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PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

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

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **ASTRAZENECA AB** Dirección: S-151 85 Sodertalje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número
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8 **Título (54):** 1,5 BENZOTIAZEPINAS Y SU USO COMO ANTIHIPERLIPIDÉMICOS

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

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $400.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] Otros

11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

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

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		TOTAL : $	400,000.00

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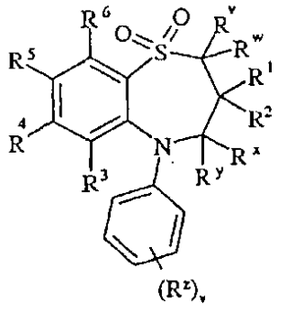
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT,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

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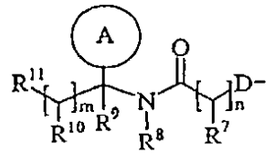
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(54) Title: CHEMICAL COMPOUNDS



(I)



(IA)

(57) Abstract: The present invention relates to compounds of the formula (I): (wherein variable groups are as defined within) pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof and their use as ileal bile acid transport (IBAT) inhibitors for the treatment of hyperlipidaemia. Processes for their manufacture and pharmaceutical compositions containing them are also described.

WO 02/50051 A1

1,5 BENZOTHIAZEPINES AND THEIR USE AS ANTIHHYPERLIPIDEMICS

This invention relates to benzothiazepine derivatives, or pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof. These benzothiazepines 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 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 I., 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 cholestipol. 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.

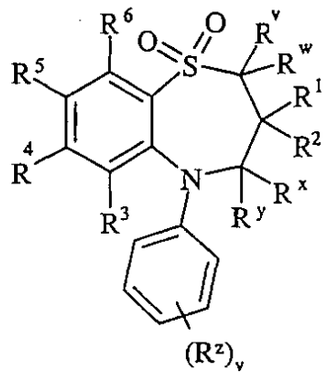
Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process which mainly takes place in the ileum by the IBAT mechanism. Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia (see for instance "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolaemic properties", Biochemica et Biophysica Acta, 1210 (1994) 255- 287). Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions. Compounds possessing such IBAT inhibitory activity have been described, see for instance 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, hypertrigliceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (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, leukocyte, monocytes and/or macrophage infiltrate, intimital 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 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^v and R^w are independently selected from hydrogen or C_{1-6}alkyl;

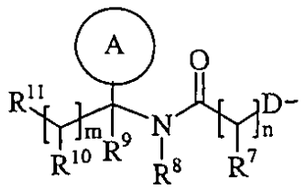
R^1 and R^2 are independently selected from C_{1-6}alkyl;

$\mathbf{R^x}$ and $\mathbf{R^y}$ are independently selected from hydrogen or C_{1-6}alkyl, or one of R^x and R^y is hydrogen or C_{1-6}alkyl and the other is hydroxy or C_{1-6}alkoxy;

$\mathbf{R^z}$ 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)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, ureido, *N'*-(C_{1-6}alkyl)ureido, *N*-(C_{1-6}alkyl)ureido, *N',N'*-(C_{1-6}alkyl)$_2$ureido, *N'*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkyl)ureido, *N',N'*-(C_{1-6}alkyl)$_2$-*N*-(C_{1-6}alkyl)ureido, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl;

v is 0-5;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula **(IA)**:



(IA)

$\mathbf{R^3}$ and $\mathbf{R^6}$ and the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ 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)$_2$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^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};

D is -O-, -N(R^a)-, -S(O)$_b$- or -CH(R^a)-; wherein R^a 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};

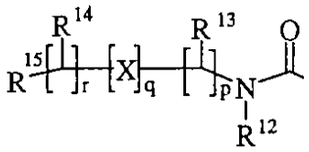
$\mathbf{R^7}$ is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{18};

$\mathbf{R^8}$ is hydrogen or C_{1-4}alkyl;

$\mathbf{R^9}$ 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, sulpho, sulphino, phosphono, tetrazolyl, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) or -P(O)(OR^c)(R^d) wherein R^c and R^d are independently selected from C_{1-6}alkyl; or R^{11} is a group of formula **(IB)**:



(IB)

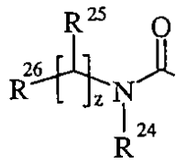
wherein:

X is –N(R^q)-, -N(R^q)C(O)-, -O-, and -S(O)$_a$-; wherein a is 0-2 and R^q 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, heterocyclyl or R^{23}; wherein said C_{1-4}alkyl, carbocyclyl or heterocyclyl may be independently optionally substituted by one or more substituents selected from R^{20};

R^{15} is carboxy, sulpho, sulphino, phosphono, tetrazolyl, -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 C_{1-6}alkyl; or R^{15} is a group of formula **(IC)**:



(IC)

wherein:

R^{24} is selected from hydrogen or C_{1-4}alkyl;

R^{25} is selected from hydrogen, C_{1-4}alkyl, carbocyclyl, heterocyclyl or R^{27}; wherein said C_{1-4}alkyl, carbocyclyl or heterocyclyl may be independently optionally substituted by one or more substituents selected from R^{28};

R^{26} is selected from carboxy, sulpho, sulphino, phosphono, tetrazolyl, -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;

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;

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

z is 0-3; wherein the values of R^{25} may be the same or different;

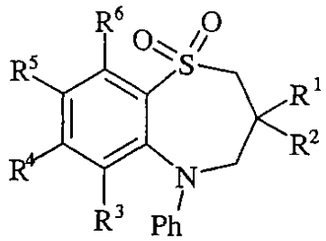
R^{16}, **R^{17}** and **R^{18}** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *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};

R^{19}, **R^{20}**, **R^{23}**, **R^{27}** and **R^{28}** 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_{1-6}alkyl; wherein R^{19}, R^{20}, R^{23}, R^{27} and R^{28} 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, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *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'**):

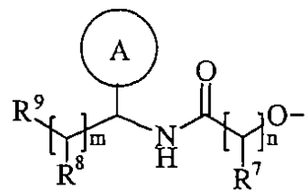


(I')

wherein:

$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from C_{1-6}alkyl;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula (**IA'**):



(IA')

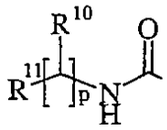
$\mathbf{R^3}$ and $\mathbf{R^6}$ and the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$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^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{12};

Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from R^{13};

$\mathbf{R^7}$ is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{14};

$\mathbf{R^8}$ is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^8 is optionally substituted by one or more substituents selected from R^{15};

$\mathbf{R^9}$ is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) or -P(O)(OR^c)(R^d) wherein R^c and R^d are independently selected from C_{1-6}alkyl; or R^9 is a group of formula (**IB'**):



(IB')

wherein:

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^{16};

R^{11} 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 C_{1-6}alkyl;

p is 1-3; wherein the values of R^{10} may be the same or different;

m is 0-2; wherein the values of R^8 may be the same or different;

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

R^{12}, **R^{13}** and **R^{14}** 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 and *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl; wherein R^{12}, R^{13} and R^{14} may be independently optionally substituted on carbon by one or more R^{17};

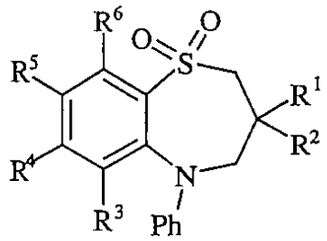
R^{15} and **R^{16}** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *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 and *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, 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_{1-6}alkyl; wherein R^{15} and R^{16} may be independently optionally substituted on carbon by one or more R^{18};

R^{17} and **R^{18}** 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,

N,N-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *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''):

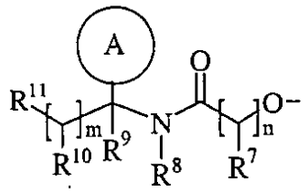


(I'')

wherein:

$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from C_{1-6}alkyl;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula (IA''):



(IA'')

$\mathbf{R^3}$ and $\mathbf{R^6}$ and the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ 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)$_2$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^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};

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

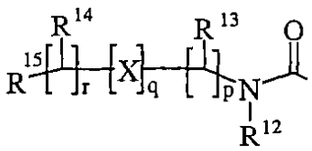
$\mathbf{R^7}$ is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{18};

$\mathbf{R^8}$ is hydrogen or C_{1-4}alkyl;

$\mathbf{R^9}$ is hydrogen or C_{1-4}alkyl;

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

$\mathbf{R^{11}}$ is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) or -P(O)(OR^c)(R^d) wherein R^c and R^d are independently selected from C_{1-6}alkyl; or R^{11} is a group of formula **(IB")**:



(IB")

wherein:

X is –N(R^q)-, -N(R^q)C(O)-, -O-, and -S(O)$_a$-; wherein a is 0-2 and R^q is hydrogen or C_{1-4}alkyl;

$\mathbf{R^{12}}$ is hydrogen or C_{1-4}alkyl;

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

$\mathbf{R^{15}}$ 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 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;

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

$\mathbf{R^{16}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ 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)$_2$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};

$\mathbf{R^{19}}$ and $\mathbf{R^{20}}$ 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_{1-6}alkyl; wherein R^{19} and R^{20} 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, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl;

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

In the following paragraphs of the description, and in the claims, where a compound of formula **(I)** is referred to, it is to be understood that this aspect also relates to compounds of formula **(I')** and compounds of formula **(I'')**.

In addition, the skilled person will appreciate that the numbering system differs between compounds of formula **(I)** and compounds of formula **(I')**. The numbering system used hereinbelow refers to compounds of formula **(I)**, but it is to be understood that these statements also apply to the corresponding values in formula **(I')**.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" includes C_{1-4}alkyl, C_{1-3}alkyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "phenylC_{1-6}alkyl" would include phenylC_{1-4}alkyl, 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. In another aspect of the invention, "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 8, 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-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouracilyl, 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, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl,

pyranyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl and 1-isoquinolonyl.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(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}alkyl$S(O)_a$ wherein a is 0 to 2" and "C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" and "C_{1-4}alkanoyl" include C_{1-3}alkanoyl, propionyl and acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" and "*N*-(C_{1-4}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" and "*N,N*-(C_{1-4}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino 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*-(C_{1-6}alkyl)sulphamoyl" and "*N*-(C_{1-4}alkyl)sulphamoyl" are *N*-(C_{1-3}alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)$_2$sulphamoyl" and "*N*-(C_{1-4}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" and "*N*-(C_{1-4}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" and "*N,N*-(C_{1-4}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{1-6}alkoxycarbonylamino" are ethoxycarbonylamino and *t*-butoxycarbonylamino. Examples of "*N'*-(C_{1-6}alkyl)ureido" are *N'*-methylureido and *N'*-ethylureido. Examples of "*N*-(C_{1-6}alkyl)ureido are *N*-methylureido and *N*-ethylureido. Examples of "*N',N'*-(C_{1-6}alkyl)$_2$ureido are *N',N'*-dimethylureido and *N'*-

methyl-*N'*-ethylureido. Examples of "*N'*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkyl)ureido are *N'*-methyl-*N*-methylureido and *N'*-propyl-*N*-methylureido. Examples of "*N',N'*-(C_{1-6}alkyl)$_2$-*N*-(C_{1-6}alkyl)ureido are *N',N'*-dimethyl-*N*-methylureido and *N'*-methyl-*N'*-ethyl-*N*-propylureido.

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 or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

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

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

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and

phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

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

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

Preferred values of R^1, R^2, R^3, R^4, R^5 and R^6 are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Preferably R^v and R^w are both hydrogen.

Preferably R^1 and R^2 are independently selected from C_{1-4}alkyl.

More preferably R^1 and R^2 are independently selected from ethyl or butyl.

More preferably R^1 and R^2 are independently selected from ethyl, propyl or butyl.

In one aspect of the invention particularly R^1 and R^2 are both butyl.

In a further aspect of the invention particularly R^1 and R^2 are both propyl.

In another aspect of the invention particularly one of R^1 and R^2 is ethyl and the other is butyl.

Preferably R^x and R^y are independently selected from hydrogen or C_{1-6}alkyl.

More preferably R^x and R^y are both hydrogen.

Preferably R^z is selected from halo, amino, C_{1-6}alkyl, C_{1-6}alkoxycarbonylamino or *N'*-(C_{1-6}alkyl)ureido.

More preferably R^z is selected from chloro, amino, *t*-butyl, *t*-butoxycarbonylamino or *N'*-(*t*-butyl)ureido.

Preferably v is 0 or 1.

In one aspect of the invention, more preferably v is 0.

In one aspect of the invention, more preferably v is 1.

In one aspect of the invention preferably R^4 is a group of formula (**IA**) (as depicted above).

In another aspect of the invention preferably R^5 is a group of formula (**IA**) (as depicted above).

Preferably R^3 and R^6 are hydrogen.

Preferably the other of R^4 and R^5 that is not the group of formula (**IA**) is selected from halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that R^4 or R^5 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy and *N,N*-(C_{1-4}alkyl)$_2$amino.

More preferably the other of R^4 and R^5 that is not the group of formula (**IA**) is selected from bromo, methoxy, isopropoxy, methylthio, ethylthio, isopropylthio or mesyl; wherein that R^4 or R^5 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy and *N,N*-dimethylamino.

Particularly the other of R^4 and R^5 that is not the group of formula (**IA**) is selected from bromo, methoxy, isopropoxy, methylthio, ethylthio, isopropylthio, 2-hydroxyethylthio, 2-(*N,N*-dimethylamino)ethylthio or mesyl.

More particularly the other of R^4 and R^5 that is not the group of formula (**IA**) is methylthio.

Preferably the other of R^4 and R^5 that is not the group of formula (**IA**) is selected from hydrogen, halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that R^4 or R^5 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy, carboxy and *N,N*-(C_{1-4}alkyl)$_2$amino.

More preferably the other of R^4 and R^5 that is not the group of formula (**IA**) is selected from hydrogen, bromo, methoxy, isopropoxy, methylthio, ethylthio, isopropylthio or mesyl; wherein that R^4 or R^5 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy, carboxy and *N,N*-dimethylamino.

Particularly the other of R^4 and R^5 that is not the group of formula (IA) is selected from hydrogen, bromo, methoxy, isopropoxy, methylthio, carboxymethylthio, ethylthio, isopropylthio, 2-hydroxyethylthio, 2-(*N,N*-dimethylamino)ethylthio or mesyl.

In another aspect of the invention, more preferably the other of R^4 and R^5 that is not the group of formula (IA) is selected from hydrogen, chloro, bromo, methoxy, isopropoxy, methylthio, ethylthio or isopropylthio; wherein that R^4 or R^5 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy, carboxy and *N,N*-dimethylamino.

In another aspect of the invention, particularly the other of R^4 and R^5 that is not the group of formula (IA) is selected from hydrogen, chloro, bromo, methoxy, isopropoxy, methylthio, carboxymethylthio, ethylthio, isopropylthio, 2-hydroxyethylthio or 2-(*N,N*-dimethylamino)ethylthio.

In another aspect of the invention, more particularly the other of R^4 and R^5 that is not the group of formula (IA) is bromo or chloro.

In another aspect of the invention, more particularly the other of R^4 and R^5 that is not the group of formula (IA) is methoxy.

In one aspect of the invention, preferably Ring A is aryl.

In another aspect of the invention, preferably Ring A is heteroaryl.

When Ring A is aryl, preferably Ring A is phenyl.

When Ring A is heteroaryl, preferably Ring A is thienyl or indolyl.

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

R^{17} is selected from halo, hydroxy or C_{1-4}alkyl; wherein R^{17} may be optionally substituted on carbon by one or more R^{21}; wherein

R^{21} is selected from halo.

Preferably D is -O- or -S-.

In one aspect of the invention, more preferably D is -O-.

In one aspect of the invention, more preferably D is -S-.

More preferably Ring A is phenyl, thienyl or indolyl; wherein Ring A is optionally substituted by one or more substituents selected from halo, hydroxy or trifluoromethyl.

Particularly Ring A is selected from phenyl, 4-hydroxyphenyl, thien-2-yl, 4-trifluoromethylphenyl, 3-hydroxyphenyl, 2-fluorophenyl, 2,3-dihydroxyphenyl or indol-3-yl.

More particularly Ring A is phenyl.

In another aspect of the invention, preferably Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from R^{17}; wherein

R^{17} is selected from halo, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy; wherein R^{17} may be optionally substituted on carbon by one or more R^{21}; wherein

R^{21} is selected from halo.

In another aspect of the invention, more preferably Ring A is phenyl, thienyl or indolyl; wherein Ring A is optionally substituted by one or more substituents selected from halo, hydroxy, methoxy or trifluoromethyl.

In another aspect of the invention, particularly Ring A is selected from phenyl, 4-hydroxyphenyl, 4-methoxyphenyl, thien-2-yl, 4-trifluoromethylphenyl, 3-hydroxyphenyl, 2-fluorophenyl, 2,3-dihydroxyphenyl or indol-3-yl.

In a further aspect of the invention, particularly Ring A is selected from phenyl, 4-hydroxyphenyl, 4-methoxyphenyl, thien-2-yl, 4-trifluoromethylphenyl, 3-hydroxyphenyl, 2-fluorophenyl, 4-fluorophenyl, 2,3-dihydroxyphenyl or indol-3-yl.

Preferably R^7 is hydrogen, C_{1-4}alkyl or carbocyclyl.

More preferably R^7 is hydrogen, methyl or phenyl.

Particularly R^7 is hydrogen.

In one aspect of the invention, preferably R^8 is hydrogen.

In another aspect of the invention, preferably R^8 is C_{1-4}alkyl.

In another aspect of the invention, more preferably R^8 is hydrogen or methyl.

In one aspect of the invention, preferably R^9 is hydrogen.

In another aspect of the invention, preferably R^9 is C_{1-4}alkyl.

In another aspect of the invention, more preferably R^9 is hydrogen or methyl.

Preferably R^{10} is hydrogen.

