s, 1H), 6 6 (s, 1H), 6 75 (d, 2H), 7 05 (t, 1H) 7 15-7.4 (m, 7H), m/z 744

Example 12

20 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-1,2,5-benzothiadiazepine

The title compound was synthesized by the procedure described in Example 10 starting from 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 (Example 18, 50mg, 0 076mmol) and *tert*-butyl *o*-(*tert*-butyl)-L-serinate hydrochloride. The intermediate ester was confirmed, m/z 755 Hydrolysis and purification by preparative HPLC yielded the title compound in 19 mg (33% yield) M/z 743 (M+1) NMR (400MHz) 0 8 (t, 6H), 1 0-1.2 (m, 6H), 1 25-1.4 (m, 2H), 1.4-1 5 (m, 2H), 1 55-1 7 (m, 2H), 2 1 (s, 3H), 3 65-3 8 (m, 2H), 3 95 (brs, 2H), 4 33 (t, 1H), 4 6 (ABq, 2H), 5 5 (s, 1H), 6 6 (s, 1H), 6 75 (d, 2H),
30 7 05 (t, 1H) 7 15-7 4 (m, 7H)

Example 13

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[N-(2-sulphoethyl)carbamoyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine ammonium salt

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)

- 5 carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50mg, 0.078mmol) was dissolved in 3ml DCM. Tetrabutylammonium taurine (88mg, 0.236mmol) was added and the mixture was stirred for 30 min. TBTU (30mg, 0.093mmol) was added and the mixture was stirred overnight. The solution was concentrated and purified by preparative HPLC using a C8 column (50x250mm). A gradient (20/80 to 60/40) of MeCN/0.1M ammonium acetate buffer was used as eluent. Lyophilization yielded 43mg of a product mixture, which was further purified by flash chromatography (5g) using a gradient of 3-20% MeOH in DCM as eluent. The fractions containing the title compound were collected and concentrated. MeOH and water were added and lyophilization yielded 17mg (29% yield).
 10 NMR (400MHz): 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 2.85-3.0 (m, 2H), 3.5-3.7 (m, 2H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.45 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), 7.15-7.45 (m, 10H), m/z. 747.

Example 14

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 -carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50mg, 0.078mmol) was dissolved in 1ml DMF and 1ml DCM. *o*-*tert*-Butyl-(L)-threonine *tert*-butyl ester (22mg, 0.095mmol) and *N*-methylmorpholine (17 μ l, 0.154mmol) were added and the mixture was stirred for 20min. TBTU (30mg, 0.093mmol) was added and the solution was stirred for 2 hours and concentrated. DCM (20ml) was added and the solution was washed with 10ml brine, dried and concentrated to 3ml. The intermediate ester was confirmed, m/z. 853. TFA (0.5ml) was added and the solution was stirred overnight. Additionally 0.5ml TFA was added and after 3h the mixture was concentrated and purified by preparative HPLC on a C8 column (50x250mm). A gradient (20/80 to 60/40) of MeCN/0.1M ammonium acetate buffer was used as eluent. Lyophilization gave the title compound in 61% yield (36mg). NMR

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✓

(400MHz) 0.8 (t, 6H), 0.9 (d, 3H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (bra, 2H), 4.15-4.25 (m, 1H), 4.35 (d, 1H), 4.6 (ABq, 2H), 5.65 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), 7.1 (d, 2H), 7.15-7.4 (m, 6H), 7.5 (d, 2H), m/z 741

5 Example 15

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 -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50mg, 0.078mmol) was dissolved in 2ml DMF. *tert*-Butyl (L)-valinate (20mg, 0.095mmol) and *N*-methylmorpholine (17 μ l, 0.154mmol) were added and the mixture was stirred for 20min. TBTU (30mg, 0.093mmol) was added and the solution was stirred overnight. Additional *N*-methylmorpholine (8 μ l, 0.078mmol) and TBTU (3x5mg, 0.047mmol) were added and the mixture was stirred overnight and concentrated. The residue was purified by flash chromatography (2g) using EtOAc/hexane (3/7) as eluent. The collected fraction was washed with 5%NaHCO₃ (10ml), 0.1M KHSO₄ (15ml) and brine before it was dried and concentrated. The intermediate *tert*-butyl ester of the title compound was confirmed, m/z 812 (M+18 (NH₄⁺)). DCM (4ml) and TFA (1.5ml) were added and the mixture was stirred overnight, concentrated and purified by preparative HPLC on a C8 column (50x250mm). A gradient (20/80 to 60/40) of MeCN/0.1M ammonium acetate buffer was used as eluent. Lyophilization gave the title compound in 31% yield (18mg). NMR (400MHz) 0.65-0.85 (m, 12H), 0.95-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.0-2.2 (m, 1H), 2.1 (s, 3H), 3.95 (bra, 2H), 4.3 (d, 1H), 4.6 (ABq, 2H), 5.65 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), 7.2 (d, 2H), 7.25-7.4 (m, 6H), 7.5 (d, 2H), m/z 739

Example 16

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-1,2,5-benzothiadiazepine

The title compound was synthesized by the procedure given in Example 15 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)

carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50mg, 0 078mmol) and *tert*-butyl (L)-leucinate (21mg, 0 095mmol). The DMF was removed and 20ml EtOAc was added and washed with NaHCO₃ (5%, 10ml), 0 1M KHSO₄ (15ml) and brine before it was dried and concentrated. The resulting residue was purified by flash chromatography as described. The intermediate *tert*-butyl ester of the title compound was confirmed, m/z 826 (M+18 (NH₄⁺)). Hydrolysis and purification by preparative HPLC gave the title compound in 21% yield (12mg). NMR (400MHz) 0 7 (dd, 6H), 0 75-0 85 (m, 6H), 0 95-1 2 (m, 6H), 1 25-1 7 (m, 9H), 2 1 (s, 3H), 3 95 (brs, 2H), 4 3-4 4 (m, 1H), 4 6 (ABq, 2H), 5 55 (s, 1H), 6 6 (s, 1H), 7 05 (t, 1H), 7 2 (d, 2H), 7 25-7 4 (m, 6H), 7 5 (d, 2H), m/z. 753

Example 17

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[N-(1-(S)-1-carboxy-2-(S)-2-methylbutyl)carbamoyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

The title compound was synthesized by the procedure given in Example 15 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50mg, 0 078mmol) and *tert*-butyl (L)-*iso*-leucinate (21mg, 0 095mmol). The DMF was removed and 20ml EtOAc was added and washed with NaHCO₃ (5%, 10ml), 0 1M KHSO₄ (15ml) and brine before it was dried and evaporated. No purification by flash chromatography was performed. The intermediate *tert*-butyl ester of the title compound was confirmed, m/z 809. Hydrolysis and purification by preparative HPLC gave the title compound in 37% yield (22mg). NMR (400MHz) 0 65-1 4 (m, 22H), 1 4-1 5 (m, 2H), 1 5-1 7 (m, 2H), 1 75-1 85 (m, 1H), 2 1 (s, 3H), 3 95 (brs, 2H), 4 25 (d, 1H), 4 6 (ABq, 2H), 5 6 (s, 1H), 6 6 (s, 1H), 7 05 (t, 1H), 7 2 (d, 2H), 7 25-7 4 (m, 6H), 7 45 (d, 2H), m/z 753.

Example 18

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3, 295mg, 0 58mmol) was dissolved in 10 ml DCM. 4-(1-

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(R)-*t*-Butoxycarbonyl-1-aminomethylphenol (Method 7, 160mg, 0.72mmol), 2,6-lutidine (140μl, 1.20mmol) and TBTU (230mg, 0.72mmol) were added successively. The mixture was stirred for 3h. Additionally 4-(1-(R)-*t*-butoxycarbonyl-1-aminomethylphenol (10mg, 0.04mmol) was added and stirring was continued for 2h. DCM (20ml) was added and the solution was washed with NaHCO₃ (5%, 20ml), KHSO₄ (0.3M, 20ml), brine (20ml) before it was dried and concentrated to a volume of 10 ml. The *tert*-butyl ester of the title compound was confirmed, *m/z*. 729 (M+18 (NH₄⁺)). TFA (1.3ml) was added and the mixture was stirred for 4.5h and concentrated. The crude product was purified by preparative HPLC using a C8 column (50x500mm) and a gradient (40/60 to 70/30 over 40 min) of MeCN/0.1M ammonium acetate buffer as eluent. Lyophilization yielded the title compound in 77.5% (302mg). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.3 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H), 7.15-7.4 (m, 7H), *m/z*. 673 (M+18 (NH₄⁺)).

Example 19

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)-α-[N-(S)-1-carboxy-4-aminobutyl]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-(*t*-butoxycarbonyl)-4-(benzyloxycarbonylamino)butyl]carbamoyl]benzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 8, 0.006 mg) was dissolved in DCM (0.2 ml), TFA (1 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. DCM and TFA were removed at reduced pressure and the residue was purified by preparative HPLC using MeCN/NH₄⁺ buffer 50/50 as eluent. The acetonitrile was evaporated and lyophilisation gave the title compound in 37% yield (21.9 mg). *M/z*. 754.4 and 752.4 (M-H).

Example 20

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(N-[(S)-1-(*t*-butoxycarbonyl)-4-(benzyloxycarbonylamino)butyl]carbamoyl)benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

- 5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(N-[(S)-1-(*t*-butoxycarbonyl)-4-(benzyloxycarbonylamino)butyl]carbamoyl)benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 8, 0 006 mg) was dissolved in DCM (0 1ml), TFA (0 15 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. DCM and TFA were removed at reduced pressure and the residue was purified by
10 preparative HPLC using MeCN/NH₄⁺ buffer 55/45 as eluent. The acetonitrile was evaporated and lyophilisation gave the title compound in 35% yield (2 mg). M/z. 888 7 and 886 7 (M-H)⁻

Example 21

- 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(S)-2-carboxypyrrolidin-1-ylcarbonyl)benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

- 15 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(S)-2-(*t*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl)benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 10, 41 mg, 0 052 mmol) was dissolved in DCM. TFA 4 1 (3 ml) and stirred for 3 hours. The reaction mixture was evaporated under reduced pressure. The
20 residue was purified by preparative HPLC using an acetonitrile/ammonium acetate buffer gradient (5/95 to 100/0) as eluent. 26 5 mg (70%) of the title compound was obtained after lyophilisation. M/z 737 3034

Example 22

- 25 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(N-(carboxymethyl)-N-methylcarbamoyl)benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

- The title compound was synthesized from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(N-(*t*-butoxycarbonylmethyl)-N-methylcarbamoyl)benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 11) by the method
30 of Example 21. NMR (500MHz, 2 rotamers 3:1 mixture). Major rotamer: 0 8 (brt, 6H), 1 0-1 24 (m, 6H), 1 25-1 4 (m, 2H), 1 4-1 51 (m, 2H), 1 56-1 68 (m, 2H), 2 09 (s, 3H), 3 0 (s, 3H), 3 75-4 21 (m, 4H), 4 60 (ABq, 2H), 6 01 (s, 1H), 6 58 (s, 1H), 7 05 (t, 1H), 7 16-7 28 (m, 3H),

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X
H

7.3-7.45 (m, 5H), 7.48 (brd, 2H) additional peaks from the minor rotamer at 2.14 (s), 3.0 (s), 4.56 (ABq), 5.81 (s), 6.61 (brs), m/z 711.4

Example 23

5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[N-(1-(R)-2-(R)-1-carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

The title compound was synthesized from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[N-[1-(R)-2-(R)-1-(*t*-butoxycarbonyl)-1-hydroxy-prop-2-yl]carbamoyl] benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 12) by the method of Example 21. M/z 741.3

Example 24

15 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[N-(sulphomethyl)carbamoyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine ammonium salt

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50 mg, 0.078 mmol), ammoniummethanesulfonic acid (15 mg, 0.088 mmol) and N-methylmorpholine (17.2 μ l, 0.156 mmol) were dissolved in DMF (2ml). Tetrabutylammoniumhydrogensulfate (35 mg, 0.103 mmol) was added and the mixture was heated for 15 minutes at 60°C. After removing heating, TBTU (45 mg, 0.14 mmol) was added. The reaction mixture was stirred in room temperature 40 minutes then 60°C for one hour. After being stirred overnight, 35 mg TBTU was added. After 6 hours, 29 mg TBTU in small portions was added and the reaction mixture was stirred overnight. The mixture was evaporated under reduced pressure. The product was purified using preparative HPLC using an acetonitrile/ammonium acetate buffer gradient (5/95 to 100/0) as eluent. To give 10 mg (17%) of the title compound as an ammonium salt. NMR (600MHz): 0.77 (brt, 6H), 0.97-1.22 (m, 6H), 1.24-1.48 (m, 4H), 1.51-1.68 (m, 2H), 2.08 (s, 3H), 3.7-4.18 (m, 2H), 4.24 (d, 1H), 4.39 (d, 1H), 4.62 (ABq, 2H), 5.62 (s, 1H), 6.58 (brs, 1H), 7.02 (brt, 1H), 7.14-7.23 (m, 2H), 7.24-7.36 (m, 6H), 7.45 (d, 2H), m/z 732.9

Example 25**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine**

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{N-[(R)- α -(*t*-butoxycarbonyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 9, 762 mg, 1.09 mmol) was dissolved in a mixture of TFA (6.65 ml) and triethylsilane (0.350 ml). The reaction mixture was stirred for one hour and then evaporated under reduced pressure to give the title compound in a quantitative yield (714 mg). NMR (500MHz) δ 0.8 (brt, 6H), 0.96-1.25 (m, 6H), 1.25-1.4 (m, 2H), 1.42-1.51 (m, 2H), 1.57-1.69 (m, 2H), 2.11 (s, 3H), 3.8-4.15 (m, 2H), 4.66 (ABq, 2H), 5.49-5.53 (m, 1H), 6.61 (s, 1H), 7.06 (t, 1H), 7.18-7.26 (m, 2H), 7.28-7.45 (m, 8H), 8.35 (d, NH), m/z 640.2

Example 26**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 -carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18, 100mg, 0.152mmol) was dissolved in 3ml DMF. *o*-*tert*-Butyl-(L)-threonine *tert*-butyl ester (50mg, 0.216mmol) and *N*-methylmorpholine (34 μ l, 0.309mmol) were added and the mixture was stirred for 5min. TBTU (60mg, 0.187mmol) was added and the solution was stirred for 30 min. Formic acid (1-2 drops) was added and the mixture was extracted between EtOAc and water. The aqueous phase was washed with EtOAc and the combined organic phases were washed with 2%NaHCO₃, brine, dried and concentrated. The intermediate *t*-butyl ester of the title compound was confirmed, m/z 869. DCM (3ml) and TFA (0.5ml) were added and the solution was stirred overnight. The mixture was concentrated and purified by preparative HPLC on a C8 column (50x250mm). A gradient (20/80 to 50/50) of MeCN/0.1M ammonium acetate buffer was used as eluent. Lyophilization gave the title compound in 61% yield (71mg). NMR (400MHz) δ 0.78 (t, 6H), 0.93 (d, 3H), 1.0-1.22 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.52 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.18-4.25 (m, 1H), 4.35 (d, 1H), 4.63 (ABq, 2H), 5.53 (s, 1H), 6.57 (s, 1H), 6.75 (d, 2H), 7.03 (t, 1H), 7.2 (d, 2H), 7.23-7.37 (m, 5H), m/z 757

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2**Example 27**

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

The title compound was synthesized by the procedure described in Example 26 starting from 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 (Example 18, 70mg, 0.108mmol) and *tert*-butyl (L)-valinate (31mg, 0.148mmol). The intermediate *tert*-butyl ester of the title compound was confirmed. M/z 811. Hydrolysis and purification by preparative HPLC yielded the title compound in 56 mg (69% yield). NMR (400MHz) δ 7.0-7.5 (m, 16H), 0.79 (t, 6H), 0.96-1.24 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.54-1.7 (m, 2H), 2.0-2.2 (m, 1H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.22 (d, 1H), 4.6 (ABq, 2H), 5.54 (s, 1H), 6.58 (s, 1H), 6.75 (d, 2H), 7.03 (t, 1H), 7.2 (d, 2H), 7.23-7.37 (m, 5H), m/z 755

Example 28

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

The title compound was synthesized by the procedure described in Example 26 starting from 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 (Example 18, 36mg, 0.054mmol) and *tert*-butyl (L)-norvalinate hydrochloride (16mg, 0.076mmol). The intermediate *tert*-butyl ester of the title compound was confirmed. M/z 811. Hydrolysis and purification by preparative HPLC yielded the title compound in 23 mg (56% yield). NMR (400MHz) δ 7.0-7.85 (m, 9H), 0.97-1.22 (m, 8H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.5-1.8 (m, 4H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.27 (dd, 1H), 4.6 (ABq, 2H), 5.45 (s, 1H), 6.58 (s, 1H), 6.75 (d, 2H), 7.03 (t, 1H), 7.19 (d, 2H), 7.23-7.37 (m, 5H), m/z 755

Example 29**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**

- 5 A solution of 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 (Example 18, 0 075 g, 0 114 mmol), butanoic acid, 2-amino-, 1,1-dimethylethyl ester, hydrochloride, (2S)- (0 031 g, 0 160 mmol) and N-methylmorpholine (0 050 ml, 0 457 mmol) in DMF (4 ml) was stirred at RT for 10 min, after which TBTU (0 048 g, 0 149 mmol) was added. After 1h, the
- 10 conversion to the ester was complete. M/z 797.4 The solution was diluted with toluene and then concentrated. The residue was dissolved in a mixture of DCM (5 ml) and TFA (2 ml) and the mixture was stirred for 7h. 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. The title compound was obtained in 0 056 g (66 %) as a white solid.
- 15 NMR (400 MHz, DMSO- d_6) 0 70 (3H, t), 0 70-0 80 (6H, m), 0 85-1 75 (14H, m), 2.10 (3H, s), 3 80 (2H, brs), 4 00-4 15 (1H, m), 4 65 (1H, d(AB)), 4 70 (1H, d(AB)), 5 50 (1H, d), 6 60 (1H, s), 6 65-7 40 (11H, m), 8 35 (1H, d), 8 50 (1H, d) 9 40 (1H, brs)

Example 30

- 20 **1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[N-((R)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine**

- A solution of 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 (Example
- 25 18, 0 075 g, 0 114 mmol), S-methyl-L-cysteine tert-butyl ester (Pestic. Sci , EN, 45, 4, 1995, 357-362, 0 031 g, 0 160 mmol) and N-methylmorpholine (0 050 ml, 0 457 mmol) in DMF (4 ml) was stirred at RT for 10 min, after which TBTU (0 048 g, 0 149 mmol) was added. After 1h, the conversion to the ester was complete. M/z 829 5 The reaction mixture was diluted with formic acid (15 ml) and stirred at 50 °C for 17h. The solution was diluted with toluene
- 30 and then concentrated. The residue was purified by preparative HPLC using a gradient of 20-60% MeCN in 0 1M ammonium acetate buffer as eluent. The title compound was obtained in 0 070 g (79 %) as a white solid. NMR (400 MHz, DMSO- d_6) 0 605-0 80 (6H, m), 0 80-1 60

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(12H, m), 1.85 (3H, s), 2.10 (3H, s), 2.60-2.80 (2H, m), 3.85 (2H, brs), 4.15-4.30 (1H, m), 4.65 (1H, d(AB)), 4.70 (1H, d(AB)), 5.50 (1H, d), 6.60 (1H, s), 6.60-7.35 (11H, m), 8.30 (1H, d), 8.40 (1H, d), 9.40 (1H, brs)

5 Example 31

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methyl-8-(N-((R)- α -[N-(carboxymethyl)carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methyl-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 5, 0.050 g, 0.105 mmol), (R)- α -[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 86 of WO 02/50051, 0.039 g, 0.148 mmol) and N-methylmorpholine (0.046 ml, 0.417 mmol) in DCM (4 ml) was stirred at RT for 20 min, after which TBTU (0.044 g, 0.137 mmol) was added. After 1h, the conversion to the ester (m/z 721.2 ($M+1$)⁺) was completed. The solvent was removed under reduced pressure and the residue was dissolved in formic acid (5 ml). The solution was stirred for 17 hours and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.044 g (63 %) as a white solid. NMR (400 MHz, DMSO- d_6) 0.65-0.80 (6H, m), 0.85-1.60 (12H, m), 2.10 (3H, s), 3.40-3.65 (2H, m), 3.70 (2H, brs), 4.60 (1H, d(AB)), 4.70 (1H, d(AB)), 5.55 (1H, d), 6.70 (1H, s), 6.80-7.50 (12H, m), 8.20-8.30 (1H, m), 8.55 (1H, d)

20 Example 32

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methyl-8-(N-((R)- α -[N-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methyl-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 16, 0.050 g, 0.105 mmol), (R)- α -[N-[(S)-1-(*t*-butoxycarbonyl)propyl]carbamoyl]-4-hydroxybenzylamine (Method 19, 0.045 g, 0.146 mmol) and N-methylmorpholine (0.047 ml, 0.427 mmol) in DCM (4 ml) was stirred at RT for 15 min, after which TBTU (0.044 g, 0.137 mmol) was added. After 17 h, the conversion to the ester (m/z 765.7 ($M+1$)⁺) was completed. The solvent was removed under reduced pressure and the residue was dissolved in formic acid (5 ml). The solution was stirred for 3 days and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.017 g (17 %)

g (23 %) as a white solid. NMR (400 MHz, DMSO) 0.60 (3H, t), 0.65-0.80 (6H, m), 0.85-1.75 (14H, m), 2.10 (3H, s), 3.75 (2H, bs), 3.90-4.05 (1H, m), 4.60 (1H, d(AB)), 4.65 (1H, d(AB)), 5.50 (1H, d), 6.65-7.30 (11H, m), 8.15 (1H, d), 8.40 (1H, d)

5 Example 33

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-[N-((S)-2-(*t*-butoxy)-1-(*t*-butoxycarbonyl)ethyl)carbamoyl]propyl)carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 20, 14 mg, 0.015 mmol) was dissolved in a mixture of DCM/TFA (3/1, 4 ml). The reaction mixture was stirred for 3.5 hours. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC using a MeCN/0.1 M ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound, 8 mg (65%). NMR (400 MHz) 0.7-0.83 (m, 9H), 0.9-1.40 (m, 8H), 1.40-1.52 (m, 2H), 1.52-1.70 (m, 3H), 1.77-1.88 (m, 1H), 2.11 (s, 3H), 3.8-4.1 (m, 4H), 4.29 (dd, 1H), 4.37 (t, 1H), 4.63 (ABq, 2H), 5.57 (s, 1H), 6.60 (s, 1H), 7.04 (brt, 1H), 7.20 (brd, 2H), 7.25-7.40 (m, 6H), 7.47 (d, 2H), m/z 812.3

20 Example 34

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[2-(S)-2-(carboxy)-4-(R)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]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 -[2-(S)-2-(methoxycarbonyl)-4-(R)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 21, 23 mg, 0.030 mmol) was dissolved in THF/H₂O (1/1, 1 ml). Lithium hydroxide (monohydrate, 2 mg, 0.048 mmol) was added and the mixture was stirred for 2 hours. 50% Starting material remained so additional lithium hydroxide (3 mg) was added and left for an hour. The reaction was still not complete so further lithium hydroxide (2 mg) was added and the reaction was stirred overnight. The product was purified by preparative HPLC using a MeCN/0.1 M ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound, 12 mg (53%) M/z 753.04

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X**Example 35**

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[2-(S)-2-(carboxy)azetidin-1-ylcarbonyl]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 -[2-(S)-2-(*t*-butoxycarbonyl)azetidin-1-ylcarbonyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 22, 27.5 mg, 0.035 mmol) was dissolved in DCM (3 ml) and TFA (1 ml) was added. The reaction was stirred for 1.5 hours. The solvent was evaporated under reduced pressure. The product was lyophilised to give 25 mg of the title compound. M/z 722.92

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Example 36

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[N-((S)-1-[N-((S)-1-(*t*-butoxycarbonyl)ethyl)carbamoyl]ethyl)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)-1-(*t*-butoxycarbonyl)ethyl)carbamoyl]ethyl)carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 26, 34 mg, 0.041 mmol) was dissolved in a mixture of DCM/TFA (3:1, 4 ml). The reaction mixture was stirred for 2 hours. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC using a MeCN/0.1 M ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound, 23 mg (72%). NMR (500 MHz, CD₃OD) δ 8.1 (bt, 6H), 8.8-1.54 (m, 16H), 1.56-1.71 (m, 2H), 2.11 (s, 3H), 3.8-4.2 (m, 2H), 4.33-4.42 (m, 2H), 4.66 (ABq, 2H), 5.55 (s, 1H), 6.61 (s, 1H), 7.07 (t, 1H), 7.22 (brd, 2H), 7.28-7.43 (m, 6H), 7.48 (d, 2H), m/z 782.1

Example 37

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[N-((R)-1-carboxy-3,3-dimethylbutyl)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-((S)-1-carboxy-3,3-dimethylbutyl)carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

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1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((*R*)- α -carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepines (Example 25, 51mg, 0.080mmol) was dissolved in 2ml DMF. *t*-Butyl 4-methyl D,L-leucinate (Method 27, 23mg, 0.114mmol), *N*-methylmorpholine (18 μ l, 0.163 mmol) and TBTU (31mg, 0.097mmol) were added successively and the mixture was stirred for 2 hours. One drop of formic acid was added and the mixture was extracted between EtOAc and water. The aqueous phase (pH=3) was washed with EtOAc. The combined organic layers were washed with 5%NaHCO₃ and brine and was then dried with Na₂SO₄ and evaporated to dryness. The intermediate *t*-butyl ester of the title compound was confirmed. *M/z* 823. DCM (2ml) and TFA (0.5ml) were added and the solution was stirred overnight. The mixture was concentrated and purified using preparative HPLC on a C8 column (50x250mm). A step gradient of MeCN (20-50%) in 0.1M ammonium acetate buffer was used as eluent. The two diastereomers separated under these conditions and they were collected and lyophilized separately. The first eluting diastereomer was obtained in 5mg (16%yield) and the second eluting diastereomer was obtained in 3mg (10% yield). The absolute configuration was assigned by comparison of NMR-spectra with related compounds and the first eluting diastereomer was found to be the (*R,R*)-diastereomer and the second eluting diastereomer was the (*R,S*)-diastereomer. *M/z* 767. NMR of the (*R,R*)-diastereomer (400MHz): 0.79 (t, 6H), 0.95 (s, 9H), 0.99-1.22 (m, 6H), 1.25-1.39 (m, 2H), 1.40-1.51 (m, 2H), 1.57-1.68 (m, 3H), 1.80 (dd, 1H), 2.08 (s, 3H), 3.95 (brs, 2H), 4.47 (dd, 1H), 4.63 (Abq, 2H), 5.61 (s, 1H), 6.58 (s, 1H), 7.04 (t, 1H), 7.20 (d, 2H), 7.25-7.35 (m, 6H), 7.43-7.47 (m, 2H). And NMR of the (*R,S*)-diastereomer (400MHz): 0.7 (s, 9H), 0.79 (t, 6H), 0.99-1.22 (m, 6H), 1.25-1.39 (m, 2H), 1.40-1.51 (m, 3H), 1.55-1.70 (m, 2H), 1.76 (dd, 1H), 2.12 (s, 3H), 3.95 (brs, 2H), 4.35 (dd, 1H), 4.60 (Abq, 2H), 5.54 (s, 1H), 6.60 (s, 1H), 7.04 (t, 1H), 7.20 (d, 2H), 7.24-7.37 (m, 6H), 7.39-7.46 (m, 2H).

Example 38

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

The title compound was prepared by the procedure of Example 37 starting from 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 (Example 18, 53mg,

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X

0 081mmol) The intermediate t-butyl ester was confirmed. M/z 839 Only one of the diastereomers were collected from the preparative HPLC purification of the racemic title compound. It was obtained in 4mg (12%) and was assigned to be the (R,R)-diastereomer from comparison of NMR-data of related compounds M/z 783 NMR (400MHz) 0 79 (t, 6H),
5 0 95 (s, 9H), 0 99-1 22 (m, 6H), 1 25-1 39 (m, 2H), 1 40-1 51 (m, 2H), 1 56-1 68 (m, 3H), 1 79 (dd, 1H), 2 08 (s, 3H), 3 96 (bra, 2H), 4 47 (dd, 1H), 4 62 (Abq, 2H), 5 47 (s, 1H), 6 58 (s, 1H), 6 73 (d, 2H), 7 04 (t, 1H), 7 19 (d, 2H), 7 24-7 35 (m, 5H)

Example 39

10 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(N-[(R)-1-carboxy-2-(trimethylsilyl)ethyl]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 -(N-[(S)-1-carboxy-2-(trimethylsilyl)ethyl]carbamoyl)-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine
15

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 (Example 18, 55mg, 0 084mmol) and methyl 3-(trimethylsilyl)alaninate (Method 28, 19mg, 0 108mmol) were dissolved in 3 5ml DMF N-Methyl morpholine (18 μ l, 0 163mmol) and TBTU (32mg, 0 101mmol) were added successively and the mixture was stirred for 2 hours One drop of formic acid was added and the mixture was then extracted between EtOAc and water The aqueous phase (pH=3) was washed with EtOAc The combined organic phases were washed with 1% NaHCO₃, brine and was then dried with Na₂SO₄ and concentrated. The intermediate methyl ester was confirmed. M/z. 813 THF (2ml), water (2ml) and LiOH (10mg, 0 418mmol)
20 were added and the mixture was stirred over night. The mixture was purified using preparative HPLC on a C8 column (50x100mm) A gradient from 20 to 50% MeCN in 0 1M ammonium acetate buffer was used as eluent. The two diastereomers were separated under these conditions and were collected separately Lyophilisation yielded 8mg (24% yield) of the first eluting diastereomer and 8 4mg (25% yield) of the second. The absolute configurations were
25 assigned from comparison with NMR-data of related compounds and the first eluting diastereomer was found to be the (R,R)-diastereomer and the second eluting diastereomer was the (R,S)-diastereomer M/z 799 NMR of the (R,R)-diastereomer (400MHz) -0 16 (s, 9H),
30

0.79 (t, 6H), 0.9-1.22 (m, 8H), 1.25-1.40 (m, 2H), 1.40-1.52 (m, 2H), 1.55-1.68 (m, 2H), 2.11 (s, 3H), 3.95 (brs, 2H), 4.29-4.35 (m, 1H), 4.58 (Abq, 2H), 5.45 (s, 1H), 6.59 (s, 1H), 6.73 (d, 2H), 7.04 (t, 1H), 7.17-7.27 (m, 5H), 7.32 (t, 2H), and of the (R,S)-diastereomer (400MHz) 0.04 (s, 9H), 0.79 (t, 6H), 1.00-1.22 (m, 8H), 1.25-1.40 (m, 2H), 1.40-1.52 (m, 2H), 1.55-1.68 (m, 2H), 2.08 (s, 3H), 3.95 (brs, 2H), 4.40-4.46 (m, 1H), 4.62 (Abq, 2H), 5.49 (s, 1H), 6.58 (s, 1H), 6.73 (d, 2H), 7.04 (t, 1H), 7.14-7.36 (m, 7H)

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard Methods from known materials. For Example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions

Method 1

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine and
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

To a suspension of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (prepared according to WO 98/38182, 0.218 g, 5.65×10^{-4} mol) in DMF (5 ml) was added NaSMc (0.210 g, 2.83 mmol, 95 %), and the mixture was stirred for 5 hours at 120°C. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.5 M HCl. The aqueous layer was extracted twice more with EtOAc and the combined organic extracts were dried (MgSO₄) and concentrated. The residue was dissolved in MeCN (7 ml) and ethyl bromoacetate (0.063 ml, 5.65×10^{-4} mol), tetrabutylammonium bromide (0.018 g, 5.65×10^{-3} mol) and sodium carbonate (0.250 g, 2.36 mmol) were added. The mixture was stirred over night at 80°C. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.5 M HCl. The organic layer was washed with brine, dried (MgSO₄) and concentrated. Flash chromatography on silica gel (Hex:EtOAc-6:1) gave the title compounds as colourless oils

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1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, 0.187 g (58 %) NMR (400 MHz, CDCl₃) 0.70-0.80 (m, 6H), 0.90-1.70 (m, 15H), 3.90 (brs, 2H), 4.25 (q, 2H), 4.35 (brs, 1H), 4.65 (s, 2H), 6.95-7.40 (m, 7H), and 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, 0.024 g (8 %) NMR (400 MHz, CDCl₃) 0.70-0.85 (m, 6H), 0.90-1.70 (m, 15H), 2.10 (s, 3H), 3.90 (brs, 2H), 4.20 (brs, 1H), 4.25 (q, 2H), 4.65 (s, 2H), 6.55 (s, 1H), 6.95-7.35 (m, 6H)

Method 2

10 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 1, 0.184 g, 3.24×10^{-4} mol) in EtOH (7 ml) was added NaOH (0.052 g, 1.30 mmol) and the mixture was stirred overnight. The solvent
15 was removed under reduced pressure and the residue was partitioned between EtOAc and 0.5 M HCl. The aqueous layer was extracted twice more with EtOAc and the combined organic extracts were washed with brine and concentrated. The crude product was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent and freeze-dried to give the title compound in 0.173 g (99 %) as a white solid. NMR (400 MHz, CD₃OD) 0.70-0.85 (m, 6H), 0.95-1.70 (m, 12H), 3.90 (brs, 2H), 4.50 (s, 2H), 6.90-7.40 (m, 7H)
20

Method 3

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

25 To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 1, 0.024 g, 4.49×10^{-5} mol) in EtOH (3 ml) was added NaOH (0.007 g, 1.80×10^{-4} mol) and the mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent and freeze-dried. The
30 title compound was obtained in 0.021 g (92 %) as a white solid. NMR (400 MHz, CD₃OD) 0.70-0.85 (m, 6H), 1.00-1.70 (m, 12H), 2.10 (s, 3H), 3.90 (brs, 2H), 4.55 (s, 2H), 6.60 (s, 1H), 6.90-7.35 (m, 6H)

Method 3**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (alternative preparation)**

1,1-Dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-methylthio-8-(*t*-
 5 butoxycarbonylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 25, 6 902 g,
 10 11 mmol) was dissolved in a mixture of TFA (50 ml) and Et₃Si (8 ml) and the solution was
 stirred for 90 min at RT. The solvent was removed under reduced pressure and the residue
 was dissolved in *t*-BuOMe (100 ml). The organic phase was washed with water (20 ml) and
 then extracted three times with diluted NaOH (2x50 ml 0.5M). The combined aqueous
 10 extracts were acidified with diluted HCl (70 ml, 1M) (pH 1-2) and were then extracted twice
 with *t*-BuOMe (2x50 ml). The ether layer was washed with brine, dried over MgSO₄ and
 concentrated. 4.694 g (92 %) of the desired product as brown oil were obtained. NMR (400
 MHz, CD₃OD) 0.70-0.85 (m, 6H), 1.00-1.25 (m, 6H), 1.25-1.50 (m, 4H), 1.55-1.70 (m, 2H),
 2.10 (s, 3H), 3.90 (brs, 2H), 4.55 (s, 2H), 6.60 (s, 1H), 6.95-7.35 (m, 6H)

Method 4**(R)-N-Benzoyloxycarbonyl-α-[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine**

(2R)-{[(Benzyloxy)carbonyl]amino}(phenyl)acetic acid (10 g, 35.0 mmol) and *t*-
 butylglycine hydrochloride (6.3 g, 37.4 mmol) was dissolved in DCM (200 ml) with 2,6-
 lutidine (8.2 ml, 70.4 mmol). After stirring 5 min at 0°C TBTU (12.4 g, 38.6 mmol) was
 20 added and stirring was continued for 1.5 hours at 0°C and 3.75 hours at room temperature.
 The reaction mixture was washed with water (2 x 100 ml), dried (MgSO₄) and purified with
 flash chromatography (DCM:EtOAc 7:1→5:1) to give the title compound (13 g, 94 %). NMR
 (500 MHz, CDCl₃) 1.45 (s, 9H), 3.84 (d, 1H), 4.00 (dd, 1H), 5.10 (m, 2H), 5.28 (brs, 1H),
 25 6.13 (brs, 1H), 6.23 (brs, 1H), 7.30-7.44 (m, 10H)

Method 5**(R)-α-[N-(*t*-Butoxycarbonylmethyl)carbamoyl]benzylamine**

(R)-N-Benzoyloxycarbonyl-α-[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine
 30 (Method 4, 12.8 g, 32.2 mmol) was dissolved in EtOH (99%, 200 ml) and toluene (50 ml).
 Pd/C (10%, 0.65 g) was added and hydrogenation was performed at atmospheric pressure for
 5.5 hours at room temperature. The reaction mixture was filtered through diatomaceous earth

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and the solvents were evaporated to give the title compound (8.4 g, 99 %) NMR (600 MHz, CDCl₃) 1.45 (s, 9H), 3.93 (m, 2H), 4.54 (s, 1H), 7.31-7.42 (m, 5H), 7.51 (brs, 1H)

Method 6

5 2-[[[(2R)-2-Amino-2-(4-hydroxyphenyl)ethanoyl]amino]ethanesulphonic acid

N-Boc-(D)-4-hydroxyphenylglycine (1.00 g, 3.21 mmol) was dissolved in DMF (5 ml) and tetrabutylammonium taurine (2.36 g, 6.42 mmol) was added together with additionally 5 ml DMF. The resulting suspension was cooled on ice and TBTU (1.24 g, 3.85 mmol) was added. The ice bath was removed after 30 min and the mixture was stirred for 2 hours before
10 it was filtered and concentrated. TFA in DCM (20%, 20ml) was added and the reaction mixture was stirred over night. Ethanol (20 ml) was added and the solvents evaporated. The crude product was refluxed in ethanol (100 ml) for 1 hour. Filtration yielded the pure title compound as a white solid, 626mg (71%) NMR (DMSO-d₆) 2.4-2.6 (m, 2H), 3.2-3.4 (m, 2H), 4.79 (s, 1H), 6.78 (d, 2H), 7.23 (d, 2H), 8.22 (t, 1H), 8.4 (brs, 3H), 9.7 (s, 1H)

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Method 7

4-(1-(R)-*t*-Butoxycarbonyl-1-aminomethyl)phenol

Sulfuric acid (conc, 1ml) was added to a solution of D-(R)-4-hydroxyphenylglycine (1.0g, 6.0mmol) in 1,4-dioxane (8ml) placed in a Teflon® flask. The flask was cooled to
20 -78°C and isobutylene (8g, 142.6mmol, condensed at -78°C) was added. The flask was placed in an autoclave at room temperature and stirred for 15h. The autoclave was cooled on ice before opened. The excess isobutylene was allowed to evaporate and the remaining solution was poured into aqueous NaOH (2M, 20ml) and was extracted with diethyl ether to remove formed by-product. The aqueous phase was slightly acidified to attain pH=10 using 2M HCl
25 and was extracted with diethyl ether (3x75ml). The organic phase was washed with brine, dried and concentrated. The obtained product was recrystallized in diethyl ether/hexane. Mass 0.55g (41%) NMR (600MHz, CDCl₃) 1.45 (s, 9H), 4.45 (s, 1H), 6.8 (d, 2H), 7.25 (d, 2H), m/z 224

30

Method 8

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(N-[(S)-1-(*t*-butoxycarbonyl)-4-(benzyloxycarbonylamino)butyl]carbamoyl)benzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 53 mg, 0.083 mmol), *tert*-butyl *N*⁶-[(benzyloxy)carbonyl]-L-ornithinate (35 mg, 0.098 mmol), N-methylmorpholine (0.027 m) were dissolved in DCM (5 ml). The mixture was stirred at room temperature for 10 min, where after TBTU (32 mg, 0.10 mmol) was added and the reaction mixture was stirred for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by chromatography using DCM:EtOAc, 5:1 as eluent to give the title compound 57 mg (72%) *M/z* = 944.7 and 942.7 (M-H).

Method 9

15 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(*t*-butoxycarbonyl)benzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3, 627 mg, 1.24 mmol) was dissolved in DCM (25 ml), *tert*-butyl (2*R*)-amino(phenyl)acetate (308 mg, 1.48 mmol), 2,6-dimethylpyridine (288 μ l, 2.47 mmol) and TBTU (477 mg, 1.48 mmol) were added. The mixture was stirred for 3.5 hours. The reaction mixture was evaporated under reduced pressure. The product was purified using an Isolute column (10g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0 then 95:5. Approximately 694mg pure compound was collected. Another fraction was purified a second time using an Isolute column (10g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5 then 90:10. The pure fraction was added to the first fraction yielding 787 mg (91%) of the title compound. NMR (400MHz, CDCl₃) 0.78 (t, 6H), 0.92-1.12 (m, 4H), 1.12-1.46 (m, 6H), 1.54 (s, 9H), 1.58-1.72 (m, 2H), 2.14 (s, 3H), 3.8-4.05 (m, 2H), 4.32 (bra, NH), 4.56 (ABq, 2H), 5.56 (d, 1H), 6.56 (s, 1H), 7.04 (t, 1H), 7.10 (brd, 2H), 7.24-7.42 (m, 8H), 7.84 (d, NH), *m/z* 694.7 (M-H).