In one aspect of the invention, preferably R^{11} is carboxy, sulpho, sulphino, phosphono, $-P(O)(OR^c)(OR^d)$, $-P(O)(OH)(OR^c)$, $-P(O)(OH)(R^d)$ or $-P(O)(OR^c)(R^d)$ wherein R^c and R^d are independently selected from C_{1-6}alkyl.

In another aspect of the invention, preferably R^{11} is a group of formula **(IB)** (as depicted above).

Preferably R^{11} is carboxy, $-P(O)(OH)(OR^c)$ or a group of formula **(IB)** (as depicted above).

More preferably R^{11} is carboxy, -P(O)(OH)(OEt) or a group of formula **(IB)** (as depicted above).

In another aspect of the invention, preferably R^{11} is carboxy, sulpho, -P(O)(OH)(OR^c) wherein R^c is selected from C_{1-4}alkyl or a group of formula **(IB)** (as depicted above).

Preferably X is –NH- or –NHC(O)-.

More preferably X is –NHC(O)-.

In one aspect of the invention, preferably R^{12} is hydrogen.

In another aspect of the invention, preferably R^{12} is C_{1-4}alkyl.

In another aspect of the invention, more preferably R^{12} is hydrogen or methyl.

Preferably R^{13} is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

R^{20} is hydroxy.

More preferably R^{13} is hydrogen, methyl or phenyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

R^{20} is hydroxy.

Particularly R^{13} is hydrogen, hydroxymethyl or phenyl.

More particularly R^{13} is hydrogen or hydroxymethyl.

In another aspect of the invention, preferably R^{13} is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

R^{20} is hydroxy, carboxy, carbocyclyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22};

R^{22} is hydroxy.

In another aspect of the invention, more preferably R^{13} is hydrogen, methyl, ethyl, butyl or phenyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

R^{20} is hydroxy, carboxy, phenyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22};

R^{22} is hydroxy.

In another aspect of the invention, particularly R^{13} is hydrogen, hydroxymethyl, 4-aminobutyl, 2-carboxyethyl, 4-hydroxybenzyl or phenyl.

In a further aspect of the invention, preferably R^{13} is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

R^{20} is hydroxy, carboxy, carbocyclyl, heterocyclyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22};

R^{22} is hydroxy.

In a further aspect of the invention, more preferably R^{13} is hydrogen, methyl, ethyl, butyl or phenyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

R^{20} is hydroxy, carboxy, phenyl, imidazolyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22};

R^{22} is hydroxy.

In a further aspect of the invention, particularly R^{13} is hydrogen, hydroxymethyl, 4-aminobutyl, 2-carboxyethyl, 4-hydroxybenzyl, imidazol-5-ylmethyl or phenyl.

In another further aspect of the invention, preferably R^{13} is hydrogen, C_{1-4}alkyl, carbocyclyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

R^{20} is hydroxy, C_{1-4}alkyl$S(O)_a$ wherein a is 0, C_{1-4}alkoxy, amino, carbocyclyl, heterocyclyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more R^{22};

R^{22} is selected from hydroxy; and

R^{23} is carboxy.

In another further aspect of the invention, more preferably R^{13} is hydrogen, methyl, ethyl, butyl or phenyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

R^{20} is hydroxy, methylthio, methoxy, amino, imidazolyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more R^{22};

R^{22} is selected from hydroxy; and

R^{23} is carboxy.

In another further aspect of the invention, particularly R^{13} is hydrogen, carboxy, hydroxymethyl, mercaptomethyl, methoxymethyl, methylthiomethyl, 2-methylthioethyl, 4-aminobutyl, 4-hydroxybenzyl, imidazol-5-ylmethyl or phenyl.

In an other aspect more particularly R^{13} is methylthiomethyl, methylsulphinylmethyl or methylsulphonylmethyl.

Preferably R^{14} is hydrogen.

In another aspect of the invention, preferably R^{14} is selected from hydrogen, C_{1-4}alkyl or carbocyclyl; wherein said C_{1-4}alkyl or carbocyclyl may be optionally substituted by one or more substituents selected from R^{20}; and

R^{20} is hydroxy.

In another aspect of the invention, more preferably R^{14} is selected from hydrogen, methyl or phenyl; wherein said methyl or phenyl may be optionally substituted by one or more substituents selected from R^{20}; and

R^{20} is hydroxy.

In another aspect of the invention, particularly R^{14} is hydrogen, phenyl or hydroxymethyl.

Particularly R^{15} is carboxy or sulpho.

In one aspect of the invention, more particularly R^{15} is carboxy.

In another aspect of the invention, more particularly R^{15} is sulpho.

Preferably R^{15} is carboxy, sulpho, $-P(O)(OR^e)(OR^f)$, $-P(O)(OH)(OR^e)$, $-P(O)(OH)(R^e)$ or $-P(O)(OR^e)(R^f)$ wherein R^e and R^f are independently selected from C_{1-4}alkyl.

More preferably R^{15} is carboxy, sulpho, $-P(O)(OR^e)(OR^f)$, $-P(O)(OH)(OR^e)$, $-P(O)(OH)(R^e)$ or $-P(O)(OR^e)(R^f)$ wherein R^e and R^f are independently selected from methyl or ethyl.

Preferably R^{15} is carboxy, sulpho, -P(O)(OEt)(OEt), -P(O)(OH)(OEt), -P(O)(OH)(Me) or -P(O)(OEt)(Me).

Preferably R^{15} is carboxy, sulpho, 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 C_{1-4}alkyl or R^{15} is a group of formula **(IC)** (as depicted above).

More preferably R^{15} is carboxy, sulpho, 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 methyl or ethyl or R^{15} is a group of formula **(IC)** (as depicted above).

Preferably R^{15} is carboxy, sulpho, phosphono, -P(O)(OEt)(OEt), -P(O)(O*t*-Bu)(O*t*-Bu), -P(O)(OH)(OEt), -P(O)(OH)(Me) or -P(O)(OEt)(Me) or R^{15} is a group of formula **(IC)** (as depicted above).

In one aspect of the invention, preferably R^{15} is a group of formula (IC) (as depicted above).

In another aspect of the invention, preferably R^{15} is not a group of formula (IC) (as depicted above).

In one aspect of the invention, preferably R^{15} is carboxy.

In another aspect of the invention, preferably R^{15} is sulpho.

In another aspect of the invention, preferably R^{15} is -P(O)(OH)(OEt).

In another aspect of the invention, preferably R^{15} is -P(O)(OH)(Me).

In another aspect of the invention, preferably R^{15} is -P(O)(OEt)(Me).

In one aspect of the invention, preferably R^{24} is hydrogen.

In another aspect of the invention, preferably R^{24} is C_{1-4}alkyl.

Preferably R^{25} is hydrogen.

Preferably R^{26} is carboxy.

Preferably p is 1 or 2; wherein the values of R^{13} may be the same or different.

In one aspect of the invention, more preferably p is 1.

In another aspect of the invention, more preferably p is 2; wherein the values of R^{13} may be the same or different.

In a further aspect of the invention, more preferably p is 3; wherein the values of R^{13} may be the same or different.

In one aspect of the invention, preferably q is 0.

In a further aspect of the invention, preferably q is 1.

In one aspect of the invention, preferably r is 0.

In one aspect of the invention, more preferably r is 1.

In another aspect of the invention, more preferably r is 2; wherein the values of R^{14} may be the same or different.

In a further aspect of the invention, more preferably r is 3; wherein the values of R^{14} may be the same or different.

Preferably m is 0.

In another aspect of the invention, preferably m is 0 or 1.

Preferably n is 1.

In another aspect of the invention, preferably n is 1 or 2.

Preferably z is 1.

The group of formula (**IA'**) wherein R^7 is hydrogen, methyl or phenyl, n is 1, Ring A is phenyl, thienyl or indolyl; wherein Ring A is optionally substituted by one or more substituents selected from halo, hydroxy or trifluoromethyl, m is 0 and R^9 is carboxy, -P(O)(OH)(OR^c) or a group of formula (**IB**).

The group of formula (**IA**) wherein:

D is -O- or -S-;

Ring A is phenyl, thienyl or indolyl; wherein Ring A is optionally substituted by one or more substituents selected from halo, hydroxy, methoxy or trifluoromethyl;

R^7 is hydrogen, methyl or phenyl;

R^8 is hydrogen or methyl;

R^9 is hydrogen or methyl;

R^{10} is hydrogen;

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

R^{11} is carboxy, -P(O)(OH)(OEt) or a group of formula (**IB**) (as depicted in claim 1);

The group of formula (**IB'**) wherein R^{10} is hydrogen, hydroxymethyl or phenyl, p is 1 or 2; wherein the values of R^{10} may be the same or different and R^{11} is carboxy or sulpho.

The group of formula (**IB**) wherein:

R^{12} is hydrogen or methyl;

R^{13} is hydrogen, methyl, ethyl, butyl or phenyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; R^{20} is hydroxy, methylthio, methoxy, amino, imidazolyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more hydroxy; R^{23} is carboxy;

X is –NH- or –NHC(O)-;

R^{14} is selected from hydrogen, methyl or phenyl; wherein said methyl or phenyl may be optionally substituted by one or more substituents selected from hydroxy;

R^{15} is carboxy, sulpho, 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 methyl or ethyl or R^{15} is a group of formula (**IC**) (as depicted in claim 1);

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

q is 0-1; and

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

The group of formula (**IC**) wherein

R^{24} is hydrogen;

R^{25} is hydrogen;

R^{26} is carboxy; and

z is 1;

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

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

$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from ethyl or butyl;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are hydrogen;

$\mathbf{R^4}$ is selected from halo, C_{1-4}alkoxy or C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2; wherein that R^4 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy and *N,N*-$(C_{1-4}alkyl)_2$amino;

$\mathbf{R^5}$ is a group of formula (IA');

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

$\mathbf{R^{17}}$ is selected from halo, hydroxy or C_{1-4}alkyl; wherein R^{17} may be optionally substituted on carbon by one or more R^{21}; wherein

$\mathbf{R^{21}}$ is selected from halo;

$\mathbf{R^7}$ is hydrogen, C_{1-4}alkyl or carbocyclyl;

$\mathbf{R^{11}}$ is carboxy, -P(O)(OH)(OR^c) or a group of formula (IB') (as depicted above);

$\mathbf{R^{13}}$ is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein

$\mathbf{R^{20}}$ is hydroxy;

$\mathbf{R^{15}}$ is carboxy or sulpho;

p is 1 or 2; wherein the values of R^{13} may be the same or different;

m is 0; and

n is 1;

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:

$\mathbf{R^1}$ and $\mathbf{R^2}$ are both butyl or one of R^1 and R^2 is ethyl and the other is butyl;

$\mathbf{R^4}$ is methylthio;

$\mathbf{R^5}$ is a group of formula (IA') (as depicted above);

R^3 and R^6 are hydrogen;

Ring A is phenyl;

R^7 is hydrogen;

R^{11} is a group of formula (**IB'**) (as depicted above);

R^{13} is hydrogen or hydroxymethyl;

R^{15} is carboxy or sulpho;

p is 1 or 2; wherein the values of R^{13} may be the same or different;

m is 0;

n is 1;

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

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

R^1 and R^2 are independently selected from ethyl or butyl;

R^3 and R^6 are hydrogen;

R^4 is selected from halo, C_{1-4}alkoxy or C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2; wherein that R^4 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy and *N,N*-(C_{1-4}alkyl)$_2$amino;

R^5 is a group of formula (**IA''**);

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 or carbocyclyl;

R^8 is hydrogen or methyl;

R^9 is hydrogen or methyl;

R^{11} is carboxy, -P(O)(OH)(OR^c) or a group of formula (**IB''**) (as depicted above);

X is –NH- or –NHC(O)-;

R^{12} is hydrogen or methyl;

R^{13} is hydrogen, C_{1-4}alkyl or carbocyclyl; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20};

R^{14} is hydrogen;

R^{15} is carboxy or sulpho;

R^{17} is selected from halo, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy; wherein R^{17} may be optionally substituted on carbon by one or more R^{21};

$\mathbf{R^{20}}$ is hydroxy, carboxy, carbocyclyl or amino; wherein R^{20} may be optionally substituted on carbon by one or more R^{22};

$\mathbf{R^{21}}$ is selected from halo;

$\mathbf{R^{22}}$ is hydroxy;

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; and wherein if q is 1, r is not 0;

m is 0 – 2; and

n is 1 – 3;

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

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

$\mathbf{R^v}$ and $\mathbf{R^w}$ are both hydrogen;

$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from C_{1-4}alkyl;

$\mathbf{R^x}$ and $\mathbf{R^y}$ are both hydrogen;

$\mathbf{R^z}$ is selected from halo, amino, C_{1-6}alkyl, C_{1-6}alkoxycarbonylamino or *N'*-(C_{1-6}alkyl)ureido;

v is 0 or 1;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are hydrogen;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula (IA) (as depicted above) and the other is selected from hydrogen, halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that R^4 or R^5 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy, carboxy and *N,N*-(C_{1-4}alkyl)$_2$amino;

D is -O- or -S-;

$\mathbf{R^7}$ is hydrogen, methyl or phenyl;

$\mathbf{R^8}$ is hydrogen or methyl;

Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from R^{17}; wherein R^{17} is selected from halo, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy; wherein R^{17} may be optionally substituted on carbon by one or more R^{21}; wherein R^{21} is selected from halo;

$\mathbf{R^9}$ is hydrogen or methyl;

$\mathbf{R^{10}}$ is hydrogen;

R^{11} is carboxy, -P(O)(OH)(OR^c) wherein R^c is selected from C_{1-4}alkyl or a group of formula (IB) (as depicted above);

R^{12} is hydrogen or methyl;

X is –NH- or –NHC(O)-;

R^{13} is hydrogen, C_{1-4}alkyl, carbocyclyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy, C_{1-4}alkyl$S(O)_a$ wherein a is 0, C_{1-4}alkoxy, amino, carbocyclyl, heterocyclyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more R^{22}; R^{22} is selected from hydroxy; and R^{23} is carboxy;

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

R^{15} is carboxy, sulpho, 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 C_{1-4}alkyl or R^{15} is a group of formula (IC) (as depicted above);

R^{24} is hydrogen;

R^{25} is hydrogen;

R^{26} is carboxy;

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;

n is 1-2; wherein the values of R^7 may be the same or different;

z is 0-1; wherein the values of R^{25} may be the same or different;

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.

In one aspect of the invention, there is provided a compound of formula (I) selected from Examples 8, 9, 46, 56, 59, 60, 61, 62, 66 and 69 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In another aspect of the invention, there is provided a compound of formula (I) which is Example 73, 74, 95, 96, 97, 98, 99 and 100 or a pharmaceutically acceptable salt, solvate,

solvate of such a salt or a prodrug thereof.

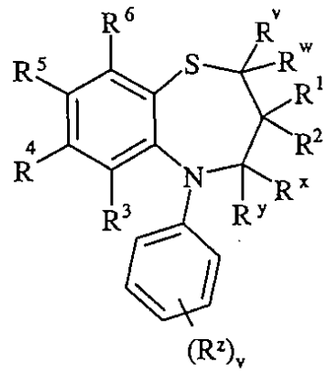
In another aspect of the invention, preferred compounds of the invention are any one of Examples 43, 50, 51 and 52 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In another additional aspect of the invention, preferred compounds of the invention are any one of Examples 43, 46, 50, 51, 56, 58, 59, 61, 62, 63, 69, 81, 83, 85, 94, 97, 98, 108, 109, 110, 111 or 117.