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X**Method 10**

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -(S)-2-(*t*-butoxycarbonyl)pyrrolidin-1-yl)carbonyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

- 5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50 mg, 0.078 mmol) and *tert*-butyl L-prolinate (15 mg, 0.088 mmol) were dissolved in DCM (2ml) and N-methylmorpholine (17.2 μ l, 0.156 mmol) and TBTU (45 mg, 0.14 mmol) were added. The reaction mixture was stirred for 3 hours then additional *tert*-butyl L-prolinate (15 mg, 0.088 mmol) was added. The reaction mixture was stirred over night. The reaction mixture was put directly on an Isolute column (2g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5, 90:10 then 80:20 to give the title compound (41 mg, 66%)
10 M/z 793.2

Method 11

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[N-(*t*-butoxycarbonylmethyl)-N-methylcarbamoyl]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 -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50 mg, 0.078 mmol) and *tert*-butyl N-methylglycinate (15 mg, 0.10 mmol) were dissolved in DCM (2ml) and N-methylmorpholine (17.2 μ l, 0.156 mmol) and TBTU (45 mg, 0.14 mmol) were added. The reaction mixture was stirred for 4 hours. The reaction mixture was put directly on an Isolute column (2g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5, 90:10 then 80:20 to give the title compound (30 mg, 50%)
20 M/z 767.4
25

Method 12

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -{N-[1-(R)-2-(R)-1-(*t*-butoxycarbonyl)-1-hydroxy-prop-2-yl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

- 30 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50 mg, 0.078 mmol)

mmol) and tert-butyl (2R,3R)-3-amino-2-hydroxybutanoate (15 mg, 0.086 mmol) were dissolved in DCM (2ml) and DMF (1ml) and N-methylmorpholine (17.2µl, 0.156 mmol) and TBTU (45 mg, 0.14 mmol) were added. The reaction mixture was stirred for 4 hours. The reaction mixture was put directly on an Isolute column (2g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5, 90:10 then 80:20 to give the title compound (33 mg, 53%) M/z 797.3

Method 13

t-Butyl N-((2R)-2-(((benzyloxy)carbonyl)amino)-2-phenylethanoyl)-O-(*t*-butyl)-L-serinate

(2R)-{[(Benzyloxy)carbonyl]amino}(phenyl)acetic acid (2.0 g, 7.0 mmol) and *t*-butyl O-(*t*-butyl)-L-serinate (2.0 g, 7.9 mmol) and 2,6-lutidine were dissolved in DCM (30 ml). After stirring 5 min at 0°C TBTU (2.5 g, 7.8 mmol) was added and stirring was continued 30 min at 0°C and 4 h. at room temperature. The reaction mixture was washed with water (2 x 100 ml), dried and purified with flash chromatography (DCM) to give the title compound (3.3 g, 97 %) NMR (300 MHz): 1.05 (s, 9H), 1.45 (s, 9H), 3.4-3.8 (m, 2H), 4.5 (bra, 1H), 4.85 (s, 2H), 5.1 (s, 2H), 5.4 (s, 1H), 7.25-7.5 (m, 10 H)

Method 14

t-Butyl N-[(2R)-2-amino-2-phenylethanoyl]-O-(*t*-butyl)-L-serinate

t-Butyl N-((2R)-2-(((benzyloxy)carbonyl)amino)-2-phenylethanoyl)-O-(*t*-butyl)-L-serinate (Method 13, 3.3 g, 6.8 mmol) was dissolved in EtOH (95%, 30 ml) and a catalytic amount of Pd/C (5%)(50% in water) was added and hydrogenation was performed at atmospheric pressure for 3 h. 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): 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 15

1,1-Dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-methyl-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

To a cooled solution (-78 °C) of 1,1-dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 23, 2.10 g, 3.41

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mmol) in THF (50 ml) was added dropwise a solution of *n*-BuLi (2.35 ml, 3.75 mmol, 1.6 M in hexane). After stirring at -78 °C for 20 minutes, MeI (2.42 g, 17.1 mmol) was added. The mixture was stirred at -78 °C for 10 minutes and at room temperature for 18 hours. Diethyl ether (50 ml) was added and the organic phase was washed with 10 % NH₄Cl (aq, 50 ml) and brine (50 ml). After drying, filtration and concentration the crude product was subjected to flash chromatography (Hexane : EtOAc -95 : 5) to give 0.4 gram (21 %) of the title product as colourless oil. NMR (300 MHz, CDCl₃) 0.60-0.70 (m, 6H), 0.70-0.90 (m, 4H), 0.90-1.35 (m, 8H), 2.00 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.00-4.20 (m, 2H), 4.35-4.60 (m, 2H), 6.65-6.85 (m, 3H), 6.90-7.10 (m, 3H), 7.15-7.30 (m, 5H).

Method 16

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methyl-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

To a solution (0 °C) of trifluoroacetic acid (30 ml) and triethylsilane (1.03 g, 8.85 mmol) was added a solution of 1,1-dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-methyl-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 15, 0.92 g, 1.77 mmol) in DCM (2 ml). The reaction mixture was stirred at room temperature for 30 minutes. After concentration of the reaction mixture, the residue was dissolved in diethyl ether (50 ml) and washed with water (25 ml) and sodium bicarbonate (10 %, 25 ml). After drying, filtration and concentration the crude product was subjected to flash chromatography on silica gel (Hexane : EtOAc -90 : 10) to give 0.58 g of a grey solid. To a solution (0 °C) of this solid in dichloromethane (30 ml) was added dropwise BBr₃ in DCM (1M in DCM, 10.2 ml, 10.2 mmol). The reaction mixture was stirred at room temperature for 45 minutes and then it was washed with sodium bicarbonate (10 %, 25 ml) and water (25 ml). After drying, filtration and concentration the crude product (0.55 g, grey solid) was dissolved in MeCN (30 ml). The solution was added K₂CO₃ (0.22 g, 1.58 mmol) and tetra-*n*-butyl ammonium bromide (10 mg) followed by ethyl bromoacetate (0.25 g, 1.51 mmol). The reaction mixture was stirred at 80 °C for 1.5 h and then evaporated under reduced pressure. The residue was dissolved in EtOAc (50 ml) and washed with NH₄Cl (aq, 10 %) and brine. After drying, filtration and concentration the crude product was subjected to flash chromatography (Hex : EtOAc 9 : 1-8 : 2) to afford 0.58 g of an off-white solid. The solid was dissolved in THF : H₂O (4 : 1, 25 ml) and LiOH (0.097 g, 2.31 mmol) was added. The reaction mixture was stirred at room temperature for 40 min. The mixture was evaporated under reduced pressure, dissolved in water (50 ml).

and acidified with 1M HCl. The aqueous layer was extracted 2x with diethyl ether. Evaporation of the solvent under reduced pressure gave 0.46 g (55%) of the title compound. NMR (300 MHz, acetone- d_6), 0.70-0.90 (m, 6H), 0.95-1.80 (m, 12H), 2.15 (s, 3H), 3.85-4.15 (m, 2H), 4.85 (s, 2H), 6.00 (s, 1H), 6.80 (s, 1H), 6.90-7.05 (m, 1H), 7.10-7.45 (m, 5H).

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Method 17

(R)-N-Benzoyloxycarbonyl- α -carboxy-4-hydroxybenzylamine

(R)-*p*-Hydroxyphenylglycine (5.00 g, 29.9 mmol) was mixed with water (50 ml). Sodium bicarbonate (6.3 g, 75.0 mmol) was added to the slurry and a white suspension was the result after 10 min stirring. Benzyl chloroformate (5.1 ml, 33.9 mmol) was added from a dropping funnel over 20 min and the mixture was stirred vigorously. After 2h, water (300 ml) was added and the suspension was extracted with ether (200 ml). The white solid did not dissolve and more water and ether were added. LC/MS indicated that the solid was product. The clear part of the aqueous phase was collected and acidified upon a white precipitate was formed. This was left over the weekend and was then filtered off. The remaining aqueous phase containing undissolved material was acidified as well and was extracted with EtOAc (3x). Also here a precipitate remained between the phases. This was collected with the organic layer. The EtOAc phase was evaporated. Toluene was added 2x to remove water. The two fractions of white solid were added together and recrystallized in DCM (200 ml). The cooled mixture was filtered and 4.77 g (53 %) of white solid were obtained. NMR (400 MHz, DMSO- d_6) 5.00 (1H, d), 5.00 (2H, s), 6.70 (2H, d), 7.05-7.50 (7H, m), 7.90 (1H, d).

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Method 18

(R)-N-Benzoyloxycarbonyl- α -(N-[(S)-1-(*t*-butoxycarbonyl)propyl]carbamoyl)-4-hydroxybenzylamine

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A solution of (R)-*N*-benzyloxycarbonyl- α -carboxy-4-hydroxybenzylamine (Method 17, 2.00 g, 6.64 mmol), (2*S*)-2-amino butanoic acid *t*-butyl ester (1.30 g, 6.64 mmol) and *N*-methylmorpholine (2.0 g, 19.8 mmol) in DCM (30 ml) was stirred at RT for 5 min, after which TBTU (2.60 g, 8.10 mmol) was added. The reaction mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (DCM: Acetone – 60:40). The product was crystallized from toluene (20 ml) giving 1.85 g of the desired product as a white solid. NMR

30

(400 MHz) 0.80 (3H, t), 1.45 (9H, s), 1.50-1.80 (2H, m), 4.10-4.20 (1H, m), 5.05 (1H, d(AB)), 5.15 (1H, d(AB)), 6.75 (2H, d), 7.20-7.40 (7H, m)

Method 19

5 (R)- α -(N-[(S)-1-(*t*-Butoxycarbonyl)propyl]carbamoyl)-4-hydroxybenzylamine

A mixture of (R)-*N*-Benzyloxycarbonyl- α -(N-[(S)-1-(*t*-butoxycarbonyl)propyl]carbamoyl)-4-hydroxybenzylamine (Method 18, 1.80 g, 4.07 mmol) and Pd/C (0.2 g, 5 %) in ethanol (30 ml, 95 %) was stirred under hydrogen gas at room temperature for 2 hours. The reaction mixture was filtered through silica gel (2g) and concentrated. The residue was dissolved in acetone (20 ml) and methanesulphonic acid (0.40 g, 4.16 mmol) was added. No crystallization was obtained and the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.350 g (28 %) as a white solid. NMR (400 MHz, DMSO- d_6) 0.75 (3H, t), 1.40 (9H, s), 1.50-1.75 (2H, m), 2.70 (1H, s), 4.00-4.10 (1H, m), 4.30 (1H, s), 6.65 (2H, d), 7.15 (2H, d), 8.15 (1H, d)

Method 20

20 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-[(R)- α -(N-[(S)-1-(*N*-(S)-2-(*t*-butoxy)-1-(*t*-butoxycarbonyl)ethyl]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-carboxypropyl]carbamoyl]benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 6, 15 mg, 0.021 mmol), *tert*-butyl *O*-(*tert*-butyl)-L-serinate hydrochloride (5.4 mg, 0.021 mmol) and *N*-methylmorpholine (4.6 μ l, 0.042 mmol) was dissolved in DMF (1 ml). TBTU (12.5 mg, 0.039 mmol) was added and the mixture was stirred for one hour. *tert*-butyl *O*-(*tert*-butyl)-L-serinate hydrochloride (0.8 mg, 0.0031 mmol) was added and the mixture was stirred for a couple of minutes. The solvent was evaporated under reduced pressure and co-evaporated a few times with toluene. The product was purified using a pre-packed ISOLUTE column (Silica, 2g) and eluted with a stepwise gradient using DCM/EtOAc 100:0 (10 ml) 95:5 (10 ml) 90:10 (10 ml) 80:20 (10 ml), to give 14 mg of the title compound. *M/z* 924.7

Method 21**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[2-(S)-2-(methoxycarbonyl)-4-(R)-4-(hydroxy)pyrrolidin-1-yl]carbonyl[benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine**

- 5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 54 mg, 0.084 mmol), methyl (4R)-4-hydroxy-L-prolinate hydrochloride (18.4 mg, 0.10 mmol) and N-methylmorpholine (13.9 μ l, 0.13 mmol) was dissolved in DMF (2 ml). TBTU (32.5 mg, 0.101 mmol) was added and the mixture was stirred for three hours. The solvent was evaporated
- 10 under reduced pressure. The product was purified two times using a pre-packed ISOLUTE column (Silica, 2g) and eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5, 90:10, 80:20 and 60:40, to give 23 mg of the title compound. M/z 767.0

Method 22

- 15 **1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[2-(S)-2-(*t*-butoxycarbonyl)azetidin-1-yl]carbonyl[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 -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 50 mg, 0.078 mmol), *tert*-butyl (2S)-azetidine-2-carboxylate (17.4 mg, 0.111 mmol) and N-methylmorpholine (10.3 μ l, 0.094 mmol) was dissolved in DMF (2 ml). TBTU (30 mg, 0.094 mmol) was added and the mixture was stirred for four hours. The solvent was evaporated
- 20 under reduced pressure. The product was purified using a pre-packed ISOLUTE column (Silica, 2g) and eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5, 90:10, 80:20,
- 25 to give 27.5 mg of the title compound. M/z 777.6 (M-H)⁺

Method 23**1,1-Dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine**

- 30 To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (prepared according to WO 98/38182, 0.200 g, 0.404 mmol) in MeCN (5 ml) where added *p*-methoxybenzyl chloride (0.066 ml, 0.486 mmol), CsI

(0.010 g, 0.038 mmol) and CaCO_3 (0.263 g, 0.807 mmol) and the mixture was stirred at 60 °C for 4h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.5M HCl (aq). The organic layer was washed with brine, dried over MgSO_4 and concentrated. The residue was filtered through silica gel (DCM: EtOAc -9:1) to give the title compound in 0.257 g (~quant) as an off-white solid. NMR (400 MHz, CDCl_3) 0.60-0.75 (m, 6H), 0.75-1.20 (m, 8H), 1.25-1.45 (m, 2H), 1.80-2.00 (m, 2H), 3.80 (s, 3H), 3.90 (s, 3H), 4.05-4.30 (m, 2H), 4.45-4.65 (m, 2H), 6.70-7.45 (m, 11H).

Method 24

10 1,1-Dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

NaSMc (0.150 g, 2.03 mmol, 95 %) was added to a solution of 1,1-dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 23, 0.249 g, 0.404 mmol) in DMF (5 ml). The mixture was stirred at RT for 2h, after which the temperature was raised to 80 °C and more NaSMc (0.090 g, 1.22 mmol) was added. After 20h at 80 °C the mixture was added water (5 ml) and 1M HCl (aq) (pH~4). The solution was extracted three times with Et_2O and the combined organic layers were washed with brine, dried over MgSO_4 and concentrated. The crude product was purified by flash chromatography on silica gel (Hex: EtOAc-4:1), which gave the title compound in 0.188 g (82%) as tan solid. NMR (500 MHz, CDCl_3) 0.60-0.75 (m, 6H), 0.75-1.20 (m, 8H), 1.25-1.40 (m, 2H), 1.80-2.00 (m, 2H), 2.20 (s, 3H), 3.80 (s, 3H), 4.20 (brs, 2H), 4.50 (brs, 2H), 6.05 (brs, 1H), 6.75-6.85 (m, 3H), 7.00-7.10 (m, 3H), 7.20-7.35 (m, 4H), 7.50 (s, 1H).

25 Method 25

1,1-Dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-methylthio-8-(t-butoxycarbonylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

A solution of 1,1-dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 24, 4.487 g, 7.889 mmol) in MeCN (100ml) was added t-butyl bromide (0.262g, 0.813 mmol), t-butyl bromoacetate (1.46ml, 9.880 mmol) and potassium carbonate (anhydrous, 3.28g, 23.7 mmol) in this order. The mixture was heated to 55°C for 2.5h, after which it was cooled to RT and left stirring over night. The solvent was evaporated until a yellowish slurry remained, which was extracted

between diethyl ether (150ml) and water (100ml) The aqueous phase was washed with ether (100ml) and the combined ether layers were washed with 0.1M KHSO₄ (aq, 100ml), brine (100ml) and were dried The ether was removed under reduced pressure and the beige solid obtained was dried under reduced pressure for 4h (5.355 g, 99 %) NMR (400 MHz, CDCl₃)
 5 0.60-1.25 (m, 14H), 1.25-1.40 (m, 2H), 1.50 (s, 9H), 1.75-2.00 (m, 2H), 2.10 (s, 3H), 3.80 (s, 3H), 4.20 (brs, 2H), 4.50 (brs, 2H), 4.60 (s, 2H), 6.45 (s, 1H), 6.75-6.85 (m, 2H), 7.00-7.15 (m, 3H), 7.20-7.40 (m, 5H)

Method 26

10 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-[N-((S)-1-(*t*-butoxycarbonyl)ethyl]carbamoyl)ethyl]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-carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25, 58 mg, 0.091
 15 mmol), *tert*-butyl L-alanyl-L-alaninate hydrochloride (27.5 mg, 0.11 mmol) and N-methylmorpholine (20 μl, 0.18 mmol) was dissolved in DMF (2 ml) TBTU (35 mg, 0.18 mmol) was added and the mixture was stirred for 2-3 hours. The solvent was evaporated under reduced pressure. The product was purified using a pre-packed ISOLUTE column (Silica, 2g) and eluted with a stepwise gradient using DCM/EtOAc 100/0, 95/5, 90/10 and
 20 80/20 to give 34 mg (45%) of the title compound. M/z 838.5

Method 27

tert-Butyl 4-methylleucinate

4-Methylleucine (500mg, 3.44mmol) was suspended in 10 ml *t*-butyl acetate.
 25 Perchloric acid (0.2ml, 3.49mmol) was added and the flask was stopped with a septum and stirred over night. Analysis was performed using TLC (DCM/MeOH, 9/1, staining with a ninhydrine/EtOH solution) The solution was poured into a flask containing 30ml EtOAc and 30 ml 5% Na₂CO₃. The aq-layer turned acidic and 2M NaOH was added until pH was approximately 7. The phases were separated and the aq-phase was washed with 2x30ml
 30 EtOAc. The combined organic phases were washed with brine, dried with Na₂SO₄ and evaporated. A oil was obtained which was co-evaporated with toluene and then with diethyl

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ether before being placed under vacuum for two days. Mass 665 mg (96% yield). NMR (CDCl₃) 1.0 (s, 9H), 1.5 (s, 9H), 1.65-1.95 (m, 2H), 3.82 (t, 1H).

Method 28

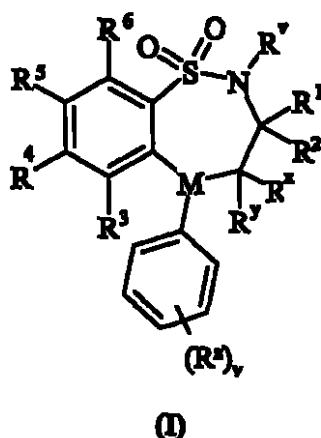
5 Methyl 3-(trimethylsilyl)alaninate

3-Trimethylsilyl alanine (J. Organomet. Chem., 628, (2001), 183-194, 19mg, 0.118mmol) was mixed with 3ml BF₃·MeOH (14%, 3.7mmol) in a sealed tube and heated to 70°C. Analysis was performed using TLC (MeOH:DCM 1:9, stained w. mahydrine in ethanol). The mixture was heated for 3h and was then cooled to ambient temperature. The mixture was poured into a mixture of 3ml EtOAc and 2ml water containing Na₂CO₃. More Na₂CO₃ (5%-aq) was added until pH ca 7. The aqueous phase was washed with EtOAc (2x3ml). The combined organic layers were washed with brine (1ml), dried with Na₂SO₄ and evaporated. The product was obtained as a white film. Mass 19mg (92% yield). NMR (CDCl₃) 0.1 (s, 9H), 1.2-1.4 (m, 2H), 3.8 (s, 3H), 4.2 (bra, 1H).

Claims

What we claim is

5 1 A compound of formula (I)



wherein

R^7 is selected from hydrogen or C_{1-6} alkyl,

10 One of R^1 and R^2 are selected from hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl and the other is selected from C_{1-6} alkyl or C_{2-6} alkenyl,

R^3 and R^7 are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, $N-(C_{1-6}alkyl)amino$, $N,N-(C_{1-6}alkyl)_2amino$, $C_{1-6}alkylS(O)_a$ wherein a is 0 to 2,

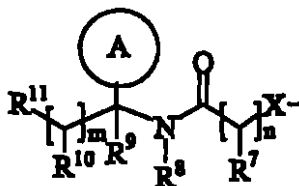
15 M is selected from $-N-$ or $-CH-$,

R^2 is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphonamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, $N-(C_{1-6}alkyl)amino$, $N,N-(C_{1-6}alkyl)_2amino$, $C_{1-6}alkanoylamino$, $N-(C_{1-6}alkyl)carbamoyl$, $N,N-(C_{1-6}alkyl)_2carbamoyl$, $C_{1-6}alkylS(O)_a$ wherein a is 0 to 2, $C_{1-6}alkoxycarbonyl$,

20 $N-(C_{1-6}alkyl)sulphonamoyl$ and $N,N-(C_{1-6}alkyl)_2sulphonamoyl$,

v is 0-5,

one of R^4 and R^5 is a group of formula (IA)



(IA)

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a, wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl)₂sulphamoyl, wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{16} ,

X is -O-, -N(R^b)-, -S(O)_b- or -CH(R^b)-, wherein R^b is hydrogen or C_{1-6} alkyl and b is 0-2,

Ring A is aryl or heteroaryl, wherein Ring A is optionally substituted by one or more substituents selected from R^{17} ,

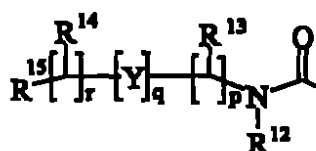
R^7 is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl, wherein R^7 is optionally substituted by one or more substituents selected from R^{18} ,

R^8 is hydrogen or C_{1-4} alkyl,

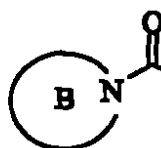
R^9 is hydrogen or C_{1-4} alkyl,

R^{10} is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl, wherein R^{10} is optionally substituted by one or more substituents selected from R^{19} ,

R^{11} is carboxy, sulphy, sulphino, phosphono, -P(O)(OR^a)(OR^d), -P(O)(OH)(OR^a), -P(O)(OH)(R^d) or -P(O)(OR^a)(R^d) wherein R^a and R^d are independently selected from C_{1-6} alkyl, or R^{11} is a group of formula (IB) or (IC)



(IB)



(IC)

wherein

Y is -N(R^b)-, -N(R^b)C(O)-, -N(R^b)C(O)(CR^aR^b)_nN(R^b)C(O)-, -O-, and -S(O)_a-, wherein a is 0-2, v is 1-2, R^b and R^t are independently selected from hydrogen or C_{1-4} alkyl optionally substituted by R^{26} and R^a is hydrogen or C_{1-4} alkyl,

R^{12} is hydrogen or C_{1-4} alkyl,

R^{13} and R^{14} are independently selected from hydrogen, C_{1-6} alkyl, carbocyclyl or heterocyclyl, and when q is 0, R^{14} may additionally be selected from hydroxy; wherein R^{13}

and R^{14} may be independently optionally substituted by one or more substituents selected from R^{20} ,

R^{15} is carboxy, sulpho, sulphino, phosphono, $-P(O)(OR^e)(OR^f)$, $-P(O)(OH)(OR^e)$, $-P(O)(OH)(R^e)$ or $-P(O)(OR^e)(R^f)$ wherein R^e and R^f are independently selected from

5 C_{1-6} alkyl,

p is 1-3, wherein the values of R^{13} may be the same or different;

q is 0-1,

r is 0-3, wherein the values of R^{14} may be the same or different,

m is 0-2, wherein the values of R^{10} may be the same or different;

10 n is 1-3, wherein the values of R^7 may be the same or different;

Ring B is a nitrogen linked heterocyclyl substituted on carbon by one group selected from R^{23} , and optionally additionally substituted on carbon by one or more R^{24} , and wherein if said nitrogen linked heterocyclyl contains an $-NH-$ moiety, that nitrogen may be optionally substituted by a group selected from R^{25} ,

15 R^{16} , R^{17} and R^{18} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, $N-(C_{1-4}alkyl)amino$, $N,N-(C_{1-4}alkyl)_2amino$, $C_{1-4}alkanoylamino$, $N-(C_{1-4}alkyl)carbamoyl$, $N,N-(C_{1-4}alkyl)_2carbamoyl$, $C_{1-4}alkylS(O)_a$ wherein a is 0 to 2, $C_{1-4}alkoxycarbonyl$, $N-(C_{1-4}alkyl)sulphamoyl$ and

20 $N,N-(C_{1-4}alkyl)_2sulphamoyl$, wherein R^{16} , R^{17} and R^{18} may be independently optionally substituted on carbon by one or more R^{21} ,

R^{19} , R^{20} , R^{24} and R^{26} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, $C_{1-4}alkanoyl$, $C_{1-4}alkanoyloxy$, $N-(C_{1-4}alkyl)amino$, $N,N-(C_{1-4}alkyl)_2amino$, $C_{1-4}alkanoylamino$, $N-(C_{1-4}alkyl)carbamoyl$, $N,N-(C_{1-4}alkyl)_2carbamoyl$, $C_{1-4}alkylS(O)_a$ wherein a is 0 to 2, $C_{1-4}alkoxycarbonyl$, $N-(C_{1-4}alkyl)sulphamoyl$, $N,N-(C_{1-4}alkyl)_2sulphamoyl$, carbocyclyl, heterocyclyl, benzyloxycarbonylamino, $(C_{1-4}alkyl)_3silyl$, sulpho, sulphino, amido, phosphono, $-P(O)(OR^a)(OR^b)$, $-P(O)(OH)(OR^a)$, $-P(O)(OH)(R^a)$ or $-P(O)(OR^a)(R^b)$, wherein R^a and R^b are independently selected from C_{1-6} alkyl, wherein R^{19} , R^{20} , R^{24} and R^{26}

30 may be independently optionally substituted on carbon by one or more R^{22} ,

R^{21} and R^{22} are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy,

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methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylearbamoyl, *N,N*-dimethylearbamoyl, methylthio, methylsulphonyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl,

5 R^{23} is carboxy, sulpho, sulphino, phosphono, $-P(O)(OR^g)(OR^h)$, $-P(O)(OH)(OR^g)$, $-P(O)(OH)(R^g)$ or $-P(O)(OR^g)(R^h)$ wherein R^g and R^h are independently selected from C_{1-6} alkyl,

R^{23} is selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6} alkyl)carbamoyl, *N,N*-(C_{1-6} alkyl)carbamoyl, benzyl, benzyloxycarbonyl,
10 benzoyl and phenylsulphonyl,
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

2 A compound of formula (I) as claimed in claim 1 wherein R^v is hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

15 3 A compound of formula (I) as claimed in either of claims 1 or 2 wherein R^1 and R^2 are both butyl or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

20 4 A compound of formula (I) as claimed in any one of claims 1-3 wherein R^x and R^y are both hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

5 A compound of formula (I) as claimed in any one of claims 1-4 wherein M is -N- or a
25 pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

6 A compound of formula (I) as claimed in any one of claims 1-5 wherein v is 0 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

30 7 A compound of formula (I) as claimed in any one of claims 1-6 wherein R^3 and R^6 are hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

8 A compound of formula (I) as claimed in any one of claims 1-7 wherein R^4 is bromo, methyl or methylthio or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

5

9 A compound of formula (I) as claimed in any one of claims 1-8 wherein R^3 is a group of formula (IA) (as depicted in claim 1) wherein

X is -O-,

Ring A is phenyl optionally substituted by one or more substituents selected from R^{17} ,

10

n is 1,

R^7 is hydrogen,

R^8 is hydrogen,

R^9 is hydrogen,

m is 0,

15

R^{11} is carboxy, a group of formula (IB) (as depicted above) or a group of formula (IC) (as depicted above) wherein

R^{12} is hydrogen or C_{1-4} alkyl,

p is 1 or 2,

R^{13} is hydrogen or C_{1-6} alkyl optionally substituted by R^{20} wherein R^{20} is hydroxy,

20

carbamoyl, amino, benzyloxycarbonylamino, C_{1-4} alkylS(O)_a wherein a is 0 or $(C_{1-4}$ alkyl)₃siyl,

R^{14} is hydrogen or hydroxy or C_{1-6} alkyl, wherein R^{14} may be optionally substituted by one or more substituents selected from R^{20} ,

Y is -N(R^n)C(O)- wherein R^n is hydrogen,

q is 0 or 1,

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r is 0 or 1,

R^{15} is carboxy or sulphy,

R^{17} is hydroxy; and

R^{20} is selected from hydroxy;

Ring B is pyrrolidin-1-yl or azetidynyl substituted on carbon by one group selected from R^{23} , and optionally additionally substituted on carbon by one or more R^{24} , wherein R^{23} is carboxy and R^{24} is hydroxy;

30

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

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- 10 A compound of formula (I) (as depicted in claim 1) wherein
 R^v is hydrogen,
 R^1 and R^2 are both butyl,
5 R^x and R^y are both hydrogen,
 M is -N-,
 v is 0;
 R^3 and R^6 are hydrogen,
 R^4 is bromo, methyl or methylthio, and
10 R^5 is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-carbamoyl-ethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl) carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3-methylbutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(S)-1-carboxy-2-(S)-2-methylbutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -carboxy-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-aminobutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-(benzyloxycarbonylamino)butyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-2-carboxypyrrolidin-1-ylcarbonyl)benzyl] carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)-*N*-methylcarbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(R)-2-(R)-1-carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-

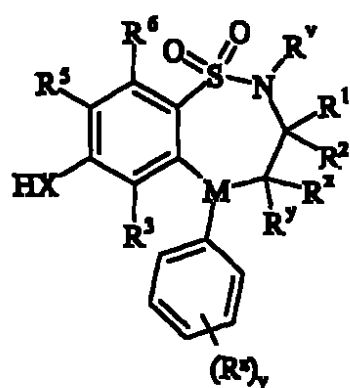
- (sulphomethyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -carboxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)-4-(R)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)azetidin-1-ylcarbonyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-{(S)-1-[*N*-((S)-1-carboxyethyl)carbamoyl]ethyl} carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3,3-dimethylbutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(trimethylsilyl)ethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy or *N*-{(R)- α -[*N*-((R)-1-carboxy-2-(trimethylsilyl)ethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy;
- or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

- 11 A compound of formula (I) selected from
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthioethyl)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,

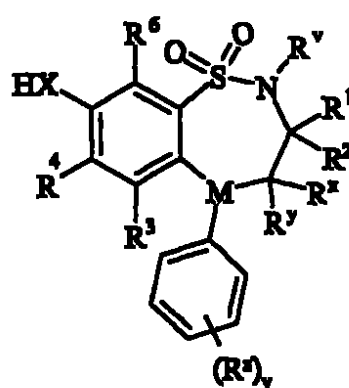
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- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[N-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl) carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[N-((S)-1-carboxypropyl) 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; and
- 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,
- or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

- 12 A process for preparing a compound of formula (I) as claimed in claims 1-11 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process comprises of
- 30 *Process 1)* for compounds of formula (I) wherein X is -O-, -NR^a or -S-, reacting a compound of formula (IIa) or (IIb)

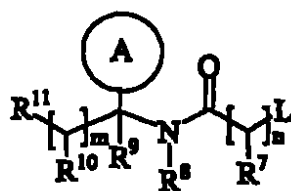


(IIa)



(IIb)

with a compound of formula (III)

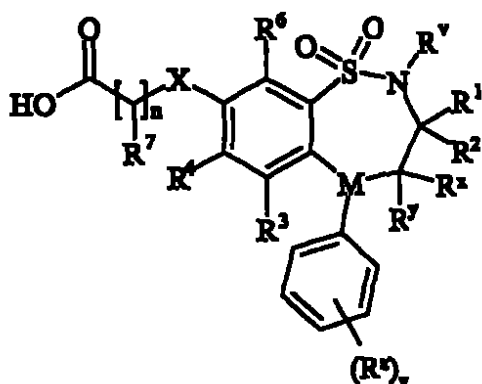


(III)

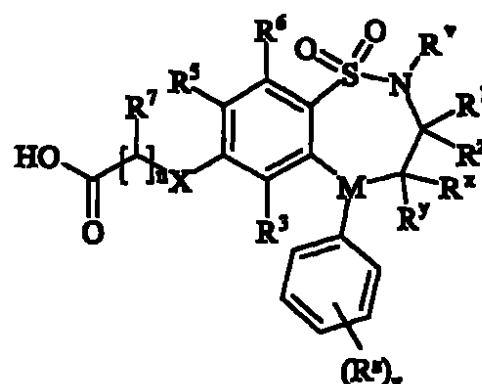
5

wherein L is a displaceable group,

Process 2) reacting an acid of formula (IVa) or (IVb)

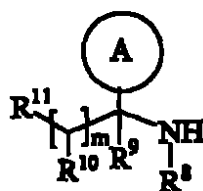


(IVa)



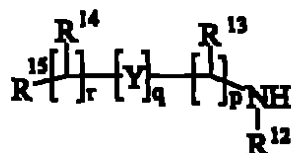
(IVb)

10 or an activated derivative thereof, with an amine of formula (V)



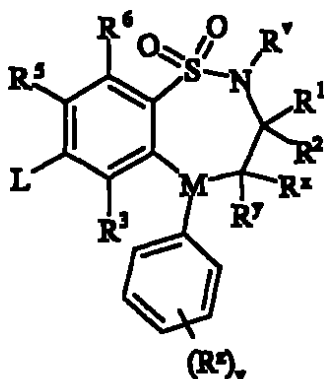
(V).

Process 3) for compounds of formula (I) wherein R^{11} is a group of formula (IB), reacting a compound of formula (I) wherein R^{11} is carboxy with an amine of formula (VI)

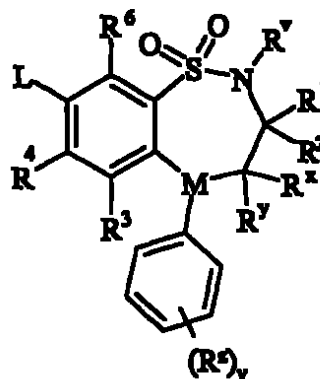


(VI)

- 5 *Process 4)* for compounds of formula (I) wherein one of R^4 and R^5 are independently selected from C_{1-6} alkylthio optionally substituted on carbon by one or more R^{17} , reacting a compound of formula (VIIa) or (VIIb)



(VIIa)



(VIIb)

- 10 wherein L is a displaceable group, with a thiol of formula (VIII)

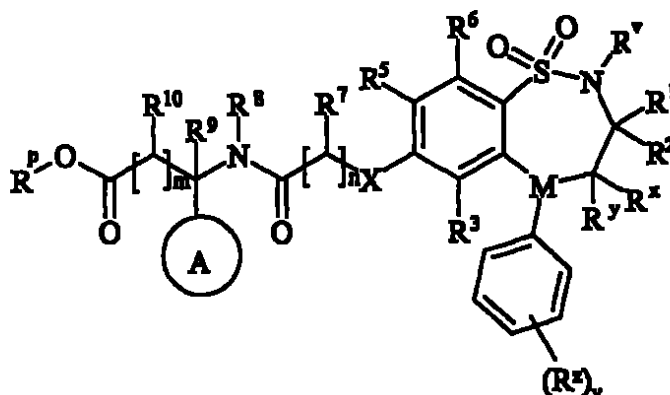


(VIII)

wherein R^m is C_{1-6} alkylthio optionally substituted on carbon by one or more R^{16} ,

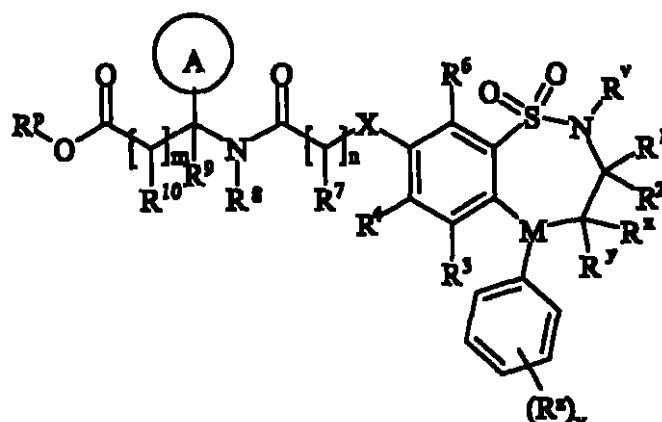
Process 5) for compounds of formula (I) wherein R^{11} is carboxy; deprotecting a compound of

- 15 formula (IXa)



(IXa)

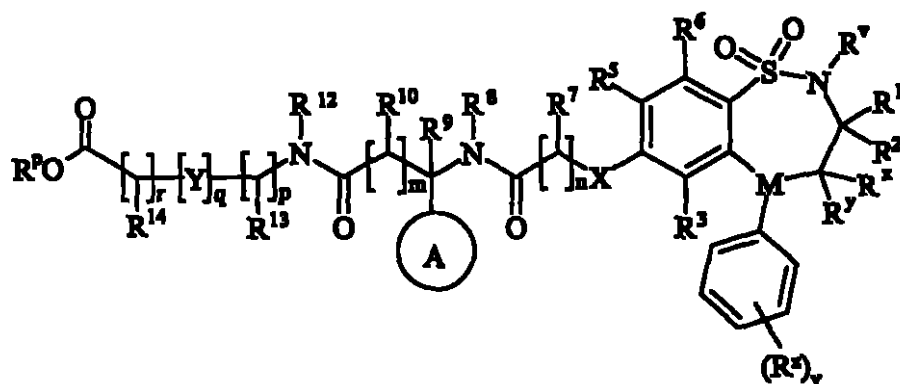
or (IXb)



(IXb)

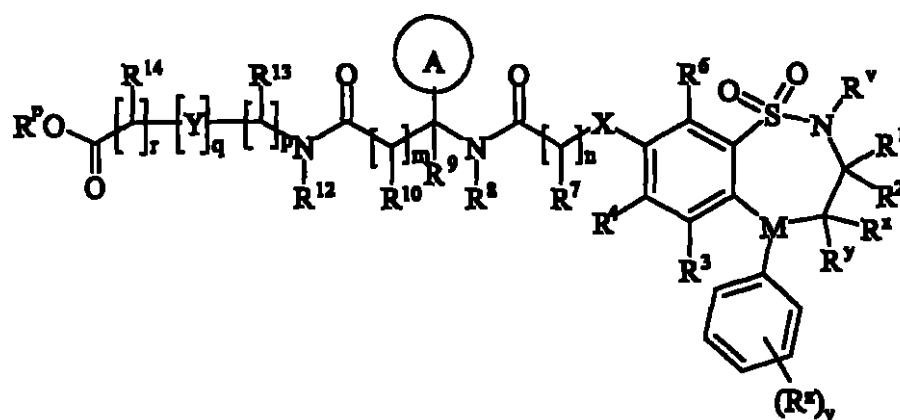
wherein R^p together with the $-OC(O)-$ group to which it is attached forms an ester;

- 5 *Process 6)* for compounds of formula (I) wherein R^{11} is a group of formula (IB) and R^{15} is carboxy; deprotecting a compound of formula (Xa)



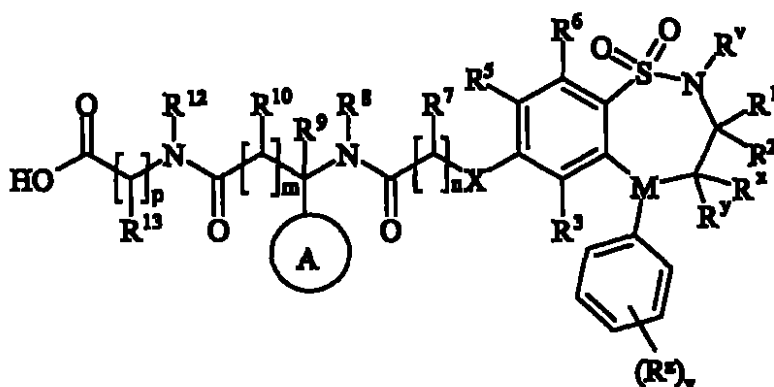
(Xa)

or (Xb)



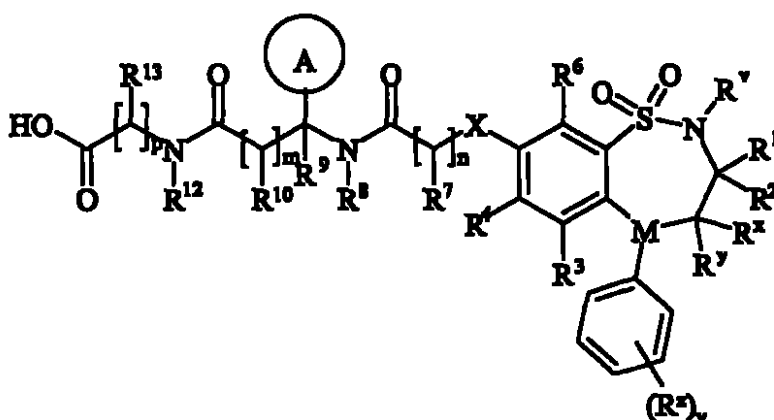
(Xb)

wherein R^p together with the $-OC(O)-$ group to which it is attached forms an ester;
 or *Process 7*) for compounds of formula (I) wherein R^{11} is a group of formula (IB) and
 $N(R^v)C(O)-$, reacting an acid of formula (XIa)



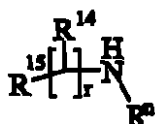
(XIa)

or (XIb)



(XIb)

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



(XII)

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

13 A compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11 for use as a medicament.

5 14 A compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11 for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

15 The use of a compound of the formula (I), or a pharmaceutically acceptable salt,
10 solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

16 The use of a compound of the formula (I), or a pharmaceutically acceptable salt,
15 solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11, in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

17 A method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective
20 amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11

18 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
25 claimed in any one of claims 1 to 11, in association with a pharmaceutically-acceptable diluent or carrier

19 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
30 claimed in any one of claims 1 to 11, 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

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20 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
claimed in any one of claims 1 to 11, and a bile acid binder, in association with a
5 pharmaceutically acceptable diluent or carrier

21 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
claimed in any one of claims 1 to 11, and an HMG Co-A reductase inhibitor, or a
10 pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile
acid binder in association with a pharmaceutically acceptable diluent or carrier

22 A composition according to claim 19 or claim 21 wherein the HMG Co-A reductase
inhibitor is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or
15 a prodrug thereof.

23 A composition according to claim 19 or claim 21 wherein the HMG Co-A reductase
inhibitor is rosuvastatin, or a pharmaceutically acceptable salt thereof.