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

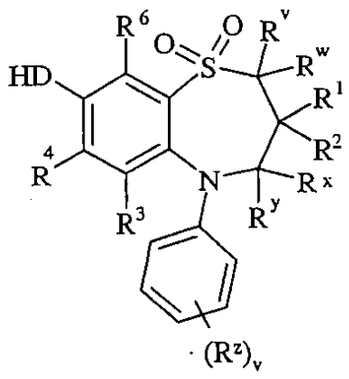
Another aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula **(I)**) comprises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

Process 1): oxidising a benzothiazepine of formula **(II)**:

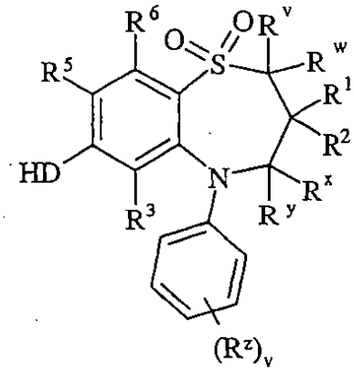


(II);

Process 2): for compounds of formula **(I)** wherein D is -O-,-NR^a or -S-; reacting a compound of formula **(IIIa)** or **(IIIb)**:

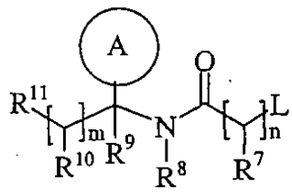


(IIIa)



(IIIb)

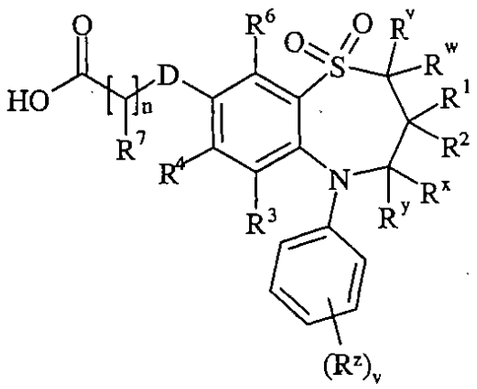
with a compound of formula **(IV)**:



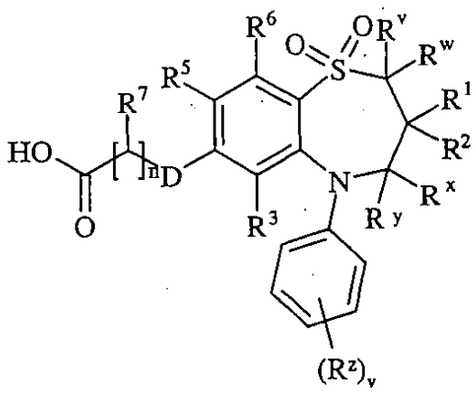
(IV)

wherein L is a displaceable group;

Process 3): reacting an acid of formula **(Va)** or **(Vb)**:

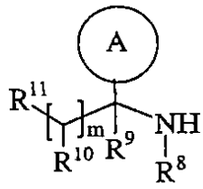


(Va)



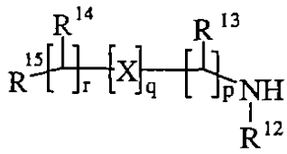
(Vb)

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



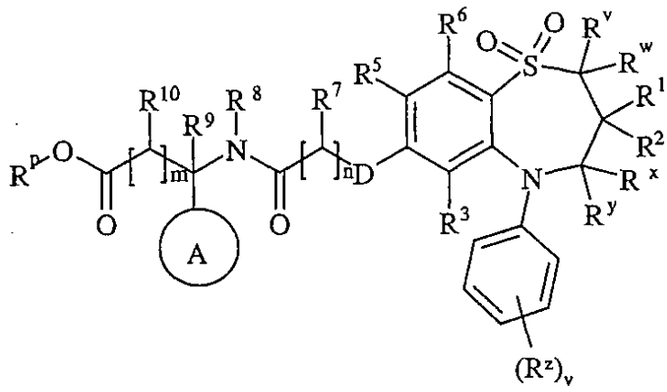
(VI);

Process 4): 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 **(VII)**:



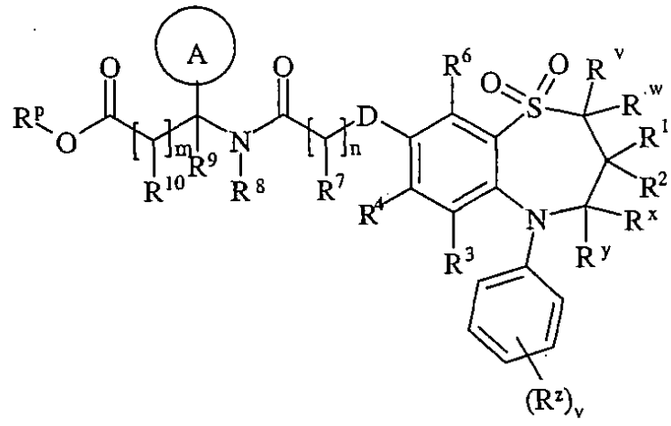
(VII)

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



(VIIIa)

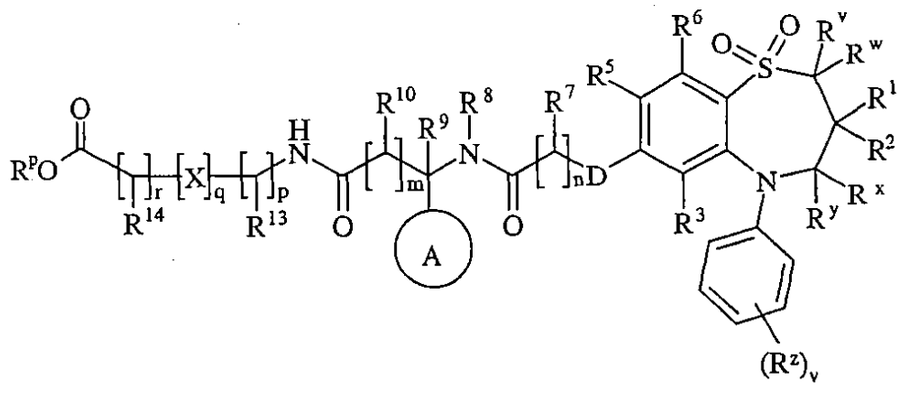
or **(VIIIb)**:



(VIIIb)

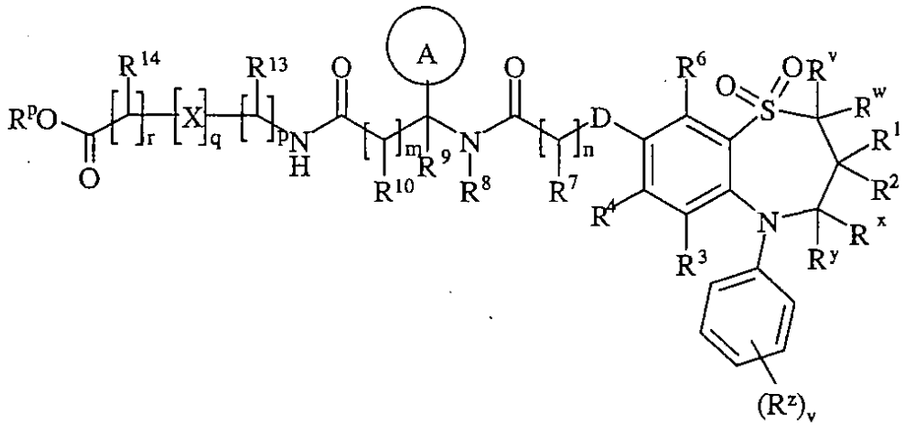
wherein R^p is C_{1-4}alkyl;

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 **(IXa)**:



(IXa)

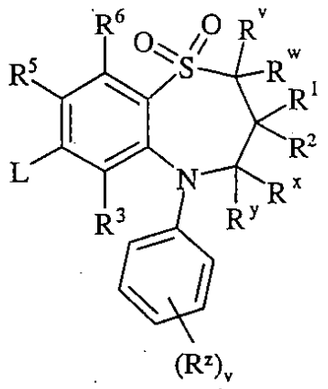
or **(IXb)**:



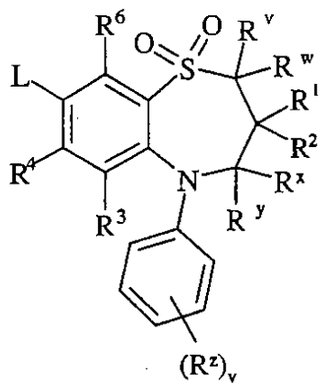
(IXb)

wherein R^p is C_{1-4}alkyl;

Process 7) for compounds of formula **(I)** wherein one of R^4 and R^5 are independently selected from C_{1-4}alkylthio optionally substituted on carbon by one or more R^{16}; reacting a compound of formula **(Xa)** or **(Xb)**:



(Xa)



(Xb)

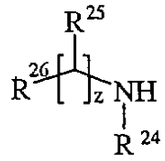
wherein L is a displaceable group; with a thiol of formula **(XI)**:

R^y-H

(XI)

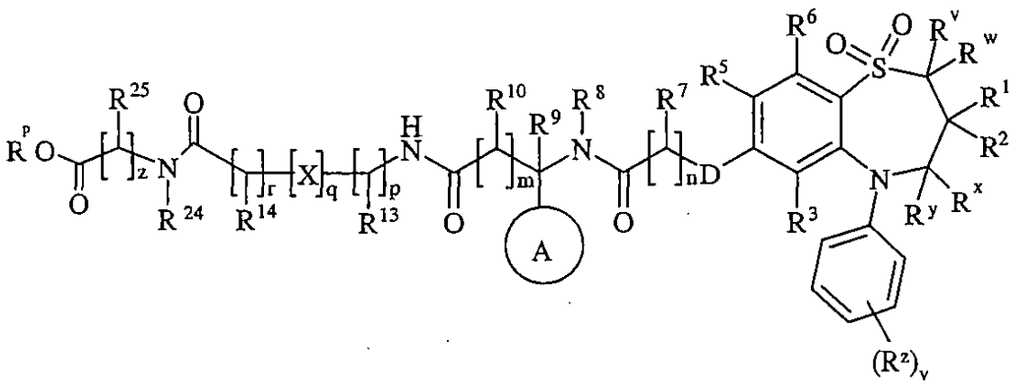
wherein R^y is C_{1-4}alkylthio optionally substituted on carbon by one or more R^{16};

Process 8) for compounds of formula **(I)** wherein R^{15} is a group of formula **(IC)** reacting a compound of formula **(IXa)** or **(IXb)** wherein R^p is hydrogen with a compound of formula **(XII)**:



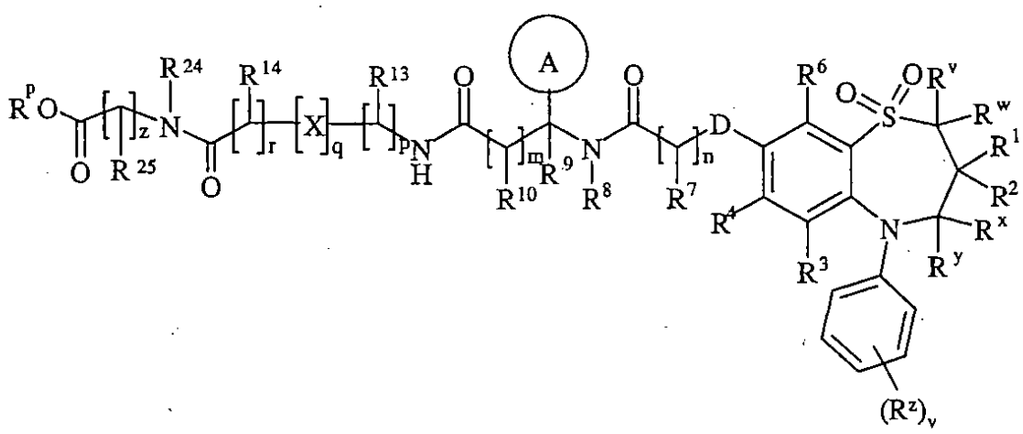
(XII)

Process 9): for compounds of formula **(I)** wherein R^{11} is a group of formula **(IB)** and R^{15} is a group of formula **(IC)** and R^{26} is carboxy; deprotecting a compound of formula **(XIIIa)**:



(XIIIa)

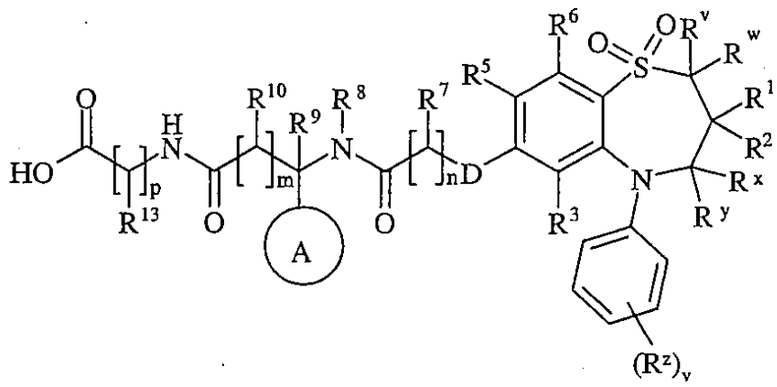
or **(XIIIb)**:



(XIIIb)

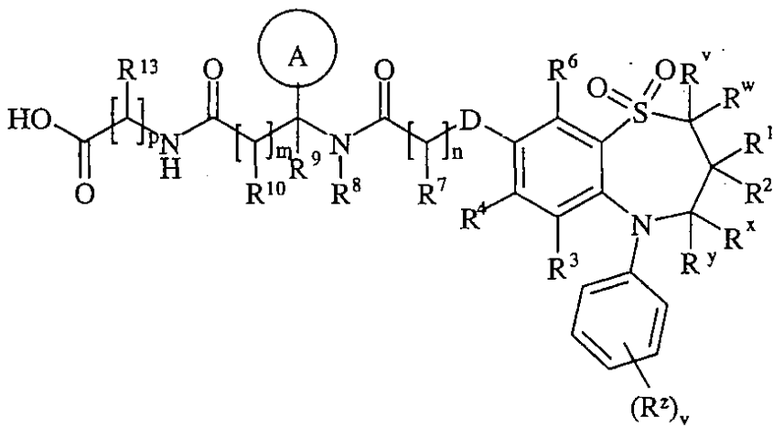
and R^p is C_{1-4}alkyl;

Process 10): for compounds of formula **(I)** wherein X is $-N(R^q)C(O)-$; reacting a compound of formula **(XIVa)**:



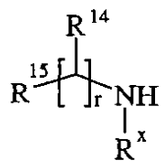
(XIVa)

or (XIVb):



(XIVb)

with a compound of formula (XV):



(XV)

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.

The skilled person will also appreciate that similar processes corresponding to the above processes can also be used to prepare compounds of formula (I') and compounds of formula (I'') wherein the definitions of the variable groups may differ.

L is a displaceable group, suitable values for L are for Example, a halogeno or

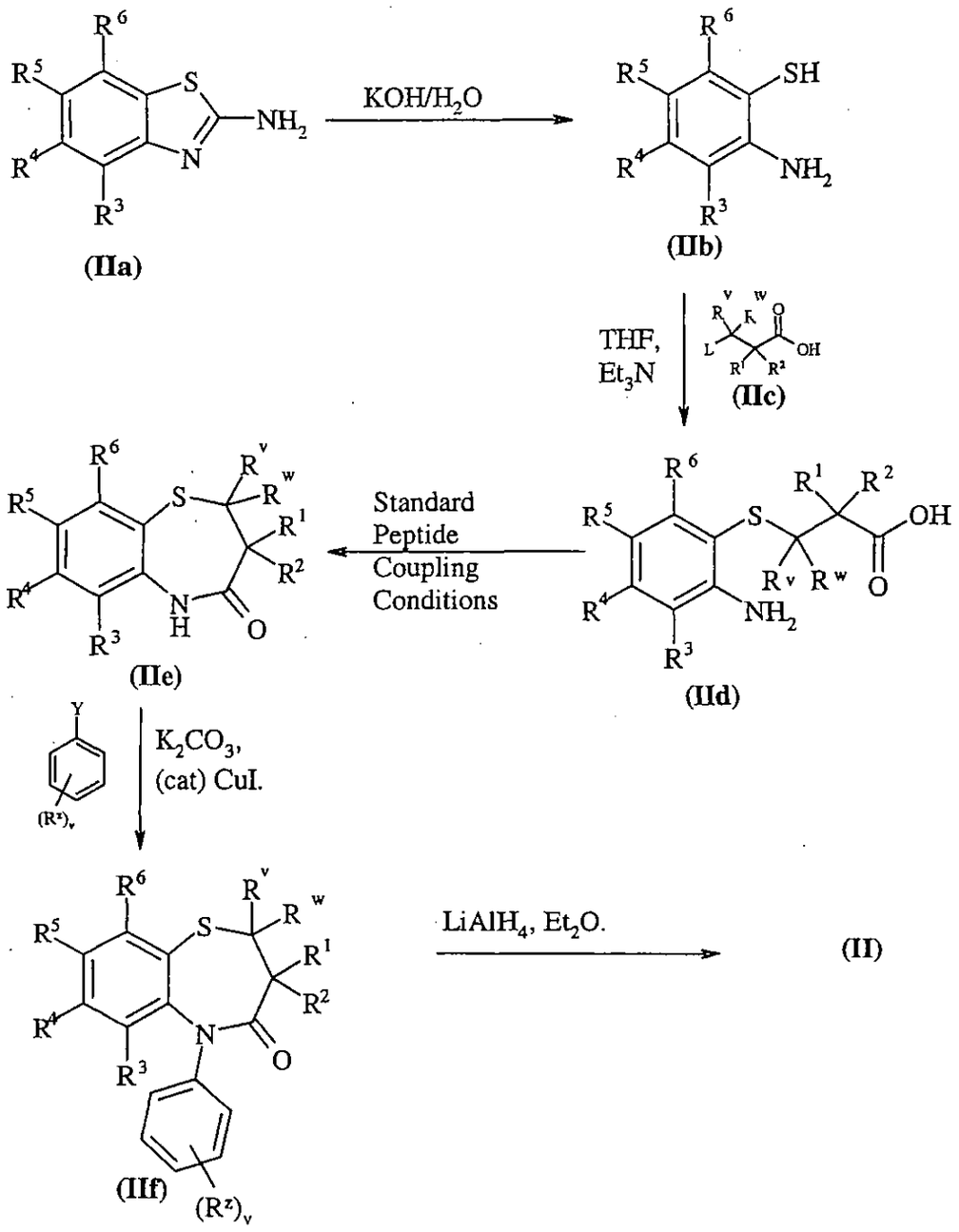
sulphonyloxy group, for Example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

R^p is C_{1-4}alkyl. Preferably R^p is methyl or ethyl. More preferably R^p is methyl.

Specific reaction conditions for the above reactions are as follows.

Process 1): Benzothiazepines of formula (II) may be oxidised under standard sulphur oxidation conditions; for Example using hydrogen peroxide and trifluoroacetic acid at a temperature in the range of 0°C to reflux, preferably at or near room temperature.

Compounds of formula (II) may be prepared according to Scheme I for compounds of formula (I) wherein R^x and R^y are hydrogen. The skilled man will appreciate that where R^x and R^y are not both hydrogen the following synthetic route needs to be manipulated using procedures known to the skilled person.



Scheme 1

wherein L is a displaceable group as defined above, and Y is a displaceable group, for Example halo.

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

Process 2): Alcohols of formula **(IIIa)** or **(IIIb)** may be reacted with compounds of formula **(IV)** 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.

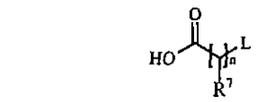
Compounds of formula **(IIIa)** or **(IIIb)** may be prepared in a similar manner to compounds of formula **(II)** (but wherein R^4 or R^5 is hydroxy) followed by the oxidation step of Process 1).