20 24 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
claimed in any one of claims 1 to 11 and a PPAR alpha and/or gamma agonist, or a
pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable
diluent or carrier

25 25 A composition according to claim 24 wherein the PPAR alpha and/or gamma agonist
is (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid or a
pharmaceutically acceptable salt thereof

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INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 02/04033

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/554 C07D285/36 A61P3/06 C07D281/02 C07K5/065
C07K5/087 A61K38/05 A61K38/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D C07K

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

Electronic data bases consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Referred to claim No.
A	WO 00 47568 A (GD SEARLE & CO (US)) 17 August 2000 (2000-08-17) cited in the application the whole document	1-25
A	WO 98 38182 A (GLAXO GROUP LTD (GB)) 3 September 1998 (1998-09-03) cited in the application the whole document	1-25
P,A	WO 01 66533 A (ASTRAZENECA UK LTD (UK)) 13 September 2001 (2001-09-13) the whole document	1-25
P,A	WO 02 50051 A (ASTRAZENECA UK LTD (UK)) 27 June 2002 (2002-06-27) the whole document	1-25

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

Special categories of cited documents

A document defining the general state of the art which is not considered to be of particular relevance

E⁺ earlier document but published on or after the international filing date

L document which may throw doubts on priority claims or which is cited to establish the publication date of another claim or other special reason (as specified)

O⁺ document referring to an oral disclosure, use, exhibition or other meansP⁺ document published prior to the international filing date but later than the priority date claimedT⁺ 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 inventionX⁺ 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 aloneY⁺ document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.A⁺ document member of the same patent family

Date of the actual completion of the international search

24 October 2002

Date of mailing of the international search report

05/11/2002

Name and mailing address of the ISA

European Patent Office, P.O. Box 1618 Patentstrasse 2
NL - 8200 HV Rijswijk
Tel (+31-70) 340-5040, Tx. 91 861 opt 4,
Fax (+31-70) 340-5010

Authorized officer

Cortés, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB 02/04033

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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

1. ☒ Claims Nos. —
because they relate to subject matter not required to be searched by this Authority namely
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos. 1-25 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid specifically claims Nos. —
4. ☐ No required additional search fees were timely paid by the applicant. Consequently this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos. —

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I 1

Although claims 16 and 17 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compounds

Continuation of Box I 1

Rule 39 1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I 2

Claims Nos 1-25 (part)

The scope of the compound group defined by the functional term "prodrugs" is unclear within the meaning of Article 6 PCT, as it is not possible to assign a molecular structure to this group

For this reason it was not possible to carry out a complete search over the whole claimed scope. Those parts of the application referring to "prodrugs" have therefore not been searched

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66 1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

PCT/GB 02/04033

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0047568	A	17-08-2000	AU 3694600 A CN 1346351 T EP 1155007 A2 HU 0105409 A2 WO 0047568 A2	29-08-2000 24-04-2002 21-11-2001 29-05-2002 17-08-2000
WO 9838182	A	03-09-1998	AU 6823898 A WO 9838182 A1	18-09-1998 03-09-1998
WO 0166533	A	13-09-2001	AU 3755601 A WO 0166533 A1	17-09-2001 13-09-2001
WO 0250051	A	27-06-2002	AU 2222802 A WO 0250051 A1	01-07-2002 27-06-2002

(42) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional



(43) Fecha de Publicación Internacional
20 de marzo de 2003 (20.03 2003)

(44) Número Internacional de Publicación

PCT

WO 03/022286 A1

(51) Clasificación Internacional de Patentes⁷ A61K 31/554,
C07D 285/38, A61P 3/08 C07D 281/02 C07K 5/085
5/087 A61K 38/05 38/06

S-431 83 (SE) SKJARET, Tore [NO/SE] Molndal
S-431 83 (SE) LEMURELL, Mallin [SE/SE]
Molndal, S-431 83 (SE)

(21) No. Solicitud Internacional PCT/GB02/04033

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(22) Fecha de Presentación Internacional
5 de septiembre de 2002 (05 09 2002)

(25) Idioma de Presentación Inglés

(26) Idioma de Publicación Inglés

(30) Datos relativos a la Prioridad
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0209483 8 25 de abril de 2002 (25 04 2002) GB

(81) Países designados (nacionales) AE AG AL, AM
AT AU AZ BA, BB BG, BR BY BZ CA, CH CN
CO, CR CU CZ DE DK DM DZ EC EE ES, FI,
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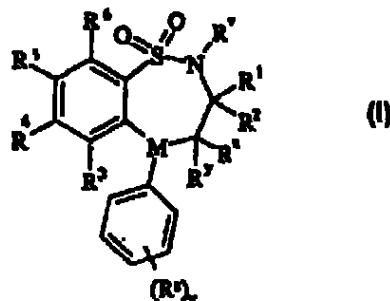
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(54) Título BENZOTIAZEPINA Y DERIVADOS DE BENZOTIADIAZEPINA CON ACTIVIDAD INHIBIDORA DE TRANSPORTE DE ÁCIDOS BILIARES EN EL ÍLEON (IBAT) PARA EL TRATAMIENTO DE HIPERLIPIDEMIA



(57) Extracto La presente invención se relaciona con compuestos de fórmula (I) en donde R¹ R², R³ R⁴ M, R⁵, v, R⁶, R⁷, R⁸ y R⁹ son como se definen allí; sales farmacéuticamente aceptables, solvatos, solvatos de tales sales y profármacos de los mismos y su uso como inhibidores de transporte de ácidos biliares en el íleon (IBAT) para el tratamiento de hiperlipidemia Asimismo se describen procesos para su manufactura y composiciones farmacéuticas que los contienen

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**DERIVADOS DE BENZOTIAZEPINA Y BENZOTIADIAZEPINA
CON ACTIVIDAD INHIBIDORA DE TRANSPORTE DE ÁCIDOS
BILIARES EN EL ÍLEON (IBAT) PARA EL TRATAMIENTO DE
HIPERLIPIDEMIA**

Esta invención se relaciona con derivados de benzotiazepina y benzotiadiazepina, o sus sales de aceptación farmacéutica, solvatos, solvatos de dichas sales y profármacos. Estas benzotiazepinas y benzotiadiazepinas poseen actividad inhibidora de transporte de ácidos biliares en el íleon (IBAT) y, por consiguiente, tienen utilidad en el tratamiento de estados patológicos asociados con condiciones hiperlipídicas y son útiles en métodos de tratamiento de un animal de sangre caliente, tal como el hombre. La invención se relaciona igualmente con procesos para la manufactura de dichos derivados de benzotiazepina y benzotiadiazepina, con composiciones farmacéuticas que los contienen y con su uso en la manufactura de medicamentos para inhibir IBAT en un animal de sangre caliente, tal como el hombre.

Es bien sabido que condiciones hiperlipídicas asociadas con concentraciones elevadas de colesterol total y colesterol de lipoproteína de baja densidad son importantes factores de riesgo para enfermedad aterosclerótica cardiovascular (por ejemplo "Coronary Heart Disease Reducing the Risk, a Worldwide View" Assman G., Carmena R. Cullen P y colaboradores, *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, y colaboradores, *Circulation*, 1999, 100, 1134-46). Se encontró que interferir la circulación de ácidos biliares en el lumen de los tractos intestinales reduce el nivel de colesterol. Terapias previas establecidas para reducir la concentración de colesterol implican, por ejemplo, tratamiento con inhibidores de HMG-CoA reductasa, preferiblemente estatinas tales como simvastatina y fluvastatina, o tratamiento con barredores de ácidos biliares, tales como resinas. Barredores de ácidos biliares de uso frecuente

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son, por ejemplo, colestiramina y colestipol. Una terapia recientemente propuesta ("Bile Acids and Lipoprotein Metabolism: a Renaissance for "Bile Acids in the Post Statin Era" Angelin B, Eriksson M, Rudling M, Current Opinion on Lipidology, 1999,10, 269-74) implicaba el tratamiento con sustancias con un efecto inhibitorio IBAT.

La reabsorción de ácido biliar del tracto gastrointestinal es un proceso fisiológico normal que tiene lugar principalmente en el íleon por el mecanismo IBAT. Inhibidores de IBAT pueden utilizarse en el tratamiento de hipercolesterolemia (véase, por ejemplo "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolaemic properties", Biochimica et Biophysica Acta, 1210 (1994) 255- 287). Así pues, compuestos apropiados que poseen dicha actividad inhibidora IBAT son también útiles en el tratamiento de condiciones hiperlipídicas.

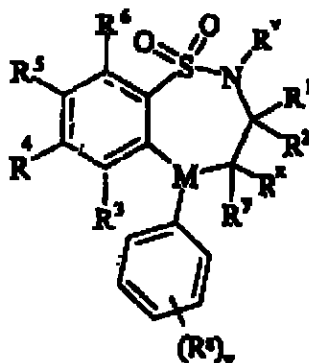
Se han descrito compuestos sustituidos que poseen dicha actividad inhibidora IBAT, véase, por ejemplo, compuestos hipolipídicos descritos en WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/05484, WO 96/16051, WO 97/33882, WO 98/38182, WO 99/35135, WO 99/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, y EP 0 854 582.

Un aspecto adicional de esta invención se relaciona con el uso de los compuestos de la invención en el tratamiento de condiciones dislipídicas y trastornos tales como hiperlipidemia, hipertrigliceridemia, hiperbetalipoproteinemia (LDL alta), hiperprebetalipoproteinemia (VLDL alta), hiperquilomicronemia, hipolipoproteinemia, hipercolesterolemia, hiperlipoproteinemia e hipoalfalipoproteinemia (HDL baja). Adicionalmente, se espera que estos compuestos sean útiles para la prevención y tratamiento de diferentes condiciones clínicas tales como aterosclerosis, arteriosclerosis, arritmia, condiciones hiper-trombóticas, 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, estrias 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

La presente invención se basa en el descubrimiento de que ciertos compuestos de benzotiazepina inhiben sorprendentemente el IBAT. Se espera que dichas propiedades tengan utilidad en el tratamiento de estados patológicos asociados con condiciones hiperlipídicas.

Por consiguiente, la presente invención provee un compuesto de fórmula (I)



(I)

en donde

R^v se selecciona de hidrógeno o C_{1-6} alquilo,

uno de R^1 y R^2 se seleccionan de hidrógeno o C_{1-6} alquilo o C_{2-6} alquénilo y el otro se selecciona de C_{1-6} alquilo o C_{2-6} alquénilo,

R^3 y R^7 se seleccionan independientemente de hidrógeno, hidroxilo, amino, mercapto, C_{1-6} alquilo, C_{1-6} alcoxilo, N -(C_{1-6} alquil)amino, N,N -(C_{1-6} alquil) $_2$ amino, C_{1-6} alquilS(O) $_a$ en donde a es 0 a 2,

M se selecciona de $-N-$ o $-CH-$,

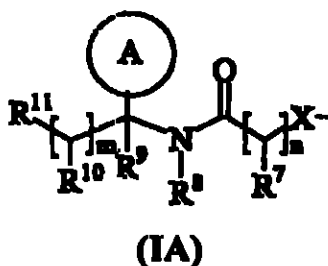
R^8 se selecciona de halo, nitrógeno, ciano, hidroxilo, amino, carboxilo, carbonilo, mercapto, sulfamilo, C_{1-6} alquilo, C_{2-6} alquénilo, C_{2-6} alquínilo, C_{1-6} alcoxilo, C_{1-6} alcanoilo, C_{1-6} alcanoiloxilo, N -(C_{1-6} alquil)amino, N,N -(C_{1-6} alquil) $_2$ amino,

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$\text{C}_{1-6}\text{alquil})_2\text{amino}$, $\text{C}_{1-6}\text{alcanoilamino}$, $N-(\text{C}_{1-6}\text{alquil})\text{carbamoilo}$, $N,N-(\text{C}_{1-6}\text{alquil})_2\text{carbamoilo}$, $\text{C}_{1-6}\text{alquilS}(\text{O})_a$ en donde a es 0 a 2, $\text{C}_{1-6}\text{alcoxycarbonilo}$, $N-(\text{C}_{1-6}\text{alquil})\text{sulfamoilo}$ y $N,N-(\text{C}_{1-6}\text{alquil})_2\text{sulfamoilo}$,

v es 0-5,

uno de R^4 y R^5 es un grupo de formula (IA)



R^3 y R^6 y los demás de R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, $\text{C}_{1-4}\text{alquilo}$, $\text{C}_{2-4}\text{alquenilo}$, $\text{C}_{2-4}\text{alquinilo}$, $\text{C}_{1-4}\text{alcoxilo}$, $\text{C}_{1-4}\text{alcanoilo}$, $\text{C}_{1-4}\text{alcanoiloxilo}$, $N-(\text{C}_{1-4}\text{alquil})\text{amino}$, $N,N-(\text{C}_{1-4}\text{alquil})_2\text{amino}$, $\text{C}_{1-4}\text{alcanoilamino}$, $N-(\text{C}_{1-4}\text{alquil})\text{carbamoilo}$, $N,N-(\text{C}_{1-4}\text{alquil})_2\text{carbamoilo}$, $\text{C}_{1-4}\text{alquilS}(\text{O})_a$ en donde a es 0 a 2, $\text{C}_{1-4}\text{alcoxycarbonilo}$, $N-(\text{C}_{1-4}\text{alquil})\text{sulfamoilo}$ y $N,N-(\text{C}_{1-4}\text{alquil})_2\text{sulfamoilo}$, en donde R^3 y R^6 y los demás de R^4 y R^5 pueden sustituirse opcionalmente en carbono por uno o mas R^{16} ,

X es $-\text{O}-$, $-\text{N}(\text{R}^a)-$, $-\text{S}(\text{O})_b-$ o $-\text{CH}(\text{R}^a)-$; en donde R^a es hidrógeno o $\text{C}_{1-6}\text{alquilo}$ y b es 0-2,

Anillo A es arilo o heteroarilo, en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{17} ,

R^7 es hidrogeno, $\text{C}_{1-4}\text{alquilo}$, carbociclilo o heterociclilo, en donde R^7 se sustituye opcionalmente por uno o mas sustituyentes seleccionados de R^{18} ,

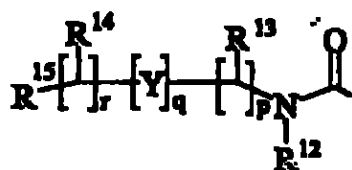
R^8 es hidrógeno o $\text{C}_{1-4}\text{alquilo}$,

R^9 es hidrogeno o $\text{C}_{1-4}\text{alquilo}$,

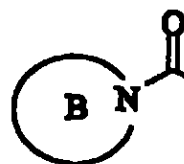
R^{10} es hidrogeno, $\text{C}_{1-4}\text{alquilo}$, carbociclilo o heterociclilo, en donde R^{10} se sustituye opcionalmente por uno o mas sustituyentes seleccionados de R^{19} ,

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R^{11} es carboxi, sulfo, sulfino, fosfona, $-P(O)(OR^e)(OR^d)$, $-P(O)(OH)(OR^e)$, $-P(O)(OH)(OR^d)$ o $-P(O)(OR^e)(R^d)$ en donde R^e y R^d se seleccionan independientemente de C_{1-6} alquilo, o R^{11} es un grupo de fórmula (IB) o (IC)



(IB)



(IC)

en donde,

Y es $-N(R^n)-$, $-N(R^n)C(O)-$, $-N(R^n)C(O)(CR^sR^t)_vN(R^n)C(O)-$, $-O-$, y $-S(O)_a-$, en donde a es 0-2, v es 1-2, R^s y R^t se seleccionan independientemente de hidrogeno o C_{1-4} alquilo opcionalmente sustituido por R^{26} y R^n es hidrógeno o C_{1-4} alquilo,

R^{12} es hidrógeno o C_{1-4} alquilo,

R^{13} y R^{14} se seleccionan independientemente de hidrogeno, C_{1-6} alquilo, carbociclilo o heterociclilo, y cuando q es 0, R^{14} puede seleccionarse adicionalmente de hidroxilo, en donde R^{13} y R^{14} puede sustituirse independientemente en forma opcional por uno o mas sustituyentes seleccionados de R^{20} ,

R^{15} es carboxi, sulfo, sulfino, fosfona, $-P(O)(OR^e)(OR^f)$, $-P(O)(OH)(OR^e)$, $-P(O)(OH)(R^f)$ o $-P(O)(OR^e)(R^f)$ en donde R^e y R^f se seleccionan independientemente de C_{1-6} alquilo,

p es 1-3, en donde los valores de R^{13} pueden ser los mismos o diferentes,

q es 0-1,

r es 0-3, en donde los valores de R^{14} pueden ser los mismos o diferentes,

m es 0-2, en donde los valores de R^{10} pueden ser los mismos o diferentes,

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n es 1-3, en donde los valores de R^7 pueden ser los mismos o diferentes,

Anillo B es un heterociclilo enlazado a nitrógeno sustituido en carbono por un grupo seleccionado de R^{23} , y sustituido opcionalmente de manera adicional en carbono por uno o mas R^{24} , y en donde si dicho heterociclilo enlazado a nitrógeno contiene una fracción -NH-, ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de R^{25} ,

R^{16} , R^{17} y R^{18} se seleccionan independientemente de halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, C_1 alquilo, C_{2-4} alquenilo, C_{2-4} alquínilo, C_{1-4} alcoxilo, C_{1-4} alcanoilo, C_{1-4} alcanoiloxilo, N -(C_{1-4} alquil)amino, N,N -(C_{1-4} alquil) $_2$ amino, C_{1-4} alcanoilamino, N -(C_{1-4} alquil)carbamoilo, N,N -(C_{1-4} alquil) $_2$ carbamoilo, C_{1-4} alquilS(O) $_a$ en donde a es 0 a 2, C_{1-4} alcoxycarbonilo, N -(C_{1-4} alquil)sulfamoilo y N,N -(C_{1-4} alquil) $_2$ sulfamoilo, en donde R^{16} , R^{17} y R^{18} pueden sustituirse independientemente en forma opcional en carbono por uno o mas R^{21} ,

R^{19} y R^{20} , R^{24} y R^{26} se seleccionan independientemente de halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, C_1 alquilo, C_{2-4} alquenilo, C_{2-4} alquínilo, C_{1-4} alcoxilo, C_{1-4} alcanoilo, C_{1-4} alcanoiloxilo, N -(C_{1-4} alquil)amino, N,N -(C_{1-4} alquil) $_2$ amino, C_{1-4} alcanoilamino, N -(C_{1-4} alquil)carbamoilo, N,N -(C_{1-4} alquil) $_2$ carbamoilo, C_{1-4} alquilS(O) $_a$ en donde a es 0 a 2, C_{1-4} alcoxycarbonilo, N -(C_{1-4} alquil) $_2$ sulfamoilo, N,N -(C_{1-4} alquil) $_2$ sulfamoilo, carbociclilo, heterociclilo, benciloxycarbonilamino, sulfo, sulfino, amidino, fosfono, $-P(O)(OR^a)(OR^b)$, $-P(O)(OH)(OR^a)$, $-P(O)(OH)(R^a)$ o $-P(O)(OR^a)(R^b)$, en donde R^a y R^b se seleccionan independientemente de C_{1-4} alquilo, en donde R^{19} y R^{20} , R^{24} y R^{26} pueden sustituirse independientemente en forma opcional en carbono por uno o más R^{22} ,

R^{21} y R^{22} se seleccionan independientemente de halo, hidroxilo, ciano, carbamoilo, ureido, amino, nitro, carboxilo, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxilo, metilo, etilo, metoxilo, etoxilo,

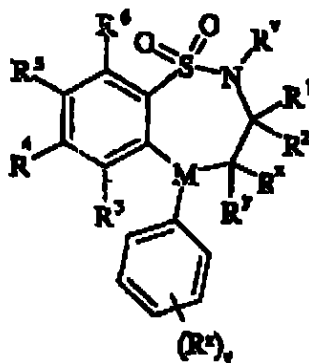
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vinilo, alilo, etinilo, metoxycarbonilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino dimetilamino, *N*-metilcarbamoilo, *N,N*-dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, *N*-metilsulfamoilo y *N,N*-dimetilsulfamoilo,

R^{23} es carboxi, sulfo, sulfino, fosfono, $-P(O)(OR^s)(OR^h)$, $-P(O)(OH)(OR^s)$, $-P(O)(OH)(R^s)$ o $-P(O)(OR^s)(R^h)$, en donde R^s y R^h se seleccionan independientemente de C_{1-6} alquilo,

R^{25} se selecciona de C_{1-6} alquilo, C_{1-6} alcanoilo, C_{1-6} alquilsulfonilo, C_{1-6} alcoxycarbonilo, carbamoilo, *N*-(C_{1-6} alquil)carbamoilo, *N,N*-(C_{1-6} alquil)carbamoilo, bencilo, benciloxycarbonilo, benzoilo y fenilsulfonilo, o su sal de aceptación farmaceutica, solvato, solvato de dicha sal o profarmaco

De acuerdo con un aspecto adicional de la presente invencion se provee un compuesto de formula (I)



(I)

en donde

R^v se selecciona de hidrogeno o C_{1-6} alquilo,

uno de R^1 y R^2 se seleccionan de hidrógeno o C_{1-6} alquilo y el otro se selecciona de C_{1-6} alquilo,

uno de R^3 y R^7 se seleccionan independientemente de hidrogeno, hidroxí, amino, mercapto, C_{1-6} alquilo, C_{1-6} alcoxi, *N*-(C_{1-6} alquil)amino, *N,N*-(C_{1-6} alquil)₂amino, C_{1-6} alquilS(O)_a, en donde a es 0 a 2,

M se selecciona de -N- o -CH-,

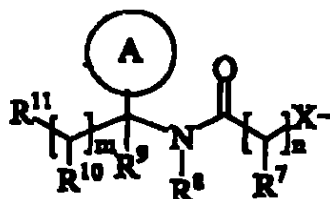
R^2 se selecciona de halo, nitro, ciano, hidroxí, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo,

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C_{1-6} alcanoilo, C_{1-6} alcanoiloxi, N -(C_{1-6} alquil)amino, N,N -(C_{1-6} alquil) $_2$ amino, C_{1-6} alcanoilamino, N -(C_{1-6} alquil)carbamoilo, N,N -(C_{1-6} alquil) $_2$ carbamoilo, C_{1-6} alquilS(O) $_a$ en donde a es 0 a 2, C_{1-6} alcoxycarbonilo, N -(C_{1-6} alquil)sulfamoilo y N,N -(C_{1-6} alquil) $_2$ sulfamoilo,

y es 0-5,

uno de R^4 y R^5 es un grupo de formula (IA)



(IA)

R^3 y R^6 y los demas de R^4 y R^5 se seleccionan independientemente de hidrogeno, halo, nitro, cloro, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, C_{1-4} alquilo, C_{2-4} alquenilo, C_{2-4} alquinilo, C_{1-4} alcoxi, C_{1-4} alcanoilo, C_{1-4} alcanoiloxi, N -(C_{1-4} alquil)amino, N,N -(C_{1-4} alquil) $_2$ amino, C_{1-4} alcanoilamino, N -(C_{1-4} alquil)carbamoilo, N,N -(C_{1-4} alquil) $_2$ carbamoilo, C_{1-4} alquilS(O) $_a$ en donde a es 0 a 2, C_{1-4} alcoxycarbonilo, N -(C_{1-4} alquil)sulfamoilo y N,N -(C_{1-4} alquil) $_2$ sulfamoilo, en donde R^3 y R^6 y los demas de R^4 y R^5 pueden sustituirse opcionalmente en carbono por uno o mas R^{16} ,

X es -O-, -N(R^a)-, -S(O) $_b$ - o -CH(R^a)-, en donde R^a es hidrogeno o C_{1-6} alquilo y b es 0-2,

Anillo A es arilo o heteroarilo, en donde Anillo A se sustituye opcionalmente por uno o mas sustituyentes seleccionados de R^{17} ,

R^7 es hidrógeno, C_{1-4} alquilo carbociclilo o heterociclilo, en donde R^7 se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{18} ,

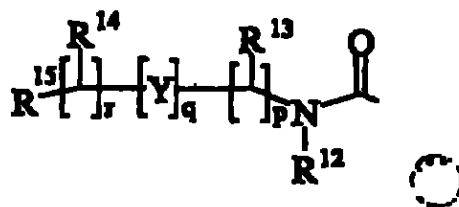
R^8 es hidrógeno o C_{1-4} alquilo,

R^9 es hidrogeno o C_{1-4} alquilo,

R^{10} es hidrógeno, C_{1-4} alquilo, carbociclilo o heterociclilo, en donde R^{10} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{19} ,

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R^{11} es carboxi, sulfo, sulfino, fosfona, $-P(O)(OR^c)(OR^d)$, $-P(O)(OH)(OR^c)$, $-P(O)(OH)(R^d)$ o $-P(O)(OR^c)(R^d)$ en donde R^c y R^d se seleccionan independientemente de C_{1-6} alquilo, o R^{11} es un grupo de formula (IB):



(IB)

en donde

Y es $-N(R^n)-$, $-N(R^n)C(O)-$, $-O-$, y $-S(O)_a-$, en donde a es 0-2 y R^n es hidrogeno o C_{1-4} alquilo,

R^{12} es hidrógeno o C_{1-4} alquilo,

R^{13} y R^{14} se seleccionan independientemente de hidrógeno, C_{1-4} alquilo, carbociclilo o heterociclilo; en donde R^{13} y R^{14} pueden sustituirse independientemente de manera opcional por uno o más sustituyentes seleccionados de R^{20} ,

R^{15} es carboxi, sulfo, sulfino, fosfona, $-P(O)(OR^e)(OR^f)$, $-P(O)(OH)(OR^e)$, $-P(O)(OH)(R^f)$ o $-P(O)(OR^e)(R^f)$ en donde R^e y R^f se seleccionan independientemente de C_{1-6} alquilo,

p es 1-3, en donde los valores de R^{13} pueden ser los mismos o diferentes,

q es 0-1,

r es 0-3, en donde los valores de R^{14} pueden ser los mismos o diferentes,

m es 0-2, en donde los valores de R^{10} pueden ser los mismos o diferentes,

n es 1-3, en donde los valores de R^7 pueden ser los mismos o diferentes,

R^{16} , R^{17} y R^{18} se seleccionan independientemente de halo, nitro, ciano, hidroxilo, amino, carboxi, carbamilo, mercapto, sulfamilo, C_{1-}

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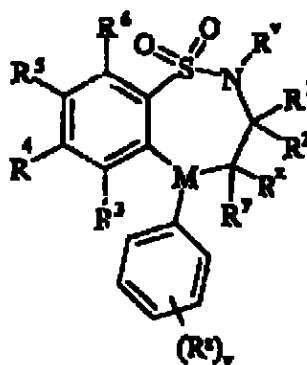
C_{1-4} alquilo, C_{2-4} alquenilo, C_{2-4} alquinilo, C_{1-4} alcoxi, C_{1-4} alcanoilo, C_{1-4} alcanoiloxi, $N-(C_{1-4}alquil)amino$, $N,N-(C_{1-4}alquil)_2amino$, $C_{1-4}alcanoilamino$, $N-(C_{1-4}alquil)carbamoilo$, $N,N-(C_{1-4}alquil)_2carbamoilo$, $C_{1-4}alquilS(O)_n$ en donde n es 0 a 2, $C_{1-4}alcoxycarbonilo$, $N-(C_{1-4}alquil)sulfamoilo$ y $N,N-(C_{1-4}alquil)_2sulfamoilo$, en donde R^{16} , R^{17} y R^{18} pueden sustituirse independientemente en forma opcional en carbono por uno o mas R^{21} ,

R^{19} y R^{20} se seleccionan independientemente de halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, C_{1-4} alquilo, C_{2-4} alquenilo, C_{2-4} alquinilo, C_{1-4} alcoxi, C_{1-4} alcanoilo, C_{1-4} alcanoiloxi, $N-(C_{1-4}alquil)amino$, $N,N-(C_{1-4}alquil)_2amino$, $C_{1-4}alcanoilamino$, $N-(C_{1-4}alquil)carbamoilo$, $N,N-(C_{1-4}alquil)_2carbamoilo$, $C_{1-4}alquilS(O)_n$ en donde n es 0 a 2, $C_{1-4}alcoxycarbonilo$, $N-(C_{1-4}alquil)sulfamoilo$ y $N,N-(C_{1-4}alquil)_2sulfamoilo$, carbociclilo, heterociclilo, sulfo, sulfino, amidino, fosfono, $-P(O)(OR^a)(OR^b)$, $-P(O)(OH)(OR^a)$, $-P(O)(OH)(R^a)$ o $-P(O)(OR^a)(R^b)$, en donde R^a y R^b se seleccionan independientemente de C_{1-4} alquilo, en donde R^{19} y R^{20} pueden sustituirse independientemente en forma opcional en carbono por uno o más R^{22} ,

R^{21} y R^{22} se seleccionan independientemente de halo, hidroxilo, ciano, carbamoilo, ureido, amino, nitro, carboxilo, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxycarbonilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, N -metilcarbamoilo, N,N -dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, N -metilsulfamoilo y N,N -dimetilsulfamoilo,

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profarmaco

De acuerdo con un aspecto adicional de la presente invencion se provee un compuesto de formula (I).

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(I)

en donde

R^v se selecciona de hidrógeno o C_{1-6} alquilo,

uno de R^1 y R^2 se seleccionan de hidrógeno o C_{1-6} alquilo y el otro se selecciona de C_{1-6} alquilo,

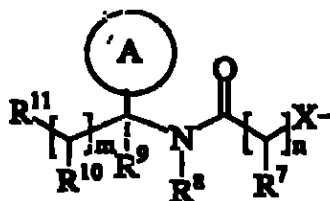
R^3 y R^4 se seleccionan independientemente de hidrógeno, hidroxilo, amino, mercapto, C_{1-6} alquilo, C_{1-6} alcoxi, N -(C_{1-6} alquil)amino, N,N -(C_{1-6} alquil) $_2$ amino, C_{1-6} alquilS(O) $_a$ en donde a es 0 a 2,

M se selecciona de $-N-$ o $-CH-$,

R^5 se selecciona de halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} alcoxi, C_{1-6} alcanoilo, C_{1-6} alcanoiloxi, N -(C_{1-6} alquil)amino, N,N -(C_{1-6} alquil) $_2$ amino, C_{1-6} alcanoilamino, N -(C_{1-6} alquil)carbamoilo, N,N -(C_{1-6} alquil) $_2$ carbamoilo, C_{1-6} alquilS(O) $_a$ en donde a es 0 a 2, C_{1-6} alcoxicarbonilo, N -(C_{1-6} alquil)sulfamoilo y N,N -(C_{1-6} alquil) $_2$ sulfamoilo,

v es 0-5,

uno de R^4 y R^5 es un grupo de formula (IA)



(IA)

R^3 y R^6 y los demás de R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, C_{1-4} alquilo, C_{2-4} alquenilo, C_{2-4} alquinilo, C_{1-4} alcoxi, C_{1-4} alcanoilo, C_{1-4} alcanoiloxi, N -(C_{1-4} alquil)amino, N,N -(C_{1-4} alquil) $_2$ amino,

C_{1-4} alcanoilamino, $N-(C_{1-4}alquilo)carbamoilo$, $N,N-(C_{1-4}alquilo)_2carbamoilo$, $C_{1-4}alquiloS(O)_a$ en donde a es 0 a 2, $C_{1-4}alcoxycarbonilo$, $N-(C_{1-4}alquilo)sulfamoilo$ y $N,N-(C_{1-4}alquilo)_2sulfamoilo$, en donde R^3 y R^6 y los demás de R^4 y R^5 pueden sustituirse opcionalmente en carbono por uno o mas R^{16} ,

X es $-O-$, $-N(R^a)-$, $-S(O)_b-$ o $-CH(R^a)-$, en donde R^a es hidrógeno o $C_{1-6}alquilo$ y b es 0-2,

Anillo A es arilo o heteroarilo, en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{17} ,

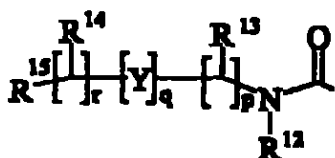
R^7 es hidrógeno, $C_{1-4}alquilo$, carbociclilo o heterociclilo, en donde R^7 se sustituye opcionalmente por uno o mas sustituyentes seleccionados de R^{18} ,

R^8 es hidrogeno o $C_{1-4}alquilo$,

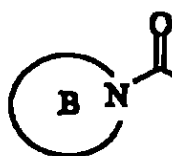
R^9 es hidrógeno o $C_{1-4}alquilo$,

R^{10} es hidrógeno, $C_{1-4}alquilo$, carbociclilo o heterociclilo, en donde R^{10} se sustituye opcionalmente por uno o mas sustituyentes seleccionados de R^{19} ,

R^{11} es carboxi, sulfo, sulfino, fosfono, $-P(O)(OR^c)(OR^d)$, $-P(O)(OH)(OR^c)$, $-P(O)(OH)(R^d)$ o $-P(O)(OR^c)(R^d)$ en donde R^c y R^d se seleccionan independientemente de $C_{1-6}alquilo$, o R^{11} es un grupo de fórmula (IB) o (IC)



(IB)



(IC)

en donde,

Y es $-N(R^n)-$, $-N(R^n)C(O)-$, $-N(R^n)C(O)(CR^sR^t)-$, $-N(R^n)C(O)-$, $-O-$, y $-S(O)_a-$, en donde a es 0-2, v es 1-2, R^s y R^t se seleccionan independientemente de hidrógeno o $C_{1-4}alquilo$ opcionalmente sustituido por R^{26} y R^n es hidrógeno o $C_{1-4}alquilo$,

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X

R^{12} es hidrogeno o C_{1-4} alquilo,

R^{13} y R^{14} se seleccionan independientemente de hidrógeno, C_{1-4} alquilo, carbociclilo o heterociclilo, en donde R^{13} y R^{14} puede sustituirse independientemente en forma opcional por uno o más sustituyentes seleccionados de R^{20} ,

R^{15} es carboxi, sulfo, sulfino, fosfona, $-P(O)(OR^e)(OR^f)$, $-P(O)(OH)(OR^e)$, $-P(O)(OH)(R^f)$ o $-P(O)(OR^e)(R^f)$ en donde R^e y R^f se seleccionan independientemente de C_{1-4} alquilo,

p es 1-3, en donde los valores de R^{13} pueden ser los mismos o diferentes,

q es 0-1,

r es 0-3, en donde los valores de R^{14} pueden ser los mismos o diferentes,

m es 0-2, en donde los valores de R^{10} pueden ser los mismos o diferentes,

n es 1-3, en donde los valores de R^7 pueden ser los mismos o diferentes,

Anillo B es un heterociclilo enlazado a nitrógeno sustituido en carbono por un grupo seleccionado de R^{23} , y sustituido opcionalmente de manera adicional en carbono por uno o más R^{24} , y en donde si dicho heterociclilo enlazado a nitrógeno contiene una fracción $-NH-$, ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de R^{25} ,

R^{16} , R^{17} y R^{18} se seleccionan independientemente de halo, nitro, ciano, hidroxil, amino, carboxil, carbamoilo, mercapto, sulfamoilo, C_{1-4} alquilo, C_{2-4} alquenilo, C_{2-4} alquinilo, C_{1-4} alcoxil, C_{1-4} alcanoilo, C_{1-4} alcanoiloxil, $N-(C_{1-4}alquil)amino$, $N,N-(C_{1-4}alquil)_2amino$, $C_{1-4}alcanoilamino$, $N-(C_{1-4}alquil)carbamoilo$, $N,N-(C_{1-4}alquil)_2carbamoilo$, $C_{1-4}alquilS(O)_a$ en donde a es 0 a 2, $C_{1-4}alcoxycarbonilo$, $N-(C_{1-4}alquil)sulfamoilo$ y $N,N-(C_{1-4}alquil)_2sulfamoilo$, en donde R^{16} , R^{17} y R^{18} pueden sustituirse independientemente en forma opcional en carbono por uno o mas R^{21} ,

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R^{19} y R^{20} , R^{24} y R^{26} se seleccionan independientemente de halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, C_{1-4} alquilo, C_{2-4} alquenilo, C_{2-4} alquinilo, C_{1-4} alcoxi, C_{1-4} alcanoilo, C_{1-4} alcanoiloxi, N -(C_{1-4} alquil)amino, N,N -(C_{1-4} alquil) $_2$ amino, C_{1-4} alcanoilamino, N -(C_{1-4} alquil)carbamoilo, N,N -(C_{1-4} alquil) $_2$ carbamoilo, C_{1-4} alquilS(O) $_a$ en donde a es 0 a 2, C_{1-4} alcoxycarbonilo, N -(C_{1-4} alquil) $_2$ sulfamoilo, N,N -(C_{1-4} alquil) $_2$ sulfamoilo, carbociclilo, heterociclilo, benciloxycarbonilamino, sulfo, sulfinilo, amidino, fosfono, $-P(O)(OR^a)(OR^b)$, $-P(O)(OH)(OR^a)$, $-P(O)(OH)(R^b)$ o $-P(O)(OR^a)(R^b)$, en donde R^a y R^b se seleccionan independientemente de C_{1-6} alquilo, en donde R^{19} y R^{20} , R^{24} y R^{26} pueden sustituirse independientemente en forma opcional en carbono por uno o mas R^{22} ,

R^{21} y R^{22} se seleccionan independientemente de halo, hidroxilo, ciano, carbamoilo, ureido, amino, nitro, carboxilo, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxycarbonilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, N -metilcarbamoilo, N,N -dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, N -metilsulfamoilo y N,N -dimetilsulfamoilo,

R^{23} es carboxilo, sulfo, sulfinilo, fosfono, $-P(O)(OR^g)(OR^h)$, $-P(O)(OH)(OR^g)$, $-P(O)(OH)(R^h)$ o $-P(O)(OR^g)(R^h)$, en donde R^g y R^h se seleccionan independientemente de C_{1-6} alquilo,

R^{25} se selecciona de C_{1-6} alquilo, C_{1-6} alcanoilo, C_{1-6} alquilsulfonilo, C_{1-6} alcoxycarbonilo, carbamoilo, N -(C_{1-6} alquil)carbamoilo, N,N -(C_{1-6} alquil) $_2$ carbamoilo, bencilo, benciloxycarbonilo, benzoilo y fenilsulfonilo, o su sal de aceptacion farmacéutica, solvato, solvato de dicha sal o profarmaco

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 ramificada unicamente. Por ejemplo, " C_{1-6} alquilo" incluye C_{1-4} alquilo, C_{1-6} alquilo, propilo, isopropilo y t -butilo. Sin embargo, referencias a grupos

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M
X

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 "fenilC₁₋₆alquilo" incluiría fenilC₁₋₆alquilo, 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.

"Heteroarilo" es un anillo mono o bicíclico, totalmente insaturado, que contiene 3-12 átomos de los cuales por lo menos un átomo se escoge de nitrógeno, azufre u oxígeno que, a menos que se especifique lo contrario, puede enlazarse con carbono o nitrógeno. Preferiblemente "heteroarilo" se refiere a un anillo monocíclico totalmente insaturado que contiene 5 o 6 átomos o un anillo bicíclico que contiene 9 o 10 átomos de los cuales por lo menos un átomo se escoge de nitrógeno, azufre u oxígeno que, a menos que se especifique lo contrario, puede enlazarse con carbono o nitrógeno. Ejemplos y valores apropiados del término "heteroarilo" son tienilo, isoxazolilo, imidazolilo, pirrolilo, tiadiazolilo, isotiazolilo, triazolilo, piranilo, indolilo, pirimidilo, pirazinilo, piridazínilo, piridilo, y quinolilo. Preferiblemente el término "heteroarilo" se refiere a tienilo o indolilo.

"Ariilo" es un anillo carbono mono o bicíclico totalmente insaturado, que contiene 3-12 átomos.

Preferiblemente "arilo" es un anillo monocíclico que contiene 5 o 6 átomos o un anillo bicíclico que contiene 9 o 10 átomos. Valores apropiados para "arilo" incluyen fenilo o naftilo. Particularmente "arilo" es fenilo.

Un "heterociclilo" es un anillo mono o bicíclico saturado, parcialmente saturado o insaturado, que contiene 3-12 átomos de los cuales por lo menos un átomo se escoge de nitrógeno, azufre u oxígeno que, a menos que se especifique lo contrario, puede enlazarse con carbono o

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nitrogeno, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un $-C(O)-$ o un átomo de azufre de anillo puede oxidarse opcionalmente para formar los S-óxidos. Preferiblemente un "heterociclilo" es un anillo mono o bicíclico saturado, parcialmente saturado o insaturado, que contiene 5 o 6 átomos de los cuales por lo menos un átomo se escoge de nitrógeno, azufre u oxígeno que, a menos que se especifique lo contrario, puede enlazarse a carbono o nitrógeno, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un $-C(O)-$ o un átomo de anillo de azufre puede oxidarse opcionalmente para formar S-óxido(s). Ejemplos y valores apropiados del término "heterociclilo" son tiazolidinilo, pirrolidinilo, pirrolinilo, 2-pirrolidonilo, 2,5-dioxopirrolidinilo, 2-benzoxazolinonilo, 1,1-dioxotetrahidrotienilo, 2,4-dioxoimidazolidinilo, 2-oxo-1,3,4-(4-triazolinil), 2-oxazolidinonilo, 5,6-dihidrouracililo, 1,3-benzodioxolilo, 1,2,4-oxadiazolilo, 2-azabicyclo[2.2.1]heptil-4-tiazolidonilo, morfolino, 2-oxotetrahidrofuranilo, tetrahidrofuranilo, 2,3-dihidrobenzofuranilo, benzotienilo, tetrahidropiranilo, piperazinilo, 1-oxo-1,3 dihidropiranilo, piperazinilo, tiomorfolino, 1,1-dioxotiomorfolino, tetrahidropiranilo, 1,3-dioxolanilo, homopiperazinilo, tienilo, isoxazolilo, imidazolilo, pirrolilo, tiadiazolilo, isotiazolilo, 1,2,4-triazolilo, 1,3,4-triazolilo, piranilo, indolilo, pirimidilo, tiazolilo, pirazinilo, piridazinilo, piridilo, 4-piridonilo, quinolilo y 1-isoquinolonilo.

Un "heterociclilo enlazado con nitrógeno" es un anillo mono o bicíclico saturado, parcialmente saturado o insaturado, que contiene 3-12 átomos de los cuales por lo menos un átomo es nitrógeno y el heterociclilo se enlaza al grupo carbonilo de fórmula (IC) mediante este nitrógeno, que puede contener adicionalmente heteroátomos adicionales seleccionados de nitrógeno, azufre u oxígeno, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un $-C(O)-$ o un átomo de azufre de anillo puede oxidarse opcionalmente para formar los S-óxidos. Preferiblemente un "heterociclilo enlazado con nitrógeno" es un anillo mono o bicíclico saturado, parcialmente saturado o insaturado, que contiene 5 o 6 átomos de los cuales por lo menos un átomo es nitrógeno y el heterociclilo se enlaza al

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grupo carbonilo de formula (IC) mediante este nitrógeno, el cual puede contener adicionalmente heteroátomos adicionales seleccionados de nitrógeno, azufre u oxígeno, en donde un grupo -CH₂- puede reemplazarse opcionalmente por un -C(O)- o un átomo de anillo de azufre puede oxidarse opcionalmente para formar S-óxido(s). Ejemplos y valores apropiados del termino "heterociclilo enlazado con nitrógeno" son morfolino, pirrolidin-1-ilo, imidazol-1-ilo, pirazolidin-1-ilo, piperidin-1-ilo y piperazin-1-ilo. Particularmente un "heterociclilo enlazado con nitrógeno" es pirrolin-1-ilo.

Un "carbociclilo" es un anillo carbono mono o biciclico saturado, parcialmente saturado o insaturado, que contiene 3-12 átomos, en donde un grupo -CH₂- puede reemplazarse opcionalmente por un -C(O)-. Preferiblemente "carbociclilo" es un anillo monocíclico que contiene 5 o 6 átomos o un anillo biciclico que contiene 9 o 10 átomos. Valores apropiados para "carbociclilo" incluyen ciclopropilo, ciclobutilo, 1-oxociclopentilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexenilo, fenilo, naftilo, tetralinilo, indanilo o 1-oxoindanilo. Particularmente "carbociclilo" es ciclopropilo, ciclobutilo, 1-oxociclopentilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexenilo, fenilo o 1-oxoindanilo.

Un ejemplo de "C₁₋₆alcanoiloxi" y "C₁₋₄alcanoiloxi" es acetoxi. Ejemplos de "C₁₋₆alcoxycarbonilo" y "C₁₋₄alcoxycarbonilo" incluyen metoxycarbonilo, etoxycarbonilo, *n*- y *t*-butoxycarbonilo. Ejemplos de "C₁₋₆alcoxi" y "C₁₋₄alcoxi" incluyen metoxi, etoxi y propoxi. Ejemplos de "C₁₋₆alcanoilamino" y "C₁₋₄alcanoilamino" incluyen formamido, acetamido y propionilamino. Ejemplos de "C₁₋₆alquilS(O)_a" en donde a es 0 a 2" y "C₁₋₄alquilS(O)_a" en donde a es 0 a 2" incluyen metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo y etilsulfonilo. Ejemplos de "C₁₋₆alcanoilo" y "C₁₋₄alcanoilo" incluyen C₁₋₃alcanoilo, propionilo y acetilo. Ejemplos de "N-(C₁₋₆alquil)amino" y "N-(C₁₋₄alquil)amino" incluyen metilamino y etilamino. Ejemplos de "N,N-(C₁₋₆alquil)₂amino" y "N,N-(C₁₋₄alquil)₂amino" incluyen di-N-metilamino, di-(N-etil)amino y N-etil-N-metilamino. Ejemplos de "C₂₋₆alquenilo" y "C₂₋₄alquenilo" son vinilo, alilo y 1-propenilo. Ejemplos de "C₂₋₆alquinilo" y "C₂₋₄alquinilo" son etinilo, 1-propinilo y 2-propinilo.

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Ejemplos de " $N-(C_{1-6}\text{alquil})\text{sulfamoilo}$ " y " $N-(C_{1-4}\text{alquil})\text{sulfamoilo}$ " son $N-(C_{1-3}\text{alquil})\text{sulfamoilo}$, $N-(\text{metil})\text{sulfamoilo}$ y $N-(\text{etil})\text{sulfamoilo}$. Ejemplos de " $N-(C_{1-6}\text{alquil})_2\text{sulfamoilo}$ " y " $N-(C_{1-4}\text{alquil})_2\text{sulfamoilo}$ " son $N,N-(\text{dimetil})\text{sulfamoilo}$ y $N-(\text{metil})-N-(\text{etil})\text{sulfamoilo}$. Ejemplos de " $N-(C_{1-6}\text{alquil})\text{carbamoilo}$ " y " $N-(C_{1-4}\text{alquil})\text{carbamoilo}$ " son metilaminocarbonilo y etilaminocarbonilo. Ejemplos de " $N,N-(C_{1-6}\text{alquil})_2\text{carbamoilo}$ " y " $N,N-(C_{1-4}\text{alquil})_2\text{carbamoilo}$ " son dimetilaminocarbonilo y metiletilaminocarbonilo. Ejemplo de " $C_{1-6}\text{alquil}\text{sulfonilo}$ " son mesilo y etilsulfonilo. Ejemplos de " $(C_{1-4}\text{alquil})_3\text{sililo}$ " comprenden trimetilsililo y metildietilsililo.

Una sal apropiada de aceptación farmacéutica de un compuesto de la invención 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, fosforico, trifluoroacético, cítrico o maleico. Además, una sal apropiada de aceptación farmacéutica de un compuesto de la invención que es suficientemente acidica es una sal de metal alcalino, por ejemplo, una sal de sodio o potasio, una sal de metal alcalinoterreo, por ejemplo, una sal de calcio o magnesio, una sal de amonio o una sal con una base orgánica que proporciona un catión de aceptación fisiológica, por ejemplo, una sal con metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina.

Los compuestos de la fórmula (I) 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) que contiene un grupo carboxi o hidroxí es, por ejemplo, un éster de aceptación farmacéutica que se hidroliza en el cuerpo humano o animal para producir el ácido o alcohol principal. Ésteres adecuados de aceptación farmacéutica para carboxi incluyen ésteres de $C_{1-6}\text{alcoximetilo}$, por ejemplo, ésteres de

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metoximetilo, C₁₋₆alcanoiloximetilo, por ejemplo, ésteres de pivaloiloiloximetilo, ftalidilo, ésteres de C₃₋₈cicloalcoxycarboniloC₁₋₆alquilo, por ejemplo, 1-ciclohexilcarboniloietilo, ésteres de 1,3-dioxolen-2-onilmetilo, por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo, u ésteres de C₁₋₆alcoxycarboniloietilo, por ejemplo 1-metoxycarboniloietilo y pueden formarse en cualquier grupo carboxi en los compuestos de esta invención

Un ester hidrolizable *in vivo* de un compuesto de la formula (I) que contiene un grupo hidroxí incluye ésteres orgánicos tales como ésteres de fosfato y éteres de α-aciloxialquilo y compuestos que como resultado de la hidrólisis *in vivo* del éster se descomponen para producir el grupo hidroxí principal. Ejemplos de éteres de α-aciloxialquilo incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi. Una selección de grupos que forman ester hidrolizable *in vivo* para hidroxí incluyen alcanilo, benzoilo, fenilacetilo y benzoilo sustituido y fenilacetilo, alcoxycarbonilo (para producir ésteres de alquil carbonato), dialquilocarbamoilo y N-(dialquilaminoetil)-N-alquilocarbamoilo (para producir carbamatos), dialquilaminoacetilo y carboxiacetilo. Ejemplos de sustituyentes en benzoilo incluyen morfolino y piperazino enlazados desde un átomo de anillo nitrógeno 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 formula (I) que contiene un grupo carboxi es, por ejemplo, una N-C₁₋₆alquil o N,N-di-C₁₋₆alquil amida tal como N-metil, N-etil, N-propil, N-dimetil, N-etil-N-metil o N,N-dietil amida.

Algunos compuestos de la formula (I) pueden tener centros quirales y/o centros isométricos geométricos (E- y Z-isómeros), y hay que entender que la invención abarca todos aquellos isómeros ópticos, diastereoisómeros e isómeros geométricos que poseen actividad inhibidora IBAT.

La invención se relaciona con cualquiera y todas las formas tautoméricas de los compuestos de la fórmula (I) que poseen actividad inhibidora IBAT.

Hay que entender igualmente que ciertos compuestos de la formula (I) pueden existir en formas solvatadas así como no solvatadas tales como,

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por ejemplo, formas hidratadas Hay que entender que invención comprende todas aquellas formas solvatadas que poseen actividad inhibidora IBAT

Valores preferidos son como sigue Dichos valores pueden usarse donde se considere apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas más arriba o mas abajo en el texto

R^y es hidrogeno

R^1 y R^2 son C_{1-4} alquilo

R^1 y R^2 son ambos butilo

Uno de R^1 y R^2 es etilo y el otro es butilo

Uno de R^x y R^y es hidrógeno y el otro es hidroxil

R^x y R^y son ambos hidrogeno

M es -N-

M es -CH-

v es 0 ó 1

v es 0

R^7 es C_{1-4} alquilo

R^3 y R^6 son hidrogeno

R^4 es metiltio o bromo

R^4 es metiltio

R^4 es halo, C_{1-4} alquilo o C_{1-4} alquilS(O)_a en donde a es 0

R^4 es bromo, metilo o metiltio

R^5 es un grupo de fórmula (IA) (como se describe anteriormente) en donde

X es -O-,

Anillo A es fenilo opcionalmente sustituido por uno o mas sustituyentes seleccionados de R^{17} ,

n es 1,

R^7 es hidrógeno,

R^8 es hidrógeno,

R^9 es hidrógeno,

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X

m es 0,

R¹¹ es un grupo de fórmula (IB) (como se describe anteriormente) en

donde

R¹² es hidrogeno,

p es 1 ó 2,

R¹³ es hidrogeno,

q es 0,

r es 0,

R¹⁵ es carboxi o sulfo, y

R¹⁷ es hidroxí

R⁵ es N-{(R)-α-[N-(carboximetil)carbamoil]bencil}carbamoilmetoxi, N-{(R)-α-[N-(carboximetil)carbamoil]bencil}carbamoilmetoxi o N-{(R)-α-[N-(2-sulfoetil)carbamoil]-4-hidrobencil}carbamoilmetoxi

R⁵ es un grupo de formula (IA) (como se describe anteriormente) en

donde

X es -O-,

Anillo A es fenilo opcionalmente sustituido por uno o más sustituyentes seleccionados de R¹⁷,

n es 1,

R⁷ es hidrógeno,

R⁸ es hidrogeno,

R⁹ es hidrógeno,

m es 0,

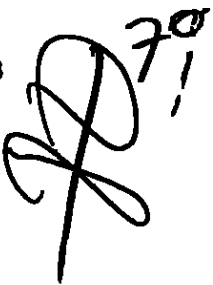
R¹¹ es carboxi, un grupo de fórmula (IB) (como se describe anteriormente) o un grupo de formula (IC) (como se describe anteriormente) en donde

R¹² es hidrógeno o C₁₋₄alquilo,

p es 1 ó 2,

R¹³ es hidrogeno o C₁₋₄alquilo sustituido opcionalmente por R²⁰ en donde R²⁰ es hidroxí, carbamoilo, amino, benciloxicarbonilamino o C₁₋₄alquilS(O)_a en donde a es 0,

R¹⁴ es hidrogeno o hidroxí,



q es 0,

r es 0 o 1,

R¹⁵ es carboxi o sulfo,

R¹⁷ es hidroxí, y

Anillo B es pirrolidin-1-ilo sustituido en carbono por un grupo seleccionado de R²³, en donde R²³ es carboxi

R⁵ es *N*-{(R)- α -[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxi-2-hidroxietyl)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxietyl)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxipropil)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((R)-1-carboxi-2-metiltio-etil)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxi-2-carbamoil-hidroxibencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-(carboximetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxietyl)carbamoil]-4-hidroxibencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxi-2-hidroxietyl)carbamoil]-4-idroxibencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-(2-sulfoetil)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxi-2-(R)-hidroxipropil)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxi-2-metilpropil)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxi-3-metilbutil)carbamoil]bencil}carbamoilmetoxi, [?] *N*-{(R)- α -[*N*-(1-(S)-1-carboxi-2-(S)-2-metilbutil)carbamoil]bencil}carbamoilmetoxi, *N*-((R)- α -carboxi-4-hidroxibencil)carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxi-4-aminobutil)carbamoil]bencil}carbamoilmetoxi, *N*-((R)- α -{*N*-[(S)-1-carboxi-4-(benciloxycarbonilamino)butil]carbamoil}bencil}carbamoilmetoxi, *N*-[(R)- α -((S)-2-carboxipirrolidin-1-ilcarbonil)bencil]carbamoilmetoxi, *N*-{(R)- α -[*N*-(carboximetil)-*N*-metilcarbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-(1-(R)-2-(R)-1-carboxi-1-hidroxi-prop-2-il)carbamoil]bencil}carbamoilmetoxi, *N*-{(R)- α -[*N*-(sulfometil)carbamoil]bencil}carbamoilmetoxi, *N*-((R)- α -carboxibencil)carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxi-2-(R)-

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hidroxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxi-2-metilpropil)carbamoil]-4-hidroxibencil}\text{-}carbamoilmetoxi,$
 $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxibutil)carbamoil]-4-hidroxibencil}\text{-}carbamoilmetoxi,$
 $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxipropil)carbamoil]-4-hidroxibencil}\text{-}carbamoilmetoxi$ o $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((R)\text{-}1\text{-carboxi-2-metiltio-etil)carbamoil]-4-hidroxibencil}\text{-}carbamoilmetoxi$

R^5 es un grupo de formula (IA) (como se describe arriba) en donde
 X es -O-,

Anillo A es fenilo sustituido de manera opcional por uno o mas
sustituyentes seleccionados de R^{17} ,

n es 1,

R^7 es hidrogeno,

R^8 es hidrógeno,

R^9 es hidrogeno,

M es 0,

R^{11} es carboxi, un grupo de formula (IB) (como se describe arriba) o
un grupo de formula (IC) (como se describe arriba) en donde

R^{12} es hidrógeno ó C_{1-4} alquilo,

p es 1 ó 2,

R^{13} es hidrogeno o C_{1-6} alquilo sustituido en forma opcional por R^{20} en
donde R^{20} es hidroxil, carbamoilo, amino, benciloxycarbonilamino, C_{1-4}
alquilS(O)_a en donde a es 0 o $(C_{1-4}$ alquil)₃sililo,

R^{14} es hidrogeno o hidroxil o C_{1-6} alquilo, en donde R^{14} puede
sustituirse forma opcional por uno o más sustituyentes seleccionados de
 R^{20} ,

Y es -N(R^n)C(O)-en donde R^n es hidrogeno,

Q es 0 ó 1,

r es 0 ó 1,

R^{15} es carboxil o sulfo,

R^{17} es hidroxil, y

R^{20} se selecciona de hidroxil,

Anillo B es pirrolidin-1-ilo o azetidínilo sustituido en carbono por un

grupo seleccionado de R^{23} , y sustituido además en forma opcional en carbono por uno o más R^{24} , en donde R^{23} es carboxi y R^{24} es hidroxí

R^5 es N -{(R)- α -[N -(carboximetil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -(carboximetil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -(2-sulfoetil)carbamoil]-4-hidroxibencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-2-hidroxi-etil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-etil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-propil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -(1-carboxi-2-metiltio-etil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-2-carbamoil-etil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -(2-sulfoetil)carbamoil]-4-hidroxibencil} carbamoilmetoxi, N -{(R)- α -[N -(carboximetil)carbamoil]-4-hidroxibencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-etil)carbamoil]-4-hidroxibencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-2-hidroxi-etil)carbamoil]-4-hidroxibencil} carbamoilmetoxi, N -{(R)- α -[N -(2-sulfoetil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-2-(R)-hidroxipropil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-2-metilpropil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-3-metilbutil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -(1-(S)-1-carboxi-2-(S)-2-metilbutil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -carboxi-4-hidroxibencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-4-aminobutil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-4-(benciloxi-carbonil-amino)butil)carbamoil]bencil} carbamoilmetoxi, N -[(R)- α -((S)-2-carboxipirrolidin-1-il-carbonil)bencil] carbamoilmetoxi, N -{(R)- α -[N -(carboximetil)- N -metilcarbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -(1-(R)-2(R)-1-carboxi-1-hidroxi-prop-2-il)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -[N -(sulfometil)carbamoil]bencil} carbamoilmetoxi, N -{(R)- α -carboxibencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-2-(R)-hidroxipropil)carbamoil]-4-hidroxibencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxi-2-metilpropil)carbamoil]-4-hidroxibencil} carbamoilmetoxi, N -{(R)- α -[N -((S)-1-carboxibutil)carbamoil]-4-hidroxibencil}

carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(S)\text{-}1\text{-carboxipropil}\}\text{carbamoil}]\text{-}4\text{-hidroxibencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(R)\text{-}1\text{-carboxi-2-metiltioetil}\}\text{carbamoil}]\text{-}4\text{-hidroxibencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(S)\text{-}1\text{-carboxipropil}\}\text{carbamoil}]\text{-}4\text{-hidroxibencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(S)\text{-}1\text{-}[N\text{-}\{(S)\text{-}2\text{-hidroxil-1-carboxietil}\}\text{carbamoil}]\text{propil}\}\text{carbamoil}\}\text{bencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}[2\text{-}(S)\text{-}2\text{-}(carboxi)\text{-}4\text{-}(R)\text{-}4\text{-}(hidroxil)pirrolidin-1-ilcarbamil}\}\text{bencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}[2\text{-}(S)\text{-}2\text{-}(carboxi)azetidil-1-ilcarbamil}\}\text{bencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(S)\text{-}1\text{-}[N\text{-}\{(S)\text{-}1\text{-carboxietil}\}\text{carbamoil}\}\text{etil}\}\text{carbamoil}\}\text{bencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(R)\text{-}1\text{-carboxi-3,3-dimetilbutil}\}\text{carbamoil}\}\text{bencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(S)\text{-}1\text{-carboxi-3,3-dimetilbutil}\}\text{carbamoil}\}\text{bencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(R)\text{-}1\text{-carboxi-3,3-dimetilbutil}\}\text{carbamoil}]\text{-}4\text{-hidroxibencil}\}\text{carbamoilmetoxi}$, $N\text{-}\{(R)\text{-}\alpha\text{-}\{N\text{-}\{(S)\text{-}1\text{-carboxi-2-(trimetilsilil)etil}\}\text{carbamoil}\}\text{-}4\text{-hidroxibencil}\}\text{carbamoilmetoxi}$ o $N\text{-}\{(R)\text{-}\alpha\text{-}\{N\text{-}\{(R)\text{-}1\text{-carboxi-2-(trimetilsilil)etil}\}\text{carbamoil}\}\text{-}4\text{-hidroxibencil}\}\text{carbamoilmetoxi}$

R^5 es hidrogeno

R^4 es un grupo de fórmula (IA)

R^5 es un grupo de fórmula (IA)

Por lo tanto, en un aspecto más de la invención, se provee un compuesto de formula (I) (como se describe arriba) en donde

R^v es hidrógeno,

R^1 y R^2 son C_{1-4} alquilo,

R^x y R^y son ambos hidrogeno,

M es-N-,

v es 0,

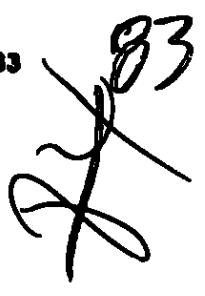
R^3 y R^6 hidrogeno,

R^4 es halo, C_{1-4} alquilo o C_{1-4} alquilS(O)_a en donde a es 0,

R^5 es un grupo de formula (IA) (como se describe arriba) en donde

X es-O-,

Anillo A es fenilo sustituido de manera opcional por uno o mas

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sustituyentes seleccionados de R^{17} ,

n es 1,

R^7 es hidrogeno,

R^8 es hidrógeno,

R^9 es hidrogeno,

m es 0,

R^{11} es carboxi, un grupo de formula (IB) (como se describe arriba) o un grupo de formula (IC) (como se describe arriba) en donde

R^{12} es hidrogeno o C_{1-4} alquilo,

p es 1 ó 2,

R^{13} es hidrogeno o C_{1-6} alquilo sustituido en forma opcional por R^{20} en donde R^{20} es hidroxí, carbamóilo, amino, benciloxícarbonilamino, C_{1-4} alquilS(O)_a en donde a es 0 ó $(C_{1-4}$ alquil)₃silo,

R^{14} es hidrógeno o hidroxí o C_{1-6} alquilo, en donde R^{14} puede sustituirse forma opcional por uno o mas sustituyentes seleccionados de R^{20} ,

Y es $-N(R^n)C(O)-$ en donde R^n es hidrógeno,

q es 0 ó 1,

r es 0 ó 1,

R^{15} es carboxí o sulfo,

R^{17} es hidroxí, y

R^{20} se selecciona de hidroxí, y

Anillo B es pirrolidin-1-ilo o azetidínilo sustituido en carbono por un grupo seleccionado de R^{23} , y sustituido ademas en forma opcional en carbono por uno o mas R^{24} , en donde R^{23} es carboxí y R^{24} es hidroxí, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

Por lo tanto, en un aspecto adicional de la invención, se provee un compuesto de fórmula (I) (como se describe arriba) en donde

R^v es hidrogeno,

R^1 y R^2 son ambos butilo,

R^x y R^y son ambos hidrogeno,

((S)-1-carboxi-2-metilpropil)carbamoil]-4-hidroxi**bencil**} carbamoilmetoxi,
N-{(R)- α -[*N*-((S)-1-carboxibutil)carbamoil]-4-hidroxi**bencil**}
 carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-carboxipropil)carbamoil]-4-
 hidroxi**bencil**} carbamoilmetoxi, *N*-{(R)- α -[*N*-((R)-1-carboxi-2-metil-
 tioetil)carbamoil]-4-hidroxi**bencil**} carbamoilmetoxi, *N*-{(R)- α -[*N*-((S)-1-
 carboxipropil)carbamoil]-4-hidroxi**bencil**} carbamoilmetoxi, *N*-{(R)- α -[*N*-
 {(S)-1-[*N*-((S)-2-hidroxi-1-carboxietil)carbamoil]propil}carbamoil]**bencil**}
 carbamoilmetoxi, *N*-{(R)- α -[2-(S)-2-(carboxi)-4-(R)-4-(hidroxi)pirrolidin-
 1-ilcarbonil]**bencil**} carbamoilmetoxi, *N*-{(R)- α -[2-(S)-2-(carboxi)azetidín-
 1-ilcarbonil]**bencil**} carbamoilmetoxi, *N*-{(R)- α -[*N*-{(S)-1-[*N*-((S)-1-
 carboxietil)carbamoil]etil}carbamoil]**bencil**} carbamoilmetoxi, *N*-{(R)- α -
 [*N*-((R)-1-carboxi-3,3-dimetilbutil)carbamoil]**bencil**} carbamoilmetoxi, *N*-
 {(R)- α -[*N*-((S)-1-carboxi-3,3-dimetilbutil)
 carbamoil]**bencil**} carbamoilmetoxi, *N*-{(R)- α -[*N*-((R)-1-carboxi-3,3-
 dimetilbutil)carbamoil]-4-hidroxi**bencil**} carbamoilmetoxi, *N*-{(R)- α -{*N*-
 [(S)-1-carboxi-2-(trimetilsilil)etil]carbamoil}-4-
 hidroxi**bencil**} carbamoilmetoxi o *N*-{(R)- α -{*N*-[(R)-1-carboxi-2-
 (trimetilsilil)etil]carbamoil}-4-hidroxi**bencil**} carbamoilmetoxi,
 o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un
 profarmaco del mismo

En otro aspecto de la invencion, compuestos preferidos de la
 invencion son cualquiera de los ejemplos 5, 6, 7, 9, 11, 14, 15, 26, 27, 28,
 30 o 33 o una sal farmacéuticamente aceptable, solvato, solvato de dicha
 sal o un profármaco del mismo

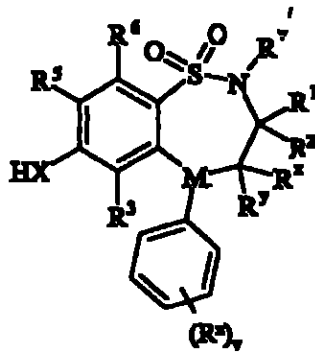
En otro aspecto de la invencion, compuestos preferidos de la
 invención son cualquiera de los ejemplos o una sal farmacéuticamente
 aceptable, solvato, solvato de dicha sal o un profármaco del mismo

Aspectos preferidos de la invencion son aquellos que se relacionan
 con el compuesto de formula (I) o una sal farmacéuticamente aceptable del
 mismo

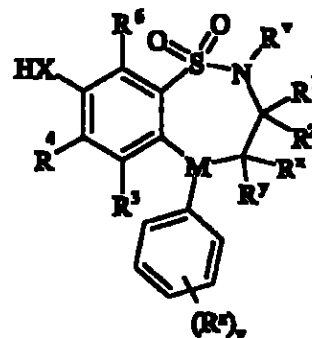
Otro aspecto de la presente invención provee un proceso para preparar
 un compuesto de fórmula (I) o una sal farmacéuticamente aceptable,

solvato, solvato de dicha sal o un profármaco del mismo, proceso que (en donde grupos variables son, a menos que se especifique lo contrario, como se define en fórmula (I)) comprende

Proceso 1) para compuestos de fórmula (I) en donde X es -O-, -NR^a o -S-, hacer reaccionar un compuesto de fórmula (IIa) ó (IIb):

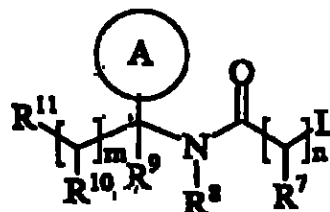


(IIa)



(IIb)

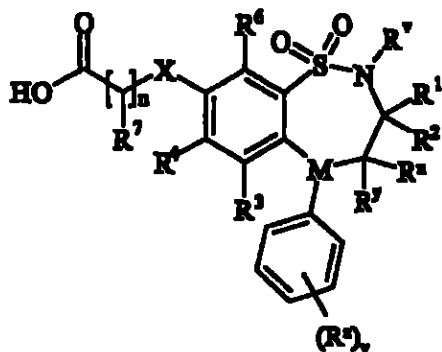
con un compuesto de formula (III):



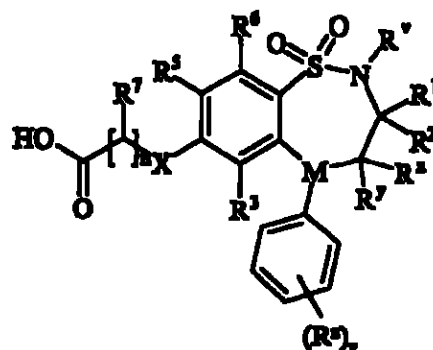
(III)

en donde L es un grupo desplazable,

Proceso 2) hacer reaccionar un ácido de fórmula (IVa) ó (IVb)



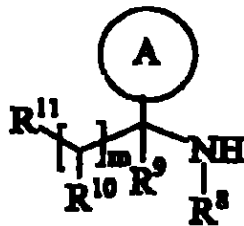
(IVa)



(IVb)

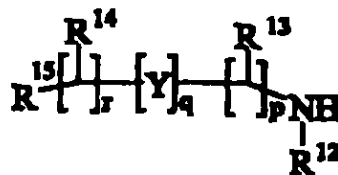
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o un derivado activado del mismo, con una amina de formula (V)



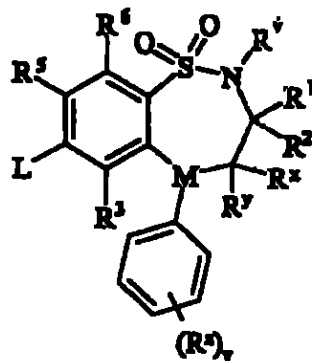
(V);

Proces 3) para compuestos de fórmula (I) en donde R^{11} es un grupo de fórmula (IB), hacer reaccionar un compuesto de formula (I) en donde R^{11} es carboxi con una amina de fórmula (VI)

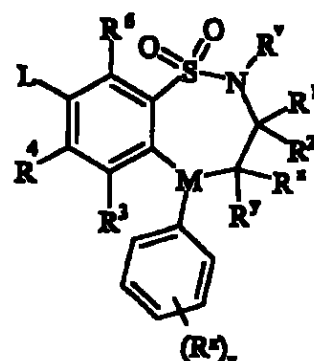


(VI)

Proceso 4) para compuestos de formula (I) en donde uno de R^4 y R^5 se seleccionan independientemente de C_{1-6} alquiltio sustituido de manera opcional en carbono por uno o mas R^{17} , hacer reaccionar un compuesto de fórmula (VIIa) o (VIIb)



(VIIa)



(VIIb)

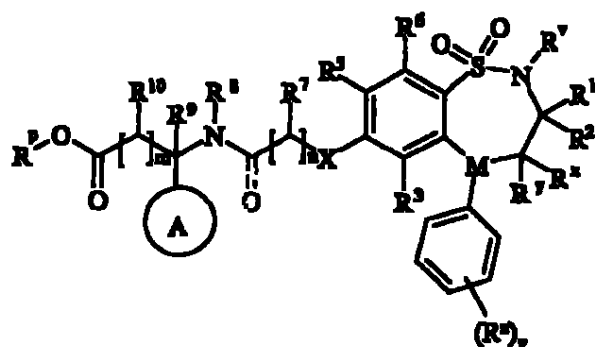
en donde L es un grupo desplazable, con un tiol de formula (VIII)



(VIII)

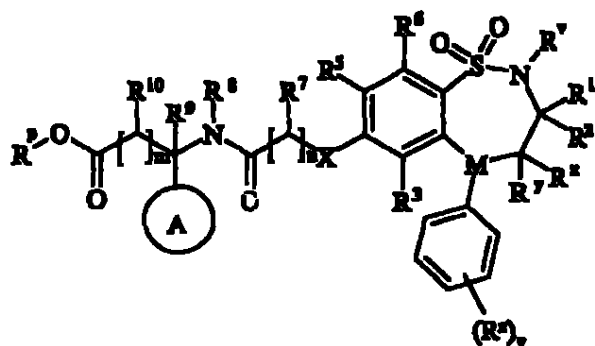
en donde R^m es C_{1-6} alquiltio sustituido de manera opcional en carbono por uno o más R^{16} ,

Proceso 5) para compuestos de fórmula (I) en donde R^{11} es carboxi, desproteger un compuesto de fórmula (IXa)



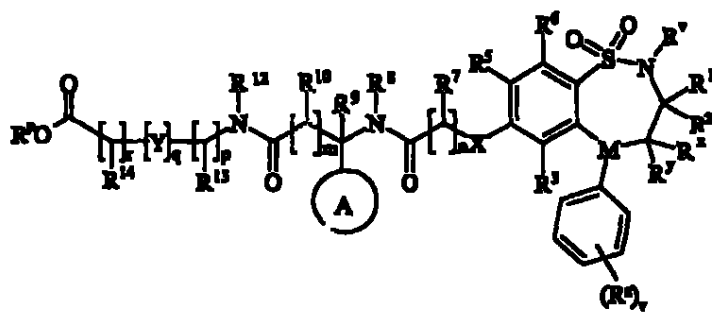
(IXa)

ó (IXb)



(IXb)

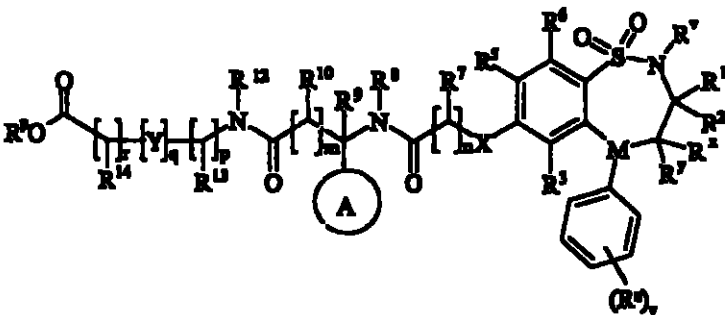
en donde R^p junto con el grupo $-OC(O)-$ al cual se une forma un éster, *Proceso 6)* para compuestos de fórmula (I) en donde R^{11} es un grupo de fórmula (IB) y R^{15} es carboxi, desproteger un compuesto de fórmula (Xa)



(Xa)

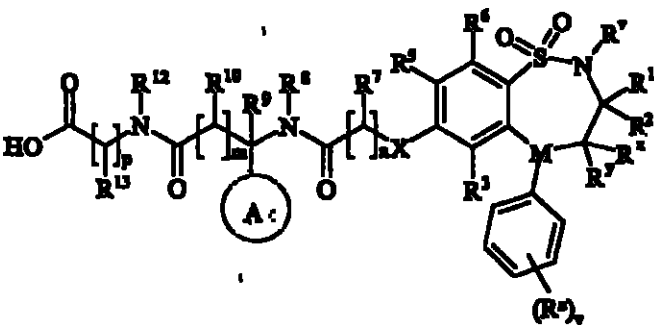
ó (Xb)

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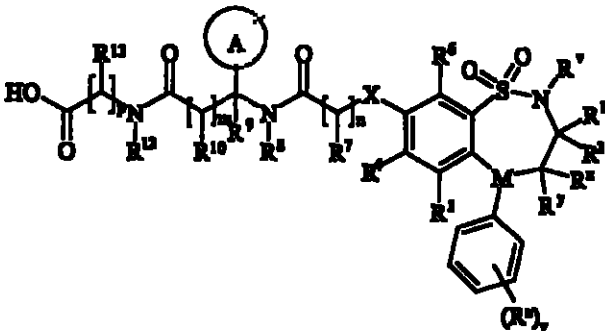
(Xb)

en donde R^p junto con el grupo -OC(O)- al cual se une forma un ester;
Proceso 7) para compuestos de fórmula (I) en donde R¹¹ es un grupo de
formula (IB) y N(Rⁿ)C(O)-, hacer reaccionar un ácido de formula (XIa)



(XIa)

o (XIb)



(XIb)

o un derivado activado del mismo, con una amina de formula (XII)



(XII)

y, a partir de entonces, si se considera necesario o deseable

i) convertir un compuesto de la fórmula (I) en otro compuesto de la fórmula

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(I),

- ii) retirar cualesquiera grupos protectores,
- iii) formar una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco

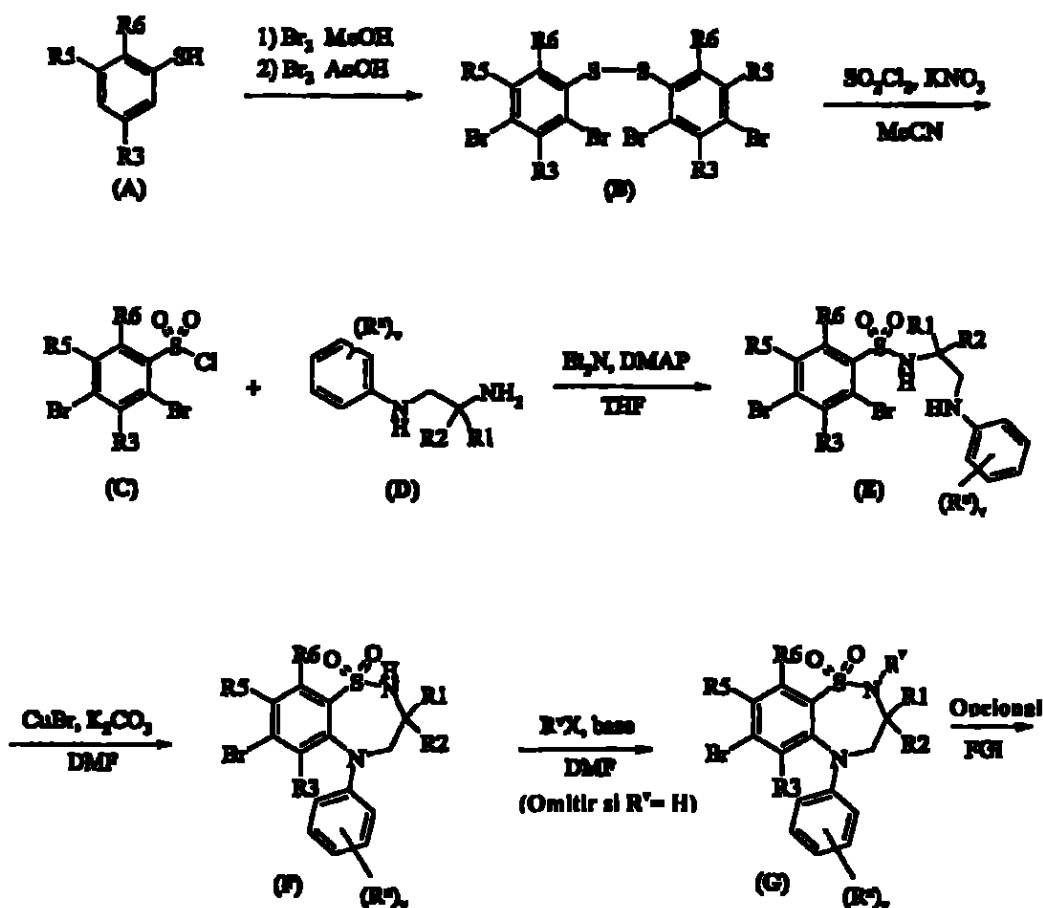
L es un grupo desplazable, valores apropiados de L son por ejemplo, un grupo halogeno o sulfonyloxi, por ejemplo un grupo cloro, bromo, metanosulfonyloxi o tolueno-4-sulfonyloxi

R^P junto con el grupo -OC(O)- al cual se une forma un éster Preferiblemente R^P es metilo o etilo Mas preferiblemente R^P es metilo En otro aspecto de la invención R_p es C₁₋₄alquilo o fenilC₁₋₄alquilo, preferiblemente C₁₋₄alquilo o bencilo, más preferiblemente t-butilo, metilo, etilo o bencilo

Condiciones específicas de reaccion para las reacciones anteriores son las siguientes

Los sistemas de anillo biciclico de la presente invencion pueden ensamblarse de acuerdo con el Esquema Ia o Esquema Ib El experto se percatara de que al hacer cualquiera de los intermedios ya identificados, el valor de R⁴ o R⁵ en los siguientes esquemas se sustituya con el grupo apropiado Por ejemplo, para sintetizar un compuesto de fórmula (IIa) R⁴ seria HX en el siguiente esquema.

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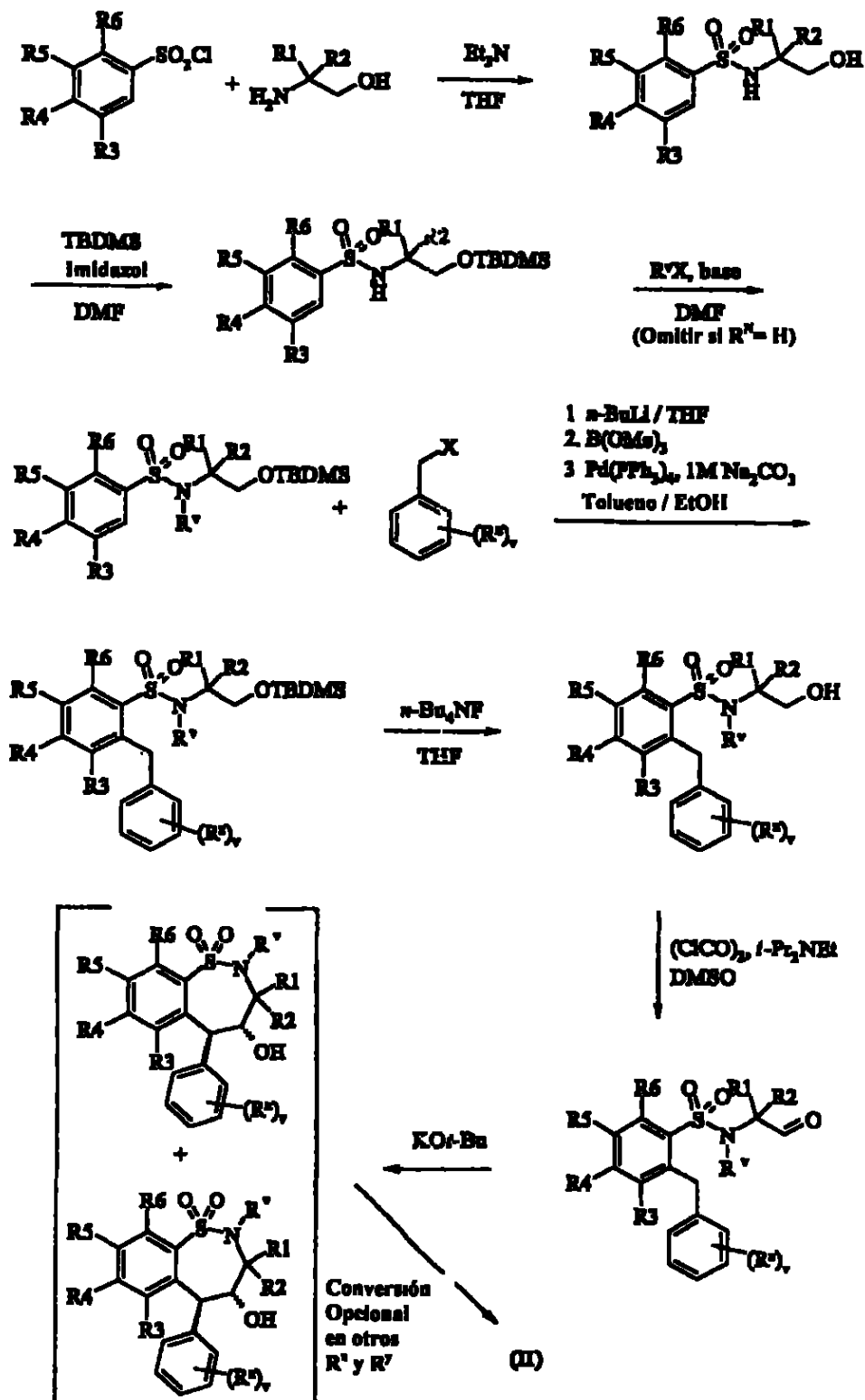


Esquema 1a

En donde FGI es la interconversión funcional de Br en otros valores de R⁴ usando procedimientos conocidos por el experto

Compuestos de fórmula (A) y (D) se consiguen en el comercio, o se conocen en la literatura, o pueden prepararse por procesos estandar conocidos en el arte

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Esquema 1b

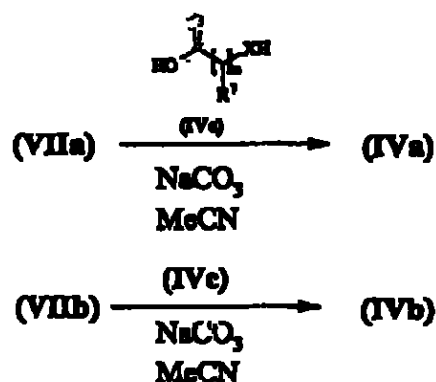
Proceso 1) Compuestos de fórmula (IIa) o (IIb) pueden hacerse reaccionar con compuestos de fórmula (III) en la presencia de una base por ejemplo una base inorgánica tal como carbonato de sodio, o una base orgánica tal como una base de Hünig, en la presencia de un solvente adecuado tal como acetonitrilo, diclorometano o tetrahydrofurano a una temperatura en el rango de 0°C a reflujo, preferiblemente a, o cerca de, reflujo

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Compuestos de fórmula (III) son compuestos disponibles en el comercio, o se conocen en la literatura, o se preparan por procesos estándar conocidos en el arte. *Proceso 2)* y *Proceso 3)* y *Proceso 7)* Ácidos y aminas pueden acoplarse juntos en la presencia de un reactivo apropiado. Reactivos de acoplamiento peptídico estándar conocidos en el arte pueden emplearse como reactivos de acoplamiento apropiados, o por ejemplo carbonildimidazol y dicitclohexil-carbodimida, opcionalmente en la presencia de un catalizador tal como dimetilaminopiridina o 4-pirrolidinopiridina, opcionalmente en la presencia de una base por ejemplo trietilamina, piridina, o 2,6-di-*alquil*-piridinas tales como 2,6-lutidina o 2,6-*tert*-butilpiridina. Los solventes adecuados 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 adecuados de ácido activado incluyen halogenuros de ácido, por ejemplo cloruros de ácido, y ésteres activos, por ejemplo ésteres de pentafluorofenilo. 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 ya descritas, en un solvente apropiado, tal como las ya descritos. La reacción puede realizarse convenientemente a una temperatura en el rango de -40 a 40°C.