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

Process 3), *Process 4*, *Process 8)* and *Process 10):* 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 **(Va)** or **(Vb)** wherein D is -O-,-NR^a- or -S- may be prepared according to Scheme 2:



(IIIa) —(Vc), $NaCO_3$, MeCN→ **(Va)**

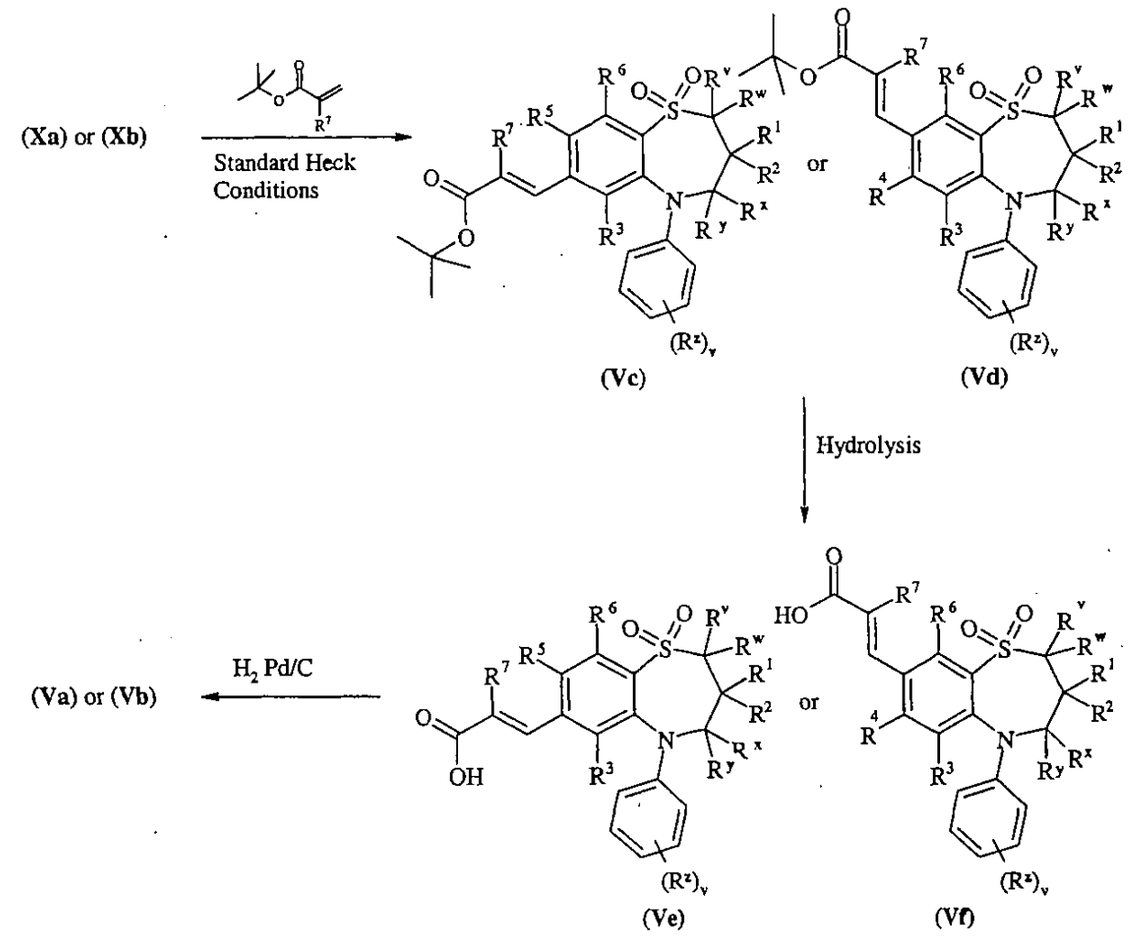
(IIIb) —**(Vc)**, $NaCO_3$, MeCN→ **(Vb)**

Scheme 2

wherein L is a displaceable group as defined above.

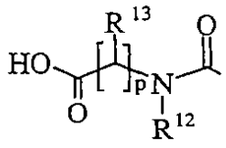
Compounds of formula **(Va)** and **(Vb)** where D is -SO- or -SO_2- may be prepared by oxidising the resulting compounds of formula **(Va)** and **(Vb)** from *Scheme 2* where D is -S-.

Compounds of formula **(Va)** or **(Vb)** wherein D is –CH_2- may be prepared according to *Scheme 3*.



Scheme 3

Compounds of formula **(XIVa)** or **(XIVa)** may be prepared by any of the processes described herein where R^{11} is a group of formula **(IB)** but wherein **(IB)** is a group of formula **(XVI)**:



(XVI)

Compounds of formula (**Vc**), (**VI**), (**VII**), (**XII**), (**XV**) and (**XVI**) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 5), *Process 6)* and *Process 9)*: Esters of formula (**VIIIa**), (**VIIIb**), (**IXa**), (**IXb**) (**XIIIa**) and (**XIIIb**) may be deprotected 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 (**VIIIa**), (**VIIIb**), (**IXa**), (**IXb**) (**XIIIa**) and (**XIIIb**) may be prepared by any of the procedures above for the preparation of compounds of formula (**I**), but wherein R^{11}, R^{15} or R^{26} is C_{1-4}alkoxycarbonyl.

Process 7): Compounds of formula (**Xa**) and (**Xb**) may be reacted with thiols of formula (**XI**) 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.

Compounds of formula (**Xa**) and (**Xb**) 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 (**XI**) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

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

hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

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

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

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

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

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., Hugnes K. T. and Jones N. R. A.; J Biomolecular Screening, 3, 227-230) or *in vivo* by studying the effect on radiolabelled bile acid absorption in mice/rats (Lewis M. C., Brieaddy 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 salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

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

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

The compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg or 0.01-50 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. In another aspect a daily dose in the rage 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.

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, hypertrigliceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (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, leukocyte, monocytes and/or macrophage infiltrate, intimital thickening, medial 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 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 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 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, hypertrigliceridemia, 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, 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,

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, leukocyte, monocytes and/or macrophage infiltrate, intimital 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.

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.

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.

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, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

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.

Suitable bile acid binders for such a combination therapy are resins, such as cholestyramine and cholestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutic dose for treatment of cholesterolaemia 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 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 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

- an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, a diuretic or a vasodilator;
- insulin;
- sulphonylureas including glibenclamide, tolbutamide;
- metformin; and/or
- acarbose;

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 combination with a compound of formula (I) include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, 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, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. 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

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 azetidinones 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;
- a nicotinic acid derivative, for example, nicotinic acid (niacin), acipimox and niceritrol;
- a phytosterol compound for example stanols;
- probucol;
- an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

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.

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.

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 **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** and **(XIIIb)** 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 **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** or **(XIIIb)**, 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 **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** or **(XIIIb)**, 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 **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** or **(XIIIb)**, 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 **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** or **(XIIIb)**, 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 **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** or **(XIIIb)**, 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 **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** or **(XIIIb)**, 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 **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** or **(XIIIb)**, 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 **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** or **(XIIIb)**, 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:

(i) evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;

(iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63 μm (Merck);

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic resonance chemical shift values were measured in deuterated $CDCl_3$ (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer unless otherwise stated data was recorded at 400MHz; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; ABq, AB quartet; ABd, AB doublet, ABdd, AB doublet of doublets; dABq, doublet of AB quartets; LCMS were recorded on a Waters ZMD, LC column xTerra MS C_8(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^+); unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Cromasil C_8, 7 μm, (Akzo Nobel); MeCN and de-ionised water 10 mM ammonium acetate as mobile phases, with suitable composition;

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

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

(ix) where an "ISOLUTE" column is referred to, this means a column containing 2 g of silica, the silica being contained in a 6 ml 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;

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

DCM	dichloromethane;
DMF	*N,N*-dimethylformamide;
TBTU	o-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate;
EtOAc	EtOAC;
MeCN	acetonitrile;
TFA	trifluoroacetic acid;
IPA	isopropanol;
DIPEA	di-isopropylethylamine; and
THF	tetrahydrofuran.

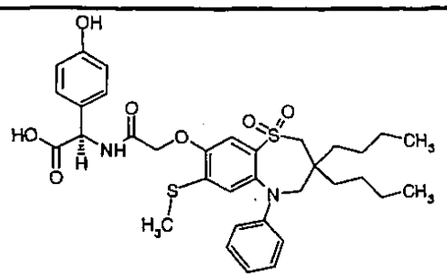
Example 1

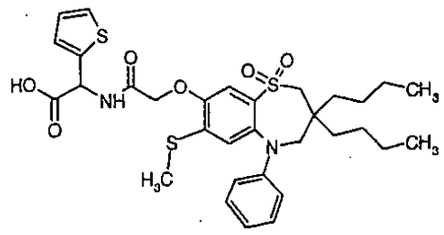
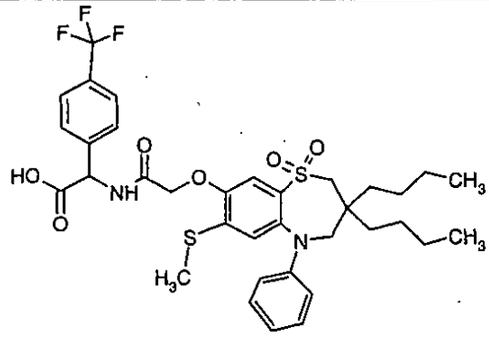
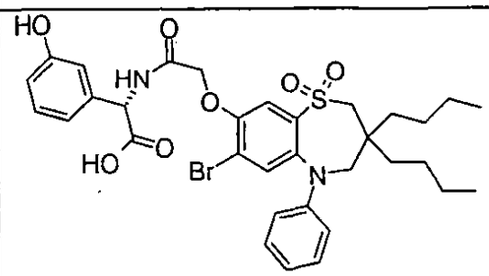
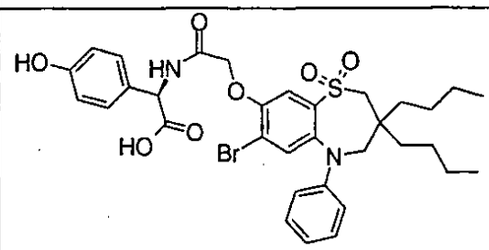
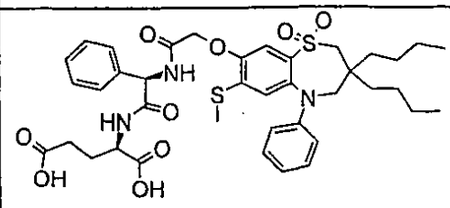
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

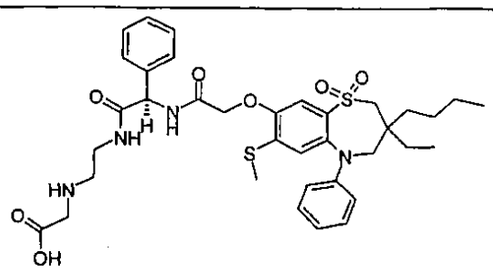
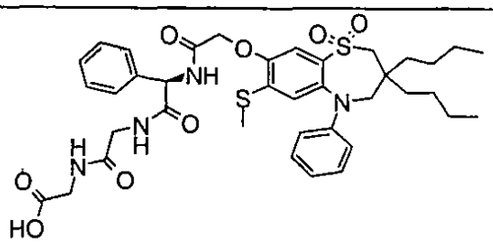
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-methoxycarbonylmethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 29; 300 mg, 0.46 mmol) was dissolved in methanol (5 ml). NaOH (100 mg in 0.2 ml water) was added to the solution and the mixture was stirred at room temperature for 1 hour. Acetic acid (0.3 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The DCM layer was separated, dried and evaporated under reduced pressure to give the title compound 270 mg (92%). NMR, 500 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 (brs, 2H), 3.6-3.8 (m, 2H), 4.6 (s, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.8 (d, 1H).

Examples 2-9

The following compounds were synthesised by the procedure of Example 1 using the appropriate starting material.

Ex	Compound	NMR	SM
2		(300 MHz, CD_3OD) 0.9-0.95 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.2 (s, 3H), 3.25 (s, 2H), 3.75 (brs, 2H), 4.65 (dd, 2H), 5.2 (s, 1H), 6.7-7.3 (m, 10H), 7.4 (s, 1H)	Meth 30

3		(300 MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 3H), 3.75 (brs, 2H), 3.25 (s, 2H), 4.6-4.7 (m, 2H), 5.7 (s, 1H), 6.7 (s, 1H), 6.9-7.3 (m, 8H), 7.4 (s, 1H)	Meth 31
4		(300 MHz, CD_3OD) 0.75-0.9 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 3H), 3.25 (s, 2H), 3.75 (brs, 2H), 4.6-4.8 (m, 2H), 5.45 (s, 1H), 6.7 (s, 1H), 6.95-7.3 (m, 5H), 7.4 (s, 1H), 7.6 (s, 4H)	Meth 32
5		(500 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 3.2 (brs, 2H), 3.6 (brs, 2H), 4.48 (m, 2H), 5.0 (s, 1H), 6.5 (d, 1H), 6.7-7.4 (m, 10H), 7.9 (s, 1H)	Meth 39
6		(DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.6 (m, 12H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.6-4.8 (m, 3H), 6.6 (d, 2H), 6.9-7.3 (m, 8H), 7.4 (s, 1H), 8.3 (d, 1H)	Meth 40
7		M/z = 768.9	Meth 67

8[1]		(300 MHz, CD_3OD) 0.75-0.9 (m, 6H), 1.0-1.25 (m, 4H), 1.4-1.6 (m, 4H), 2.15 (s, 3H), 3.1-3.3 (m, 4H), 3.5-3.8 (m, 5H), 4.75 (ABq, 2H), 5.45 (s, 2H), 6.75 (s, 1H), 6.95-7.5 (11H); m/z 711.3	Meth 42
9		(500 MHz, DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.6 (m, 12H), 2.2 (s, 3H) 3.2-3.8 (m, 8H), 4.8 (ABq, 2H), 5.6 (d, 1H), 6.7 (s, 1H), 6.8-7.5 (m, 11H), 7.8 (brs, 1H), 8.6 (d, 1H), 8.8 (t, 1H)	Meth 69

[1] Ethanol instead of methanol, purified by preparative HPLC using MeCN and ammonium acetate buffer (55:45) as eluent

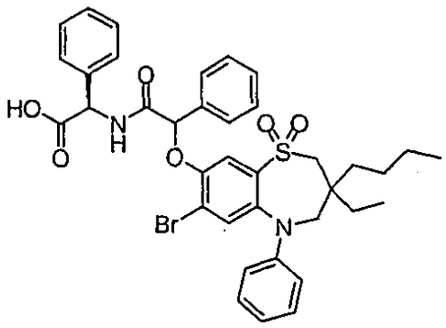
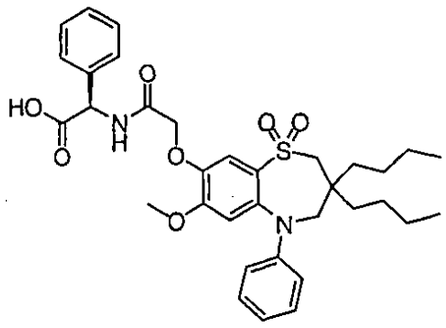
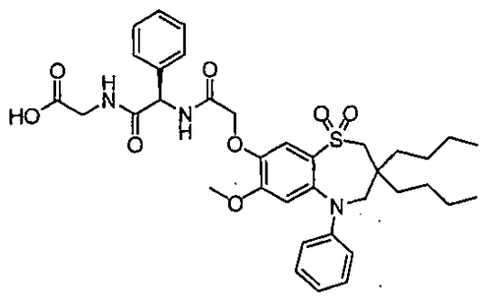
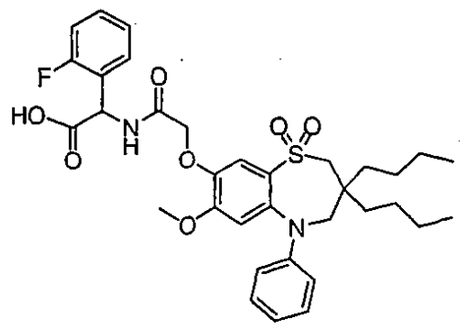
Example 10

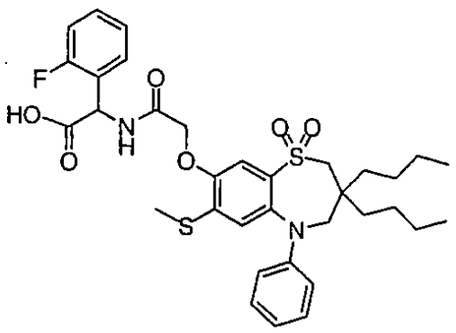
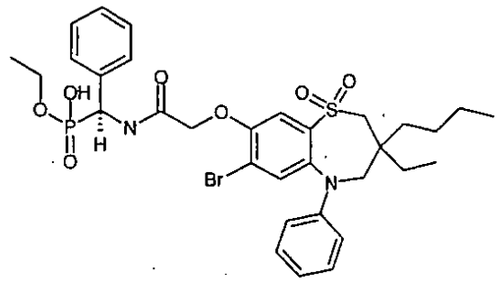
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-{1-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoyl]ethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-{1-[*N*-((R)-1'-phenyl-1'-methoxycarbonylmethyl)carbamoyl]ethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 33; 103 mg, 0.15 mmol) was dissolved in a mixture of THF and H_2O (2:1, 3 ml). LiOH (7 mg, 0.3 mmol) was added and the mixture was stirred for 7 hours at ambient temperature. Most of the solvent was removed under reduced pressure and the crude product was purified by preparative HPLC using MeCN and ammonium acetate buffer (45:55) as eluent to give the title compound 97 mg (96 %). NMR (DMSO-d_6) 0.60-0.80 (m, 6H), 0.90-1.60 (m, 11H), 3.15-3.45 (m, 2H), 3.50-3.90 (m, 2H), 4.95-5.25 (m, 2H), 6.85-7.55 (m, 12H), 8.55-8.95 (m, 1H).

Examples 11-16

The following compounds were synthesised by the procedure of Example 10 using the appropriate starting material.