Compuestos de fórmula (IVa) ó (IVb) en donde X=O-, -NR^a, -S- pueden prepararse de acuerdo con Esquema 2

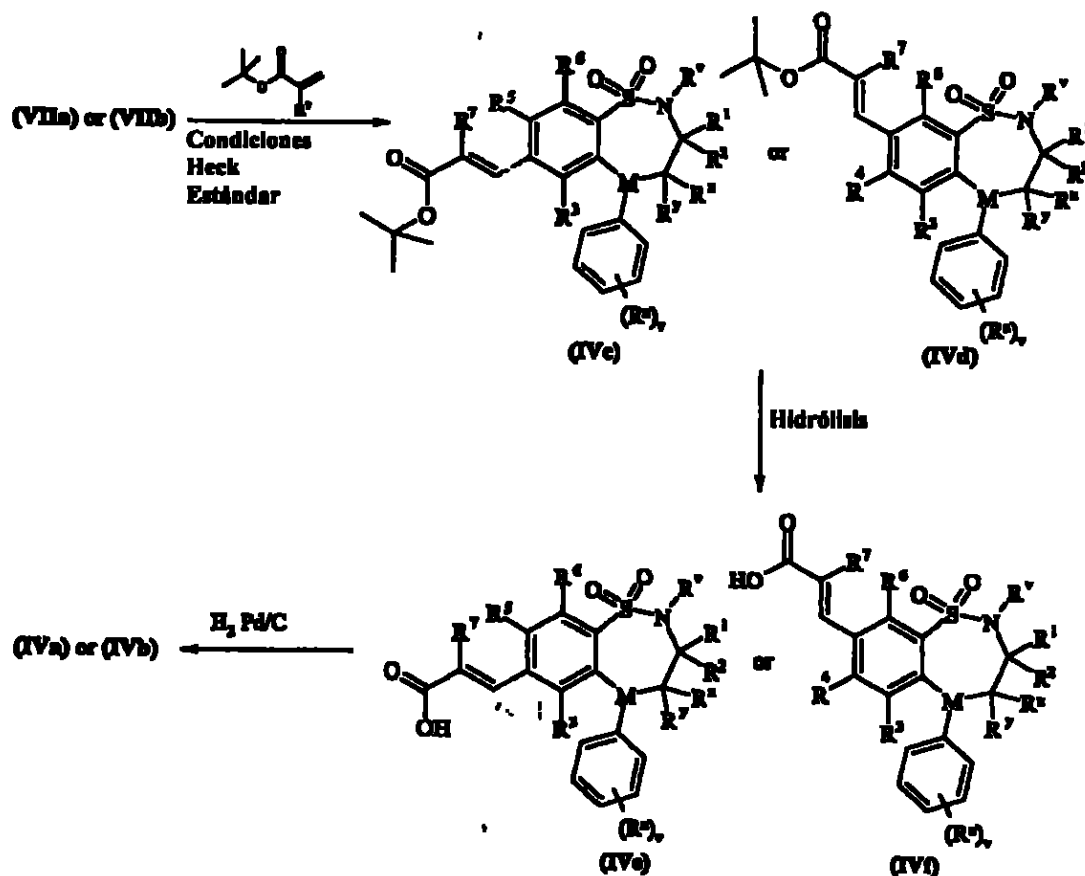


Esquema 2

En donde L en (VIIa) y (VIIb) es un grupo desplazable por ejemplo bromo, cloro, fluoro, mesilo o tosilo y en donde X es -O-, -S-, NR^a (opcionalmente para -SO- y -SO₂- seguido por el paso de oxidación de Proceso 1)

Compuestos de formula (IVa) y (IVb) donde X es -SO- o -SO₂- pueden prepararse oxidando los compuestos resultantes de fórmula (IVa) y (IVb) de *Esquema 2* donde X es -S-

Compuestos de formula (Va) ó (Vb) en donde X es -CH₂- y n es 1 pueden prepararse de acuerdo con *Esquema 3*



Esquema 3

El experto se percatará de que el anterior esquema de reacción puede manipularse para preparar compuestos de fórmula (Va) ó (Vb) donde n es 2 o 3

Compuestos de fórmula (XIa) y (XIb) pueden prepararse por manipulaciones conocidas por el experto de los procesos descritos aquí

Compuestos de fórmula (IVc), (V), (VI), (XII) y (VII) son compuestos disponibles en el comercio, o se conocen en la literatura, o se

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preparan por procesos estandar conocidos en el arte

Proceso 4) Compuestos de formula (VIIa) y (VIIb) pueden hacerse reaccionar con tioles de fórmula (VIII) 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 solvente adecuado tal como DMF o THF a una temperatura en el rango de 0°C a reflujo

Compuestos de formula (VIIa) y (VIIb) pueden prepararse por cualquiera de los procedimientos anteriores para la preparación de compuestos de fórmula (I), pero en donde uno de R^4 y R^5 es L

Compuestos de formula (VIII) son compuestos disponibles en el comercio, o se conocen en la literatura, o se preparan por procesos estandar conocidos en el arte *Proceso 5)* y *Proceso 6)* Esteres de formula (IXa), (IXb), (Xa) y (Xb) pueden desprotegerse bajo condiciones estandar tales como las descritas más adelante, por ejemplo pueden desprotegerse con hidroxido de sodio en metanol a temperatura ambiente

Ésteres de formula (IXa), (IXb), (Xa) y (Xb) pueden prepararse por cualquiera de los procedimientos anteriores para la preparación de compuestos de formula (I), pero en donde R^{11} ó R^{15} es C_{1-4} alkoxycarbonilo

Se apreciara que ciertos de los diferentes sustituyentes de anillo en los compuestos de la presente invencion pueden introducirse por reacciones de sustitucion aromática estándar o generarse por modificaciones convencionales de grupo funcional bien sea antes o inmediatamente despues de los procesos ya mencionados, 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 reaccion de sustitucion aromática, reduccion de sustituyentes, alquilación de sustituyentes y oxidación de sustituyentes Los reactivos y condiciones de reaccion para tales procedimientos son bien conocidos en el arte quimico Ejemplos particulares de reacciones de sustitucion aromática incluyen la introduccion de un grupo nitro usando acido nitrico

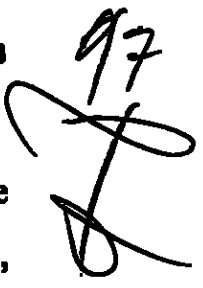
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X

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 nitró 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 alquilo 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. Un caso particular en donde puede usarse un grupo protector se presenta en proteger el nitrógeno en la posición 2 del anillo benzotiadiazepina durante la síntesis de ciertos intermedios.

Grupos protectores convencionales pueden usarse de 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 hidroxilo, 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 alcanilo tal como un grupo acetilo, un grupo alcóxicarbonilo, por ejemplo un grupo metóxicarbonilo, etóxicarbonilo o *t*-butoxicarbonilo, un grupo arilmetóxicarbonilo, por ejemplo bencilóxicarbonilo, 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 alcanilo o

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alkoxycarbonilo o un grupo aroilo pueden retirarse por ejemplo, mediante hidrolisis con una base adecuada tal como un hidroxido de metal alcalino, por ejemplo hidroxido 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, sulfurico o fosfórico o ácido trifluoroacético, y un grupo arilmetoxycarbonilo tal como un grupo benciloxycarbonilo puede retirarse, por ejemplo, mediante hidrogenacion sobre un catalizador tal como paladi-sobre-carbono, 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 hidroxilo es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanilo tal como acetilo, un grupo aroilo, por ejemplo benzoilo, o un grupo arilmetilo, por ejemplo bencilo. Las condiciones de desproteccion para los grupos protectores anteriores variaran necesariamente con la elección del grupo protector. Así, por ejemplo, un grupo acilo tal como un alcanilo o un grupo aroilo pueden retirarse, por ejemplo, mediante hidrolisis con una base apropiada tal como un hidroxido de metal alcalino, por ejemplo hidroxido de litio o de sodio. Alternativamente, un grupo arilmetilo tal como un grupo bencilo pueden retirarse, por ejemplo, mediante hidrogenacion sobre un catalizador tal como paladio-sobre-carbono.

Un grupo protector adecuado para un grupo carboxilo, por ejemplo, un grupo esterificante, por ejemplo un grupo metilo o etilo que puede retirarse, por ejemplo, mediante hidrolisis 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 organico tal como ácido trifluoroacetico, o por ejemplo un grupo bencilo que puede retirarse, por ejemplo, mediante hidrogenacion sobre un catalizador tal como paladio-sobre-carbono.

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✓

Los grupos protectores pueden retirarse en cualquier fase convencional en la síntesis usando técnicas convencionales bien conocidas en el arte químico

Como ya se afirmó anteriormente en el texto, los compuestos definidos en la presente invención poseen actividad inhibidora IBAT. Estas propiedades pueden evaluarse, por ejemplo, usando un análisis de prueba *in vitro* para estudiar el efecto de la absorción de ácido biliar en células transfectadas con IBAT (Smith L., Price-Jones M. J., Hugnes K. T. and Jones N. R. A., J Biomolecular Screening, 3,227-230) o *in vivo* estudiando el efecto sobre la absorción de ácido biliar radiomarcado en ratones/ratas (Lewis M. C., Brieddy L. E. and Root C. J., J Lip Res 1995, 36, 1098-1105)

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se define anteriormente en el texto en asociación con un diluyente o transportador 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 unguento o crema o para administración rectal como un supositorio

En general las composiciones anteriores pueden prepararse en una manera convencional usando excipientes convencionales

El compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, se administrará normalmente a un animal de sangre caliente en una dosis unitaria en el rango 5-5000 mg por metro cuadrado de área corporal del animal, es decir, aproximadamente 0.02-100 mg/kg, preferiblemente 0.02-50 mg/kg, y esto normalmente proporciona una dosis terapéuticamente efectiva. Una 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 0.02-20 mg/kg No obstante, la dosis diaria variará necesariamente dependiendo del anfitrión tratado, la vía particular de administración, y la gravedad de la afección que se está tratando En consecuencia la dosificación óptima puede determinarse por el médico que está tratando a cualquier paciente particular

De acuerdo con un aspecto más de la presente invención se provee un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se define anteriormente en el texto para uso en un método de tratamiento terapéutico o profiláctico de un animal de sangre caliente, tal como el hombre

Hemos encontrado que los compuestos definidos en la presente invención, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, son inhibidores efectivos de IBAT y, en consecuencia, tienen utilidad en el tratamiento de estados patológicos asociados con afecciones hiperlipídicas

Así, de acuerdo con este aspecto de la invención se provee un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se define anteriormente 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 una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se define anteriormente en el texto en la manufactura de un medicamento para uso en la producción de un efecto inhibidor IBAT 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 una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se define anteriormente en el texto en la manufactura de un medicamento para uso en

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el tratamiento de afecciones hiperlipidámicas 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 una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se define anteriormente en el texto en la manufactura de un medicamento para uso en el tratamiento afecciones y trastornos dislipidémicos tales como hiperlipidaemia, hipertrigliceridemia, hiperbetalipoproteinemia (alta LDL), hiperprebetalipoproteinemia (alta VLDL), hiperquilomicronemia, hipolipoproteinemia, hipercolesterolemia, hiperlipoproteinemia e hipoalfalipoproteinemia (baja HDL) en un animal de sangre caliente, tal como el hombre

De acuerdo con otra característica de la invencion se provee el uso de un compuesto de la formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, como se define anteriormente en el texto en la mañufactura de un medicamento para uso en el tratamiento de diferentes afecciones clínicas tales como aterosclerosis, arteriosclerosis, arritmia, afecciones hiper-tromboticas, disfuncion vascular, disfunción endotelial, falla cardiaca, cardiopatias isquémicas, enfermedades cardiovasculares, infarto del miocardio, angina pectoris, vasculopatias perifericas, inflamacion de tejidos cardiovasculares tales como corazón, válvulas, sistema vascular, arterias y venas, aneurismas, estenosis, restenosis, placas vasculares, estrias vasculares adiposas, leucocitos, monocitos y/o infiltracion de macrófagos, engrosamiento de la capa íntima, adelgazamiento de la media, trauma infeccioso y quirurgico y trombosis vascular, apoplejía y accidentes isquemicos transitorios 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 una sal farmaceuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se define anteriormente en el texto en la manufactura de un medicamento para uso en el tratamiento de aterosclerosis, cardiopatias isquemicas, infarto del

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miocardio, angina pectoris, vasculopatias perifericas, apoplejia y accidentes isquémicos transitorios en un animal de sangre caliente, tal como el hombre

De acuerdo con otra característica de este aspecto de la invención se provee un método para producir un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

De acuerdo con otra característica de este aspecto de la invención se provee un método de tratar afecciones hiperlipidemicas en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

De acuerdo con otra característica de este aspecto de la invencion se provee un metodo de tratar afecciones y trastornos dislipidemicos tales como hiperlipidaemia, hipertrigliceridemia, hiperbetalipoproteinemia (alta LDL), hiperprebetalipoproteinemia (alta VLDL), hiperquilomicronemia, hipolipoproteinemia, hipercolesterolemia, hiperlipoproteinemia e hipoalfalipoproteinemia (baja HDL) en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

De acuerdo con otra característica de este aspecto de la invencion se provee un metodo de tratar diferentes afecciones clinicas tales como aterosclerosis, arteriosclerosis, arritmia, afecciones hiper-tromboticas, disfuncion vascular, disfuncion endotelial, falla cardíaca, cardiopatias isquemicas, enfermedades cardiovasculares, infarto del miocardio, angina pectoris, vasculopatias perifericas, inflamacion de tejidos cardiovasculares tales como corazon, valvulas, sistema vascular, arterias y venas, aneurismas,

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estenosis, restenosis, placas vasculares, estrias vasculares adiposas, leucocitos, monocitos y/o infiltración de macrófagos, engrosamiento de la capa intima, adelgazamiento de la media, trama infeccioso y quirurgico y trombosis vascular, apoplejía y accidentes isquémicos transitorios necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

De acuerdo con otra característica de este aspecto de la invención se provee un método aterosclerosis, cardiopatías isquémicas, infarto del miocardio, angina pectoris, vasculopatías periféricas, apoplejía y accidentes isquémicos transitorios en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

Existe evidencia de que un inhibidor IBAT podría ser potencialmente útil en el tratamiento y/o prevención de cálculos biliares. De acuerdo con otra característica de este aspecto de la invención se provee un método de tratar y / o prevenir cálculos biliares en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

El tamaño de la dosis requerida para el tratamiento terapéutico o profiláctico se variara necesariamente dependiendo del anfitrión tratado, la vía de administración y la gravedad de la enfermedad que se está tratando. Se contempla una dosis unitaria en el rango, por ejemplo, 0.1-50mg/kg preferiblemente 0.1-10 mg/kg

La actividad inhibidora IBAT definida más arriba en el texto puede aplicarse como terapia individual o puede incluir, además de un compuesto de la invención, una o más de otras sustancias y/o tratamientos. Tal

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tratamiento conjunto puede lograrse por medio de la administración simultanea, secuencial o separada de los componentes individuales de tratamiento. De acuerdo con este aspecto de la invención se provee un producto farmaceutico que comprende un compuesto de la formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se define anteriormente en el texto y una sustancia adicional inhibidora IBAT como se define anteriormente en el texto y un agente hipolipidemico adicional para el tratamiento conjunto de hiperlipidaemia.

En otro aspecto de la invencion, el compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, puede administrarse en asociacion con un inhibidor de HMG Co-A reductasa, o sales farmaceuticamente aceptables, solvatos, solvatos de dichas sales o profarmacos de los mismos. Inhibidores adecuados de HMG Co-A reductasa, sales farmaceuticamente aceptables, solvatos, solvatos de dichas sales o profarmacos de los mismos son estatinas bien conocidas en el arte. Estatinas particulares son fluvastatina, lovastatina, pravastatina, simvastatina, atorvastatina, cerivastatina, bervastatina, dalvastatina, mevastatina y ácido (E)-7-[4-(4-fluorofenil)-6-isopropil-2-[metil(metilsulfonyl)amino]pirimidin-5-il](3R,5S)-3,5-dihidroxihept-6-enoico (rosuvastatina), o una sal farmaceuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo. Una estatina particular es atorvastatina, o una sal farmaceuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo. Una estatina mas particular es sal de calcio de atorvastatina. Otra estatina particular es ácido (E)-7-[4-(4-fluorofenil)-6-isopropil-2-[metil(metilsulfonyl)amino]pirimidin-5-il](3R,5S)-3,5-dihidroxihept-6-enoico (rosuvastatina), o una sal farmaceuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo. Una estatina particular preferible es sal de calcio de rosuvastatina.

En un aspecto adicional de la invencion, el compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un

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profarmaco del mismo puede administrarse en asociación con un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y/o un secuestrante de ácido biliar evitando así un posible riesgo de exceso de ácidos biliares en el colon causado por la inhibición del sistema de transporte de ácidos biliares en el íleon. Un exceso de ácidos biliares en los contenidos viscerales puede ocasionar diarrea. Así, la presente invención provee además un tratamiento de un posible efecto adverso tal como diarrea en pacientes durante la terapia que comprende el compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo.

Un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo disminuirá mediante su acción el colesterol endógeno disponible para la síntesis de ácidos biliares y tendrá un efecto suplementario en combinación con el compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo sobre la disminución de lípidos.

Barredores apropiados de ácidos biliares para tal terapia de combinación son resinas, tales como colestiramina y colestipol. Una ventaja es que la dosis de secuestrante de ácido biliar podría mantenerse más baja que la dosis terapéutica para tratamiento de colesterolaemia en tratamiento único que comprende únicamente un secuestrante de ácido biliar. Con una dosis baja de secuestrante de ácido biliar podrían evitarse además cualesquiera efectos adversos causados por una pobre tolerancia del paciente a la dosis terapéutica.

Por lo tanto, en una característica adicional de la invención, se provee un método para producir un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo en la administración simultánea, secuencial o separada con una cantidad efectiva de un inhibidor

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de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

Por lo tanto en una característica adicional de la invención, se provee un metodo para producir un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo en administracion simultánea, secuencial o separada con un secuestrante de ácido biliar

Por lo tanto en una característica adicional de la invencion, se provee un metodo para producir un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmaceuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo en administracion simultanea, secuencial o separada con una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o una sal farmaceuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, en administracion simultánea, secuencial o separada con un secuestrante de ácido biliar

Por lo tanto en una característica adicional de la invención, se provee un metodo de tratar afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo en administración simultanea, secuencial o separada con una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

Por lo tanto en una característica adicional de la invencion, se provee un metodo de tratar afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un

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compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo en administración simultánea, secuencial o separada con una cantidad efectiva de un secuestrante de ácido biliar

Por lo tanto en una característica adicional de la invención, se provee un método de tratar afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo en administración simultánea, secuencial o separada con una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, en administración simultánea, secuencial o separada con un secuestrante de ácido biliar

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, en asociación con un diluyente o transportador farmacéuticamente aceptables

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y un secuestrante de ácido biliar, en asociación con un diluyente o transportador farmacéuticamente aceptables

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y un secuestrante de ácido biliar en asociación con un diluyente

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o transportador farmacéuticamente aceptables

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, y un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, y un secuestrante de ácido biliar

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, y un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo y un secuestrante de ácido biliar

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende

- a) un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en una primera forma farmacéutica unitaria,
- b) un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en una segunda forma farmacéutica unitaria, y
- c) un recipiente para contener dichas formas farmacéuticas unitaria primera y segunda

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende

- a) un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en una primera forma farmacéutica unitaria,

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- b) un secuestrante de ácido biliar; en una segunda forma farmacéutica unitaria, y
- c) un recipiente para contener dichas formas farmacéuticas unitaria primera y segunda.

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende

- a) un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en una primera forma farmacéutica unitaria,
- b) un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en una segunda forma farmacéutica unitaria,
- c) un secuestrante de ácido biliar, en una tercera forma farmacéutica unitaria, y
- d) un recipiente para contener dichas formas farmacéuticas unitaria primera, segunda y tercera

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende

- a) un compuesto de fórmula (II), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, junto con un diluyente o transportador farmacéuticamente aceptables, en una primera forma farmacéutica unitaria,
- b) un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en una segunda forma farmacéutica unitaria, y
- c) un recipiente para contener dichas formas farmacéuticas unitaria primera y segunda

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende

- a) un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, junto con un diluyente o transportador farmacéuticamente aceptables, en una primera

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forma farmacéutica unitaria,

b) un secuestrante de ácido biliar, en una segunda forma farmacéutica unitaria, y

c) un recipiente para contener dichas formas farmacéuticas unitaria primera y segunda

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende

a) un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, junto con un diluyente o transportador farmacéuticamente aceptables, en una primera forma farmacéutica unitaria,

b) un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, en una segunda forma farmacéutica unitaria, y

c) un secuestrante de ácido biliar, en una tercera forma farmacéutica unitaria, y

d) un recipiente para contener dichas formas farmacéuticas unitaria primera, segunda y tercera

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor IBAT 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 una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo y un secuestrante de ácido biliar, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre

De acuerdo con otra característica de la invención se provee el uso de

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un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y un secuestrante de ácido biliar, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor IBAT 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 una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, en la manufactura de un medicamento para uso en el tratamiento afecciones hiperlipidémicas 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 una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, un secuestrante de ácido biliar, en la manufactura de un medicamento para uso en el tratamiento afecciones hiperlipidémicas 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 una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y un secuestrante de ácido biliar, en la manufactura de un medicamento para uso en el tratamiento afecciones hiperlipidémicas 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 efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco

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del mismo, opcionalmente junto con un diluyente o transportador farmacéuticamente aceptables, con la administración simultánea, secuencial o separada de una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, opcionalmente junto con un diluyente o transportador farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre necesitado de dicho tratamiento terapéutico

De acuerdo con un aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, opcionalmente junto con un diluyente o transportador farmacéuticamente aceptables, con la administración simultánea, secuencial o separada de una cantidad efectiva de un secuestrante de ácido biliar, opcionalmente junto con un diluyente o transportador farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre necesitado de dicho tratamiento terapéutico

De acuerdo con un aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, opcionalmente junto con un diluyente o transportador farmacéuticamente aceptables, con la administración simultánea, secuencial o separada de una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, opcionalmente junto con un excipiente farmacéuticamente aceptable, con la administración simultánea, secuencial o separada de una cantidad efectiva de un secuestrante de ácido biliar, opcionalmente junto con un diluyente o transportador 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

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provee un tratamiento de combinacion que comprende la administraci3n de una cantidad efectiva de un compuesto de la formula (I), o una sal farmac3uticamente aceptable, solvato, solvato de dicha sal o un prof3rmaco del mismo, opcionalmente junto con un diluyente o trasportador farmac3uticamente aceptables, con la administracion simultanea, secuencial o separada de uno o mas de los siguientes agentes seleccionados de

- un inhibidor CETP (proteina transportadora de los 3steres de colesterol), por ejemplo los referenciados y descritos en WO 00/38725 pagina 7 rengl3n 22 - pagina 10, rengl3n 17 que se incorporan aqui por referencia,
- un antagonista de absorci3n de colesterol por ejemplo azetudinonas tales como SCH 58235 y los descritos en US 5,767,115 que se incorporan aqui por referencia,
- un inhibidor MTP (proteina transportadora microsomal) por ejemplo los descritos en Science, 282, 751-54, 1998 que se incorporan aqui por referencia,
- un derivado de 3cido fibrico, por ejemplo clofibrato, gemfibrozil, fenofibrato, ciprofibrato y bezafibrato,
- un derivado de 3cido nic3t3nico, por ejemplo, 3cido nic3t3nico (niacina), acipimox y niceritrol,
- un compuesto de fitosterol por ejemplo estanoles,
- probucol,
- un compuesto anti-obesidad por ejemplo orlistat (EP 129,748) y sibutramina (GB 2,184,122 y US 4,929,629),
- un compuesto antihipertensor por ejemplo un inhibidor de la enzima de conversion de angiotensina, un antagonista de receptor de angiotensina II, un bloqueador adren3rgico, un bloqueador alfa andrenergico, un bloqueador beta andrenergico, un bloqueador alfa/beta andrenergico mixto, un estimulante andrenergico, bloqueador de canales de calcio, un diuretico o un vasodilatador,
- insulina,
- sulfonilureas incluidas glibencl3mida, tolbutamida,

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➤ metformina, y/o

➤ acarbosa,

o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, opcionalmente junto con un diluyente o transportador farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre necesitado de dicho tratamiento terapéutico

Inhibidores ACE particulares o sales farmacéuticamente aceptables, solvatos, solvatos de dichas sales o profármacos de los mismos, incluidos metabolitos activos, que pueden usarse en combinación con un compuesto de fórmula (I) comprenden pero no se limitan a, los siguientes compuestos alacepril, alatriopril, altiopril calcio, ancovenin, benazepril, benazepril clorhidrato, benazeprilat, benzoilcaptopril, captopril, captopril-cisteína, captopril-glutation, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacido, enalapril, enalaprilat, enapril, epicaptopril, foroximitina fosfenopril, fosenopril, fosenopril sodio, fosinopril, fosinopril sodio, fosinoprilat, ácido fosinoprilico, glicopril, hemorfin-4, idrapril, ímidapril, 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. Inhibidores ACE preferidos para uso en la presente invención son ramipril, ramiprilat, lisinopril, enalapril y enalaprilat. Inhibidores ACE mas preferidos para usos en la presente invención son ramipril y ramiprilat.

Antagonistas preferidos de angiotensina II, sales farmacéuticamente aceptables, solvatos, solvatos de dichas sales o profármacos de los mismos para uso en combinación con un compuesto de fórmula (I) incluyen, pero no se limitan a, los compuestos candesartan, candesartan cilexetilo, losartan, valsartan, irbesartan, tasosartan, telmisartan y eprosartan. Antagonistas de angiotensina II particularmente preferidos o derivados

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farmacéuticamente aceptable de los mismos para uso en la presente invención son candesartan y candesartan cilexetilo

En otro aspecto de la invención, el compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, puede administrarse en asociación con un agonista alfa y/o gamma PPAR, sales farmacéuticamente aceptables, solvatos, solvatos de dichas sales o profármacos de los mismos. Agonistas alfa y/o gamma PPAR adecuados, sales farmacéuticamente aceptables, solvatos, solvatos de dichas sales o profármacos de los mismos 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, 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 página 634) y J Med Chem, 2000, 43, 527 todos los cuales se incorporan aquí por referencia. Un agonista alfa y/o gamma PPAR se refiere particularmente a WY-14643, clofibrato, fenofibrato, bezafibrato, GW 9578, troglitazona, pioglitazona, rosiglitazona, eglitazona, proglitazona, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 y GW 2433. Un agonista alfa y/o gamma PPAR se refiere particularmente a ácido (S)-2-etoxi-3-[4-(2-{4-metanosulfoniloxifenil}etoxi)fenil]propanoico y sales farmacéuticamente aceptables del mismo. Agonistas adicionales adecuados alfa y/o gamma PPAR alfa y/o gamma son NN622/Ragaglitazar y BMS 298585.

Por lo tanto en una característica adicional de la invención, se provee un método para producir un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo en administración simultánea, secuencial o separada con una cantidad efectiva de un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable, solvato,

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X
X

solvato de dicha sal o un profarmaco del mismo

Por lo tanto en una característica adicional de la invención, se provee un método de tratar afecciones hiperlipídemicas en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo en administración simultánea, secuencial o separada con una cantidad efectiva de un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, y un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en asociación con un diluyente o transportador farmacéuticamente aceptables

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, y un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

De acuerdo con un aspecto adicional de la presente invención se provee un maletín que comprende

- a) un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en una primera forma farmacéutica unitaria,
- b) un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en una segunda forma farmacéutica unitaria, y
- c) un recipiente para contener dichas formas farmacéuticas unitaria primera

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X
X

y segunda

De acuerdo con un aspecto adicional de la presente invencion se provee un maletín que comprende

- a) un compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, junto con un diluyente o trasportador farmacéuticamente aceptables, en una primera forma farmaceutica unitaria,
- b) un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, en una segunda forma farmaceutica unitaria, y
- c) un recipiente para contener dichas formas farmaceuticas unitaria primera y segunda

De acuerdo con otra característica de la invencion se provee el uso de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, y un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en la manufactura de un medicamento para uso en la produccion de un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre

De acuerdo con otra característica de la invencion se provee el uso de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en la manufactura de un medicamento para uso en el tratamiento afecciones hiperlipidemicas en un animal de sangre caliente, tal como el hombre

De acuerdo con un aspecto adicional de la presente invencion se provee un tratamiento de combinación que comprende la administracion de una cantidad efectiva de un compuesto de la formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, opcionalmente junto con un diluyente o trasportador farmacéuticamente aceptables, con la administracion simultanea, secuencial

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o separada de una cantidad efectiva de un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, opcionalmente junto con un diluyente o transportador farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre necesitado de dicho tratamiento terapéutico

Además de su uso en medicina terapeutica, los compuestos de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, son tambien utiles como herramientas farmacológicas en el desarrollo y estandarización de sistemas de prueba *in vitro* e *in vivo* para la evaluación de los efectos de inhibidores de IBAT en animales de laboratorio tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la investigación de nuevos agentes terapeuticos

Muchos de los intermedios descritos aquí son novedosos y se proveen en consecuencia como una característica de la invencion. Por ejemplo compuestos de formula (IXa), (IXb), (Xa) y (Xb) muestran actividad inhibidora IBAT cuando se prueban en el análisis de prueba *in vitro* referenciado arriba y se reivindicari por lo tanto como una característica adicional de la invencion

Así pues en una característica adicional de la invención, se provee un compuesto de fórmula (IXa), (IXb), (Xa) o (Xb), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

Por lo tanto de acuerdo con un aspecto adicional de la invención se provee una composición farmaceutica que comprende compuesto de fórmula (IXa), (IXb), (Xa) o (Xb), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, como se define anteriormente en el texto en asociación con un diluyente o transportador farmacéuticamente aceptables

De acuerdo con un aspecto adicional de la presente invencion se provee un compuesto de la formula (IXa), (IXb), (Xa) o (Xb), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco

del mismo, como se define anteriormente en el texto para uso en un metodo de tratamiento terapeutico o profiláctico de un animal de sangre caliente, tal como el hombre

Por lo tanto, de acuerdo con este aspecto de la invencion se provee un compuesto de la fórmula (IXa), (IXb), (Xa) y (Xb), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se define anteriormente en el texto para uso como un medicamento

De acuerdo con otra característica de la invencion se provee el uso de un compuesto de la fórmula (IXa), (IXb), (Xa) o (Xb), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo como se define anteriormente en el texto en la manufactura de un medicamento para uso en la produccion de un efecto inhibidor IBAT 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 formula (IXa), (IXb), (Xa) o (Xb), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo como se define anteriormente en el texto en la manufactura de un medicamento para uso en el tratamiento afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre

De acuerdo con otra característica de este aspecto de la invención se provee un metodo para producir un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (IXa), (IXb), (Xa) o (Xb), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

De acuerdo con otra característica de este aspecto de la invención se provee un metodo de tratar afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (IXa), (IXb), (Xa) o (Xb), o una sal

farmaceuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

En las anteriores diferentes características de composición farmaceutica, proceso, método, uso y manufactura de un medicamento, se aplican también las incorporaciones alternativas y preferidas de los compuestos de la invención descritas 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 μ m (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 CD₃OD 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, y los múltiplos de picos se muestran como sigue s, singlete, d, doblete, dd,

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doble doblete, t, triplete, tt, triple triplete, q, cuartete, tq, triple cuartete, m, multiplete, br, amplio, LCMS se registraron en una Waters ZMD, LC columna x Terra MS C₈(Waters), detección con un HP 1100 MS-detector equipado con arreglo de diodos, los espectros de masa (MS) (bucle) se registraron en VG Platform II (Fisons Instruments) con un HP-1100 MS-detector equipado con arreglo de diodos, a menos que se indique lo contrario el ión de masa citado es (MH⁺),

(vi) a menos que se especifiquen mas detalles en el texto, la cromatografía analítica de líquido de alto rendimiento (HPLC) se realizó en Prep LC 2000 (Waters), Kromasil Cg, 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,

(ix) donde se menciona una columna "ISOLUTE", esto significa una columna que contenía 2g de sílice, estando contenido el sílice en una jeringa desechable de 6ml y soportada por un disco poroso de tamaño de poro 54Å, obtenida de International Sorbent Technology bajo el nombre "ISOLUTE", "ISOLUTE" es una marca registrada,

(x) las siguientes abreviaturas pueden usarse antes o mas arriba en el texto

DCM	diclorometano,
DMF	N,N-dimetilformamida;
TFA	ácido trifluoroacético,
TBTU	o-Benzotriazol-1-il-N,N',N'-tetrametiluronio tetrafluoroborato,
EtOAc	acetato de etilo, y
MeCN	acetonitrilo

Ejemplo 1

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1,1-Dioxo-3,3-dibutil-5-fenil-7-bromo-8-(N-{(R)- α -[N-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-bromo-8-carboximetoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Método 2, 0 020 g, 3.71×10^{-5} mol) en DCM (4 ml) se agregó (R)- α -[N-(t-butoxicarbonilmetil)carbamoil]bencilamina (Método 5, 0 013 g, 4.82×10^{-5} mol) y N-metilmorfolina (0 015 ml, 1.48×10^{-4} mol). La mezcla se agitó durante 5 minutos y luego se agregó TBTU (0 015 g, 4.82×10^{-5} mol). La mezcla de reacción se agitó durante la noche y luego se agregó TFA (1 5 ml). Después de 1 hora, la solución se diluyó con tolueno, antes que se retirara el solvente bajo presión reducida. El residuo se purificó por HPLC preparativa usando un tampón MeCN / acetato de amonio como eluyente, y se secó por congelamiento, para producir el compuesto del título en 0 026 g (96 %) como un sólido blanco. NMR (400 MHz, DMSO-d₆) 0 60-0 80 (m, 6H), 0 80-1 60 (m, 12H), 3 30 (dd (AB), 1H), 3 45 (dd (AB), 1H), 3 85 (brs, 2H), 4 70 (d (AB), 1H), 4 75 (d (AB), 1H), 5 60 (d, 1H), 6 90-7 50 (m, 12H), 8 00-8 10 (m, 1H) 8 55 (d, 1H).

Ejemplo 2

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Método 3, 0 016 g, 3.16×10^{-5} mol) en DCM (4 ml) se agregó (R)- α -[N-(t-butoxicarbonilmetil)carbamoil]bencilamina (Método 5, 0 012 g, 4.54×10^{-5} mol) y N-metilmorfolina (0 015 ml, 1.48×10^{-4} mol). La mezcla se agitó durante 5 minutos y luego se agregó TBTU (0 015 g, 4.82×10^{-5} mol). La mezcla de reacción se agitó durante la noche y luego se agregó TFA (1 5 ml). Después de 1 hora, la solución se diluyó con tolueno, antes que se retirara el solvente bajo presión reducida. El residuo se purificó por HPLC preparativa usando un tampón MeCN / acetato de amonio como eluyente y se seco por

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congelamiento, para producir el compuesto del título en 0 018 g (82 %) como un sólido blanco NMR (400 MHz, DMSO-d₆) 0 65-0 80 (m, 6H), 0 85-1 60 (m, 12H), 2 10 (s, 3H), 3 65 (dd (AB), 1H), 3 75 (dd (AB), 1H), 3 85 (brs, 2H), 4 65 (d (AB), 1H), 4 75 (d (AB), 1H), 5 60 (d, 1H), 6 55 (s, 1H), 6 90-7 50 (m, 11H), 8 45 (d, 1H), 8 50-8 60 (m, 1H)

Ejemplo 3

1,1-Dioxo-3,3-dibutil-5-fenil-7-bromo-8-(N-((R)-α-[N-(2-sulfoetil) carbamoil]-4-hidroxibencil)carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-bromo-8-carboximetoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 2, 0 050 g, 9.27×10^{-5} mol) en DMF (6 ml) se agregó ácido 2-[[[(2R)-2-amino-2-(4-hidroxifenil)etanoil]amino]etanosulfónico (Metodo 6, 0 033 g, 1.20×10^{-4} mol) y N-metil morfolina (0 041 ml, 3.72×10^{-4} mol) La mezcla se agito durante 10 minutos y luego se agrego TBTU (0 039 g, 1.21×10^{-4} mol) La mezcla de reacción se agito durante la noche y el solvente se retiró bajo presión reducida. El residuo se purifico por HPLC preparativa usando un tampón MeCN / acetato de amonio como eluyente y se secó por congelamiento, para producir el compuesto del título en 0 039 g (53 %) como un sólido blanco NMR (400 MHz, DMSO-d₆) 0 60-0 80 (m, 6H), 0 80-1 60 (m, 12H), 2 40-2 60 (m, 2H), 3 10-3 50 (m, 2H), 3 85 (brs, 2H), 4 70 (d (AB), 1H), 4 75 (d (AB), 1H), 5 25 (d, 1H), 6 70 (s, 1H), 6 75 (s, 1H), 6 85-7 80 (m, 10H), 8 15-8 25 (m, 1H) 8 45 (d, 1H), 9 40 (brs, 1H)

Ejemplo 4

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-((R)-α-[N-((S)-1-carboxi-2-hidroxi-etil)carbamoil]bencil)carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

Una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 3, 0 050 g, 0 099 mmol), *t*-butil N-[(2R)-2-amino-2-feniletanoil]-*o*-(*t*-butil)-L-serinato (Método 14, 0 042 g, 0 120 mmol) y N-metil morfolina (0 033 ml, 0 299 mmol)

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X

en DCM (4 ml) se agito a temperatura ambiente durante 10 minutos, despues de lo cual se agregó TBTU (0 041 g, 0 128 mmol) Despues de 8 horas, la conversión se concluyo, m/z 839 7 Se agrego TFA (2 ml) y la mezcla de reaccion se agitó durante 12 horas La solución se transfirió a un embudo separado y se lavo con agua y luego se concentró El residuo se purificó por HPLC preparativa usando una gradiente de 40-60% MeCN en 0 1M tampon de acetato de amonio como eluyente El compuesto del titulo se obtuvo en 0 045 g (63 %) como un sólido blanco NMR (400 MHz, DMSO-d₆) 0 60-0 80 (6H, m), 0 85-1 60 (12H, m), 2 10 (3H, s), 3 40-3 65 (2H, m), 3 85 (2H, brs), 4 10-4 20 (1H, m), 4 70 (1H, d(AB)), 4 75 (1H, d(AB)), 5 70 (1H, d), 6 60 (1H, s), 6 85-7 50 (12H, m), 8 50 (1H, d), 8 60 (1H, d), m/z 839 7

Ejemplo 5

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-((R)-α-[N-((S)-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

Una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-((R)-α-carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 0 055 g, 0 086 mmol), L-alanina, 1,1-dimetiletil éster, clorhidrato (0 017 g, 0 098 mmol) y N-metilmorfolina (0 028 ml, 0 254 mmol) en DCM (5 ml) se agitó a temperatura ambiente durante 10 minutos, después de lo cual se agrego TBTU (0 033 g, 0 103 mmol) Despues de 16 horas la conversión se concluyó, m/z 767 4 Se agrego TFA (2 5 ml) y la mezcla de reaccion se agitó durante 2 horas La solución se diluyó con tolueno y luego se concentró El residuo se purificó por HPLC preparativa usando una gradiente de 40-60% MeCN en 0 1M tampon de acetato de amonio como eluyente El compuesto del titulo se obtuvo en 0 044 g (72 %) como un sólido blanco NMR (400 MHz) 0 70-0 85 (6H, m), 0 90-1 70 (12H, m), 1 30 (3H, d), 2 10 (3H, s), 3 95 (2H, brs), 4 25-4 40 (1H, m), 4 60 (1H, d(AB)), 4 65 (1H, d(AB)), 5 60 (1H, s), 6 60 (1H, s), 6 95-7 50 (11H, m), m/z 767 4

Ejemplo 6

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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

Una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 0 055 g, 0 086 mmol), ácido butanoico, 2-amino-, 1,1-dimetiletil éster, clorhidrato, (2S)- (0 020 g, 0 102 mmol) y N-metilmorfolina (0 035 ml, 0 316 mmol) en DCM (5 ml) se agitó a temperatura ambiente durante 10 minutos, después de lo cual se agregó TBTU (0 036 g, 0 112 mmol). Después de 19 horas se agregaron más ácido butanoico, 2-amino-, 1,1-dimetiletil éster, clorhidrato, (2S)- (0 020 g, 0 102 mmol), N-metilmorfolina (0 035 ml, 0 316 mmol) y TBTU (0 036 g, 0 112 mmol). Después de 68 horas, la conversión se concluyó, m/z 781 5. Se agregó TFA (2 ml) y la mezcla de reacción se agitó durante 7 horas y luego se agregó más TFA (2 ml). Después de 18 horas se concluyó la reacción. La solución se transfirió a un embudo separado y se lavó con agua y luego se concentró. El residuo se purificó por HPLC preparativa usando una gradiente de 40-60% MeCN en 0 1M tampón de acetato de amonio como eluyente. El compuesto del título se obtuvo en 0 026 g (41 %) como un sólido blanco. NMR (400 MHz, DMSO-d₆) 0 65 (3H, t), 0 65-0 80 (6H, m), 0 85-1 75 (14H, m), 2 10 (3H, s), 3 80 (2H, brs), 3 95-4 10 (1H, m), 4 65 (1H, d(AB)), 4 75 (1H, d(AB)), 5 65 (1H, d), 6 55 (1H, s), 6 85-7 50 (12H, m), 8 50 (1H, d), 8 60 (1H, d), m/z 781 5.