Ex	Compound	NMR	SM
11		($(CD_3)_2CO$) 0.70-0.90 (m, 6H), 0.95-1.35 (m, 4H), 1.40-1.75 (m, 4H), 3.15-3.35 (m, 2H), 3.80 (brs, 2H), 5.40 (d, 1H), 5.90-6.15 (2s, 1H), 6.95-7.75 (m, 18H)	Meth 34
12		(CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.60 (s, 3H), 3.75 (brs, 2H), 4.60 (ABq, 2H), 5.40 (s, 1H), 6.50 (s, 1H), 6.95-7.45 (m, 10H), 7.55 (s, 1H)	Meth 35
13		(CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.55 (s, 3H), 3.75 (brs, 2H), 3.90 (ABq, 2H), 4.60 (ABq, 2H), 5.60 (s, 1H), 6.50 (s, 1H), 6.95-7.45 (m, 10H), 7.55 (s, 1H)	Meth 36
14		(CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.60 (m, 4H), 3.20 (s, 2H), 3.60 (s, 3H), 3.75 (brs, 2H), 4.55 (ABq, 2H), 5.55 (s, 1H), 6.50 (s, 1H), 6.95-7.45 (m, 9H), 7.50 (s, 1H)	Meth 37

15		(CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.60 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.75 (brs, 2H), 4.65 (ABq, 2H), 5.60 (s, 1H), 6.70 (s, 1H), 6.90-7.45 (m, 10H)	Meth 38
16		(CD_3OD) 7.55-7.41 (3H, m), 7.35-7.20 (5H, m), 7.15-7.08 (3H, m), 7.04-6.98 (1H, m), 5.48-5.32 (1H, m), 4.80-4.60 (2H, m), 4.00-3.56 (4H, m), 3.27-3.22 (2H, m), 1.61-1.00 (11H, m), 0.83-0.74 (6H, m)	Meth 70

Example 17

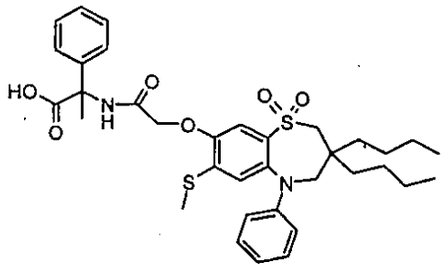
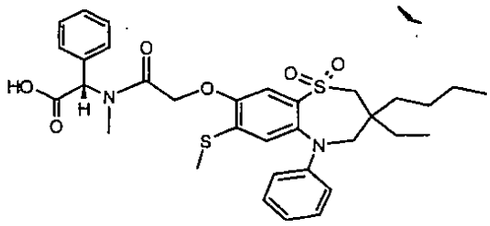
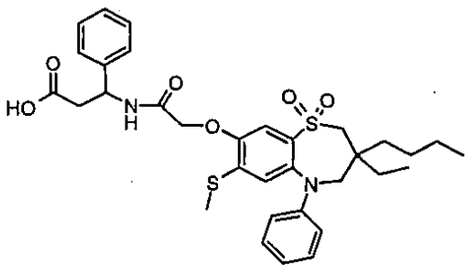
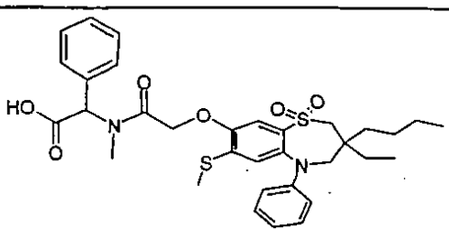
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((S)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((S)-1'-phenyl-1'-methoxycarbonylmethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 46; 60 mg, 0.091 mmol) was dissolved in THF (1 ml) and added to a solution of lithium hydroxide monohydrate (12.6 mg, 0.29 mmol) in water (1 ml). The mixture was stirred occasionally for 30 minutes. 2M HCl solution (0.3 ml) was added and the water layer was extracted with DCM. The organic layer was washed once with brine, dried, filtered and evaporated at reduced pressure to give the title compound 48 mg (82%). NMR (CD_3OD) 0.73-0.84 (m, 6H), 1.0-1.6 (m, 8H), 3.27 (brs, 2H), 3.60-3..90 (m, 2H), 4.71 (ABq, 2H), 5.47-5.55 (m, 1H), 7.02 (brt, 1H), 7.08-7.17 (m, 3H), 7.25-7.46 (m, 7H), 7.52 (s, 1H), 8.43 (d, NH); m/z 643.5.

Examples 18-21

The following compounds were synthesised by the procedure of Example 17 using the appropriate starting material.

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Ex	Compound	NMR or m/z	SM
18[1]		M/z 670 ($M+NH_4^+$)	Meth 43
19[2]		(CD_3OD) 0.70-0.90 (m, 6H), 1.0-1.32 (m, 4H), 1.32-1.70 (m, 4H), 2.15 (s, 3H), 2.85 (brs, 3H), 3.23 (brs, 2H), 3.53-3.93 (m, 2H), 4.99 (ABq, 2H), 6.27 (s, 1H), 6.71 (s, 1H), 6.94 (t, 1H), 7.07 (d, 2H), 7.25 (t, 2H), 7.3-7.47 (m, 6H); m/z 625.3	Meth 62
20		(CD_3OD) 0.75-0.84 (m, 6H), 1.0-1.29 (m, 4H), 1.36-1.65 (m, 4H), 2.15 (s, 3H), 2.82-2.97 (m, 2H), 3.22 (brs, 2H), 3.6-3.85 (m, 2H), 4.66 (ABq, 2H), 5.43 (t, 1H), 6.71 (s, 1H), 6.96 (t, 1H), 7.09 (d, 2H), 7.2-7.38 (m, 7H), 7.40 (s, 1H); m/z 625.4	Meth 112
21		(600 MHz, CD_3OD) 0.77-0.88 (m, 6H), 1.0-1.32 (m, 4H), 1.39-1.70 (m, 4H), 2.16 (s, 3H), 2.88 (brs, 3H), 3.25 (brs, 2H), 3.52-3.93 (m, 2H), 5.03 (ABq, 2H), 6.28 (s, 1H), 6.73 (s, 1H), 6.96 (t, 1H), 7.09 (brd, 2H), 7.27 (t, 2H), 7.32-7.46 (m, 6H)	Meth 79

[1] 2.2 equivalents of LiOH in THF/water (4/1)

[2] Purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent

Example 22

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

The title compound was synthesised from 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((R)-1'-phenyl-1'-methoxycarbonylmethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 61) by the procedure of Example 17, except that the water layer was extracted with EtOAc. The product was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent. NMR 0.75-0.83 (m, 6H), 1.0-1.25 (m, 4H), 1.32-1.52 (m, 3H), 1.55-1.70 (m, 1H), 3.20 (ABq, 2H), 3.65-3.83 (m, 2H), 4.62 (ABq, 2H), 5.68 (d, 1H), 7.04-7.15 (m, 4H), 7.3-7.5 (m, 8H), 7.87 (brd, 1H); m/z 643.1.

Example 23

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-(*N*-{(S)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine ammonium salt

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((S)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 17; 48 mg, 0.075 mmol) and 2-aminoethanesulphonic acid (17 mg, 0.14 mmol) was dissolved in DMF (2 ml) and DIPEA (0.052 ml, 0.30 mmol). The mixture was stirred for 15 min at 60°C. TBTU (31 mg, 0.097 mmol) was added and the mixture was stirred for 2 hours at 60°C. The solvent was evaporated at reduced pressure. The residue was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent. Lyophilisation gave the title compound 4 mg (7%). NMR (CD_3OD) 0.75-0.83 (m, 6H), 0.95-1.65 (m, 8H), 2.85-3.0 (m, 2H), 3.27 (brs, 2H), 3.5-3.9 (m, 4H), 4.72 (ABq, 2H), 5.48 (s, 1H), 7.02 (brt, 1H), 7.09-7.15 (m, 3H), 7.25-7.52 (m, 8H); m/z 750.3.

36

Examples 24-37

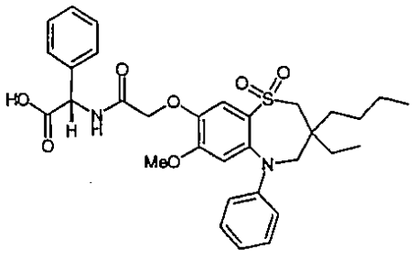
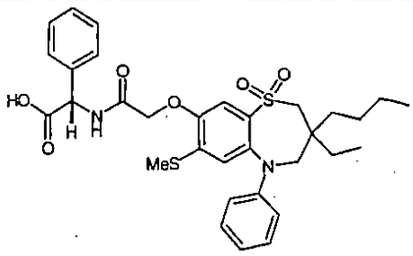
The following compounds were prepared by the same procedure. The acid (1 equiv) was dissolved in THF (1 ml) and added to a solution of lithium hydroxide monohydrate (12.6 mg, 2.9-6.6 equiv) in water (1 ml). The mixture was stirred occasionally and after 1.5-6 hours the deprotection was completed (according to LC-MS). 2M HCl-solution (0.3 ml) was added.

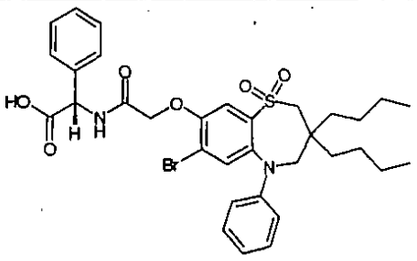
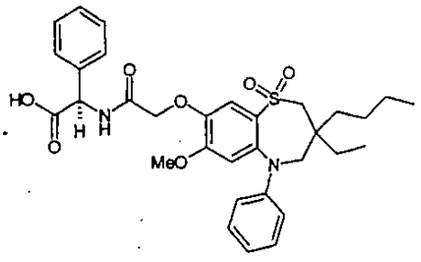
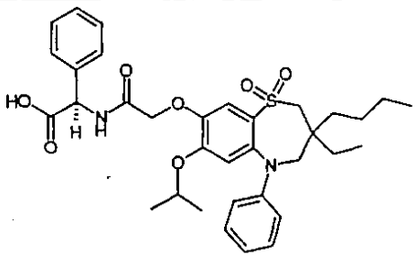
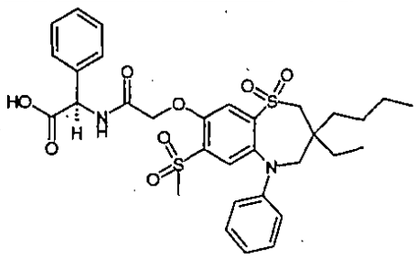
Examples 24-33

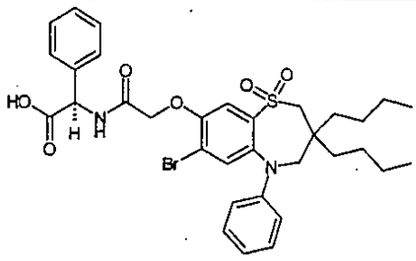
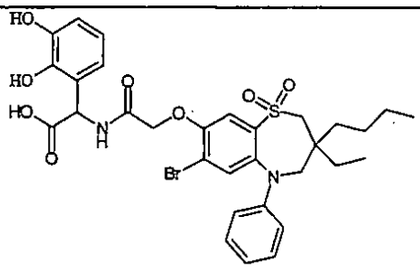
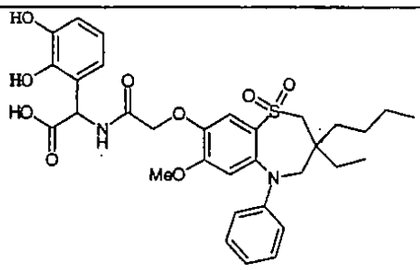
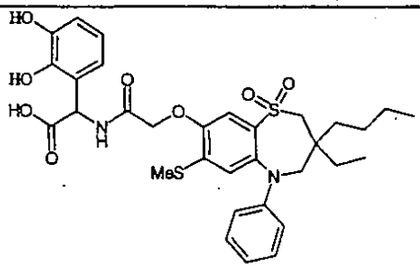
The reaction mixture was put on a syringe filled with hydramatrix®. The product was eluted with DCM. The DCM was dried, filtered and evaporated at reduced pressure. The product was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent.

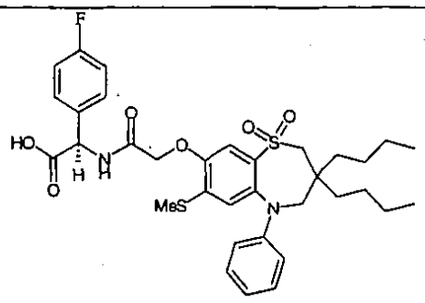
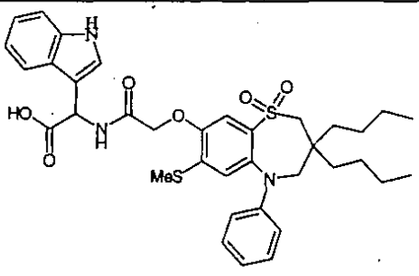
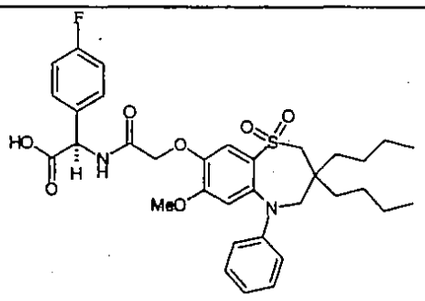
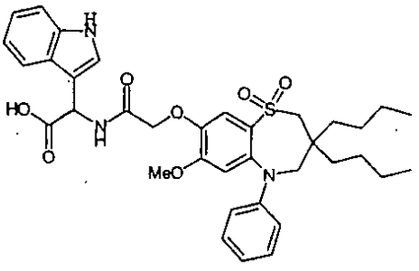
Examples 34-37

The water layer was extracted two times with DCM. The organic layer was dried, filtered and evaporated at reduced pressure.

Ex	Compound	NMR (CD_3OD)	m/z	SM
24		0.75-0.84 (m, 6H), 1.0-1.25 (m, 4H), 1.37-1.65 (m, 4H), 3.20 (brs, 2H), 3.55-3.90 (m, 5H), 4.58 (ABq, 2H), 5.33 (s, 1H), 6.51 (s, 1H), 6.97 (brt, 1H), 7.12 (brd, 2H), 7.2-7.33 (m, 5H), 7.41 (brd, 2H), 7.54 (s, 1H)	595.4	Meth 47
25		0.73-0.85 (m, 6H), 1.0-1.3 (m, 4H), 1.35-1.65 (m, 4H), 2.17 (s, 3H), 3.23 (brs, 2H), 3.55-3.90 (m, 2H), 4.71 (ABq, 2H), 5.49-5.52 (m, 1H), 6.73 (s, 1H), 6.96 (brt, 1H), 7.10 (brd, 2H), 7.23-7.45 (m, 8H), 8.36 (brd, NH)	611.2	Meth 48

26		0.74-0.84 (m, 6H), 1.0-1.3 (m, 8H), 1.37-1.54 (m, 4H), 3.28 (brs, 2H), 3.65-3.85 (m, 2H), 4.72 (ABq, 2H), 5.49-5.52 (m, 1H), 7.04 (brt, 1H), 7.09-7,18 (m, 3H), 7.28-7.46 (m, 7H), 7.52 (s, 1H), 8.45 (brd, NH)	671.2	Meth 49
27		0.74-0.84 (m, 6H), 1.0-1.3 (m, 4H), 1.35-1.65 (m, 4H), 3.21 (brs, 2H), 3.59 (s, 3H), 3.62-3.90 (m, 2H), 4.62 (ABq, 2H), 5.49 (s, 1H), 6.50 (s, 1H) 6.98 (brt, 1H), 7.12 (brd, 2H), 7.24-7,43 (m, 7H), 7.54 (s, 1H)	595.3	Meth 50
28		0.74-0.85 (m, 6H), 0.85-1.65 (m, 14H), 3.21 (brs, 2H), 3.6-3.9 (m, 2H), 4.25-4.36 (m, 1H), 4.53-4.66 (m, 2H), 5.49 (s, 1H), 6.47 (s, 1H) 6.91-7.0 (m, 1H), 7.04-7.16 (m, 2H), 7.22-7,46 (m, 7H), 7.51 (s, 1H)	623.3	Meth 51
29		0.73-0.85 (m, 6H), 0.85-1.65 (m, 8H), 3.24 (brs, 3H), 3.34 (brs, 2H), 3.6-3.95 (m, 2H), 4.8-4.95 (m, 2H), 5.52 (s, 1H), 7.06 (brt, 1H), 7.17 (brd, 2H), 7.27-7.40 (m, 5H), 7.40-7.50 (m, 3H), 7.69 (s, 1H)	643.3	Meth 52

30		0.74-0.84 (m, 6H), 0.85-1.55 (m, 12H), 3.24-3.33 (m, 2H), 3.65-3.85 (m, 2H), 4.65-4.78 (m, 2H), 5.50 (brs, 1H), 6.99-7.2 (m, 4H), 7.25-7.48 (m, 7H), 7.51 (s, 1H)	671.2	Meth 53
31		0.72-0.84 (m, 6H), 0.85-1.65 (m, 8H), 3.27 (brs, 2H), 3.54-3.9 (m, 2H), 4.70 (ABq, 2H), 5.70 (s, 1H), 6.63-6.69 (m, 1H), 6.71-6.77 (m, 2H), 7.02 (brt, 1H), 7.08-7.17 (m, 3H), 7.30 (brt, 2H), 7.52 (s, 1H)	675.4	Meth 54
32		0.72-0.84 (m, 6H), 0.98-1.67 (m, 8H), 3.21 (brs, 2H), 3.54-3.9 (m, 5H), 4.62 (ABq, 2H), 5.57 (s, 1H), 6.51 (s, 1H), 6.59-6.73 (m, 3H), 6.97 (brt, 1H), 7.12 (brd, 2H), 7.28 (brt, 2H), 7.56 (s, 1H)	627.5	Meth 55
33		0.73-0.86 (m, 6H), 1.0-1.68 (m, 8H), 2.19 (s, 3H), 3.24 (brs, 2H), 3.55-3.9 (m, 2H), 4.71 (ABq, 2H), 5.53 (s, 1H), 6.60-6.73 (m, 3H), 6.75 (s, 1H), 6.96 (brt, 1H), 7.10 (brd, 2H), 7.27 (brt, 2H), 7.44 (s, 1H)	643.4	Meth 56

34		0.74-0.86 (m, 6H), 1.0-1.3 (m, 8H), 1.35-1.57 (m, 4H), 2.19 (s, 3H), 3.23 (brs, 2H), 3.62-3.85 (m, 2H), 4.65 (ABq, 2H), 5.28 (s, 1H), 6.72 (s, 1H), 6.94-7.05 (m, 3H), 7.12 (brd, 2H), 7.28 (brt, 2H), 7.39 (s, 1H), 7.43 (dd, 2H)	657.3	Meth 57
35		0.75-0.86 (m, 6H), 1.0-1.3 (m, 8H), 1.35-1.55 (m, 4H), 2.01 (s, 3H), 3.11-3.26 (ABq, 2H), 3.6-3.8 (m, 2H), 4.58 (d, 1H), 4.70 (d, 1H), 5.64 (s, 1H), 6.62 (s, 1H), 6.91-7.0 (m, 2H), 7.01-7.12 (m, 3H), 7.23-7.33 (m, 4H), 7.37 (s, 1H), 7.69 (brd, 1H)	678.4	Meth 58
36		0.76-0.84 (m, 6H), 1.0-1.3 (m, 8H), 1.36-1.53 (m, 4H), 3.21 (brs, 2H), 3.64 (s, 3H), 3.67-3.87 (m, 2H), 4.57 (ABq, 2H), 5.31 (s, 1H), 6.50 (s, 1H), 6.95-7.06 (m, 3H), 7.14 (brd, 2H), 7.28 (brt, 2H), 7.38-7.46 (m, 2H), 7.51 (s, 1H)	641.4	Meth 59
37		0.75-0.87 (m, 6H), 1.0-1.3 (m, 8H), 1.34-1.53 (m, 4H), 3.18 (ABq, 2H), 3.27 (s, 3H), 3.65-3.85 (m, 2H), 4.52 (d, 1H), 4.65 (d, 1H), 5.66 (s, 1H), 6.30 (s, 1H), 6.90-7.02 (m, 2H), 7.03-7.16 (m, 3H), 7.23-7.34 (m, 4H), 7.50 (s, 1H), 7.59 (brd, 1H)	662.4	Meth 60

Example 38

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 22; 50 mg, 0.078 mmol) was dissolved in DMF (1.5 ml). Sodium methanethiolate (20 mg, 0.29 mmol) was added and the mixture was stirred for 1.5 hours at 50°C. Acetic acid (40 mg) was added and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (45:55) as eluent to give the title compound 29 mg (61%). NMR (DMSO-d_6): 0.7-0.8 (m, 6H), 0.9-1.6 (m, 8H), 2.2 (s, 3H), 3.1-3.7 (m, 4H), 4.6-4.8 (m, 3H), 6.7 (s, 1H), 6.8-7.4 (m, 11H), 8.3 (d, 1H).

Example 39

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-ethylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 22; 50 mg, 0.078 mmol), ethanethiol (99 mg, 1.59 mmol) and caesium carbonate (253 mg, 0.78 mmol) were added to DMF (5 ml) and the mixture was stirred for 30 h at 44°C. The solvent was filtered, evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (45:55) as eluent. The residue was purified by column chromatography using DCM : methanol (100:15) to give the title compound 15 mg (31%). NMR (300 MHz, CD_3OD) 0.7-0.85 (m, 6H), 1.0-1.6 (m, 11H), 2.65 (q, 2H), 3.2 (s, 2H), 3.7 (brs, 2H), 4.6 (q, 2H), 5.3 (s, 1H), 6.75 (s, 1H), 6.9-7.5 (m, 11H).

Example 40

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-(2-hydroxyethylthio)-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 22; 50 mg, 0.078 mmol), 2-mercaptoethanol (281 mg, 3.59 mmol) and caesium carbonate (228 mg, 0.7 mmol) were added to DMF (5 ml) and the mixture was stirred for 9 hours at 70°C. The solvent was evaporated under reduced pressure. The residue was purified by preparative

HPLC using MeCN/ammonium acetate buffer (45:55) as eluent. The collected fractions were lyophilised to give the title compound 20 mg (40%). NMR (300 MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.6 (m, 8H), 2.9 (t, 2H), 3.2 (s, 2H), 3.55 (t, 2H), 3.7 (brs, 2H), 4.65 (q, 2H), 5.3 (s, 1H), 6.9 (s, 1H), 6.95-7.5 (m, 11H).

Example 41

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-(2-*N'*,*N'*-dimethylaminoethylthio)-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 22; 50 mg, 0.078 mmol), dimethylaminoethanethiol hydrochloride (99 mg, 0.94 mmol), potassium carbonate (129 mg, 0.94 mmol), DIPEA (100 mg, 0.77 mmol) and sodium borohydride (35 mg, 0.93 mmol) were added to DMF (10 ml) and the mixture was stirred for 24 hours at 85°C. The solvent was filtered and evaporated under reduced pressure. The residue was purified twice by preparative HPLC using MeCN/ammonium acetate buffer (40:60) as eluent. The collected fractions were lyophilised to give the title compound 15 mg (30%). NMR (300 MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.65 (m, 8H), 2.65 (s, 6H), 3.05 (t, 2H), 3.2 (t, 2H), 3.3 (s, 2H), 3.75 (brs, 2H), 4.75 (s, 2H), 5.2 (s, 1H), 6.95-7.4 (m, 11), 7.5 (s, 1H).

Example 42

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-isopropylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 22; 50 mg, 0.078 mmol), 2-propanethiol (126 mg, 1.65 mmol), caesium carbonate (152 mg, 0.47 mmol), sodium borohydride (25 mg, 0.66 mmol) were added to DMF (5 ml) and the mixture was stirred for 5 min at 100°C. The solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (45:55) as eluent. The collected fractions were lyophilised to give the title compound 15 mg (30%). NMR (300 MHz, DMSO-d_6) 0.7-0.85 (m, 6H), 0.95-1.65 (m, 14H), 3.3 (s, 2H), 3.7 (brs, 2H), 4.75 (dd, 2H), 5.05 (brs, 1H), 6.75-7.4 (m, 12H), 8.5 (brs, 1H).

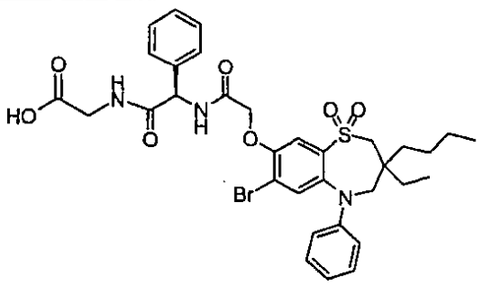
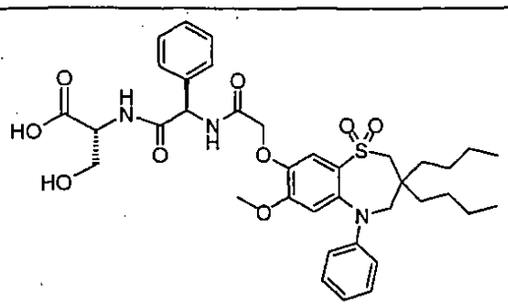
Example 43

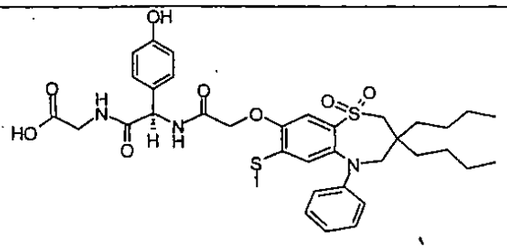
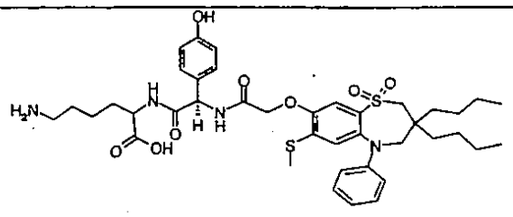
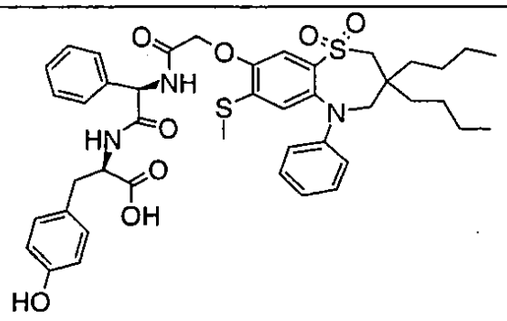
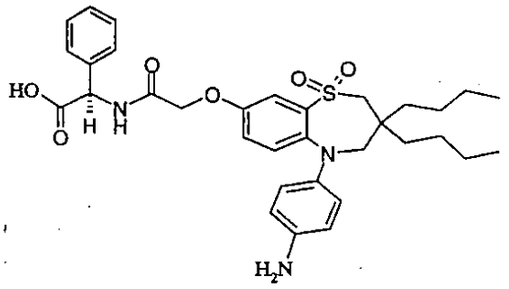
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(*t*-butoxycarbonylmethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 63; 120 mg, 0.17 mmol) was dissolved in DCM (2 ml). TFA (0.7 ml) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (50:50) as eluent to give the title compound 95 mg (85%). NMR (300 MHz, DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.6 (m, 12H), 2.2 (s, 3H) 3.2-3.3 (m, 2H), 3.5-3.8 (m, 4H), 4.8 (ABq, 2H), 5.6 (d;1H), 6.7 (s, 1H), 6.8-7.5 (m, 11H), 8.5-8.7 (m, 2H).

Examples 44-49

The following compounds were synthesised by the procedure of Example 43 using the appropriate starting material.

Ex	Compound	NMR or m/z	SM
44		(300 MHz) 0.7-0.9 (m, 6H), 1.0-1.7 (m, 8H), 3.2 (m, 2H), 3.75 (brs, 2H), 3.9-4.0 (m, 1H), 4.15-4.25 (m, 1H), 4.5-4.7 (m, 2H), 5.75-5.9 (m, 1H), 7.05- 7.2 (m, 4H), 7.25-7.4 (m, 5H), 7.45-7.55 (m, 3H), 8.2 (d, 1H)	Meth 64
45		(CD_3OD) 0.70-0.90 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.55 (s, 3H), 3.75 (brs, 2H), 3.80-4.00 (m, 2H), 4.40-4.70 (m, 3H), 5.65 (s, 1H), 6.50 (s, 1H), 6.95-7.50 (m, 10H), 7.55 (s, 1H)	Meth 41

46		(300 MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.2 (s, 3H), 3.25 (2H), 3.7-3.95 (m, 4H), 4.7 (ABq, 2H), 5.5 (s, 1H), 6.7 (s, 1H), 6.75-7.35 (m, 9H), 7.4 (s, 1H)	Meth 65
47		783.5	Meth 66
48		802.7	Meth 68
49		(500 MHz, CD_3OD) 0.82 (brt, 6H), 1.05-1.26 (m, 8H), 1.42-1.56 (m, 4H), 3.27 (brs, 2H), 3.6-3.75 (m, 2H), 4.58 (ABq, 2H), 5.41 (s, 1H), 6.73-6.82 (m, 3H), 7.0 (d, 2H), 7.05 (dd, 1H), 7.25-7.36 (m, 3H), 7.41 (brd, 2H), 7.48 (d, 1H); m/z 608.3	Ex 119

Example 50

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 22; 150 mg, 0.30 mmol) and 2-((2'R)-2'-amino-2'-phenylethanoylamino)ethanesulphonic acid (Method 28; containing DIPEA hydrochloride, 150 mg, 0.36 mmol) was dissolved in DMF (6 ml). DIPEA (0.2 ml, 1.15 mmol) and TBTU (114 mg, 0.36 mmol) were added and the mixture was stirred for 2 hours at room temperature.

The solvent was evaporated at reduced pressure. The residue was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound 73 mg (32%). NMR (CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.3 (m, 8H), 1.3-1.6 (m, 4H), 2.16 (s, 3H), 2.85-3.0 (m, 2H), 3.24 (brs, 2H) 3.5-3.85 (m, 4H), 4.70 (ABq, 2H), 5.47 (s, 1H), 6.71 (s, 1H), 6.97 (brt, 1H), 7.11 (brd, 2H), 7.23-7.45 (m, 8H); m/z 746.2.

Example 51

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

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 17; 49 mg, 0.10 mmol) and 2-((2'R)-2'-amino-2'-phenylethanoylamino)ethanesulphonic acid (Method 28; containing DIPEA hydrochloride; 52 mg, 0.12 mmol) was dissolved in DMF (2 ml). DIPEA (0.071 ml, 0.41 mmol) and TBTU (39 mg, 0.12 mmol) was added and the mixture was stirred for 2 hours at room temperature. The solvent was evaporated at reduced pressure. The residue was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound 59 mg (78%). NMR (CD_3OD) 0.74-0.90 (m, 6H), 0.98-1.3 (m, 4H), 1.35-1.67 (m, 4H), 2.16 (s, 3H), 2.85-3.02 (m, 2H), 3.23 (brs, 2H) 3.52-3.90 (m, 4H), 4.70 (ABq, 2H), 5.47 (s, 1H), 6.71 (s, 1H), 6.96 (brt, 1H), 7.09 (brd, 2H), 7.21-7.48 (m, 8H); m/z 718.4.

Example 52

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

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N*-(ethoxycarbonylmethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 72; 44 mg, 0.063 mmol) was dissolved in THF : H_2O, 1:1, (2 ml) and NaOH (1 M, 0.126 mmol) was added. The mixture was stirred at ambient temperature for 1 hour. The reaction mixture was acidified with HCl (1 M), diluted to 10 ml and extracted with DCM (3 x 10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated to give the title compound 33 mg (78%). NMR (300 MHz) 0.78-0.85 (m, 6H),

1.02- 1.70 (m, 8H), 2.20 (s, 3H), 3.15/3.21 (ABq, 2H), 3.78 (m, 2H), 3.94/4.20 (dABq, 2H), 4.64 (q, 2H), 5.91 (d, 1H), 6.65 (s, 1H), 6.98-7.52 (m, 11H), 8.17 (d, 1H).

Example 53

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

The title compound was synthesised from 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N*-(1"-methoxycarbonyl-1"-phenylmethyl)carbamoyl] methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 73) by the procedure of Example 52. NMR (500 MHz) 0.76-0.84 (m, 6H), 1.05-1.73 (m, 8H), 2.14 (s, 3H), 3.16 (m, 2H), 3.74 (m, 2H), 4.48 (m, 2H), 5.53 (d, 2H), 5.96 (d, 2H), 6.63 (s, 1H), 6.97-7.48 (m, 13H), 7.86 (m, 1H), 8.17 (m, 1H).

Example 54

1,1-Dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-{1-[*N*-((R)-α-carboxybenzyl)carbamoyl] ethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-{1-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoyl]ethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 10, 0.050 g, 7.6×10^{-5} mol) in DMF (4 ml) was added sodium thiomethylate (0.021 g, 3.0×10^{-4} mol) and the solution was stirred for 4 hours at ambient temperature. The mixture was concentrated and the residue was partitioned between water and ether. The aqueous phase was extracted two more times with ether and the combined organic extracts were dried ($MgSO_4$), concentrated and purified by HPLC. The title compound was obtained in 0.030 g (63 %) as a white solid. NMR (CD_3OD) 0.75-0.90 (m, 6H), 1.00-1.30 (m, 4H), 1.40-1.70 (m, 7H), 2.15 (d, 3H), 3.10-3.30 (m, 2H), 3.55-3.95 (m, 2H), 4.80-4.95 (m, 2H), 5.30 (d, 1H), 6.70-7.50 (m, 12H); m/z 625.3.

Example 55

1,1-Dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-{α-[*N*-((R)-α-carboxybenzyl)carbamoyl] benzyloxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-{α-[*N*-((R)-α-carboxybenzyl)carbamoyl]benzyloxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 11; 0.018 g, 2.5×10^{-5} mol) in DMF (3 ml) was added sodium thiomethylate (0.007 g, 1.0×10^{-4}

mol) and the solution was stirred for 4 hours at ambient temperature. The mixture was concentrated and the residue was partitioned between water and ether. The aqueous phase was extracted two more times with ether and the combined organic extracts were dried ($MgSO_4$), concentrated and purified by HPLC. The title compound was obtained in 0.015 g (89 %) as a white solid. NMR (CD_3OD) 0.70-0.85 (m, 6H), 1.00-1.25 (m, 4H), 1.35-1.65 (m, 4H), 2.20 (d, 3H), 3.10-3.20 (m, 2H), 3.50-3.85 (m, 2H), 5.30 (d, 1H), 5.80 (d, 1H), 6.70 (s, 1H), 6.90-7.65 (m, 16H).

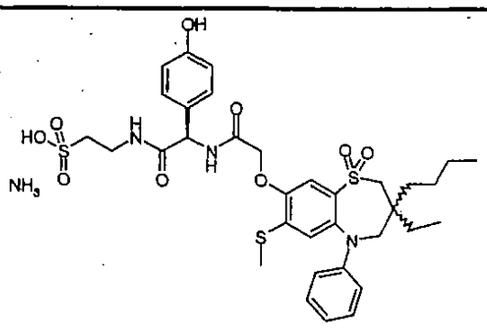
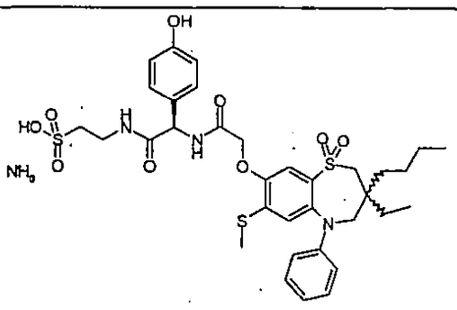
Example 56

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

2-{[(2R)-2-Amino-2-(4-hydroxyphenyl)ethanoyl]amino}ethanesulphonic acid (Method 80; 32.5 mg, 0.119 mmol) was mixed with DMF (4 ml) and N-methylmorpholine (30 µl, 0.272 mmol). A clear solution was obtained and 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 22; 50 mg, 0.099 mmol) and TBTU (38 mg, 0.119 mmol) were added successively. The reaction was stirred at ambient temperature for 30 min and the DMF was removed. The crude product was purified by preparative HPLC using an MeCN/ammonium acetate buffer (1:1). Lyophilisation gave 55 mg of the title compound (71%). NMR (500 MHz, MeOD) 0.78-0.86 (m, 6H), 1.0-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.15 (s, 3H), 2.85-3.00 (m, 2H), 3.25 (s, 2H), 3.55-3.68 (m, 2H), 3.75 (brs, 2H), 4.65 (ABq, 2H), 5.36 (s, 1H), 6.70 (s, 1H), 6.75 (d, 2H), 6.98 (t, 1H), 7.12 (d, 2H), 7.22 (d, 2H) 7.28 (t, 2H), 7.4 (s, 1H); m/z 762.