Ejemplo 7

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

Una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 0 055 g, 0 086 mmol), S-metil-L-cisteína tert-butil éster (Pestic Sci, EN, 45, 4, 1995, 357-362, 0 020 g, 0 105 mmol) y N-metilmorfolina (0 035 ml, 0 317 mmol) en DCM (5 ml) se agitó a temperatura ambiente

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durante 10 minutos, después de lo cual se agregó TBTU (0.036 g, 0.112 mmol). Después de 19 horas se agregaron más S-metil-L-cisteina tert-butil éster (0.020 g, 0.105 mmol), N-metilmorfolina (0.035 ml, 0.317 mmol) y TBTU (0.036 g, 0.112 mmol). Después de 68 horas la conversión se concluyó, m/z 811.6 (M-1). Se agregó TFA (1.5 ml) y la mezcla de reacción se agitó durante 7 horas y se agregó más TFA (1.5 ml). Después de 18 horas se concluyó la reacción. La solución se transfirió a un embudo separado y se lavó con agua y luego se concentró. El residuo se purificó por HPLC preparativa usando una gradiente de 40-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. El compuesto del título se obtuvo en 0.042 g (65 %) como un sólido blanco. NMR (400 MHz, DMSO-d₆) 0.65-0.80 (6H, m), 0.85-1.60 (12H, m), 1.85 (3H, s), 2.10 (3H, s), 2.60-2.80 (2H, m), 3.80 (2H, brs), 4.20-4.35 (1H, m), 4.65 (1H, d(AB)), 4.75 (1H, d(AB)), 5.65 (1H, d), 6.55 (1H, s), 6.85-7.50 (12H, m), 8.45 (1H, d), 8.65 (1H, d).

Ejemplo 8

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-((R)-α-[N-((S)-1-carboxi-2-carbamoyl-etil)carbamoyl]bencil)carbamoylmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

N-Metilmorfolina (0.034 ml, 0.314 mmol), TBTU (0.033 g, 0.103 mmol) y L-asparagina, 1,1-dimetiletil éster, monohidrato (0.021 g, 0.093 mmol) se agregaron sucesivamente a una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-((R)-α-carboxibencil)carbamoylmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 0.050 g, 0.078 mmol) en DCM (5 ml). Después de 2 horas aún había restos de material inicial y se agregaron más N-metilmorfolina (0.035 ml, 0.314 mmol) y TBTU (0.033 g, 0.103 mmol). Después de 12 horas la conversión se concluyó, m/z 810.5. La solución se diluyó con agua (~5 ml) y luego se extrajo tres veces con éter. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron. El residuo se disolvió en una mezcla de DCM (5 ml) y TFA (2.5 ml) y la solución se agitó durante 21 horas. La solución se transfirió a un embudo separado y se lavó con agua y luego se concentró. El residuo se purificó por

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HPLC preparativa usando una gradiente de 40-60% MeCN en 0.1M tampón de acetato de amonio como eluyente. El compuesto del título se obtuvo en 0.022 g (37 %) como un sólido blanco. NMR (400 MHz, DMSO-d₆) 0.60-0.80 (6H, m), 0.80-1.60 (12H, m), 2.10 (3H, s), 2.25-2.70 (2H, m), 3.80 (2H, brs), 4.35-4.45 (1H, m), 4.65 (1H, d(AB)), 4.75 (1H, d(AB)), 5.60 (1H, d), 6.55 (1H, s), 6.70-7.60 (14H, m), 8.45 (1H, d), 8.55-8.70 (1H, m), m/z 810.5

Ejemplo 9

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-(N-((R)-α-[N-(2-sulfoetil)carbamoyl]-4-hidroxibencil)carbamoylmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina sal de amonio

El compuesto del título se sintetizó usando el procedimiento de Ejemplo 3 a partir de 1,1-dioxo-3,3-dibutil-5-fenil-7-metil-8-carboximetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Método 3, 43mg, 0.085mmol). El solvente se evaporó después de 3 horas y el producto crudo se purificó por HPLC preparativa (columna C8, 50x250mm) usando una gradiente (40/60 a 60/40) de MeCN/0.1M tampón de acetato de amonio como eluyente. La liofilización produjo 38mg (57% rendimiento) del compuesto del título. NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 2.8-3.0 (m, 2H), 3.55-3.7 (m, 2H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.35 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H), 7.15-7.4 (m, 7H), 8.15 (t, 1H), m/z 763

Ejemplo 10

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-(N-((R)-α-[N-(carboximetil)carbamoyl]-4-hidroxibencil)carbamoylmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-((R)-α-carboxi-4-hidroxibencil)carbamoylmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 18, 50mg, 0.076mmol) se disolvió en DCM (4ml). Glicina *tert*-butil éster (12mg, 0.091mmol), 2,6-lutidina (20μl 0.15mmol) y TBTU (30mg, 0.091mmol) se agregaron sucesivamente. Después de 3 horas se agregó

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DMF (2ml) y se obtuvo una solución clara. Se agregaron glicina *tert*-butil éster (0.04mmol), 2,6-lutidina (0.15mmol) y TBTU (2x0.03mmol) y la mezcla se agitó durante 3 horas más. La mezcla de reacción se concentró y luego se extrajo entre KHSO₄ acuoso (0.05M, pH=1) y EtOAc (2x20ml). La fase orgánica se lavó con salmuera, se secó y se concentró para producir un aceite que contenía el *tert*-butil éster del compuesto del título. M/z 769 y 786 (M+18 (NH₄⁺)). Se agregaron DCM (4ml) y TFA (1.5ml). La mezcla se agitó durante 2 horas y luego se concentró y se purificó por HPLC preparativa en una columna C8 (50x250mm) usando una gradiente (20/80 a 50/50) de MeCN/0.1M tampón de acetato de amonio como eluyente. La liofilización produjo el compuesto del título en 52% (28mg). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.9 ABq, 2H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.45 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H) 7.15-7.4 (m, 7H), m/z 730 (M+18 (NH₄⁺)).

Ejemplo 11

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-(N-{(R)-α-[N-((S)-1-carboxietil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

El compuesto del título se sintetizó por el procedimiento descrito en Ejemplo 10 a partir de 1,1-dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-((R)-α-carboxi-4-hidroxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 18, 50mg, 0.076mmol) y *tert*-butil L-alaninato clorhidrato. Se confirmó el intermedio *tert*-butil éster del compuesto del título. M/z 783 y 800 (M+18 (NH₄⁺)). La hidrólisis y purificación por HPLC preparativa produjeron el compuesto del título en 20 mg (37% rendimiento). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.3 (d, 3H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.35 (q, 1H), 4.6 (ABq, 2H), 5.45 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H) 7.15-7.4 (m, 7H), m/z 744.

Ejemplo 12

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1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -[N-((S)-1-carboxi-2-hidroxi-2-
hidroxietil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-
1,2,5-benzotiadiazepina

El compuesto del título se sintetizó por el procedimiento descrito en Ejemplo 10 a partir de 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 (Ejemplo 18, 50mg, 0.076mmol) y *tert*-butil *o*-(*tert*-butil)-L-serinato clorhidrato. Se confirmó el intermedio ester, m/z 755. La hidrólisis y purificación por HPLC preparativa produjeron el compuesto del título en 19 mg (33% rendimiento). M/z 743 (M+1). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.65-3.8 (m, 2H), 3.95 (brs, 2H), 4.33 (t, 1H), 4.6 (ABq, 2H), 5.5 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H), 7.15-7.4 (m, 7H).

Ejemplo 13

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -[N-(2-sulfoetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina sal de amonio

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50mg, 0.078mmol) se disolvió en 3ml DCM. Se agregó taurina de tetrabutilamonio (88mg, 0.236mmol) y la mezcla se agitó durante 30 minutos. Se agregó TBTU (30mg, 0.093mmol) y la mezcla se agitó durante la noche. La solución se concentró y se purificó por HPLC preparativa usando una columna C8 (50x250mm). Una gradiente (20/80 a 60/40) de MeCN/0.1M tampón de acetato de amonio se usó como eluyente. La liofilización produjo 43mg de una mezcla de producto, la cual se purificó posteriormente por cromatografía de destello (5g) usando una gradiente de 3-20% MeOH en DCM como eluyente. Se recogieron y concentraron las fracciones que contenían el compuesto. Se agregaron MeOH y agua y la liofilización produjo 17mg (29% rendimiento). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 2.85-3.0 (m, 2H), 3.5-3.7 (m, 2H), 3.95 (brs, 2H),

4 6 (ABq, 2H), 5 45 (s, 1H), 6 6 (s, 1H), 7 05 (t, 1H) 7 15-7 45 (m, 10H), m/z 747

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Ejemplo 14

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 -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50mg, 0 078mmol) se disolvió en 1ml DMF y 1ml DCM Se agregaron *o-tert*-butil-(L)-treonina *tert*-butil éster (22mg, 0 095mmol) y *N*-metilmorfolina (17 μ l, 0 154mmol) y la mezcla se agito durante 20min Se agregó TBTU (30mg, 0 093mmol) y la solución se agitó durante 2 horas y se concentró Se agregó DCM (20ml) y la solución se lavo con 10ml salmuera, se seco y se concentró a 3ml Se confirmó el intermedio éster, m/z 853 Se agregó TFA (0 5ml) y la solución se agitó durante la noche Se agrego 0 5ml TFA mas y despues de 3 horas la mezcla se concentró y se purificó por HPLC preparativa en una columna C8 (50x250mm) Una gradiente (20/80 a 60/40) de MeCN/0 1M tampon de acetato de amonio se uso como eluyente La liofilizacion produjo el compuesto del título en 61% rendimiento (36mg) NMR (400MHz) 0 8 (t, 6H), 0 9 (d, 3H), 1 0-1 2 (m, 6H), 1 25-1 4 (m, 2H), 1 4-1 5 (m, 2H), 1 55-1 7 (m, 2H), 2 1 (s, 3H), 3 95 (brs, 2H), 4 15-4 25 (m, 1H), 4 35 (d, 1H), 4 6 (ABq, 2H), 5 65 (s, 1H), 6 6 (s, 1H), 7 05 (t, 1H), 7 1 (d, 2H), 7 15-7 4 (m, 6H), 7 5 (d, 2H), m/z 741

Ejemplo 15

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 -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50mg, 0 078mmol) se disolvio en 2ml DMF Se agregaron *tert*-

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X

nutril (L)-valinato (20mg, 0.095mmol) y *N*-metilmorfolina (17μl, 0.154mmol) y la mezcla se agitó durante 20 minutos. Se agregó TBTU (30mg, 0.093mmol) y la solución se agitó durante la noche. Se agregaron más *N*-metilmorfolina (8μl, 0.078mmol) y TBTU (3x5mg, 0.047mmol) y la mezcla se agitó durante la noche y se concentró. El residuo se purificó por cromatografía de destello (2g) usando EtOAc/hexano (3/7) como eluyente. La fracción recogida se lavó con 5% NaHCO₃ (10ml), 0.1M KHSO₄ (15ml) y salmuera antes de secarla y concentrarla. Se confirmó el intermedio *tert*-butil ester del compuesto del título, *m/z* 812 (M+18 (NH₄⁺)). Se agregaron DCM (4ml) y TFA (1.5ml) y la mezcla se agitó durante la noche, se concentró y se purificó por HPLC preparativa en una columna C8 (50x250mm). Un gradiente (20/80 a 60/40) de MeCN/0.1M tampón de acetato de amonio se usó como eluyente. La liofilización produjo el compuesto del título en 31% rendimiento (18mg). NMR (400MHz) 0.65-0.85 (m, 12H), 0.95-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.0-2.2 (m, 1H), (s, 3H), 3.95 (brs, 2H), 4.3 (d, 1H), 4.6 (ABq, 2H), 5.65 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), (d, 2H), 7.25-7.4 (m, 6H), 7.5 (d, 2H), *m/z* 739.

Ejemplo 16

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-1,2,5-benzotiadiazepina

El compuesto del título se sintetizó por el procedimiento dado en Ejemplo 15 a partir de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-{(R)-α-carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50mg, 0.078mmol) y *tert*-butil (L)-leucinato (21mg, 0.095mmol). Se retiró el DMF y se agregó 20ml EtOAc y se lavó con NaHCO₃ (5%, 10ml), 0.1M KHSO₄ (15ml) y salmuera antes de secarlo y concentrarlo. El residuo resultante se purificó por cromatografía de destello como se describe. Se confirmó el intermedio *tert*-butil ester del compuesto del título, *m/z* 826 (M+18 (NH₄⁺)). La hidrólisis y purificación por HPLC preparativa produjeron el compuesto del título en 21% rendimiento (12mg).

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NMR (400MHz) 0.7 (dd, 6H), 0.75-0.85 (m, 6H), 0.95-1.2 (m, 6H), 1.25-1.7 (m, 9H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.3-4.4 (m, 1H), 4.6 (ABq, 2H), 5.55 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), 7.2 (d, 2H), 7.25-7.4 (m, 6H), 7.5 (d, 2H), m/z 753

Ejemplo 17

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -[N-(1-(S)-1-carboxi-2-(S)-2-metilbutil)carbamoil]bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

El compuesto del título se sintetizó por el procedimiento dado en Ejemplo 15 a partir de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50mg, 0.078mmol) y *tert*-butil (L)-*iso*-leucinato (21mg, 0.095mmol). Se retiró el DMF y se agregó 20ml EtOAc y se lavó con NaHCO₃ (5%, 10ml), 0.1M KHSO₄ (15ml) y salmuera antes de secarlo y evaporarlo. No se realizó purificación por cromatografía de destello. Se confirmó el intermedio *tert*-butil éster del compuesto del título, m/z 809. La hidrólisis y purificación por HPLC preparativa produjeron el compuesto del título en 37% rendimiento (22mg). NMR (400MHz) 0.65-1.4 (m, 22H), 1.4-1.5 (m, 2H), 1.5-1.7 (m, 2H), 1.75-1.85 (m, 1H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.25 (d, 1H), 4.6 (ABq, 2H), 5.6 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), 7.2 (d, 2H), 7.25-7.4 (m, 6H), 7.45 (d, 2H), m/z 753

Ejemplo 18

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

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 3, 295mg, 0.58mmol) se disolvió en 10 ml DCM. 4-(1-(R)-*t*-butoxicarbonil-1-aminometil)fenol (Metodo 7, 160mg, 0.72mmol), 2,6-lutidina (140 μ l, 1.20mmol) y TBTU (230mg, 0.72mmol) se agregaron sucesivamente. La mezcla se agitó durante 3 horas. Se agregó más 4-(1-(R)-*t*-butoxicarbonil-1-aminometil)fenol (10mg,

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0.04 mmol) y la agitación se continuó durante 2 horas. Se agregó DCM (20 ml) y la solución se lavó con NaHCO₃ (5%, 20 ml), KHSO₄ (0.3 M, 20 ml), salmuera (20 ml) antes de secarla y concentrarla a un volumen de 10 ml. Se confirmó el *tert*-butil éster del compuesto del título, m/z 729 (M+18 (NH₄⁺)). Se agregó TFA (1.3 ml) y la mezcla se agitó durante 4.5 horas y se concentró. El producto crudo se purificó por HPLC preparativa usando una columna C8 (50x500 mm) y una gradiente (40/60 a 70/30 durante 40 minutos) de MeCN/0.1 M tampón de acetato de amonio como eluyente. La liofilización produjo el compuesto del título en 77.5% (302 mg). NMR (400 MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.3 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H), 7.15-7.4 (m, 7H), m/z 673 (M+18 (NH₄⁺)).

Ejemplo 19

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-{(R)-α-[N-((S)-1-carboxi-4-aminobutil)carbamoil]bencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-{(R)-α-[N-((S)-1-(*t*-butoxicarbonil)-4-(benciloxycarbonilamino)butil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Método 8, 0.006 mg) se disolvió en DCM (0.2 ml), TFA (1 ml) se agregó y la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Se retiraron DCM y TFA a presión reducida y el residuo se purificó por HPLC preparativa usando MeCN/NH₄⁺ buffer 50/50 como eluyente. Se evaporó el acetonitrilo y la liofilización produjo el compuesto del título en 37% rendimiento (21.9 mg). M/z 754.4 y 752.4 (M-H)⁻.

Ejemplo 20

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-{(R)-α-[N-((S)-1-carboxi-4-(benciloxycarbonilamino)butil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

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X
X
X

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -{N-[(S)-1-(*t*-butoxicarbonil)-4-(benciloxicarbonilamino)butil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 8, 0 006 mg) se disolvió en DCM (0 1 ml), se agrego TFA (0 15 ml) y la mezcla de reaccion se agito a temperatura ambiente durante 1 hora. Se retiraron DCM TFA a presion reducida y el residuo se purificó por HPLC preparativa usando tampon MeCN/NH₄⁺ 55/45 como eluyente Se evaporo el acetonitrilo y la liofilización produjo el compuesto del título en 35% rendimiento (2 mg) M/z 888 7 y 886 7 (M-H)

Ejemplo 21

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{N-[(R)- α -[(S)-2-carboxipirrolidin-1-ilcarbonil]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 -[(S)-2-(*t*-butoxicarbonil)pirrolidin-1-ilcarbonil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 10, 41 mg, 0 052 mmol) se disolvió en DCM TFA 4 1 (3 ml) y se agito durante 3 horas La mezcla de reacción se evaporó bajo presion reducida. El residuo se purifico por HPLC preparativa usando una gradiente acetonitrilo/tampon de acetato de amonio (5/95 a 100/0) como eluyente Se obtuvieron 26 5 mg (70%) del compuesto del titulo despues de la liofilizacion M/z 737 3034

Ejemplo 22

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-(carboximetil)-N-metilcarbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

El compuesto del titulo se sintetizó a partir de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-(*t*-butoxicarbonilmetil)-N-metilcarbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 11) por el método de Ejemplo 21 NMR (500MHz, 2 rotameros mezcla 3 1) . Rotámero mayor 0 8 (brt, 6H), 1 0-1.24

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(m, 6H), 1.25-1.4 (m, 2H), 1.4-1.51 (m, 2H), 1.56-1.68 (m, 2H), 2.09 (s, 3H), 3.0 (s, 3H), 3.75-4.21 (m, 4H), 4.60 (ABq, 2H), 6.01 (s, 1H), 6.58 (s, 1H), 7.05 (t, 1H), 7.16-7.28 (m, 3H), 7.3-7.45 (m, 5H), 7.48 (brd, 2H) picos adicionales del rotamero menor a 2.14 (s), 3.0 (s), 4.56 (ABq), 5.81 (s), 6.61 (brs), m/z 711.4

Ejemplo 23

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-{(R)- α -[N-(1-(R)-2-(R)-1-carboxi-1-hidroxiprop-2-il)carbamoil]bencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

El compuesto del título se sintetizó a partir de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -{N-[1-(R)-2-(R)-1-*t*-butoxicarbonil]-1-hidroxiprop-2-il]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 12) por el método de Ejemplo 21 M/z 741.3

Ejemplo 24

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-{(R)- α -[N-(sulfometil)carbamoil]bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina sal de amonio

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50 mg, 0.078 mmol), ácido aminometanosulfónico (15 mg, 0.088 mmol) y N-metilmorfolina (17 μ l, 0.156 mmol) se disolvieron en DMF (2ml). Se agregó sulfato hidrogenado de tetrabutilamonio (35 mg, 0.103 mmol) y la mezcla se calentó durante 15 minutos a 60°C. Después de retirar por calentamiento, se agregó TBTU (45 mg, 0.14 mmol). La mezcla de reacción se agitó a temperatura ambiente 40 minutos, luego 60°C durante una hora. Después de agitarse durante la noche, se agregaron 35 mg TBTU. Luego de 6 horas se agregaron 29 mg TBTU en porciones pequeñas y la mezcla de reacción se agitó durante la noche. La mezcla se evaporó bajo presión reducida. El producto se purificó usando HPLC preparativa usando

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una gradiente acetonitrilo/tampón de acetato de amonio (5/95 a 100/0) como eluyente para producir 10 mg (17%) del compuesto del título como una sal de amonio NMR (600MHz) 0 77 (brt, 6H), 0 97-1 22 (m, 6H), 1 24-1 48 (m, 4H), 1 51-1 68 (m, 2H), 2 08 (s, 3H), 3 7-4 18 (m, 2H), 4 24 (d, 1H), 4 39 (d, 1H), 4 62 (ABq, 2H), 5 62 (s, 1H), 6 58 (brs, 1H), 7 02 (brt, 1H), 7 14-7 23 (m, 2H), 7 24-7 36 (m, 6H), 7 45 (d, 2H), m/z 732 9

Ejemplo 25

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{N-[(R)- α -(*t*-butoxicarbonil)bencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Método 9, 762 mg, 1 09 mmol) se disolvió en una mezcla de TFA (6 65 ml) y trietilsilano (0 350 ml) La mezcla de reacción se agitó durante una hora y luego se evaporó bajo presión reducida para producir el compuesto del título en un rendimiento cuantitativo (714 mg) NMR (500MHz) 0 8 (brt, 6H), 0 96-1 25 (m, 6H), 1 25-1 4 (m, 2H), 1 42-1 51 (m, 2H), 1 57-1 69 (m, 2H), 2 11 (s, 3H), 3 8-4 15 (m, 2H), 4 66 (ABq, 2H), 5 49-5 53 (m, 1H), 6 61 (s, 1H), 7 06 (t, 1H), 7 18-7 26 (m, 2H), 7 28-7 45 (m, 8H), 8 35 (d, NH), m/z 640 2

Ejemplo 26

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 -carboxi-4-hidroxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 18, 100mg, 0 152mmol) se disolvió en 3ml DMF Se agregaron α -*tert*-butil-(L)-treonina *tert*-butil éster (50mg, 0 216mmol) y N-metilmorfolina (34 μ l, 0 309mmol) y la mezcla se agitó durante 5 minutos Se agregó TBTU (60mg, 0 187mmol) y la solución se agitó durante 30 minutos Se agregó ácido fórmico (1-2 gotas) y la mezcla se extrajo entre EtOAc y agua La fase

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H

acuosa se lavo con EtOAc y las fases orgánicas combinadas se lavaron con 2%NaHCO₃, salmuera, se secaron y se concentraron. Se confirmó el intermedio *t*-butil ester del compuesto del título, m/z 869 Se agregaron DCM (3ml) y TFA (0.5ml) y la solución se agitó durante la noche. La mezcla se concentró y se purificó por HPLC preparativa en una columna C8 (50x250mm). Una gradiente (20/80 a 50/50) de MeCN/0.1M tampón de acetato de amonio se usó como eluyente. La liofilización produjo el compuesto del título en 61% rendimiento (71mg). NMR (400MHz) 0.78 (t, 6H), 0.93 (d, 3H), 1.0-1.22 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.52 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.18-4.25 (m, 1H), 4.35 (d, 1H), 4.63 (ABq, 2H), 5.53 (s, 1H), 6.57 (s, 1H), 6.75 (d, 2H), 7.03 (t, 1H), 7.2 (d, 2H), 7.23-7.37 (m, 5H), m/z 757

Ejemplo 27

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-(N-((R)-α-[N-((S)-1-carboxi-2-metilpropil)carbamoil]-4-hidroxibencil)carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

El compuesto del título se sintetizó por el procedimiento descrito en Ejemplo 26 a partir de 1,1-dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-((R)-α-carboxi-4-hidroxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 18, 70mg, 0.108mmol) y *tert*-butil (L)-valinato (31mg, 0.148mmol). Se confirmó el intermedio *tert*-butil éster del compuesto del título. M/z 811. La hidrólisis y purificación por HPLC preparativa produjeron el compuesto del título en 56 mg (69% rendimiento). NMR (400MHz) 0.7-0.75 (m, 16H), 0.79 (t, 6H), 0.96-1.24 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.54-1.7 (m, 2H), 2.0-2.2 (m, 1H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.22 (d, 1H), 4.6 (ABq, 2H), 5.54 (s, 1H), 6.58 (s, 1H), 6.75 (d, 2H), 7.03 (t, 1H), 7.2 (d, 2H), 7.23-7.37 (m, 5H), m/z 755

Ejemplo 28

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-(N-((R)-α-[N-((S)-1-carboxibutil)carbamoil]-4-hidroxibencil)carbamoilmetoxi)-2,3,4,5-tetrahidro-

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X1,2,5-benzotriazepina

El compuesto del título se sintetizó por el procedimiento descrito en Ejemplo 26 a partir de 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-benzotriazepina (Ejemplo 18, 36mg, 0.054mmol) y *tert*-butil (L)-norvalinato clorhidrato (16mg, 0.076mmol). Se confirmó el intermedio *tert*-butil éster del compuesto del título. M/z 811. La hidrólisis y purificación por HPLC preparativa produjeron el compuesto del título en 23 mg (56% rendimiento). NMR (400MHz) 0.7-0.85 (m, 9H), 0.97-1.22 (m, 8H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.5-1.8 (m, 4H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.27 (dd, 1H), 4.6 (ABq, 2H), 5.45 (s, 1H), 6.58 (s, 1H), 6.75 (d, 2H), 7.03 (t, 1H), 7.19 (d, 2H), 7.23-7.37 (m, 5H), m/z 755.

Ejemplo 291,1-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-benzotriazepina

Una solución de 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-benzotriazepina (Ejemplo 18, 0.075 g, 0.114 mmol), ácido butanoico, 2-amino-, 1,1-dimetiletil éster, clorhidrato, (2S)-(0.031 g, 0.160 mmol) y N-metilmorfolina (0.050 ml, 0.457 mmol) en DMF (4 ml) se agitó a temperatura ambiente durante 10 minutos, después de lo cual se agregó TBTU (0.048 g, 0.149 mmol). Después de 1 hora, se concluyó la conversión al éster. M/z 797.4. La solución se diluyó con tolueno y luego se concentró. El residuo se disolvió en una mezcla de DCM (5 ml) y TFA (2 ml) y la mezcla se agitó durante 7 horas. El solvente se retiró 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. El compuesto del título se obtuvo en 0.056 g (66%) como un sólido blanco. NMR (400 MHz, DMSO- d_6) 0.70 (3H, t), 0.70-0.80 (6H, m), 0.85-1.75 (14H, m), 2.10 (3H, s), 3.80 (2H, brs), 4.00-4.15 (1H, m), 4.65 (1H, d(AB)), 4.70 (1H, d(AB)), 5.50 (1H,

d), 6 60 (1H, s), 6 65-7 40 (11H, m), 8 35 (1H, d), 8 50 (1H, d) 9 40 (1H, brs)

Ejemplo 30

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

Una solución de 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 (Ejemplo 18, 0 075 g, 0 114 mmol), S-metil-L-cisteína tert-butil éster (Pestic Sci, EN, 45, 4, 1995, 357-362, 0 031 g, 0 160 mmol) y N-metilmorfolina (0 050 ml, 0 457 mmol) en DMF (4 ml) se agitó a temperatura ambiente durante 10 minutos, después de lo cual se agregó TBTU (0 048 g, 0 149 mmol). Después de 1 hora, se concluyó la conversión al éster. M/z 829 5. La mezcla de reacción se diluyó con ácido fórmico (15 ml) y se agitó a 50 °C durante 17 horas. La solución se diluyó con tolueno y luego se concentró. El residuo se purificó por HPLC preparativa usando una gradiente de 20-60% MeCN en 0 1M tampón de acetato de amonio como eluyente. El compuesto del título se obtuvo en 0 070 g (79 %) como un sólido blanco. NMR (400 MHz, DMSO-d₆) 0 605-0 80 (6H, m), 0 80-1 60 (12H, m), 1 85 (3H, s), 2 10 (3H, s), 2 60-2 80 (2H, m), 3 85 (2H, brs), 4 15-4 30 (1H, m), 4 65 (1H, d(AB)), 4 70 (1H, d(AB)), 5 50 (1H, d), 6 60 (1H, s), 6 60-7 35 (11H, m), 8 30 (1H, d), 8 40 (1H, d), 9 40 (1H, brs).

Ejemplo 31

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-((R)- α -[N-(carboximetil)carbamoil]bencil)carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

Una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metil-8-carboximetoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 5, 0 050 g, 0 105 mmol), (R)- α -[N-(*t*-butoxicarbonilmetil)carbamoil]bencilamina (Metodo 86 de WO 02/50051, 0 039 g, 0 148 mmol) y N-metilmorfolina (0 046 ml, 0 417 mmol) en DCM (4 ml) se agitó a temperatura ambiente durante 20 minutos, después de lo cual se agregó TBTU (0 044 g, 0 137 mmol). Después de 1 hora, se

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concluyo la conversión al éster (m/z 721 2 ($M+1$)⁺) El solvente se retiro bajo presión reducida y el residuo se disolvió en ácido fórmico (5 ml) La solución se agitó durante 17 horas y luego se concentró El residuo se purificó por HPLC preparativa usando una gradiente de 40-60% MeCN en 0 1M tampón de acetato de amonio como eluyente El compuesto del título se obtuvo en 0 044 g (63 %) como un sólido blanco NMR (400 MHz, DMSO- d_6) 0 65-0 80 (6H, m), 0 85-1 60 (12H, m), 2 10 (3H, s), 3 40-3 65 (2H, m), 3 70 (2H, bs), 4 60 (1H, d(AB)), 4 70 (1H, d(AB)), 5 55 (1H, d), 6 70 (1H, s), 6 80-7 50 (12H, m), 8 20-8 30 (1H, m), 8 55 (1H, d)

Ejemplo 32

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-(N-{(R)- α -[N-((S)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

Una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metil-8-carboximetoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 16, 0 050 g, 0 105 mmol), (R)- α -{N-[(S)-1-(*t*-butoxicarbonil)propil]carbamoil}-4-hidroxibencilamina (Metodo 19, 0 045 g, 0 146 mmol) y N-metilmorfolina (0 047 ml, 0 427 mmol) en DCM (4 ml) se agitó a temperatura ambiente durante 15 minutos, después de lo cual se agregó TBTU (0 044 g, 0 137 mmol) Después de 17 horas, se concluyó la conversión al éster (m/z 765 7 ($M+1$)⁺) El solvente se retiró bajo presión reducida y el residuo se disolvió en ácido fórmico (5 ml) La solución se agitó durante 3 días y luego se concentró El residuo se purificó por HPLC preparativa usando una gradiente de 40-60% MeCN en 0 1M tampón de acetato de amonio como eluyente El compuesto del título se obtuvo en 0 017 g (23 %) como un sólido blanco NMR (400 MHz, DMSO), 0 60 (3H, t), 0 65-0 80 (6H, m), 0 85-1 75 (14H, m), 2 1 0 (3H, s), 3 75 (2H, bs), 3 90-4 05 (1H, m), 4 60 (1H, d(AB)), 4 65 (1H, d(AB)), 5 50 (1H, d), 6 65-7 30 (11H, m), 8 15 (1H, d), 8 40 (1H, d)

Ejemplo 33

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-[N-{(R)- α -[N-((S)-1-[N-((S)-2-

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~~X~~

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-{*N*-[(S)-2-(*t*-butoxi)-1-(*t*-butoxicarbonil)etil]carbamoil}propil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 20, 14 mg, 0 015 mmol) se disolvio en una mezcla de DCM TFA (3 1,4 ml) La mezcla de reacción se agitó durante 3 5 horas El solvente se evaporó bajo presión reducida. El producto se purificó por HPLC preparativa usando una gradiente MeCN/0 1 M tampon de acetato de amonio (5/95 a 100/0) como eluyente para producir el compuesto del título, 8 mg (65%) NMR (400 MHz) 0 7-0 83 (m, 9H), 0 9-1 40 (m, 8H), 1 40-1 52 (m, 2H), 1 52-1 70 (m, 3H), 1 77-1 88 (m, 1H), 2 11 (s, 3H), 3 8-4 1 (m, 4H), 4 29 (dd, 1H), 4 37 (t, 1H), 4 63 (ABq, 2H), 5 57 (s, 1H), 6 60 (s, 1H), 7 04 (brt, 1H), 7 20 (brd, 2H), 7 25-7 40 (m, 6H), 7 47 (d, 2H), m/z 812 3

Ejemplo 34

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[2-(S)-2-(carboxi)-4-(R)-4-(hidroxi)pirrolidin-1-ilcarbonil]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 -[2-(S)-2-(metoxicarbonil)-4-(R)-4-(hidroxi)pirrolidin-1-ilcarbonil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Método 21, 23 mg, 0 030 mmol) se disolvio en THF H₂O (1 1, 1ml) Se agrego hidroxido de litio (monohidrato, 2 mg, 0 048 mmol) y la mezcla se agitó durante 2 horas Como quedo 50% de material inicial, se agrego mas hidroxido de litio (3 mg) y se dejó durante hora La reacción no habia concluido aún de modo que se agrego más hidroxido de litio (2 mg) y la reacción se agitó durante la noche El producto se purifico por HPLC preparativa usando una gradiente MeCN/0 1 M tampón de acetato de amonio (5/95 a 100/0) como eluyente para producir el compuesto del título, 12 mg (53%) M/z 753 04

Ejemplo 35

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7/2

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[2-(S)-2-(carboxi)-azetidín-1-ylcarbonil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[2-(S)-2-(*t*-butoxicarbonil)azetidín-1-ylcarbonil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina (Metodo 22, 27.5 mg, 0.035 mmol) se disolvió en DCM (3 ml) y se agregó TFA (1 ml). La reacción se agitó durante 1.5 horas. El solvente se evaporó bajo presión reducida. El producto se liofilizó para producir 25 mg del compuesto del título. M/z 722.92

Ejemplo 36

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-{(S)-1-[N-{(S)-1-carboxietil}carbamoil]etil}carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-{(S)-1-[N-{(S)-1-(*t*-butoxicarbonil)etil}carbamoil]etil}carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina (Método 26, 34 mg, 0.041 mmol) se disolvió en una mezcla de DCM/TFA (3.1, 4 ml). La mezcla de reacción se agitó durante 2 horas. El solvente se evaporó bajo presión reducida. El producto se purificó por HPLC preparativa usando una gradiente MeCN/0.1 M tampón de acetato de amonio (5/95 a 100/0) como eluyente para producir el compuesto del título, 23 mg (72%). MMR (500 MHz, CD₃OD) 0.81 (bt, 6H), 0.88-1.54 (m, 16H), 1.56-1.71 (m, 2H), 2.11 (s, 3H), 3.8-4.2 (m, 2H), 4.33-4.42 (m, 2H), 4.66 (ABq, 2H), 5.55 (s, 1H), 6.61 (s, 1H), 7.07 (t, 1H), 7.22 (brd, 2H), 7.28-7.43 (m, 6H), 7.48 (d, 2H), m/z 782.1

Ejemplo 37

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-{(R)-1-(carboxi)-3,3-dimetilbutil}carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina, y

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-{(S)-1-carboxi-3,3-dimetilbutil}carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahydro-1,2,5-

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benzotiadiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-(R)- α -carboxibencil]carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 51mg, 0.080mmol) se disolvió en 2ml DMF. Se agregaron sucesivamente t-butil 4-metil D,L-leucinato (Método 27, 23mg, 0.114mmol), N-metilmorfolina (18 μ l, 0.163 mmol) y TBTU (31mg, 0.097mmol) y la mezcla se agitó durante 2 horas. Se agregó una gota de ácido fórmico y la mezcla se extrajo entre EtOAc y agua. La fase acuosa (pH=3) se lavó con EtOAc. Las capas orgánicas combinadas se lavaron con 5%NaHCO₃ y salmuera y luego se secaron con Na₂SO₄ y se evaporaron a sequedad. Se confirmó el intermedio t-butil éster del compuesto del título M/z 823. Se agregaron DCM (2ml) y TFA (0.5ml) y la solución se agitó durante la noche. La mezcla se concentró y se purificó usando HPLC preparativa en una columna C8 (50x250mm). Se usó como eluyente una gradiente gradual de MeCN (20-50%) en 0.1M tampón de acetato de amonio. Se separaron los dos diastereómeros bajo estas condiciones y se recogieron y liofilizaron por separado. El primer diastereómero eluyente se obtuvo en 5mg (16% rendimiento) y el segundo diastereómero eluyente se obtuvo en 3mg (10% rendimiento). Se asignó la configuración absoluta por comparación de espectros NMR con compuestos relacionados y se encontró que el primer diastereómero eluyente era el (R,R)-diastereómero y el segundo diastereómero eluyente era el (R,S)-diastereómero. M/z 767. NMR del (R,R)-diastereómero (400MHz) 0.79 (t, 6H), 0.95 (s, 9H), 0.99-1.22 (m, 6H), 1.25-1.39 (m, 2H), 1.40-1.51 (m, 2H), 1.57-1.68 (m, 3H), 1.80 (dd, 1H), 2.08 (s, 3H), 3.95 (brs, 2H), 4.47 (dd, 1H), 4.63 (Abq, 2H), 5.61 (s, 1H), 6.58 (s, 1H), 7.04 (t, 1H), 7.20 (d, 2H), 7.25-7.35 (m, 6H), 7.43-7.47 (m, 2H). Y NMR del (R,S)-diastereómero (400MHz) 0.7 (s, 9H), 0.79 (t, 6H), 0.99-1.22 (m, 6H), 1.25-1.39 (m, 2H), 1.40-1.51 (m, 3H), 1.55-1.70 (m, 2H), 1.76 (dd, 1H), 2.12 (s, 3H), 3.95 (brs, 2H), 4.35 (dd, 1H), 4.60 (Abq, 2H), 5.54 (s, 1H), 6.60 (s, 1H), 7.04 (t, 1H), 7.20 (d, 2H), 7.24-7.37 (m, 6H), 7.39-7.46 (m, 2H).

Ejemplo 38

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1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -[N-((R)-1-carboxi-3,3-dimetilbutil)carbamoil]-4-hidroxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

Se preparó el compuesto del título por el procedimiento de Ejemplo 37 a partir de 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 (Ejemplo 18, 53mg, 0.081mmol). Se confirmó el intermedio t-butil ester M/z 839. Únicamente se recogió uno de los diastereómeros a partir de la purificación con HPLC preparativa del compuesto del título racémico. Se obtuvo en 4mg (12%) y se señaló que era el (R,R)-diastereómero de la comparación de los datos NMR de compuestos relacionados. M/z 783 NMR (400MHz) 0.79 (t, 6H), 0.95 (s, 9H), 0.99-1.22 (m, 6H), 1.25-1.39 (m, 2H), 1.40-1.51 (m, 2H), 1.56-1.68 (m, 3H), 1.79 (dd, 1H), 2.08 (s, 3H), 3.96 (brs, 2H), 4.47 (dd, 1H), 4.62 (Abq, 2H), 5.47 (s, 1H), 6.58 (s, 1H), 6.73 (d, 2H), 7.04 (t, 1H), 7.19 (d, 2H), 7.24-7.35 (m, 5H).

Ejemplo 39

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -{N-[(R)-1-carboxi-2-(trimetilsilil)etil]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 -{N-[(R)-1-(carboxi)-2-(trimetilsilil)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 -carboxi-4-hidroxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 18, 55mg, 0.084mmol) y metil 3-(trimetilsilil)alaninato (Método 28, 19mg, 0.108mmol) se disolvieron en 3.5ml DMF. N-Metil morfolina (18 μ l, 0.163mmol) y TBTU (32mg, 0.101mmol) se agregaron sucesivamente y la mezcla se agitó durante 2 horas. Se agregó una gota de ácido fórmico y la mezcla se extrajo entonces entre EtOAc y agua. La fase acuosa (pH=3) se lavó con EtOAc. Las fases orgánicas combinadas se lavaron con 1% NaHCO₃, salmuera y luego se secaron con Na₂SO₄ y se concentraron. Se

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confirmó el intermedio metil éster M/z 813. Se agregaron THF (2ml), agua (2ml) y LiOH (10mg, 0.418mmol) y la mezcla se agitó durante la noche. La mezcla se purificó usando HPLC preparativa en una columna C8 (50x100mm). Una gradiente de 20 a 50% MeCN en 0.1M tampón de acetato de amonio se usó como eluyente. Se separaron los dos diastereómeros bajo estas condiciones y se recogieron por separado. La liofilización produjo 8mg (24% rendimiento) del primer diastereómero eluyente y 8.4mg (25% rendimiento) del segundo. Se asignaron las configuraciones absolutas a partir de la comparación con datos NMR de compuestos relacionados y se encontró que el primer diastereómero eluyente era el (R,R)-diastereómero y el segundo diastereómero eluyente era el (R,S)-diastereómero. M/z 799. NMR del (R,R)-diastereómero (400MHz) δ 0.16 (s, 9H), 0.79 (t, 6H), 0.9-1.22 (m, 8H), 1.25-1.40 (m, 2H), 1.40-1.52 (m, 2H), 1.55-1.68 (m, 2H), 2.11 (s, 3H), 3.95 (brs, 2H), 4.29-4.35 (m, 1H), 4.58 (Abq, 2H), 5.45 (s, 1H), 6.59 (s, 1H), 6.73 (d, 2H), 7.04 (t, 1H), 7.17-7.27 (m, 5H), 7.32 (t, 2H), y del (R,S)-diastereómero (400MHz) δ 0.04 (s, 9H), 0.79 (t, 6H), 1.00-1.22 (m, 8H), 1.25-1.40 (m, 2H), 1.40-1.52 (m, 2H), 1.55-1.68 (m, 2H), 2.08 (s, 3H), 3.95 (brs, 2H), 4.40-4.46 (m, 1H), 4.62 (Abq, 2H), 5.49 (s, 1H), 6.58 (s, 1H), 6.73 (d, 2H), 7.04 (t, 1H), 7.14-7.36 (m, 7H).

Preparación de Materiales Iniciales

Los materiales iniciales de los Ejemplos ya citados se obtienen en el comercio o se preparan fácilmente por Métodos estándar a partir de materiales conocidos. Por Ejemplo, las siguientes reacciones son una ilustración, mas no una limitación, de algunos de los materiales iniciales usados en las reacciones anteriores.

Método 1

1,1-Dioxo-3,3-dibutil-5-fenil-7-bromo-8-etoxycarbonilmetoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina y

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-etoxycarbonilmetoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina

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A una suspensión de 1,1-dioxo-3,3-dibutil-5-fenil-7-bromo-8-metoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina (preparada de acuerdo con WO 98/38182, 0.218 g, 5.65×10^{-4} mol) en DMF (5 ml) se agregó NaSMe (0.210 g, 2.83 mmol, 95 %), y la mezcla se agitó durante 5 horas a 120°C. El solvente se retiró bajo presión reducida y el residuo se repartió en porciones entre EtOAc y 0.5 M HCl. La capa acuosa se extrajo dos veces más con EtOAc y los extractos orgánicos combinados se secaron (MgSO_4) y se concentraron. El residuo se disolvió en MeCN (7 ml) y se agregaron bromoacetato de etilo (0.063 ml, 5.65×10^{-4} mol), bromuro de tetrabutilamonio (0.018 g, 5.65×10^{-5} mol) y carbonato de sodio (0.250 g, 2.36 mmol). La mezcla se agitó durante la noche a 80°C. El solvente se retiró bajo presión reducida y el residuo se repartió en porciones entre EtOAc y 0.5 M HCl. La capa orgánica se lavó con salmuera, se secó (MgSO_4) y se concentró. Cromatografía de destello en gel de sílice (Hex EtOAc-6:1) produjo los compuestos del título como aceites incoloros.

1,1-dioxo-3,3-dibutil-5-fenil-7-bromo-8-etoxycarbonilmetoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina, 0.187 g (58 %). NMR (400 MHz, CDCl_3) 0.70-0.80 (m, 6H), 0.90-1.70 (m, 15H), 3.90 (brs, 2H), 4.25 (q, 2H), 4.35 (brs, 1H), 4.65 (s, 2H), 6.95-7.40 (m, 7H), y 1,1-dioxo-3,3-dibutil-5-fenil-7-metil-8-etoxycarbonilmetoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina, 0.024 g (8 %). NMR (400 MHz, CDCl_3) 0.70-0.85 (m, 6H), 0.90-1.70 (m, 15H), 2.10 (s, 3H), 3.90 (brs, 2H), 4.20 (brs, 1H), 4.25 (q, 2H), 4.65 (s, 2H), 6.55 (s, 1H), 6.95-7.35 (m, 6H).

Método 2

1,1-Dioxo-3,3-dibutil-5-fenil-7-bromo-8-etoxycarbonilmetoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-bromo-8-etoxycarbonilmetoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina (Método 1, 0.184 g, 3.24×10^{-4} mol) en EtOH (7 ml) se agregó NaOH (0.052 g, 1.30 mmol) y la mezcla se agitó durante la noche. El solvente se retiró bajo presión reducida y el residuo se repartió en porciones entre EtOAc y 0.5 M HCl. La

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capa acuosa se extrajo dos veces más con EtOAc y los extractos organicos combinados se lavaron con salmuera y se concentraron. El producto crudo se purifico por HPLC preparativa usando un tampón MeCN / acetato de amonio como eluyente y se seco por congelamiento para producir el compuesto del titulo en 0.173 g (99 %) como un sólido blanco. NMR (400 MHz, CD₃OD) 0.70-0.85 (m, 6H), 0.95-1.70 (m, 12H), 3.90 (brs, 2H), 4.50 (s, 2H), 6.90-7.40 (m, 7H).

Método 3

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-etoxycarbonil-metoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 1, 0.024 g, 4.49×10^{-5} mol) en EtOH (3 ml) se agregó NaOH (0.007 g, 1.80×10^{-4} mol) y la mezcla se agito durante la noche. El solvente se retiró bajo presión reducida y el residuo se purifico por HPLC preparativa usando un tampón MeCN / acetato de amonio como eluyente y se secó por congelamiento. El compuesto del titulo se obtuvo en 0.021 g (92 %) como un solido blanco. NMR (400 MHz, CD₃OD) 0.70-0.85 (m, 6H), 1.00-1.70 (m, 12H), 2.10 (s, 3H), 3.90 (brs, 2H), 4.55 (s, 2H), 6.60 (s, 1H), 6.90-7.35 (m, 6H).

Método 3

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (preparación alternativa)

1,1-Dioxo-2-(4-metoxibencil)-3,3-dibutil-5-fenil-7-metiltio-8-(*t*-butoxycarbonilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 25, 6.902 g, 10.11 mmol) se disolvió en una mezcla de TFA (50 ml) y Et₃Si (8 ml) y la solución se agitó durante 90 minutos a temperatura ambiente. El solvente se retiró bajo presión reducida y el residuo se disolvió en *t*-BuOMe (100 ml). La fase orgánica se lavó con agua (20 ml) y luego se extrajo tres veces con NaOH diluido (2x50 ml 0.5M). Los extractos acuosos combinados se acidificaron con HCl diluido (70 ml, 1M) (pH 1-2) y luego se extrajeron dos

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veces con *t*-BuOMe (2x50 ml) La capa éter se lavó con salmuera, se secó sobre MgSO₄ y se concentro Se obtuvieron 4 694 g (92 %) del producto deseado como un aceite marrón NMR (400 MHz, CD₃OD) 0 70-0 85 (m, 6H), 1 00-1 25 (m, 6H), 1 25-1 50 (m, 4H), 1 55-1 70 (m, 2H), 2 10 (s, 3H), 3 90 (brs, 2H), 4 55 (s, 2H), 6 60 (s 1H), 6 95-7 35 (m, 6H)

Método 4

(R)-N-Benciloxycarbonil- α -[N-(*t*-butoxycarbonilmetil)carbamoil] bencilamina

Ácido (2R)-{[(Benciloxi)carbonil]amino}(fenil)acetico (10 g, 35 0 mmol) y *t*-butilglicina clorhidrato (6 3 g, 37 4 mmol) se disolvió en DCM (200 ml) con 2,6-lutidina (8 2 ml, 70 4 mmol) Despues de agitar 5 minutos a 0°C se agregó TBTU (12 4 g, 38 6 mmol) y la agitación se continuo durante 1 5 horas a 0°C y 3 75 horas a temperatura ambiente La mezcla de reaccion se lavó con agua (2 x 100 ml), se seco (MgSCO₄) y se purifico con cromatografia de destello (DCM EtOAc 7 1→5 1) para producir el compuesto del titulo (13 g, 94 %) NMR (500 MHz, CDCl₃) 1 45 (s, 9H), 3 84 (d, 1H), 4 00 (dd, 1H), 5 10 (m, 2H), 5 28 (brs, 1H), 6 13 (brs, 1H), 6 23 (brs, 1H), 7 30-7 44 (m, 10H)

Método 5

(R)- α -[N-(*t*-Butoxycarbonilmetil]bencilamina

(R)-N-Benciloxycarbonil- α -[N-(*t*-butoxycarbonilmetil)carbamoil] bencilamina (Método 4, 12 8 g, 32 2 mmol) se disolvio en EtOH (99%, 200 ml) y tolueno (50 ml) Se agregó Pd/C (10%, 0 65 g) y se realizó hidrogenacion a presion atmosférica durante 5 5 horas a temperatura ambiente La mezcla de reacción se filtraron a traves de tierras de diatomeas y los solventes se evaporaron para producir el compuesto del título (8 4 g, 99 %) NMR (600 MHz, CDCl₃) 1 45 (s, 9H), 3 93 (m, 2H), 4 54 (s, 1H), 7 31-7 42 (m, 5H), 7 51 (brs, 1H)

Método 6

Ácido 2-{[(2R)-2-amino-2-(4-hidroxifenil)etanoil]amino}etanosulfónico

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N-Boc-(D)-4-hidroxifenilglicina (1 00 g, 3 21 mmol) se disolvio en DMF (5 ml) y se agregó taurina de tetrabutilamonio (2 36 g, 6 42 mmol) junto con 5 ml DMF mas La suspensión resultante se enfrió sobre hielo y se agregó TBTU (1 24 g, 3 85 mmol) Se retiro el baño de hielo despues de 30 minutos y la mezcla se agitó durante 2 horas antes de filtrarla y concentrarla. Se agrego TFA en DCM (20%, 20ml) y la mezcla de reacción se agitó durante la noche Se agrego etanol (20 ml) y se evaporaron los solventes El producto crudo se hizo refluir en etanol (100 ml) durante 1 hora. La filtracion produjo el compuesto del titulo puro como un sólido blanco, 626mg (71%) MMR (DMSO- d_6) 2 4-2 6 (m, 2H), 3 2-3 4 (m, 2H), 4 79 (s, 1H), 6 78 (d, 2H), 7 23 (d, 2H), 8 22 (t, 1H), 8 4 (brs, 3H), 9 7 (s, 1H)

Método 7

4-(1-(R)-*t*-Butoxicarbonil-1-aminometil)fenol

Ácido sulfurico (conc, 1ml) se agrego a una solucion de D-(R)-4-hidroxifenilglicina (1 0g, 6 0mmol) en 1,4-dioxane (8ml) contenida en un matraz de Teflon® El matraz se enfrio a -78°C y se agrego isobutileno (8g, 142 6mmol, condensado a -78°C) El matraz se puso en un autoclave a temperatura ambiente y se agito durante 15 horas El autoclave enfrio sobre hielo antes de abrirlo Se dejó evaporar el exceso de isobutileno y la solucion restante se vertio en NaOH acuoso (2M, 20ml) y se extrajo con eter dietilico para retirar el sub-producto formado La fase acuosa se acidifico levemente para alcanzar un pH=10 usando 2M HCl y se extrajo con eter dietílico (3x75ml) La fase orgánica se lavo con salmuera, se seco y se concentro El producto obtenido se recristalizo en éter dietilico/hexano Masa 0 55g (41%) NMR (600MHz, $CDCl_3$) 1 45 (s, 9H), 4 45 (s, 1H), 6 8 (d, 2H), 7 25 (d, 2H), m/z 224

Método 8

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N((R)- α -{N-[(S)-1-(*t*-butoxicarbonil)-4-benciloxycarbonilamino]butil]carbamoil}bencil]carbamoilmetoxi]-2,3,4,5-

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149tetrahydro-1,2,5-benzotriazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahydro-1,2,5-benzotriazepina (Ejemplo 25, 53 mg, 0.083 mmol), *tert*-butil *N*⁶-[(benciloxi)carbonil]-L-ornitinato (35 mg, 0.098 mmol), N-metil morfolina (0.027 m) se disolvieron en DCM (5 ml). La mezcla se agitó a temperatura ambiente durante 10 minutos, tras lo cual se agregó TBTU (32 mg, 0.10 mmol) y la mezcla de reacción se agitó durante 1.5 horas. El solvente se retiró bajo presión reducida y el residuo se purificó por cromatografía usando DCM EtOAc, 5:1 como eluyente para producir el compuesto del título 57 mg (72%) *M/z* = 944.7 y 942.7 (M-H).

Método 91,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-[(R)- α -(*t*-butoxicarbonil)bencil]carbamoilmetoxi)-2,3,4,5-tetrahydro-1,2,5-benzotriazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahydro-1,2,5-benzotriazepina (Método 3, 627 mg, 1.24 mmol) se disolvió en DCM (25 ml), se agregaron *tert*-butil (2*R*)-amino(fenil)acetato (308 mg, 1.48 mmol), 2,6-dimetilpiridina (288 μ l, 2.47 mmol) y TBTU (477 mg, 1.48 mmol). La mezcla se agitó durante 3.5 horas. La mezcla de reacción se evaporó bajo presión reducida. El producto se purificó usando una columna Isolute (10g, sílice). El producto se eluyó con un gradiente gradual usando DCM EtOAc 100:0, luego 95:5. Se recogieron aproximadamente 694 mg de compuesto puro. Otra fracción se purificó una segunda vez usando una columna Isolute (10g, sílice). El producto se eluyó con un gradiente gradual usando DCM EtOAc 100:0, 95:5, luego 90:10. La fracción pura se agregó a la primera fracción proporcionando 787 mg (91%) del compuesto del título. NMR (400 MHz, CDCl₃) 0.78 (t, 6H), 0.92-1.12 (m, 4H), 1.12-1.46 (m, 6H), 1.54 (s, 9H), 1.58-1.72 (m, 2H), 2.14 (s, 3H), 3.8-4.05 (m, 2H), 4.32 (brs, NH), 4.56 (ABq, 2H), 5.56 (d, 1H), 6.56 (s, 1H), 7.04 (t, 1H), 7.10 (brd, 2H), 7.24-7.42 (m, 8H), 7.84 (d, NH), *m/z* 694.7 (M-H).

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X**Método 10**

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -[(S)-2-(*t*-butoxicarbonil)pirrolidin-1-ilcarbonil]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 -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50 mg, 0 078 mmol) y *tert*-butil L-prolinato (15 mg, 0 088 mmol) se disolvieron en DCM (2ml) y se agregaron N-metilmorfolina (17 2 μ l, 0 156 mmol) y TBTU (45 mg, 0 14 mmol) La mezcla de reacción se agito durante 3 horas, luego se agrego mas *tert*-butil L-prolinato (15 mg, 0 088 mmol) La mezcla de reaccion se agitó durante la noche La mezcla de reaccion se puso directamente en una columna Isolute (2g, sílice) El producto se eluyó con una gradiente gradual usando DCM EtOAc 100 0, 95 5,90 10, luego 80 20 para producir el compuesto del titulo (41 mg, 66%) M/z 793 2

Método 11

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -[N-(*t*-butoxicarbonilmetil)-N-metilcarbamoil]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 -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50 mg, 0 078 mmol) y *tert*-butil N-metilglicinato (15 mg, 0 10 mmol) se disolvieron en DCM (2ml) y se agregaron N-metilmorfolina (17 2 μ l, 0 156 mmol) y TBTU (45 mg, 0 14 mmol) La mezcla de reaccion se agitó durante 4 horas La mezcla de reacción se puso directamente en una columna Isolute (2g, sílice) El producto se eluyo con una gradiente gradual usando DCM EtOAc 100 0, 95 5,90 10, luego 80 20 para producir el compuesto del titulo (30 mg, 50%) M/z 767 4

Método 12

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1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -(N-[1-(R)-2-(R)-1-(*t*-butoxycarbonyl)-1-hidroxi-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 -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50 mg, 0 078 mmol) y *tert*-butil (2R,3R)-3-amino-2-hidroxibutanoato (15 mg, 0 086 mmol) se disolvieron en DCM (2ml) y se agregaron DMF (1ml) y N-metilmorfolina (17 2 μ l, 0 156 mmol) y TBTU (45 mg, 0 14 mmol) La mezcla de reacción se agito durante 4 horas La mezcla de reacción se puso directamente en una columna Isolute (2g, sílice) El producto se eluyó con una gradiente gradual usando DCM EtOAc 100 0,95 5, 90 10, luego 80 20 para producir el compuesto del titulo (33 mg, 53%) M/z 797 3

Método 13

t-Butil N-((2R)-2-([(benciloxi)carbonil]amino)-2-feniletanoil)-*o*-(*t*-butil)-L-serinato

Ácido (2R)-{[(Benciloxi)carbonil]amino}(fenil)acetico (2 0 g, 7 0 mmol) y *t*-butil *o*-(*t*-butil)-L-serinato (2 0 g, 7 9 mmol) y 2 6-lutidina se disolvieron en DCM (30 ml) Despues de agitar 5 minutos a 0°C se agrego TBTU (2 5 g, 7 8 mmol) y la agitación se continuo 30 minutos a 0°C y 4 horas a temperatura ambiente La mezcla de reaccion se lavo con agua (2 x 100 ml), se seco y purificó con cromatografía de destello (DCM) para producir el compuesto del título (3 3g, 97 %) NMR (300 MHz) 1 05 (s, 9H), 1 45 (s, 9H), 3 4-3 8 (m, 2H), 4 5 (brs, 1H), 4 85 (s, 2H), 5 1 (s, 2H), 5 4 (s, 1H), 7 25-7 5 (m, 10 H)

Método 14

t-Butil N-((2R)-2-amino-2-feniletanoil)-*o*-(*t*-butil)-L-serinato

t-Butil N-((2R)-2-([(benciloxi)carbonil]amino)-2-feniletanoil)-*o*-(*t*-butil)-L-serinato (Metodo 13, 3 3 g, 6 8 mmol) se disolvio en EtOH (95%, 30 ml) y se agregó una cantidad catalítica de Pd/C (5%)(50% en agua) y se realizo hidrogenación a presión atmosférica durante 3 horas a temperatura

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ambiente La mezcla de reacción se filtro a través de tierras de diatomeas y el solvente se evaporo para producir el compuesto del titulo (2.35 g, 98 %) NMR (500 MHz) 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 15

1,1-Dioxo-2-(4-metoxibencil)-3,3-dibutil-5-fenil-7-metil-8-metoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina

A una solución enfriada (-78 °C) de 1,1-dioxo-2-(4-metoxibencil)-3,3-dibutil-5-fenil-7-bromo-8-metoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina (Método 23, 2.10 g, 3.41 mmol) en THF (50 ml) se agregó gota a gota una solución de *n*-BuLi (2.35 ml, 3.75 mmol, 1.6 M en hexano) Después de agitar a -78 °C durante 20 minutos, se agregó MeI (2.42 g, 17.1 mmol) La mezcla se agitó a -78 °C durante 10 minutos y a temperatura ambiente durante 18 horas Se agregó éter dietílico (50 ml) y la fase orgánica se lavó con 10 % NH₄Cl (acuoso, 50 ml) y salmuera, (50 ml) Después de secar, filtrar y concentrar el producto crudo se sometió a cromatografía de destello (Hexano EtOAc -95/5) para producir 0.4 gram (21 %) del producto del título como un aceite incoloro NMR (300 MHz, CDCl₃) 0.60-0.70 (m, 6H), 0.70-0.90 (m, 4H), 0.90-1.35 (m, 8H), 2.00 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.00-4.20 (m, 2H), 4.35-4.60 (m, 2H), 6.65-6.85 (m, 3H), 6.90-7.10 (m, 3H), 7.15-7.30 (m, 5H)

Método 16

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-carboximetoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina

A una solución (0 °C) de ácido trifluoroacético (30 ml) y trietilsilano (1.03 g, 8.85 mmol) se agregó una solución de 1,1-dioxo-2-(4-metoxibencil)-3,3-dibutil-5-fenil-7-metil-8-metoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina (Método 15, 0.92 g, 1.77 mmol) en DCM (2 ml) La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos Después de la concentración de la mezcla de reacción, el residuo se disolvió en éter dietílico

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(50 ml) y se lavo con agua (25 ml) y bicarbonato de sodio (10 %, 25 ml). Después de secar, filtrar y concentrar el producto crudo se sometio a cromatografia de destello en gel de sílice (Hexano EtOAc -90 10) para producir 0.58 g de un sólido gris. A una solución (0 °C) de este sólido en diclorometano (30 ml) se agrego gota a gota BBr_3 en DCM (1M en DCM, 10.2 ml, 10.2 mmol). La mezcla de reacción se agito a temperatura ambiente durante 45 minutos y luego se lavó con bicarbonato de sodio (10 %, 25 ml) y agua (25 ml). Después de secar, filtrar y concentrar el producto crudo (0.55g, sólido gris) se disolvió en MeCN (30 ml). A la solución se agrego K_2CO_3 (0.22g, 1.58 mmol) y bromuro de tetra-*n*-butil amonio (10 mg) seguidos por bromoacetato de etilo (0.25 g, 1.51 mmol). La mezcla de reacción se agitó a 80 °C durante 1.5 hora y luego se evaporo bajo presión reducida. El residuo se disolvió en EtOAc (50 ml) y se lavo con NH_4Cl (acuoso, 10 %) y salmuera. Después de secar, filtrar y concentrar el producto crudo se sometio a cromatografia de destello (Hex EtOAc 9 1-8 2) para proporcionar 0.58 g de un sólido blancuzco. El sólido se disolvió en THF H_2O (4 1,25ml) y se agrego LiOH (0.097 g, 2.31 mmol). La mezcla de reacción se agito a temperatura ambiente durante 40 minutos. La mezcla se evaporo bajo presión reducida, se disolvió en agua (50 ml) y se acidificó con 1M HCl. La capa acuosa se extrajo 2x con eter dietílico. La evaporación del solvente bajo presión reducida produjo 0.46 g (55%) del compuesto del título. NMR (300 MHz, acetona- d_6) 0.70-0.90 (m, 6H), 0.95-1.80 (m, 12H), 2.15 (s, 3H), 3.85-4.15 (m, 2H), 4.85 (s, 2H), 6.00 (s, 1H), 6.80 (s, 1H), 6.90-7.05 (m, 1H), 7.10-7.45 (m, 5H).

Método 17

(R)-N-Benciloxycarbonil- α -carboxi-4-hidroxibencilamina

(R)-*p*-Hidroxifenilglicina (5.00 g, 29.9 mmol) se mezcló con agua (50 ml). Se agregó bicarbonato de sodio (6.3g, 75.0 mmol) a la lechada y una suspensión blanca fue el resultado después de agitar durante 10 minutos. Se agrego cloroformato de bencilo (5.1ml, 33.9 mmol) de un embudo de goteo durante 20 minutos y la mezcla se agito vigorosamente. Después de 2 horas,

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se agrego agua (300ml) y la suspensión se extrajo con éter (200ml) El solido blanco no se disolvió y se agregaron mas agua y éter LC/MS indico que el sólido era el producto Se recogio la parte clara de la fase acuosa y se acidificó cuando se formó un precipitado blanco Éste se dejó durante el fin de semana y luego se extrajo por filtracion La fase acuosa restante que contenia material no disuelto se acidificó igualmente y se extrajo con EtOAc (3x) También aqui quedo un precipitado entre las fases Éste se recogio con la capa organica. La fase EtOAc se evaporó Se agregó tolueno 2x para retirar agua Se juntaron las dos fracciones de solido blanco y se recrystalizaron en DCM (200ml) Se filtró la mezcla enfriada y se obtuvieron 4 77g (53 %) de solido blanco NMR (400 MHz, DMSO-d₆) 5 00 (1H, d), 5 00 (2H, s), 6 70 (2H, d), 7 05-7 50 (7H, m), 7 90 (1H, d)

Método 18

(R)-N-Benciloxycarbonil- α -{N-[(S)-1-(t-butoxycarbonil)propil]carbamoyl}-4-hidroxibencilamina

Una solución de (R)-N-benciloxycarbonil- α -carboxi-4-hidroxibencilamina (Método 17, 2 00 g, 6 64 mmol), ácido (2S)-2-amino butanico *t*-butil ester (1 30 g, 6 64 mmol) y N-metilmorfolina (2 0 g, 19 8 mmol) en DCM (30 ml) se agito a temperatura ambiente durante 5 minutos, después de lo cual se agregó TBTU (2 60 g, 8 10 mmol) La mezcla de reacción se agito a temperatura ambiente durante la noche El solvente se retiro bajo presión reducida y el residuo se purificó por cromatografia de destello en gel de sílice (DCM Acetona - 60 40) El producto se cristalizó de tolueno (20 ml) produciendo 1 85 g del producto deseado como un solido blanco NMR (400 MHz) 0 80 (3H, t), 1 45 (9H, s), 1 50-1 80 (2H, m), 4 10-4 20 (1H, m), 5 05 (1H, d(AB)), 5 15 (1H, d(AB)), 6 75 (2H, d), 7 20-7 40 (7H, m)

Método 19

(R)- α -{N-[(S)-1-(t-Butoxycarbonil)propil]carbamoyl}-4-hidroxibencilamina

Una mezcla de (R)-N-Benciloxycarbonil- α -{N-[(S)-1-(t-butoxycarbonil)

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propil]carbamoil}-4-hidroxibencilamina (Método 18, 1.80 g, 4.07 mmol) y Pd/C (0.2 g, 5 %) en etanol (30 ml, 95 %) se agitó bajo gas hidrogeno a temperatura ambiente durante 2 horas. La mezcla de reacción se filtro a traves de gel de sílice (2g) y se concentró. El residuo se disolvió en acetona (20 ml) y se agregó ácido metanosulfónico (0.40 g, 4.16 mmol). No se obtuvo cristalización y el solvente se retiró bajo presión reducida. El producto crudo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0.1M tampón de acetato de amonio como eluyente. El compuesto del título se obtuvo en 0.350 g (28 %) como un sólido blanco. NMR (400 MHz, DMSO- d_6) 0.75 (3H, t), 1.40 (9H, s), 1.50-1.75 (2H, m), 2.70 (1H, s), 4.00-4.10 (1H, m), 4.30 (1H, s), 6.65 (2H, d), 7.15 (2H, d), 8.15 (1H, d).

Método 20

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-(N-{(R)- α -[N-((S)-1-{N-((S)-2-(*t*-butoxi)-1-(*t*-butoxicarbonil)etil]carbamoil}propil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-(N-{(R)- α -[N-((S)-1-carboxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 6, 15 mg, 0.021 mmol), *tert*-butil *O*-(*tert*-butil)-L-serinato clorhidrato (5.4 mg, 0.021 mmol) y N-metilmorfolina (4.6 μ l, 0.042 mmol) se disolvió en DMF (1 ml). Se agregó TBTU (12.5 mg, 0.039 mmol) y la mezcla se agitó durante una hora, se agregó *tert*-butil *O*-(*tert*-butil)-L-serinato clorhidrato (0.8 mg, 0.0031 mmol) y la mezcla se agitó durante un par de minutos. El solvente se evaporó bajo presión reducida y se co-evaporó unas cuantas veces con tolueno. El producto se purificó usando una columna ISOLUTE pre-empacada (Sílice, 2g) y se eluyó con una gradiente gradual usando DCM EtOAc 100:0 (10 ml) 95:5 (10 ml) 90:10 (10 ml) 80:20 (10 ml), para producir 14 mg del compuesto del título. M/z 924.7

Método 21

1,1-Dioxo-3,3-dibutil-5-fenil-7-metil-8-(N-{(R)- α -[2-(S)-2-(metoxycarbonil)-4-(R)-4-(hidroxipirrolidin-1-ilcarbonil]bencil}

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X
X
Xcarbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 54 mg, 0 084 mmol), metil (4R)-4-hidroxi-L-prolinato clorhidrato (18 4 mg, 0 10 mmol) y N-metilmorfolina (13 9 μ l, 0 13 mmol) se disolvio en DMF (2 ml) Se agregó TBTU (32 5 mg, 0 101 mmol) y la mezcla se agito durante tres horas El solvente se evaporo bajo presión reducida. El producto se purificó dos veces usando una columna ISOLUTE pre-empacada (Silice, 2g) y se eluyo con una gradiente gradual usando DCM EtOAc 100 0, 95 5, 90 10, 80 20 y 60 40, para producir 23 mg del compuesto del titulo M/z 767 0

Método 221,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)- α -[2-(S)-2-(t-butoxicarbonil)azetidin-1-ylcarbonil]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 -carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 50 mg, 0 078 mmol), *tert*-butil (2S)-azetidino-2-carboxilato (17 4 mg, 0 111 mmol) y N-metilmorfolina (10 3 μ l, 0 094 mmol) se disolvio en DMF (2 ml) Se agrego TBTU (30 mg, 0 094 mmol) y la mezcla se agito durante cuatro horas El solvente se evaporo bajo presion reducida El producto se purifico usando una columna ISOLUTE pre-empacada (Silice, 2g) y se eluyo con una gradiente gradual usando DCM EtOAc 100 0, 95 5, 90 10, 80 20, para producir 27 5 mg del compuesto del titulo M/z 777 6 (M-H)⁺

Método 231,1-Dioxo-2-(4-metoxibencil)-3,3-dibutil-5-fenil-7-bromo-8-metoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-bromo-8-metoxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (preparada de acuerdo con WO 98/38182, 0 200 g, 0 404 mmol) en MeCN (5 ml) se agregaron cloruro de p-

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F

metoxibencilo (0 066 ml, 0 486 mmol), CsI (0 010 g, 0 038 mmol) y Cs_2CO_3 (0 263 g, 0 807 mmol) y la mezcla se agito a 60 °C durante 4 horas El solvente se retiro bajo presion reducida y el residuo se repartio en porciones entre EtOAc y 0 5M HCl (acuoso) La capa orgánica se lavo con salmuera, se secó MgSO_4 y se concentro El residuo se filtró a través de gel de sílice (DCM EtOAc -9 1) para producir el compuesto del titulo en 0 257 g (~cuantitativo) como un sólido blancuzco NMR (400 MHz, CDCl_3) 0 60-0 75 (m, 6H), 0 75-1 20 (m, 8H), 1 25-1 45 (m, 2H), 1 80-2 00 (m, 2H), 3 80 (s, 3H), 3 90 (s, 3H), 4 05-4 30 (m, 2H), 4 45-4 65 (m, 2H), 6 70-7 45 (m, 11H)

Método 24

1,1-Dioxo-2-(4-metoxibencil)-3,3-dibutil-5-fenil-7-metiltio-8-hidroxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina

NaSMe (0 150 g, 2 03 mmol, 95 %) se agregó a una solución de 1,1-dioxo-2-(4-metoxibencil)-3,3-dibutil-5-fenil-7-bromo-8-metoxi-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina (Método 23, 0 249 g, 0 404 mmol) en DMF (5 ml) La mezcla se agitó a temperatura ambiente durante 2 horas, después de lo cual se elevó la temperatura a 80 °C y se agregó más NaSMe (0 090 g, 1 22 mmol) Después de 20 horas a 80 °C se agregó agua (5 ml) y 1M HCl (acuoso) (pH~4) a la mezcla La solución se extrajo tres veces con Et_2O y las capas organicas combinadas se lavaron con salmuera, se secaron sobre MgSO_4 y se concentraron El producto crudo se purifico por cromatografia de destello en gel de sílice (Hex EtOAc-4 1), lo cual produjo el compuesto del titulo en 0 188 g (82%) como un solido color marrón NMR (500 MHz, CDCl_3) 0 60-0 75 (m, 6H), 0 75-1 20 (m, 8H), 1 25-1 40 (m, 2H), 1 80-2 00 (m, 2H), 2 20 (s, 3H), 3 80 (s, 3H), 4 20 (brs, 2H), 4 50 (brs, 2H), 6 05 (brs, 1H), 6 75-6 85 (m, 3H), 7 00-7 10 (m, 3H), 7 20-7 35 (m, 4H), 7 50 (s, 1H)

Método 25

1,1-Dioxo-2-(4-metoxibencil)-3,3-dibutil-5-fenil-7-metiltio-8-(t-butoxicarbonilmetoxi)-2,3,4,5-tetrahydro-1,2,5-benzotiadiazepina

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✓

A una solución de 1,1-dioxo-2-(4-metoxibencil)-3,3-dibutil-5-fenil-7-metiltio-8-hidroxi-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Metodo 24, 4 487 g, 7 889 mmol) en MeCN (100ml) se agregó bromuro de t-butilo (0 262g, 0 813 mmol), bromoacetato de t-butilo (1 46ml, 9 880 mmol) y carbonato de potasio (anhidro, 3 28g, 23 7 mmol) en este orden. La mezcla se calentó a 55°C durante 2 5 horas, después de lo cual se enfrió a temperatura ambiente y se dejó agitando durante la noche. El solvente se evaporó hasta que quedó una lechada amarillenta, la cual se extrajo entre éter dietílico (150ml) y agua (100ml). La fase acuosa se lavó con éter (100ml) y las capas éter combinadas se lavaron con 0 1M KHSO₄ (aq, 100ml), salmuera (100ml) y se secaron. Se retiró el éter bajo presión reducida y el sólido color crema obtenido se secó bajo presión reducida durante 4 horas (5 355 g, 99 %). NMR (400 MHz, CDCl₃) 0 60-1 25 (m, 14H), 1 25-1 40 (m, 2H), 1 50 (s, 9H), 1 75-2 00 (m, 2H), 2 10 (s, 3H), 3 80 (s, 3H), 4 20 (brs, 2H), 4 50 (brs, 2H), 4 60 (s, 2H), 6 45 (s, 1H), 6 75-6 85 (m, 2H), 7 00-7 15 (m, 3H), 7 20-7 40 (m, 5H).

Método 26

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)-α-[N-((S)-1-[N-((S)-1-(t-butoxicarbonil)etil]carbamoil}etil]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-carboxibencil]carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (Ejemplo 25, 58 mg, 0 091 mmol), *tert*-butil L-alanil-L-alaninato clorhidrato (27 5 mg, 0 11 mmol) y N-metilmorfolina (20 µl, 0 18 mmol) se disolvió en DMF (2 ml). Se agregó TBTU (35 mg, 0 18 mmol) y la mezcla se agitó durante 2-3 horas. El solvente se evaporó bajo presión reducida. El producto se purificó usando una columna ISOLUTE pre-empacada (Silice, 2g) y se eluyó con un gradiente gradual usando DCM EtOAc 100 0, 95 5, 90 10 y 80 20 para producir 34 mg (45%) del compuesto del título. M/z 838 5.

Método 27

tert-Butil 4-metileucinato

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X

4-Metilleucina (500mg, 3.44mmol) se suspendió en 10 ml de acetato de *t*-butilo. Se agregó ácido perclórico (0.2ml, 3.49mmol) se agregó y el matraz se taponó con un tabique y se agitó durante la noche. Se llevó a cabo el análisis usando TLC (DCM/MeOH, 9:1, tiñendo con una solución de ninhidrina/EtOH). La solución se vertió en un matraz que contenía 30ml EtOAc y 30 ml 5% Na₂CO₃. La capa acuosa se volvió ácida y se agregó 2M NaOH hasta que el pH fue de aproximadamente 7. Las fases se separaron y la fase acuosa se lavó con 2x30ml EtOAc. Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na₂SO₄ y se evaporaron. Se obtuvo un aceite el cual se co-evaporó con tolueno y luego con éter dietílico antes de ponerse bajo vacío durante dos días. Masa 665 mg (96% rendimiento). NMR (CDCl₃) 1.0 (s, 9H), 1.5 (s, 9H), 1.65-1.95 (m, 2H), 3.82 (t, 1H).

Metodo 28

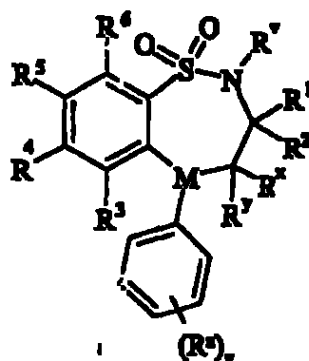
Metil 3-(trimetilsilil)alaninato

3-Trimetilsilil alanina (J. Organomet. Chem., 628, (2001), 183-194, 19mg, 0.118mmol) se mezcló con 3ml BF₃·MeOH (14%, 3.7mmol) en un tubo sellado y se calentó a 70°C. Se realizó el análisis usando TLC (MeOH/DCM 1:9, teido con ninhidrina en etanol). La mezcla se calentó durante 3 horas y luego se enfrió a temperatura ambiente. La mezcla se vertió en una mezcla de 3ml EtOAc y 2ml de agua que contenía Na₂CO₃. Se agregó más Na₂CO₃ (5%-acuoso) hasta un pH de aproximadamente 7. La fase acuosa se lavó con EtOAc (2x3ml). Las capas orgánicas combinadas se lavaron con salmuera (1ml), se secaron con Na₂SO₄ y se evaporaron. El producto se obtuvo como una película blanca. Masa 19mg (92% rendimiento). NMR (CDCl₃) 0.1 (s, 9H), 1.2-1.4 (m, 2H), 3.8 (s, 3H), 4.2 (brs, 1H).

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X**Reivindicaciones**

Lo que se reivindica es

1 un compuesto de fórmula (I)



(I)

en donde

R^v se selecciona de hidrógeno o C_{1-6} alquilo,

uno de R^1 y R^2 se seleccionan de hidrógeno o C_{1-6} alquilo o C_{2-6} alquenilo y el otro se selecciona de C_{1-6} alquilo o C_{2-6} alquenilo,

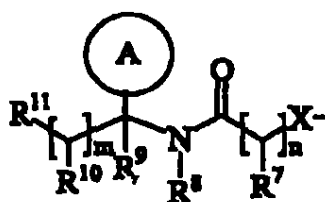
R^x y R^y se seleccionan independientemente de hidrógeno, hidroxilo, amino, mercapto, C_{1-6} alquilo, C_{1-6} alcoxi, N -(C_{1-6} alquil)amino, N,N -(C_{1-6} alquil) $_2$ amino, C_{1-6} alquilS(O) $_a$ en donde a es 0 a 2,

M se selecciona de -N- o -CH-,

R^z se selecciona de halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamilo, mercapto, sulfamilo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} alcoxi, C_{1-6} alcanoilo, C_{1-6} alcanoiloxi, N -(C_{1-6} alquil)amino, N,N -(C_{1-6} alquil) $_2$ amino, C_{1-6} alcanoilamino, N -(C_{1-6} alquil)carbamilo, N,N -(C_{1-6} alquil) $_2$ carbamilo, C_{1-6} alquilS(O) $_a$ en donde a es 0 a 2, C_{1-6} alcoxycarbonilo, N -(C_{1-6} alquil)sulfamilo y N,N -(C_{1-6} alquil) $_2$ sulfamilo,

v es 0-5,

uno de R^4 y R^5 es un grupo de fórmula (IA)



(IA)

R^3 y R^6 y los demás de R^4 y R^5 se seleccionan independientemente de hidrogeno, halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamilo, mercapto, sulfamilo, C_{1-4} alquilo, C_{2-4} alquenilo, C_{2-4} alquinilo, C_{1-4} alcoxi, C_{1-4} alcanoilo, C_{1-4} alcanoiloxi, N -(C_{1-4} alquil)amino, N,N -(C_{1-4} alquil) $_2$ amino, C_{1-4} alcanoilamino, N -(C_{1-4} alquil)carbamilo, N,N -(C_{1-4} alquil) $_2$ carbamilo, C_{1-4} alquilS(O) $_a$ en donde a es 0 a 2, C_{1-4} alcoxycarbonilo, N -(C_{1-4} alquil)sulfamilo y N,N -(C_{1-4} alquil) $_2$ sulfamilo, en donde R^3 y R^6 y los demás de R^4 y R^5 pueden sustituirse opcionalmente en carbono por uno o más R^{16} .

X es -O-, -N(R^a)-, -S(O)_b- o -CH(R^a)-, en donde R^a es hidrógeno o C₁ alquilo y b es 0-2,

Anillo A es ariilo o heteroarillo, en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de R¹⁷,

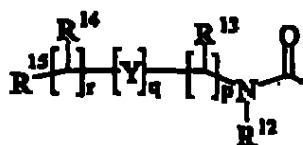
R⁷ es hidrogeno, C₁₋₄alquilo, carbociclilo o heterociclilo, en donde R⁷ se sustituye opcionalmente por uno o mas sustituyentes seleccionados de R¹⁸,

R⁸ es hidrógeno o C₁₋₄alquilo,

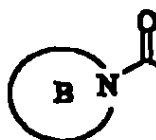
R⁹ es hidrógeno o C₁₋₄alquilo,

R¹⁰ es hidrógeno, C₁₋₄alquilo, carbociclilo o heterociclilo, en donde R¹⁰ se sustituye opcionalmente por uno o más sustituyentes seleccionados de R¹⁹,

R^{11} es carboxi, sulfo, sulfino, fosfona, $-P(O)(OR^c)(OR^d)$, $-P(O)(OH)(OR^c)$, $-P(O)(OH)(OR^d)$ o $-P(O)(OR^c)(R^d)$ en donde R^c y R^d se seleccionan independientemente de C_{1-6} alquilo, o R^{11} es un grupo de formula (IB) o (IC).