Examples 57-58

The following compounds were synthesised by the procedure of Example 56 using the appropriate starting material except that the reaction was left to proceed for 64 hours (Example 57) or 2 hours (Example 58) and the product was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (45/55 to 60/40) as eluent.

Ex	Compound	NMR (CD_3OD) and m/z	SM
57	 Enantiomer 1	0.75-0.84 (m, 6H) 1.00-1.27 (m, 4H), 1.37-1.64 (m, 4H) 2.14 (s, 3H), 2.86-3.00 (m, 2H), 3.22 (s, 2H), 3.53-3.68 (m, 2H), 3.85 brd, 2H), 4.68 (ABq, 2H), 5.35 (s, 1H), 6.70 (s, 1H), 6.75 (d, 2H), 6.95 (t, 1H), 7.08 (d, 2H), 7.20-7.29 (m, 4H), 7.37 (s, 1H); m/z 751 ($M+NH_4^+$)	Meth 23
58	 Enantiomer 2	0.77-0.85 (m, 6H) 1.06-1.27 (m, 4H), 1.40-1.62 (m, 4H) 2.17 (s, 3H), 2.87-3.00 (m, 2H), 3.24 (s, 2H), 3.56-3.68 (m, 2H), 3.75 (brd, 2H), 4.71 (ABq, 2H), 5.37 (s, 1H), 6.72 (s, 1H), 6.77 (d, 2H), 6.97 (t, 1H), 7.10 (d, 2H), 7.23 (d, 2H), 7.28 (t, 2H), 7.40 (s, 1H); m/z 751 ($M+NH_4^+$)	Meth 24

Example 59

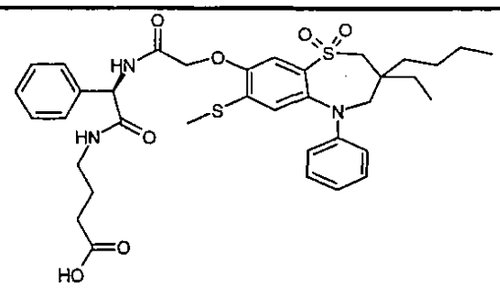
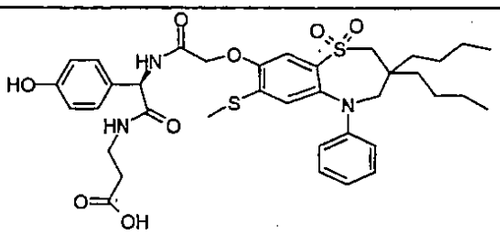
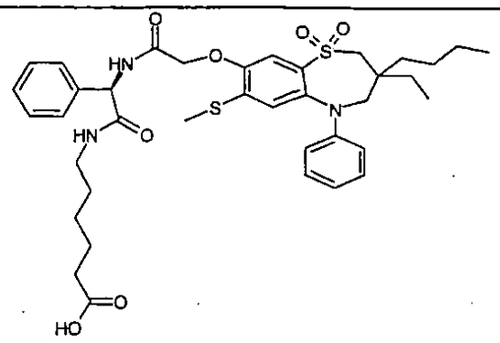
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

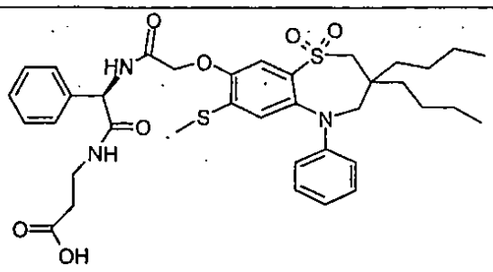
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 38; 66.8 mg, 0.109 mmol) and β-alanine ethylester hydrochloride (23.0 mg, 0.15 mmol) was dissolved in DCM (2.5 ml) and *N*-methyl morpholine (0.07 ml, 0.64 mmol) was added. After stirring at ambient temperature for 5 min TBTU (45.6 mg, 0.142 mmol) was added followed by stirring for 2 hours. The reaction mixture was filtered through a short column and concentrated. The crude ester was dissolved in THF (1.5 ml) and water (1.5 ml) and NaOH (1 M, 0.20 mmol) was added. After stirring at ambient temperature for 1 hour the reaction was quenched with 1 M HCl. The reaction mixture was diluted with water (10 ml) and extracted with DCM (3 x 5 ml).

The organic layers was concentrated and purified with preparative HPLC to give the title compound (60 mg, 81%). NMR (300 MHz) 0.80 (m, 6H), 1.00-1.70 (m, 8H), 2.17 (s, 3H), 2.48 (m, 2H), 3.17 (ABq, 2H), 3.35 (m, 1H), 3.57 (m, 1H), 3.70 (m, 2H), 4.62 (ABq, 2H), 5.77 (d, 1H), 6.64 (s, 1H), 6.98 (t, 1H), 7.06 (d, 2H), 7.28 (m, 4H), 7.42 (m, 3H), 7.56 (m, 1H), 8.10 (m, 1H).

Examples 60-63

The following compounds were synthesised by the procedure of Example 59 using the appropriate starting material.

Ex	Compound	NMR	SM
60		0.81 (m, 6H), 1.00-1.95 (m, 10H), 2.22 (s, 3H), 3.37 (m, 2H), 3.18 (ABq, 2H), 3.48 (m, 2H), 3.75 (m, 2H), 4.66 (q, 2H), 5.75 (d, 1H), 6.67 (s, 1H), 7.00 (t, 1H), 7.09 (m, 2H), 7.20 (m, 1H), 7.30 (m, 4H), 7.44 (m, 2H), 8.25 (m, 1H)	Ex 38
61		(300 MHz, DMSO-d_6) 0.74 (m, 6H), 0.95-1.50 (m, 12H), 2.16 (s, 3H), 2.28 (t, 2H), 3.24 (m, 2H), 4.74 (q, 2H), 5.33 (d, 1H), 6.69 (m, 2H), 6.85 (t, 1H), 6.99 (m, 2H), 7.16 (m, 4H), 8.33-8.45 (m, 2H)	Ex 2
62		(300 MHz) 0.81 (m, 6H), 1.00-1.74 (m, 14H), 2.22 (s, 3H), 2.31 (m, 2H), 3.10-3.35 (m, 4H), 3.73 (m, 2H), 4.62 (ABq, 2H), 5.64 (d, 1H), 6.39 (brs, 1H), 6.67 (s, 1H), 6.96-7.10 (m, 3H), 7.25-7.48 (m, 7H), 8.21 (d, 1H)	Ex 38

63		0.81 (m, 6H), 1.03-1.55 (m, 12H), 2.19 (s, 3H), 2.55 (m, 2H), 3.18 (m, 2H), 3.46 (m, 1H), 3.58 (m, 1H), 3.74 (m, 2H), 4.64 (ABq, 2H), 5.80 (m, 1H), 6.64 (s, 1H), 7.01 (t, 1H), 7.08 (d, 2H), 7.30 (m, 5H), 7.44 (m, 3H), 8.11 (m, 1H)	Ex 1

Example 64

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-carboxy-4-methoxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*t*-butoxycarbonyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 78; 48 mg, 0.070 mmol), bromoethyl(trimetylammoniumbromide) (57 mg, 0.230 mmol), tetrabutylammonium bromide (3 mg, 0.009 mmol) and Cs_2CO_3 (71 mg, 0.22 mmol) were added to CH_3CN (1.0 ml) and the reaction mixture was heated at reflux overnight. The solvent was evaporated and the residue was added to water (10 ml), extracted with DCM (3 x 5 ml) and dried ($MgSO_4$). The crude ester was dissolved in DCM (2.5 ml), TFA (0.3 ml) was added and the reaction mixture was stirred at room temperature overnight. The solvents were evaporated and the crude product was purified with preparative HPLC to give the title compound (23 mg, 51 %). NMR (DMSO-d_6) 0.74 (m, 6H), 0.94-1.60 (m, 8H), 2.17 (s, 3H), 3.25 (m, 2H), 3.69 (s, 3H), 4.70 (ABq, 2H), 4.95 (brs, 1H), 6.71 (s, 1H), 6.83 (m, 3H), 6.97 (d, 2H), 7.20 (m, 4H), 7.27 (s, 1H), 8.37 (brs, 1H).

Example 65

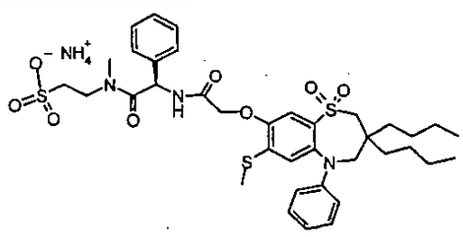
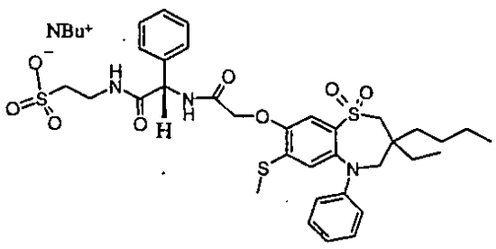
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(α-[*N'*-(2-sulphoethyl)carbamoyl]-α-methylbenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine ammonium salt

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-(α-carboxy-α-methylbenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 18; 27 mg, 0.041 mmol) was dissolved in DCM (2 ml). Taurine tetrabutylammonium salt (45 mg, 0.123 mmol) and TBTU (16 mg, 0.050 mmol) was added successively and the mixture was stirred for 5 hours at ambient temperature. The solvent was evaporated and the product was purified by preparative HPLC using an MeCN/ammonium acetate buffer (50/50) as eluent. Lyophilisation

gave the title compound in 62% yield (20 mg). NMR showed 16% of the product to remain as a tetrabutylammonium salt. NMR (500 MHz) 0.75-0.9 (m, 6H), 1.0-1.3 (m, 8H), 1.3-1.6 (m, 4H), 1.95 (s, 3H), 2.1 (s, 3H), 2.9 (brs, 2H), 3.05 (brs, 2H), 3.55 (ABd, 2H), 3.75 (brs, 2H), 4.55 (ABq, 2H), 6.6 (s, 1H), 6.9-7.6 (m, 12H), 8.2-8.3 (brs, 1H); m/z 777 ($M+NH4^+$).

Examples 66-67

The following compounds were synthesised by the procedure of Example 65 using the appropriate starting material.

Ex	Compound	NMR (CD_3OD) and M/z	SM
66		777 ($M+NH_4^+$)	Ex 1
67		0.75-0.85 (m, 6H), 1.02 (t, 12H), 1.05-1.3 (m, 4H), 1.3-1.7 (m, 20H), 2.17 (s, 3H), 2.85-2.99 (m, 2H), 3.19-3.26 (m, 10H), 3.52-3.92 (m, 4H), 4.71 (ABq, 2H), 5.47 (s, 1H), 6.72 (s, 1H), 6.96 (t, 1H), 7.09 (brd, 2H), 7.23-7.44 (m, 8H); m/z 735.2 ($M+NH_4^+$)	Ex 25

Example 68

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(methoxycarbonylmethyl) carbamoyl]-α-methylbenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 44; 20 mg, 0.028 mmol) was dissolved in 2.5 ml of a THF/water mixture (4/1). LiOH (2 mg, 0.084 mmol) was added and the mixture was stirred for 1 hour at ambient temperature. The title compound was purified with preparative HPLC using an MeCN/ammonium acetate buffer (50/50) as eluent. The MeCN was evaporated and the remaining buffer was acidified with acetic acid. Lyophilisation gave 10 mg product (51%).

NMR 0.7-0.9 (m, 6H), 1.0-1.35 (m, 8H), 1.35-1.6 (m, 4H), 2.0 (s, 3H), 2.2 (s, 3H), 3.2 (brs, 2H), 3.65-3.85 (brs, 2H), 3.9-4.1 (d, 2H), 4.5-4.7 (ABq, 2H), 6.6 (s, 1H), 6.8 (brs, 1H), 6.9-7.5 (m, 11H), 8.1 (s, 1H); m/z 727 ($M + NH_4^+$).

Example 69

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[α-carboxy-2-fluorobenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 15; 20 mg, 0.030 mmol), taurine tetrabutylammonium salt (20 mg, 0.054 mmol) and DIPEA (25 mg, 0.19 mmol) was dissolved in DMF (0.4 ml). TBTU (15 mg, 0.047 mmol) was added and the mixture was stirred for 30 min at room temperature. The product was separated from the reaction mixture by preparative HPLC using MeCN/ammonium acetate buffer (50:50) as eluent. 7 mg (29%) of the title compound was obtained. M/z = 764.5.

Example 70

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 43; 35 mg, 0.050 mmol) and (R)-α-[*N*-(*t*-butoxycarbonylmethyl) carbamoyl]benzylamine (Method 86; 20 mg, 0.076 mmol) were dissolved in DCM (2 ml) and 2,6-lutidine (0.03 ml, 0.26 mmol) was added. After stirring at ambient temperature for 5 min, TBTU (20 mg, 0.062 mmol) was added and stirring was continued for 3 hours. The reaction mixture was filtered through a column using DCM : EtOAc; 3 : 1 as eluent. The t-butyl ester was then dissolved in DCM (6 ml) and TFA (1 ml) was added. After stirring at ambient temperature overnight the solvents were evaporated. Toluene was added and evaporated twice. No further purification was necessary to give the title compound (40 mg, 93 %). NMR (500 MHz, DMSO-d_6) 0.75 (m, 6H), 0.95-1.50 (m, 12H), 2.16 (s, 3H), 3.25 (m, 2H), 3.75 (m, 2H), 3.90 (dd, 1H), 4.73/4.84 (ABq, 2H), 5.54 (m, 2H), 5.58 (d, 1H), 6.68 (s, 1H), 6.85 (t, 1H), 6.99 (d, 2H), 7.18-7.46 (m, 13H), 8.51-8.73 (m, 4H).

Example 71

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 22; 61 mg, 0.12 mmol) and methyl (2S)-amino(4-hydroxyphenyl)acetate hydrochloride (31 mg, 0.14 mmol) were dissolved in DCM (4 ml) and 2,6-lutidine (0.04 ml, 0.34 mmol) was added. After stirring at room temperature for 5 min TBTU (53 mg, 0.17 mmol) was added and stirring was continued for 2 hours. The reaction mixture was filtered through a short column. The crude methyl ester was dissolved in THF (1.5 ml) and water (1.0 ml) and NaOH (aq., 1 M, 0.39 mmol) was added. The reaction mixture was stirred at room temperature for 8 hours, quenched with HCl (1 M) and extracted with DCM (3 x 5 ml). The collected organic layers were concentrated and purified with preparative HPLC using MeCN/ammonium acetate buffer (50:50) to give the title compound (57 mg, 72 %). NMR (500 MHz, CD_3OD) 0.81 (m, 6H), 1.05-1.26 (m, 8H), 1.40-1.55 (m, 4H), 2.17 (s, 3H), 3.24 (brs, 2H), 3.74 (brs, 1H), 4.66 (ABq, 2H), 6.70-6.75 (m, 3H), 6.99 (t, 1H), 7.11 (d, 2H), 7.22-7.30 (m, 4H), 7.40 (s, 1H).

Example 72

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-(S)-(α-carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 71; 31 mg, 0.047 mmol) and tetrabutylammonium taurine (57 mg, 0.155 mmol) were dissolved in DCM (2 ml). After stirring at room temperature for 5 min TBTU (24 mg, 0.075 mmol) was added and stirring was continued for 6 hours. The solvent was evaporated and the residue was purified with preparative HPLC (twice to remove all tetrabutylammonium salt) using MeCN/ammonium acetate buffer to give the title compound 6 mg (16%). M/z 762.2.

Example 73 and Example 74

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

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 38; 56.4 mg, 0.092 mmol) and methyl D-histidinate dihydrochloride (25.2 mg, 0.104 mmol) were added to DCM (3 ml). N-methyl morpholine (0.05 ml, 0.41 mmol) was added followed by TBTU (40 mg, 0.12 mmol). The reaction mixture was stirred at 4°C for 1 hour 30 min and at room temperature for 3 hours. More TBTU (15 mg, 0.047 mmol) and DIPEA (0.025 ml, 0.14 mmol) were added and the reaction mixture was stirred at room temperature for another 30 min. The solvent was evaporated and the residue was filtered through a short column with MeOH as eluent. The crude methyl ester was dissolved in THF (1.0 ml) and water (1.0 ml) and NaOH (aq., 1 M, 0.15 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours and was quenched with HCl (1 M). The solvents were evaporated the residue was purified with preparative HPLC using MeCN/ammonium acetate buffer. The compound eluted as two peaks, assumed to be the two diastereomers. First peak (10 mg, 14%). Second peak (16.8 mg, 24%). First peak: NMR (DMSO-d_6) 0.74 (m, 6H), 0.95-1.60 (m, 8H), 2.17 (s, 3H), 2.82 (m, 2H), 3.23 (m, 2H), 4.27 (m, 1H), 4.80 (ABq, 2H), 5.60 (d, 1H), 6.55 (brs, 1H), 6.70 (s, 1H), 6.84 (t, 1H), 6.96 (d, 2H), 7.14-7.28 (m, 6H), 7.33 (s, 1H), 7.44 (brs, 1H), 8.54 (d, 1H), 8.60 (brs, 1H); m/z 748.4. Second peak: NMR (DMSO-d_6) 0.74 (m, 6H), 0.95-1.60 (m, 8H), 2.17 (s, 3H), 2.92 (dABq, 2H), 3.23 (m, 2H), 4.41 (m, 1H), 4.79 (ABq, 2H), 5.60 (d, 1H), 6.70 (s, 1H), 6.78 (s, 1H), 6.84 (t, 1H), 6.96 (d, 2H), 7.16-7.34 (m, 6H), 7.40 (m, 2H), 7.55 (s, 1H), 8.55 (d, 1H), 8.71 (d, 1H); m/z 748.4.