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(IB)



(IC)

en donde,

Y es $-N(R^n)-$, $-N(R^n)C(O)-$, $-N(R^n)C(O)(CR^sR^t)_vN(R^n)C(O)-$, $-O-$, y $-S(O)_a-$, en donde a es 0-2, v es 1-2, R^s y R^t se seleccionan independientemente de hidrogeno o C_{1-4} alquilo opcionalmente sustituido por R^{26} y R^n es hidrógeno o C_{1-4} alquilo,

R^{12} es hidrogeno o C_{1-4} alquilo,

R^{13} y R^{14} se seleccionan independientemente de hidrogeno, C_{1-6} alquilo, carbociclilo o heterociclilo, y cuando q es 0, R^{14} puede seleccionarse adicionalmente de hidroxilo, en donde R^{13} y R^{14} puede sustituirse independientemente en forma opcional por uno o mas sustituyentes seleccionados de R^{20} ,

R^{15} es carboxilo, sulfo, sulfino, fosfono, $-P(O)(OR^e)(OR^f)$, $-P(O)(OH)(OR^e)$, $-P(O)(OH)(R^e)$ o $-P(O)(OR^e)(R^f)$ en donde R^e y R^f se seleccionan independientemente de C_{1-6} alquilo,

p es 1-3, en donde los valores de R^{13} pueden ser los mismos o diferentes,

q es 0-1,

r es 0-3, en donde los valores de R^{14} pueden ser los mismos o diferentes,

m es 0-2, en donde los valores de R^{10} pueden ser los mismos o diferentes,

n es 1-3, en donde los valores de R^7 pueden ser los mismos o diferentes,

Anillo B es un heterociclilo enlazado a nitrógeno sustituido en carbono por un grupo seleccionado de R^{23} , y sustituido opcionalmente de manera adicional en carbono por uno o mas R^{24} , y en donde si dicho heterociclilo enlazado a nitrógeno contiene una fraccion $-NH-$, ese

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nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de R^{25} ,

R^{16} , R^{17} y R^{18} se seleccionan independientemente de halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, C_{1-4} alquilo, C_{2-4} alquenilo, C_{2-4} alquinilo, C_{1-4} alcoxi, C_{1-4} alcanoilo, C_{1-4} alcanoiloxi, $N-(C_{1-4}alquil)amino$, $N,N-(C_{1-4}alquil)_2amino$, $C_{1-4}alcanoilamino$, $N-(C_{1-4}alquil)carbamoilo$, $N,N-(C_{1-4}alquil)_2carbamoilo$, $C_{1-4}alquilS(O)_a$ en donde a es 0 a 2, $C_{1-4}alcoxycarbonilo$, $N-(C_{1-4}alquil)sulfamoilo$ y $N,N-(C_{1-4}alquil)_2sulfamoilo$, en donde R^{16} , R^{17} y R^{18} pueden sustituirse independientemente en forma opcional en carbono por uno o más R^{21} ,

R^{19} y R^{20} , R^{24} y R^{26} se seleccionan independientemente de halo, nitro, ciano, hidroxilo, amino, carboxilo, carbamoilo, mercapto, sulfamoilo, C_{1-4} alquilo, C_{2-4} alquenilo, C_{2-4} alquinilo, C_{1-4} alcoxi, C_{1-4} alcanoilo, C_{1-4} alcanoiloxi, $N-(C_{1-4}alquil)amino$, $N,N-(C_{1-4}alquil)_2amino$, $C_{1-4}alcanoilamino$, $N-(C_{1-4}alquil)carbamoilo$, $N,N-(C_{1-4}alquil)_2carbamoilo$, $C_{1-4}alquilS(O)_a$ en donde a es 0 a 2, $C_{1-4}alcoxycarbonilo$, $N-(C_{1-4}alquil)_2sulfamoilo$, $N,N-(C_{1-4}alquil)_2sulfamoilo$, carbociclilo, heterociclilo, benciloxycarbonilamino, sulfo, sulfino, amídino, fosfono, $-P(O)(OR^a)(OR^b)$, $-P(O)(OH)(OR^a)$, $-P(O)(OH)(R^a)$ o $-P(O)(OR^a)(R^b)$, en donde R^a y R^b se seleccionan independientemente de C_{1-4} alquilo, en donde R^{19} y R^{20} , R^{24} y R^{26} pueden sustituirse independientemente en forma opcional en carbono por uno o mas R^{22} ,

R^{21} y R^{22} se seleccionan independientemente de halo, hidroxilo, ciano, carbamoilo, ureido, amino, nitro, carboxilo, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxycarbonilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, N -metilcarbamoilo, N,N -dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, N -metilsulfamoilo y N,N -dimetilsulfamoilo,

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✓

R^{23} es carboxi, sulfo, sulfino, fosfono, $-P(O)(OR^s)(OR^h)$, $-P(O)(OH)(OR^s)$, $-P(O)(OH)(R^s)$ o $-P(O)(OR^s)(R^h)$, en donde R^s y R^h se seleccionan independientemente de C_{1-6} alquilo,

R^{25} se selecciona de C_{1-6} alquilo, C_{1-6} alcanoilo, C_{1-6} alquilsulfonilo, C_{1-6} alcoxycarbonilo, carbamoilo, $N-(C_{1-6}$ alquil)carbamoilo, $N,N-(C_{1-6}$ alquil)carbamoilo, bencilo, benciloxycarbonilo, benzoilo y fenilsulfonilo, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco

2 Un compuesto de formula (I) como se reivindica en reivindicacion 1 en donde R^v es hidrógeno o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

3 Un compuesto de formula (I) como se reivindica en cualquiera de las dos reivindicaciones 1 ó 2 en donde R^1 y R^2 son ambos butilo o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

4 Un compuesto de formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-3 en donde R^x y R^y son ambos hidrogeno o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

5 Un compuesto de formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-4 en donde M es -N- o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

6 Un compuesto de fórmula (I) como se reivindica en una cualquiera de las reivindicaciones 1-5 en donde v es 0 o una sal farmaceuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

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20
X

7 Un compuesto de fórmula (I) como se reivindica en una cualquiera de las reivindicaciones 1-6 en donde R^3 y R^6 son hidrógeno o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

8 Un compuesto de formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-7 en donde R^4 es bromo, metilo o metiltio o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

9 Un compuesto de formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-8 en donde R^5 es un grupo de formula (IA) (como se describe en reivindicación 1) en donde

X es -O-,

Anillo A es fenilo opcionalmente sustituido por uno o mas sustituyentes seleccionados de R^{17} ,

n es 1,

R^7 es hidrogeno,

R^8 es hidrogeno,

R^9 es hidrógeno,

m es 0,

R^{11} es carboxi, un grupo de fórmula (IB) (como se describe anteriormente) o un grupo de fórmula (IC) (como se describe anteriormente) en donde

R^{12} es hidrógeno o C_{1-4} alquilo,

p es 1 o 2,

R^{13} es hidrógeno o C_{1-6} alquilo sustituido opcionalmente por R^{20} en donde R^{20} es hidroxil, carbamilo, amino, benciloxycarbonilamino o C_{1-4} alquilS(O)_a en donde a es 0 o (C₁₋₄alquil)₃silo,

R^{14} es hidrógeno o hidroxil o C_{1-6} alquilo, en donde R^{14} puede sustituirse forma opcional por uno o más sustituyentes seleccionados de R^{20} ,

Y es -N(Rⁿ)C(O)-en donde Rⁿ es hidrógeno,

Qes 0 ó 1,

resol.

R¹⁵ es carboxi o sulfo.

R¹⁷ es hidroxilo, y

R²⁰ se selecciona de hidroxil.

Anillo B es pirrolidin-1-ilo o azetidínilo sustituido en carbono por un grupo seleccionado de R^{23} , y sustituido además en forma opcional en carbono por uno o más R^{24} , en donde R^{23} es carboxi y R^{24} es hidroxí o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

11 Un compuesto de formula (I) (como se describe arriba) en donde

R^v es hidrógeno,

R¹ y R² son ambos butilo.

R^x y R^y son ambos hidrógeno,

M es -N-,

v es 0,

R^3 y R^6 son hidrógeno,

R⁴ es bromo, metilo o metiltio, y

R³ es N-{(R)-α-[N-(carboximetil)carbamoil]bencil}carbamoilmetoxi, N-{(R)-α-[N-(carboximetil)carbamoil]bencil}carbamoilmetoxi, N-{(R)-α-[N-(2-sulfoetil)carbamoil]-4-hidroxi-bencil}carbamoilmetoxi, N-{(R)-α-[N-((S)-1-carboxi-2-hidroxi-etil)carbamoil]bencil}carbamoilmetoxi, N-{(R)-α-[N-((S)-1-carboxi-etil)carbamoil]bencil}carbamoilmetoxi, N-{(R)-α-[N-((S)-1-carboxi-propil)carbamoil]bencil}carbamoilmetoxi, N-{(R)-α-[N-((R)-1-carboxi-2-metil-tio-etil)carbamoil]bencil}carbamoilmetoxi, N-{(R)-α-[N-((S)-1-carboxi-2-carbamoil-etil)carbamoil]bencil}carbamoilmetoxi, N-{(R)-α-[N-(2-sulfoetil)carbamoil]-4-hidroxi-bencil}carbamoilmetoxi, N-{(R)-α-[N-(carboximetil)carbamoil]-4-hidroxi-bencil}carbamoilmetoxi, N-{(R)-α-[N-((S)-1-carboxi-etil)carbamoil]-4-hidroxi-bencil}carbamoilmetoxi, N-{(R)-α-[N-((S)-1-carboxi-2-hidroxi-etil)carbamoil]-4-hidroxi-bencil}

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carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}(2\text{-sulfoetil})\text{carbamoil}]\text{bencil}\}$
 carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxi-2-(R)-hidroxi}propil)$
 carbamoil]bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxi-2-}$
 metilpropil)carbamoil]bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}(S)\text{-}1\text{-carboxi-}$
 3-metilbutil)carbamoil]bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}(1\text{-}(S)\text{-}1\text{-}$
 carboxi-2-(S)-2-metilbutil)carbamoil]bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}$
 carboxi-4-hidroxi bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxi-4-}$
 aminobutil)carbamoil]bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}\{N\text{-}[(S)\text{-}1\text{-}$
 carboxi-4-(benciloxi carbonil amino)butil]carbamoil} bencil)
 carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}((S)\text{-}2\text{-carboxi}prrrolidin\text{-}1\text{-il carbonil})\text{bencil}\}$
 carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}(\text{carboxi metil})\text{-}N\text{-metil carbamoil}]\text{bencil}\}$
 carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}(1\text{-}(R)\text{-}2\text{-}(R)\text{-}1\text{-carboxi-1-hidroxi}prop\text{-}2\text{-}$
 il)carbamoil]bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}(\text{sulfometil})\text{carbamoil}]\}$
 bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-carboxi bencil}\}$ carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}$
 $[N\text{-}((S)\text{-}1\text{-carboxi-2-(R)-hidroxi}propil)\text{carbamoil}]\text{-4-hidroxi bencil}\}$
 carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxi-2-metil}propil)\text{carbamoil}]\text{-4-}$
 hidroxi bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxi}butil)$
 carbamoil]\text{-4-hidroxi bencil}\} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-}$
 carboxi propil)carbamoil]\text{-4-hidroxi bencil}\} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}$
 $((R)\text{-}1\text{-carboxi-2-metil}tio\text{-etil})\text{carbamoil}]\text{-4-hidroxi bencil}\}$ carbamoilmetoxi,
 $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxi}propil)\text{carbamoil}]\text{-4-hidroxi bencil}\}$
 carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(S)\text{-}1\text{-}[N\text{-}((S)\text{-}2\text{-hidroxi-1-carboxi}etil)$
 carbamoil]propil} carbamoil]bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[2\text{-}(S)\text{-}2\text{-}$
 (carboxi)-4-(R)-4-(hidroxi)prrrolidin\text{-}1\text{-il carbonil}]\text{bencil}\} carbamoilmetoxi,
 $N\text{-}\{(R)\text{-}\alpha\text{-}[2\text{-}\{(S)\text{-}2\text{-}(\text{carboxi})\text{azetidin-1-il carbonil}]\text{bencil}\}$ carbamoilmetoxi,
 $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}\{(S)\text{-}1\text{-}[N\text{-}((S)\text{-}1\text{-carboxi}etil)\text{carbamoil}]\text{etil}\}$ carbamoil]bencil}
 carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((R)\text{-}1\text{-carboxi-3,3-dimetil}butil)\text{carbamoil}]\}$
 bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((S)\text{-}1\text{-carboxi-3,3-dimetil}butil)$
 carbamoil]bencil} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}[N\text{-}((R)\text{-}1\text{-carboxi-3,3-}$
 dimetilbutil)carbamoil]\text{-4-hidroxi bencil}\} carbamoilmetoxi, $N\text{-}\{(R)\text{-}\alpha\text{-}\{N\text{-}$
 $[(S)\text{-}1\text{-carboxi-2-(trimetil}silil)\text{etil}]\text{carbamoil}\}\text{-4-hidroxi bencil}\}$
 carbamoilmetoxi o $N\text{-}\{(R)\text{-}\alpha\text{-}\{N\text{-}[(R)\text{-}1\text{-carboxi-2-(trimetil}silil)\text{etil}]\}$

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X

carbamoil}-4-hidroxibencil)carbamoilmetoxi,

o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

11 Un compuesto de fórmula (I) seleccionado 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,

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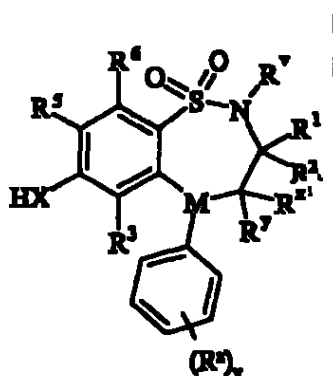
1,1-dioxo-3,3-dibutyl-5-fenil-7-metiltio-8-[N-{(R)- α -[N-{(S)-1-[N-((S)-2-hidroxi-1-carboxietil)carbamoil]propil}carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina, y

1,1-dioxo-3,3-dibutyl-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,

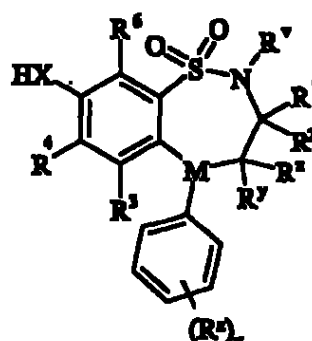
o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo

12 Un proceso para preparar un compuesto de fórmula (I) como se reivindica en reivindicaciones 1-11 o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, proceso que comprende

Proceso 1) para compuestos de fórmula (I) en donde X es -O-, -NR^a o -S-, hacer reaccionar un compuesto de fórmula (IIa) o (IIb):

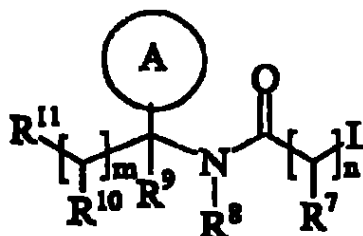


(IIa)



(IIb)

con un compuesto de fórmula (III):

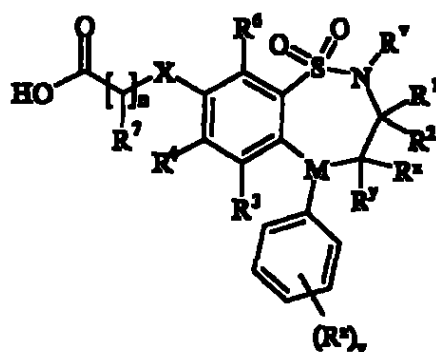


(III)

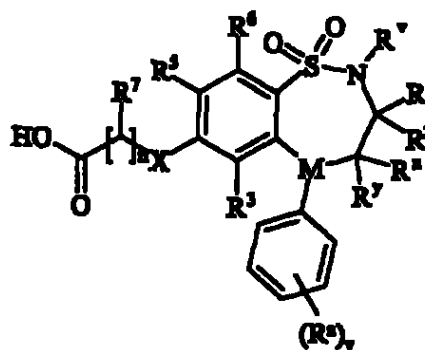
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en donde L es un grupo desplazable,

Proceso 2) hacer reaccionar un ácido de fórmula (IVa) o (IVb)

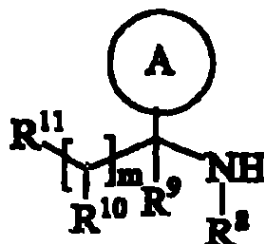


(IVa)



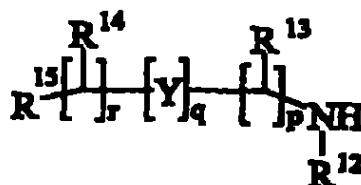
(IVb)

o un derivado activado del mismo, con una amina de fórmula (V)



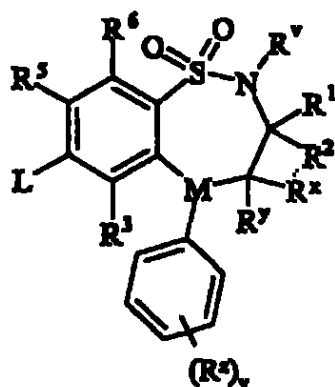
(V);

Proces 3) para compuestos de fórmula (I) en donde R^{11} es un grupo de fórmula (IB), hacer reaccionar un compuesto de fórmula (I) en donde R^{11} es carboxi con una amina de formula (VI)

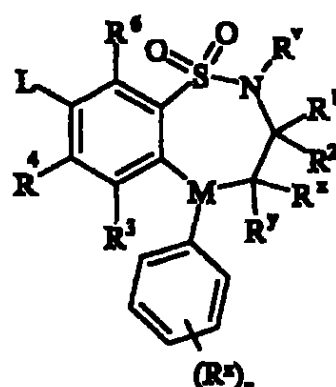


(VI)

Proceso 4) para compuestos de fórmula (I) en donde uno de R^4 y R^5 se seleccionan independientemente de C_{1-6} alquiltio sustituido de manera opcional en carbono por uno o mas R^{17} , hacer reaccionar un compuesto de formula (VIIa) o (VIIb)

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(VIIa)



(VIIb)

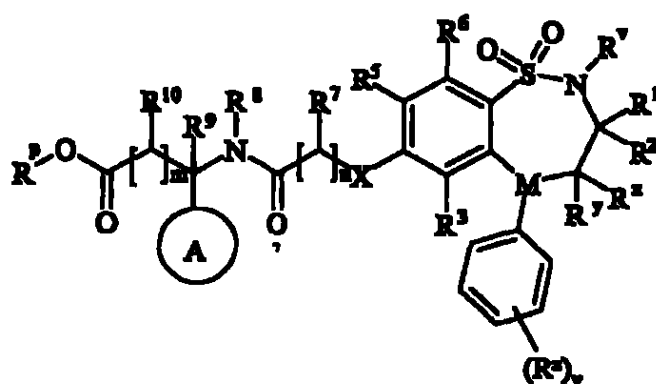
en donde L es un grupo desplazable, con un tiol de fórmula (VIII)



(VIII)

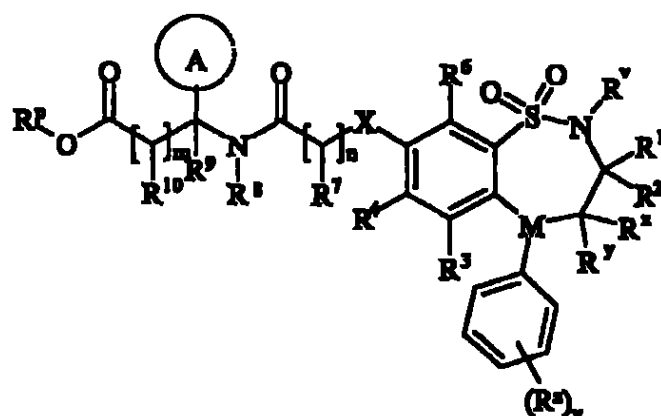
en donde R^m es C_{1-6} alquiltio sustituido de manera opcional en carbono por uno o más R^{16} ,

Proceso 5) para compuestos de fórmula (I) en donde R^{11} es carboxi, desproteger un compuesto de formula (IXa)



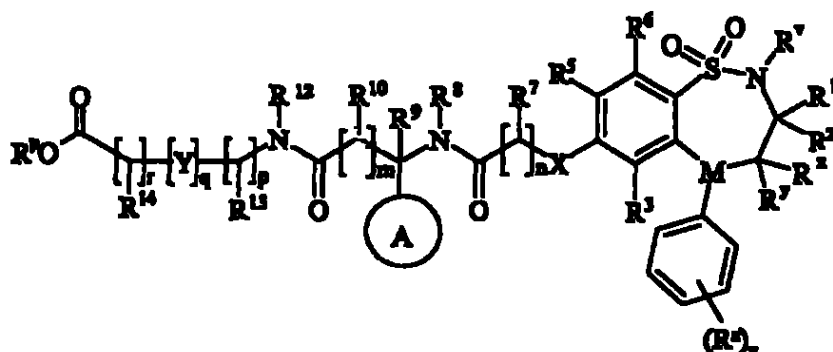
(IXa)

ó (IXb)



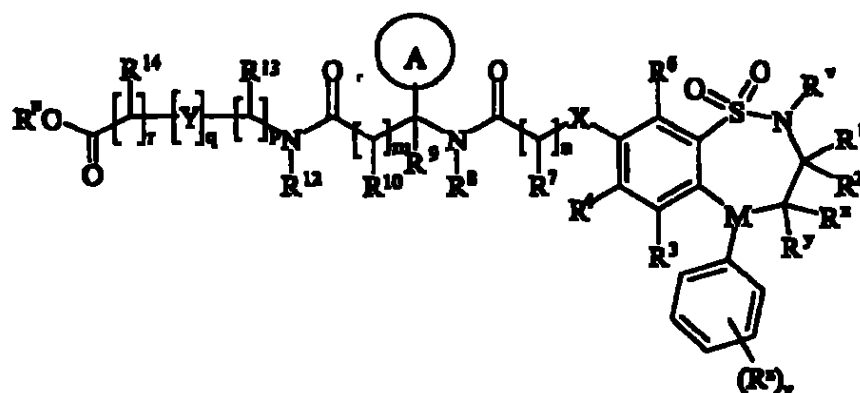
(IXb)

en donde R^p junto con el grupo $-OC(O)-$ al cual se une forma un ester;
Proceso 6) para compuestos de formula (I) en donde R^{11} es un grupo de
 formula (IB) y R^{15} es carboxi, desproteger un compuesto de formula (Xa)



(Xa)

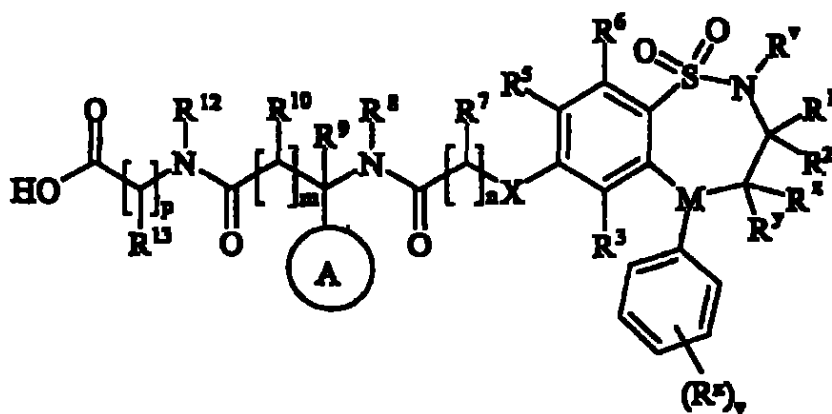
ó (Xb)



(Xb)

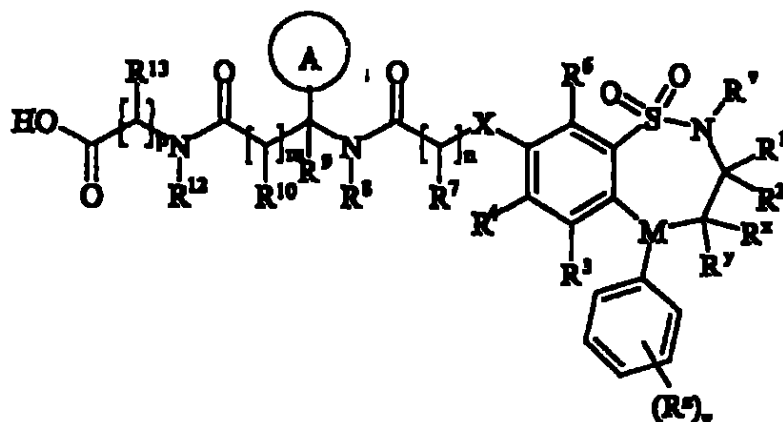
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en donde R^p junto con el grupo $-OC(O)-$ al cual se une forma un éster, *Proceso 7)* para compuestos de fórmula (I) en donde R^{11} es un grupo de fórmula (IB) y $N(R^n)C(O)-$, hacer reaccionar un ácido de fórmula (XIa)



(XIa)

ó (XIb)



(XIb)

o un derivado activado del mismo, con una amina de fórmula (XII)



(XII)

y, a partir de entonces, si se considera necesario o deseable

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1) convertir un compuesto de la fórmula (I) en otro compuesto de la fórmula (I),

11) retirar cualesquiera grupos protectores,

111) formar una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco

13 Un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11 para uso como un medicamento

14 Un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11 para uso en un método de tratamiento terapéutico o profiláctico de un animal de sangre caliente, tal como el hombre

15 El uso de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11 en la manufactura de un medicamento para uso en la producción de un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre

16 El uso de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11, en la producción de un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre

17 Un método para producir un efecto inhibidor IBAT en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un

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1

compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11

18 Una composición farmacéutica que comprende un compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11, en asociación con un diluyente o transportador farmacéuticamente aceptables

19 Una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11, y un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, en asociacion con un diluyente o transportador farmacéuticamente aceptables

20 Una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11, y un secuestrante de acido biliar, en asociación con un diluyente o transportador farmacéuticamente aceptables

21 Una composición farmacéutica que comprende un compuesto de formula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profármaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11, y un inhibidor de HMG Co-A reductasa, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, y un secuestrante de ácido biliar en asociacion con un diluyente o transportador farmacéuticamente aceptables

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22 Una composición de acuerdo con reivindicación 19 o reivindicación 21 en donde el Inhibidor de HMG Co-A reductasa es atorvastatina, o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo

23 Una composición de acuerdo con reivindicación 19 o reivindicación 21 en donde el inhibidor de HMG Co-A reductasa es rosuvastatina, o una sal farmacéuticamente aceptable de la misma

24 Una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato, solvato de dicha sal o un profarmaco del mismo, como se reivindica en una cualquiera de las reivindicaciones 1 a 11 y un agonista alfa y/o gamma PPAR, o una sal farmacéuticamente aceptable de la misma, en asociación con un diluyente o transportador farmacéuticamente aceptables

25 Una composición de acuerdo con reivindicación 24 en donde el agonista alfa y/o gamma PPAR es ácido (S)-2-etoxi-3-[4-(2-{4-metanosulfoniloxifenil}etoxi)fenil]propanoico o una sal farmacéuticamente aceptable del mismo

PATENT COOPERATION TREATY

25 APR 2003

PCT *

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

CODE	DATE	NTD
ANKOM	24 APR 2003	NO
DATA		
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FINAL		
CHECK		

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

To:
KRYANT, Tracey
ASTRAZENECA
Global Intellectual Property
Mercedes, Alderley Park
Macclesfield
Cheshire SK10 4TG
GRANDE BRETAGNE

Date of mailing
(day/month/year) 14/04/2003

Applicant's or agent's file reference
100479/WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB 02/04033

International filing date (day/month/year)
05/09/2002

Priority date (day/month/year)
08/09/2001

Applicant

ASTRAZENECA AB et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example to exemptions from patentability requirements for enabling disclosure clarity and support for the claims

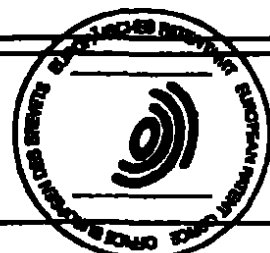
Name and mailing address of the IPEA/



European Patent Office
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Tel (+49-89) 2399-0, Tx 523656 epmu d
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Authorized officer

FERRO VASCONCELOS M
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 100479/WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPBA/416)	
International application No. PCT/GB 02/ 04033	International filing date (day/month/year) 05/09/2002	Priority date (day/month/year) 08/09/2001	
International Patent Classification (IPC) or national classification and IPC A61K31/554			
Applicant ASTRAZENECA AB et al			

- 1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- 2 This REPORT consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

CODE	DATE	NTD
ANKOM	24 APR 2003	GIPS
DATA ENTERED		
FINAL CHECK		

Date of submission of the demand 25/03/2003	Date of completion of this report 09/04/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx 523656 epmu d Fax. (+49-89) 2399-4465	Authorized officer GELLIE B R Tel. (+49-89) 2399 2828

Form PCT/IPBA/409 (cover sheet) P20476 (October 2002)



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/GB 02/04023

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I Basis of the report

The basis of this international preliminary examination is the application as originally filed

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66 1(e) PCT), see also international search report)

V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable

TRATADO SOBRE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

180
7
180

Remitente

OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A

BRYANT, Tracey
ASTRAZENECA
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
GRAN BRETAÑA

PCT

COMUNICACIÓN SOBRE EL ENVÍO DEL INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Regla 71.1 PCT)

Fecha de envío
(Día/Mes/Año)

14/04/2003

No de Expediente del Solicitante o Apoderado

100479/WO

COMUNICACIÓN IMPORTANTE

No de Solicitud Internacional

PCT / GB 02/ 04033

Fecha Internacional de Presentación
(día/mes/año)

05/09/2002

Fecha de Prioridad
(día/mes/año)

08/09/2001

Solicitante

ASTRAZENECA AB et al

- 1 Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el informe de examen preliminar internacional elaborado para la solicitud internacional en caso dado con los anexos correspondientes
- 2 Una copia del informe en caso dado con los anexos correspondientes se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas
- 3 A solicitud de una oficina seleccionada la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina

4 RECORDATORIO

Para ingresar en la fase nacional el solicitante dentro de los 30 meses a partir de la fecha de prioridad (o en algunas oficinas incluso después) tiene que realizar ante cada oficina seleccionada ciertos actos (entrega de traducciones y desembolso de honorarios nacionales) (Artículo 39 (1)) (véase también la información remitida por la Oficina Internacional en el Formulario PCT/IB/301)

Si se tiene que enviar a una oficina seleccionada una traducción de la solicitud internacional entonces esta traducción tiene que incluir traducciones de todos los anexos al informe de examen preliminar internacional. Es obligación del solicitante elaborar dichas traducciones y hacerlas llegar directamente a las oficinas seleccionadas respectivas.

Mayores detalles en cuanto a los plazos normativos y los requisitos de las oficinas seleccionadas se desprenden del Volumen II de la guía PCT para solicitantes.

Se llama la atención del solicitante al Artículo 33(5) que establece que los criterios de novedad, actividad inventiva y posibilidad de aplicación industrial descritos en Artículo 33(2) a (4) sirven meramente los propósitos del examen preliminar internacional y que "todo Estado Contratante puede aplicar criterios adicionales o diferentes para efectos de decidir si la invención reivindicada es patentable o no" (véase también Artículo 27 (5)). Los criterios adicionales pueden incluir, por ejemplo, exención de patentabilidad y los requerimientos al ser permitida la divulgación y de claridad y soporte de las reivindicaciones.

Nombre y dirección postal de la Oficina Encargada del
Examen Preliminar Internacional IPEA

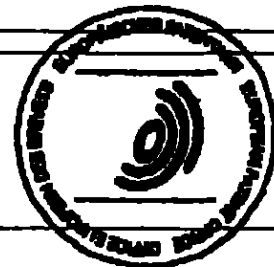


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Empleado Autorizado

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TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 38 y Regla 70 PCT)

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No de Expediente del Solicitante o Apoderado 100479/WO	PROCEDIMIENTO POSTERIOR véase comunicación sobre el envío del Informe de examen preliminar internacional (Formulario PCT/IPEA/418)	
No de Expediente Internacional PCT / GB 02/ 04033	Fecha Internacional de Presentación (día/mes/año) 05/09/2002	Fecha de Prioridad (día/mes/año) 08/09/2001
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC A61K31 / 554		
Solicitante ASTRAZENECA AB et al		

1 Este Informe de examen preliminar Internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 38

2 Este INFORME comprende un total de 2 hojas, inclusive esta portada

☐ Además se adjuntan ANEXOS al Informe en este caso se trata de hojas con descripciones reivindicaciones y/o dibujos, que se modificaron y que sirven de base a este Informe y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70.18 y Sección 807 de las Instrucciones administrativas al PCT)

Estos anexos comprenden en total de _____ hojas.

3. Este Informe contiene datos con respecto a los siguientes puntos

I ☒ Base del Informe

II ☐ Prioridad

III ☒ Sin elaboración de un dictamen sobre novedad actividad inventiva y posibilidad de aplicación industrial

IV ☐ Uniformidad deficiente de la invención

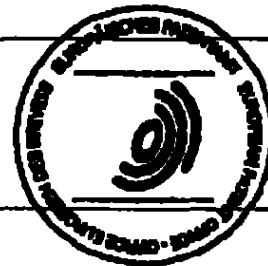
V ☒ Declaración justificada según Artículo 35(2) con respecto a la novedad la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración

VI ☐ Ciertos documentos enumerados

VII ☐ Ciertas deficiencias del registro internacional

VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición 25/03/2003	Fecha de la conclusión de este informe 09/04/2003
Nombre y dirección postal de la Oficina Encargada del Examen Preliminar Internacional IPEA  Oficina Europea de Patentes D-80298 Munich Tel (+49-89) 2399-0 Tx 523856 epmu d Fax (+49-89) 2399-4485	Empleado Autorizado GELLIE B R Tel (+49-89) 2399 2828



**INFORME DE EXAMEN PRELIMINAR
INTERNACIONAL**

No. de Solicitud Internacional PCT / GB 02/04033

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[Handwritten signature]

I Base del Informe

La base de este informe de examen preliminar la constituye la solicitud tal como se radicó originalmente

III Ausencia de formulación de opinión en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial

La cuestión de si la invención reivindicada parece ser novedosa, implicar una actividad inventiva o ser aplicable industrialmente no ha sido objeto del examen preliminar internacional con respecto a las reivindicaciones que no se han investigado (Artículo 17(2) (a) ó (3) y Regla 66 1 (e) PCT), véase también el informe de búsqueda internacional)

V Declaración motivada bajo Regla 66 2(a)(II) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial

En la medida en que se ha llevado a cabo el examen preliminar internacional (véase ítem III más arriba en el texto), se señala lo siguiente

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención como se define en las reivindicaciones, que han sido objeto de un informe de búsqueda internacional, satisface los criterios mencionados en Artículo 33(1) PCT, es decir, parece ser novedosa, implicar actividad inventiva y ser industrialmente aplicable

183 (4)
100479/WO

PCT REQUEST

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0	For receiving Office use only	
0-1	International Application No	
0-2	International Filing Date	
0-3	Name of receiving Office and PCT International Application*	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	100479/WO
I	Title of invention	CHEMICAL COMPOUNDS
II	Applicant	
II 1	This person is	applicant only
II-2	Applicant for	AP: (GH GM KE LS MW NZ SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MK MN MW MX NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address.	Sodertalje S-151 85 Sweden
II-6	State of nationality	SE
II 7	State of residence	SE
II-8	Telephone No.	+44 1625 230148
II-9	Facsimile No.	+44 1625 510752

PCT REQUEST

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100428/100

III-1	Applicant and/or inventor	
III-1-1	This person is	applicant only
III-1-2	Applicant for	MG
III-1-4	Name	ASTRAZENECA UK LIMITED
III-1-5	Address	15 Stanhope Gate London, Greater London W1Y 6LN United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB
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)	STARKE, Ingemar
III-2-5	Address	Molndal S-431 83 Sweden
III-2-6	State of nationality	SE
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)	DAHLSTROM, Mikael, Ulf, Johan
III-3-5	Address	Molndal S-431 83 Sweden
III-3-6	State of nationality	FI
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)	BLOMBERG, David
III-4-5	Address	Molndal S-431 83 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)	ALLENFALK, Suzanne
III-5-5	Address	Molndal S-431 83 Sweden
III-5-6	State of nationality	SE
III-5-7	State of residence	SE

PCT REQUEST

3/6

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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)	SKJARET, Tore
III-6-5	Address.	Molndal S-431 83 Sweden
III-6-6	State of nationality	NO
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)	LENDRELL, Malin
III-7-5	Address.	Molndal S-431 83 Sweden
III-7-6	State of nationality	SE
III 7 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 (LAST First)	BRYANT, Tracey, et al
IV 1-2	Address	ASTRAZENECA Global Intellectual Property Merreside Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
IV 1-3	Telephone No.	+44 1625 513228
IV 1-4	Facsimile No	+44 1625 510752

PCT REQUEST

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1004784/0

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V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-3	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3 the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-4	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1.1	Filing date	08 September 2001 (08.09.2001)
VI-1.2	Number	0121768.6
VI-1.3	Country	GB

PCT REQUEST

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100470/WO

VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	25 April 2002 (25.04.2002)	
VI-2-2	Number	0209463.9	
VI-2-3	Country	GB	
VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s)	VI-1, VI-2	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX 1	Request (including declaration sheets)	6	-
IX-2	Description	86	-
IX-3	Claims	14	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	107	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX 17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X 1 1	Name (LAST First)	BRYANT, Tracey, et al	

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10-1	Date of actual receipt of the purported international application	
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The demand must be filed directly with the competent International Preliminary Examining Authority or if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below.

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 100479/WG	
International application No. PCT/GB02/04033	International filing date (day/month/year) 05 September 2002 (05 09 2002)	(Earliest) Priority date (day/month/year) 08 September 2001 (08 09 2001)	
Title of invention BENZOTHIAZEPINE AND BENZOTHIADIAZEPINE DERIVATIVES WITH ILEAL BILE ACID TRANSPORT (IBAT) INHIBITORY ACTIVITY FOR THE TREATMENT HYPERLIPIDAEMIA			
Box No. II APPLICANT(S)			
Name and address (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.) AstraZeneca AB S-151 85 Södertälje Sweden		Telephone No. +44 1625 230148	
		Facsimile No. +44 1625 510752	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality SE		State (that is, country) of residence SE	
Name and address. (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.) ASTRAZENECA UK LIMITED 15 Stanhope Gate London, Greater London W1Y 6LN GB			
State (that is, country) of nationality GB		State (that is, country) of residence GB	
Name and address. (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.) STARKE, Ingemar Molndal S-431 83 Sweden			
State (that is, country) of nationality SE		State (that is, country) of residence SE	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

DAHLSTROM, Mikael Ulf Johan
Molndal
S-431 83
Sweden

State (that is, country) of nationality
FIState (that is, country) of residence:
SE

Name and address (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BLOMBERG, David
Molndal
S-431 83
Sweden

State (that is, country) of nationality
SEState (that is, country) of residence:
SE

Name and address (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ALENFALK, Suzanne
Molndal
S-431 83
Sweden

State (that is, country) of nationality
SEState (that is, country) of residence:
SE

Name and address (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

SKJARET, Tore
Molndal
S-431 83
Sweden

State (that is, country) of nationality
NOState (that is, country) of residence:
SE☒ Further applicants are indicated on another continuation sheet.

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~~191~~

Sheet No. 3

International application No.
PCT/GB02/04033

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LEMURELL, Malin
Molndal
S-431 83
Sweden

State (that is, country) of nationality
SE

State (that is, country) of residence:
SE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality

State (that is, country) of residence

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet

Box No. III AGENT OR COMMON REPRESENTATIVE, OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority in addition to the agent(s)/common representative appointed earlierName and address. (Family name followed by given name, for a legal entity, full official designation.
The address must include postal code and name of country.)BRYANT, Tracey et al
ASTRAZENECA
Global Intellectual Property
Merseyside, Alderley Park
Macclesfield,
Cheshire SK10 4TG
United Kingdom

Telephone No

+44 1625 513228

Facsimile No

+44 1625 510752

Teleprinter No.

Agent's registration No with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1 The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69 1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination.

- | | | |
|----|---|--------|
| 1 | translation of international application | sheets |
| 2 | amendments under Article 34 | sheets |
| 3 | copy (or, where required, translation) of amendments under Article 19 | sheets |
| 4 | copy (or where required, translation) of statement under Article 19 | sheets |
| 5 | letter | sheets |
| 6. | other (specify) | sheets |

For International Preliminary Examining Authority use only

received	not received
----------	--------------

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below

- | | |
|---|---|
| 1 ☒ fee calculation sheet | 5 ☐ statement explaining lack of signature |
| 2 ☐ original separate power of attorney | 6 ☐ sequence listing in computer readable form |
| 3 ☐ original general power of attorney | 7 ☐ other (specify) |
| 4 ☐ copy of general power of attorney reference number, if any | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



BRYANT, Tracey et al
Global Intellectual Property, Patents, AstraZeneca AB

For International Preliminary Examining Authority use only

1 Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b)

3 ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply

☐ The applicant has been informed accordingly

4 ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5

5 ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on

Brigard & Castro

BOGOTA - COLOMBIA

PODER

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 enseñanzas 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 desistirse 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 creyeran 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 desistirse, 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 16-56 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

POWER OF ATTORNEY

I (We) **ASTRAZENECA AB**

domiciled in **SE-151-3odertalje, 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 vegetable 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

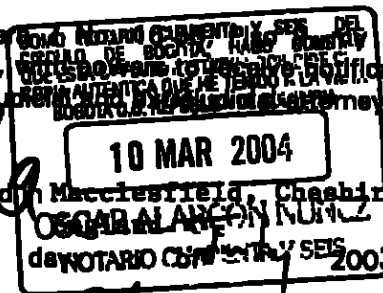
To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims, to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting, 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 16-56 Piso 9, my (our) attorney(s) in fact, with power to receive notifications and to designate judicial or extrajudicial attorneys

Granted and signed in **Macclesfield, Cheshire,**
this **18th** day of **March** 2003

Signature

Name **KEVIN BILL**
Title **Director, TB Services**



110816

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

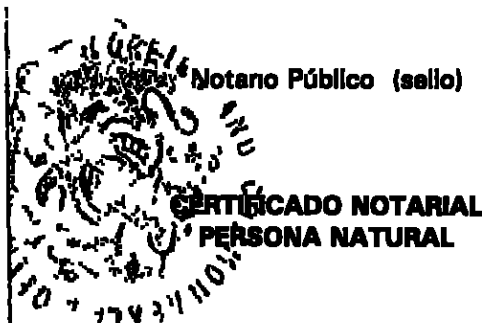
de

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

que quien confiere el presente poder es su representante



by de de , compareció(eron)
nte 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)

LEGALIZACION POR APOSTILLA ES REQUERIDA

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of
personally appeared before me

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

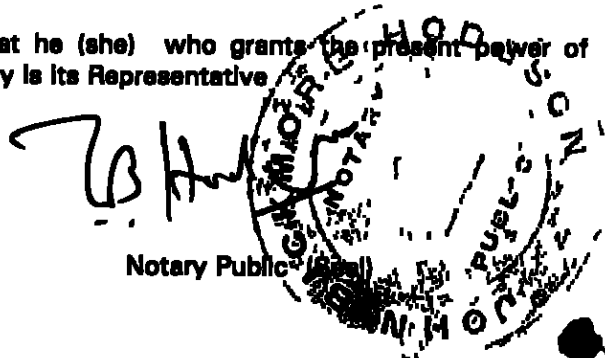
ATTORNEY
of
ATRAZENECA AS

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 the purpose for which this instrument is granted is 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

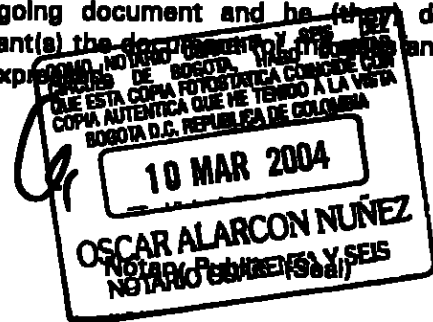
State of Sweden
under date of 1st January 2003

and that he (she) who grants the present power of attorney is its Representative



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 and purposes therein expressed



LEGALIZATION BY APOSTILLE IS REQUIRED

194
X

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 J B Hodgson
a été signé par

- 3 Acting in the capacity of Notary Public
agissant en qualité de

- 4 Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/tambour de

- 5 at London/Londres

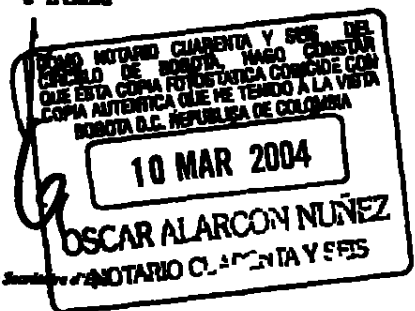
Certified/Attesté
6. the/le 17 February 2004

- 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/num No **G348987**

- 9 Stamp,
tambour

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

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención	()	()
- Dibujos de ser estos pertinentes	()	()
- Comprobante de Pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
Firma Responsable		
SUPERINDUSTRIA Y COMERCIO		
Radicación : 04032561 00000000	Folios: 195	
Fecha (GMB): 2004-04-06 16:30:06		
Trámite : 011 PCT-PATENT 379 FINE NACI 411 PRESENTAR		
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES		

2020
Bogotá, D C ,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
ASTRAZENECA AB

Oficio N°

05219

ASUNTO	Radicación N°	04-32561
	Solicitud Internacional	PCT/GB02/04033
	Fecha inicio fase nacional	08/04/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Unica de la Superintendencia de Industria y Comercio, se le comunica que

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante (Art 26-k) Decisión 486)

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 21/04/2004

202060

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Bogotá D C Colombia