Example 75

1,1-Dioxo-3,3-dibutyl-5-(4-*t*-butylphenyl)-7-methylthio-8-(*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

The title compound was isolated as a byproduct in synthesis of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 43). Approximately 1 g of this compound was purified with preparative HPLC (MeCN/ammonium acetate buffer (50:50)) to give the title compound (32 mg). NMR (500 MHz, DMSO-d_6) 0.73 (m, 6H), 0.90-

1.40 (m, 12H), 1.24 (s, 9H), 2.16 (s, 3H), 3.23 (m, 2H), 3.65/3.75 (dABq, 2H), 4.72/4.82 (ABq, 2H), 5.60 (d, 1H), 6.65 (s, 1H), 6.97 (d, 2H), 7.23-7.35 (m, 6H), 7.45 (d, 2H), 8.58 (d, 1H), 8.62 (t, 1H).

Example 76

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-(*N*-((R)-α-carboxybenzyl)carbamoylmethylthio)-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-carboxymethylthio-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 81; 38 mg, 0.080 mmol) and D-phenylglycine methyl ester hydrochloride (24 mg, 0.12 mmol) were dissolved in DCM (2 ml) and N-methyl morpholine (0.05 ml, 0.42 mmol) was added. After stirring at room temperature for 5 min TBTU (44 mg, 0.14 mmol) was added and stirring was continued for 2 hours. The reaction mixture was filtered through a short column. The resulting product was dissolved in THF (1 ml) and water (1 ml) and NaOH (aq., 0.2 ml, 1 M) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched with HCl (1 M), diluted with water (10 ml) and extracted with DCM (3 x 3 ml). Purification with preparative HPLC yielded the title compound (40 mg, 82 %). NMR (DMSO-d_6) 0.75 (m, 6H), 0.96-1.60 (m, 8H), 3.22 (m, 2H), 3.56 (ABq, 2H), 3.89 (s, 3H), 4.81 (d, 1H), 6.78 (t, 1H), 6.83 (d, 2H), 6.89 (s, 1H), 7.11-7.23 (m, 7H), 7.31 (s, 1H), 8.37 (m, 1H).

Example 77

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-carboxymethylthio-8-[*N*-(α-carboxybenzyl) carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-ethoxycarbonylmethylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 82; 21 mg, 0.038 mmol) and phenylglycine methyl ester hydrochloride (12 mg, 0.061 mmol) were dissolved in DCM (1.5 ml) and N-methyl morpholine (0.02 ml, 0.19 mmol) was added. After stirring at ambient temperature for 5 min TBTU (18 mg, 0.056 mmol) was added and stirring was continued for 2 hours. The reaction mixture was filtered through a short column. The crude diester was dissolved in THF (1 ml) and water (1 ml) and NaOH (aq., 0.1 ml, 1 M) was added. The reaction mixture was stirred at ambient temperature for 2 hours, quenched with HCl (1 M), diluted with water (10 ml) and extracted with DCM (3 x 3 ml). The collected organic layers were concentrated and purified with preparative HPLC using MeCN/ammonium acetate buffer (30:70 → 40:60) to

give the title compound (20 mg, 80%). NMR (CD_3OD) 0.80 (m, 6H), 1.03-1.26 (m, 4H), 1.38-1.65 (m, 4H), 1.96 (s, 3H), 3.20 (s, 2H), 3.44 (s, 2H), 3.67 (brs, 1H), 3.76 (brs, 1H), 4.67 (ABq, 2H), 5.29 (s, 1H), 6.89 (s, 1H), 6.92 (t, 1H), 7.05 (d, 2H), 7.19-7.32 (m, 5H), 7.41 (s, 1H), 7.45 (d, 2H).

Example 78

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 43; 50 mg, 0.072 mmol), *tert*-butyl *o*-(*tert*-butyl)-D-serinate hydrochloride (22 mg, 0.087 mmol) and N-methylmorpholine (40 mg, 0.40 mmol) were dissolved in DCM (1 ml). TBTU (29 mg, 0.090 mmol) was added and the mixture was stirred for 1 hour at room temperature. The reaction mixture was evaporated and the residue was filtered through a short column (DCM : EtOAc, 1:4). The substance obtained (ca. 60 mg) was dissolved in DCM (1 ml). TFA (0.59 g, 5.2 mmol) was added and the mixture was stirred for 2 hours at room temperature. The solvent was evaporated and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (50:50) as eluent. 38 mg (72%) of the title compound was obtained. NMR (300 MHz, DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.5 (m, 12H), 2.2 (s, 3H), 3.2-3.9 (m, 10H), 4.2 (brs, 1H), 4.8 (ABq, 2H), 5.6 (d, 1H), 6.7 (s, 1H), 6.8-7.5 (m, 11H), 8.0 (d, 1H), 8.6 (d, 1H), 8.7 (t, 1H).

Example 79

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 43; 50 mg, 0.072 mmol), *tert*-butyl *O*-(*tert*-butyl)-L-serinate hydrochloride (22 mg, 0.087 mmol) and N-methylmorpholine (40 mg, 0.40 mmol) were dissolved in DCM (1 ml). TBTU (29 mg, 0.090 mmol) was added and the mixture was stirred for 1 h at room temperature. The reaction mixture was evaporated and the residue was filtered

through a short column (DCM : EtOAc, 1:4). The substance obtained (ca. 60 mg) was dissolved in DCM (1 ml). TFA (0.44 g, 3.9 mmol) was added and the mixture was stirred for 18 hours at room temperature. The solvent was evaporated and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (50:50) as eluent. 33 mg (63%) of the title compound was obtained. NMR (300 MHz, DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.5 (m, 12H), 2.2 (s, 3H), 3.2-3.9 (m, 10H), 4.2 (m, 1H), 4.8 (ABq, 2H), 5.6 (d, 1H), 6.7 (s, 1H), 6.8-7.5 (m, 11H), 7.9 (d, 1H), 8.6 (d, 1H), 8.7 (t, 1H).

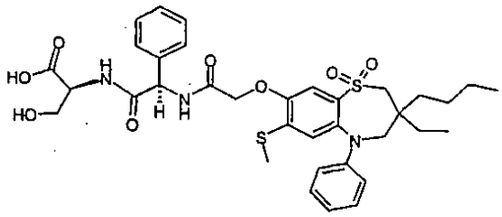
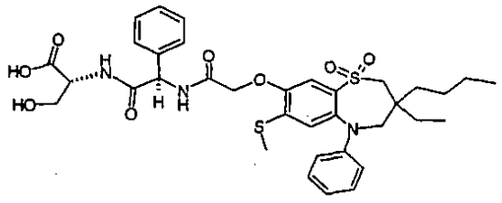
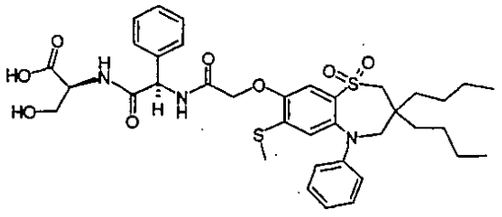
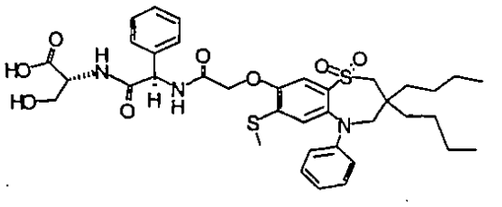
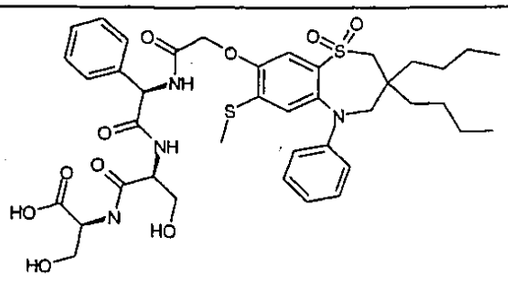
Example 80

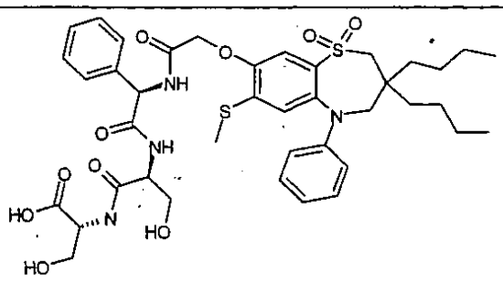
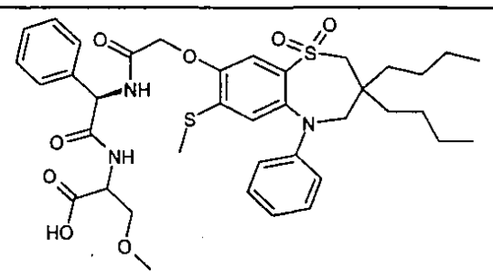
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(1,1-dicarboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 38; 50 mg, 0.082 mmol), dimethylaminomalonate (60 mg, 0.13 mmol) and N-methylmorpholine (55 µl, 0.5 mmol) were dissolved in DCM (3 ml), TBTU (42 mg, 0.13 mmol) was added and the mixture was stirred for 15 mins. The solvent was evaporated under reduced pressure. The residue was dissolved in ethanol (95%) (2 ml) and a solution of NaOH (80 mg, 2 mmol) in water (80 µl) was added. The reaction mixture was stirred for 4 hours. The mixture was neutralized with acetic acid. The solvent was evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (40:60) as eluent. The collected fractions were lyophilised to obtain 4 mg (7%) of the title compound. NMR (300 MHz, CD_3OD) 0.75-0.9 (m, 6H), 1.0-1.3 (m, 4H), 1.4-1.65 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.7 (brs, 2H), 4.65-4.8 (m, 2H), 5.75 (s, 1H), 6.75 (s, 1H), 6.9-7.55 (m, 11H).

Examples 81-87

The following compounds were synthesised by the procedure of Example 80 using the appropriate starting material except that 2,6-lutedine was used instead of *N*-methylmorpholine and the ration of eluent was MeCN/ammonium acetate buffer (45:55). Reaction time at each stage varied slightly.

Ex	Compound	NMR (300 MHz, CD_3OD)	SM
81		(500 MHz) 0.8-0.95 (m, 6H), 1.05-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 3H), 3.25 (s, 2H), 3.7-3.9 (m, 4H), 4.4-4.45 (m, 1H), 4.7-4.8 (m, 2H), 5.7 (s, 1H), 6.75 (s, 1H), 6.95-7.6 (m, 11H)	Ex 38
82		0.75-0.9 (m, 6H), 1.05-1.3 (m, 4H), 1.4-1.6 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.7-3.95 (m, 4H), 4.25-4.3 (m, 1H), 4.75 (ABq, 2H), 5.65 (s, 1H), 6.75 (s, 1H), 7.95-7.55 (m, 11H)	Ex 38
83		0.75-0.9 (m, 6H), 1.05-1.35 (m, 8H), 1.4-1.6 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.7-3.9 (m, 4H), 4.35-4.45 (m, 1H), 4.7 (ABq, 2H), 5.7 (s, 1H), 6.75 (s, 1H), 6.95-7.55 (m, 11H)	Ex 1
84[1]		0.75-0.9 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.7-3.9 (m, 4H), 3.3-3.4 (m, 1H), 4.7 (ABq, 2H), 5.65 (s, 1H), 6.7 (s, 1H), 6.95-7.55 (m, 11H)	Ex 1
85[2]		0.75-0.9 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 3.25 (s, 3H), 3.6-3.9 (m, 6H), 4.3-4.5 (m, 2H), 4.7 (ABq, 2H), 5.65 (s, 1H), 6.7 (s, 1H), 6.95-7.5 (m, 11H)	Ex 83

86 [3]		0.75-0.9 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.6-3.9 (m, 6H), 4.35-4.5 (m, 2H), 4.7 (ABq, 2H), 5.6 (s, 1H), 6.7 (s, 1H), 6.95-7.55 (m, 11H)	Ex 83
87 [4]		0.75-0.9 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.2 (d, 3H), 3.15-3.35 (m, 5H), 3.5-3.85 (4H), 4.4-4.5 (m, 1H), 4.6-4.7 (m, 2H), 5.6 (s, 1H), 6.7 (s, 1H), 6.95-7.55 (m, 11H)	Ex 1

[1] Eluent ratio (55:45); [2] Eluent ratio - variable gradient; [3] Eluent ratio (50:50); [4] Eluent ratio (60:40)

Example 88

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-(S)-(α-carboxybenzyl) carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-(S)-(α-methoxycarbonylbenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 87; 55.2 mg, 0.064 mmol) was dissolved in THF (2 ml) and 0.5 ml water. LiOH (3.1 mg, 0.127 mmol) was added and the mixture was stirred for 1hour. Water (1 ml) was added and the mixture was acidified with 0.1M HCl and extracted with DCM (3 x 2 ml). The DCM phase was dried with and concentrated. The solid product was co-evaporated with diethyl ether and dissolved in HPLC grade water. Lyophilisation gave the title compound as a white solid in 68% yield (28 mg). NMR 0.77-0.85 (m, 6H), 1.03-1.25 (m, 8H), 1.34-1.57 (m, 4H), 2.16 (s, 3H), 3.18 (brs, 2H), 3.75 (brs, 2H), 4.65 (ABq, 2H), 5.7 (d, 1H), 6.63 (s, 1H), 7.0 (t, 1H), 7.1 (d, 2H), 7.26-7.48 (m, 8H), 7.85 (d, 1H); m/z 639.

Example 89

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(S)-α-[*N'*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(S)-α-[*N'*-(methoxycarbonylmethyl)carbamoyl]benzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 88; 19 mg, 0.027 mmol) was hydrolysed by LiOH (1.3 mg, 0.054 mmol) in THF (1 ml) and water (0.3 ml). After 1 hour water (3 ml) was added and the mixture acidified using 0.1M HCl and extracted with DCM (3 x 3 ml). The organic layer was dried and evaporated yielding 16 mg (82% yield) of the title compound. NMR 0.77-0.85 (m, 6H), 1.0-1.3 (m, 8H), 1.34-1.57 (m, 4H), 2.17 (s, 3H), 3.18 (s, 2H), 3.75 (brs, 2H), 3.90-4.20 (m, 2H), 4.65 (ABq, 2H), 5.87 (m, 1H), 6.63 (s, 1H), 6.98-7.50 (m, 12H), 8.12-8.20 (m, 1H); m/z 696.

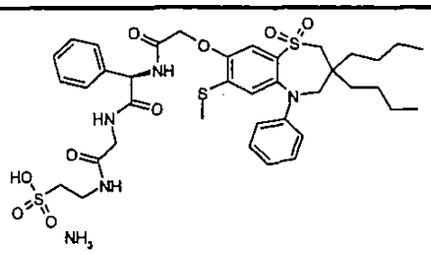
Example 90

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(S)-α-[*N'*-(2-sulphoethyl)carbamoyl] benzyl}carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine sodium salt

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-(S)-(α-carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 88; 41 mg, 0.064 mmol) was dissolved in 3 ml DCM. Taurine tetrabutylammonium salt (70 mg, 0.191 mmol) and TBTU (25 mg, 0.078 mmol) were added successively and the mixture was stirred overnight at ambient temperature. The solvent was evaporated and the product was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (45/55 to 55/45) as eluent. Lyophilisation of the collected fractions and then ion-exchange chromatography over 4 g Amberlite CG 120, Na^+-form, gave the title compound in 85% yield (42 mg). NMR 0.7-0.8 (m, 6H), 0.9-1.2 (m, 8H), 1.3-1.5 (m, 4H), 2.0 (s, 3H), 2.9-3.2 (m, 2H+2H), 3.3-3.8 (m, 2H+2H), 4.4-4.7 (m, 2H), 5.6 (m, 1H), 6.57 (s, 1H), 6.9-7.5 (m, 11H), 7.8-8.1 (m, 2H); m/z 746.

Example 91

The following compound was synthesised by the procedure of Example 90 using the appropriate starting material except the product was purified using a buffer gradient of 40/60 to 70/30 and then lyophilised to give the ammonium salt.

Ex	Compound	NMR (CD_3OD) and m/z	SM
91		0.76-0.84 (m, 6H), 1.03-1.27 (m, 8H), 1.38-1.55 (m, 4H), 2.15 (s, 3H), 2.95 (t, 2H), 3.24 (s, 2H), 3.58 (dt, 2H), 3.75 (brs, 2H), 3.85 (ABdd, 2H), 4.72 (ABq, 2H), 5.51 (s, 1H), 6.70 (s, 1H), 6.97 (t, 1H), 7.11 (d, 2H), 7.25-7.40 (m, 6H), 7.46 (d, 2H); m/z 803	Ex 43

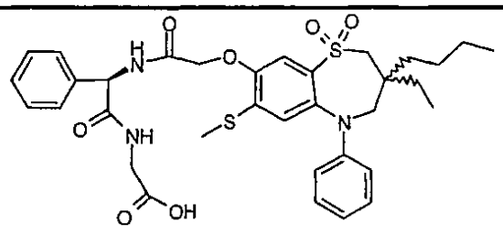
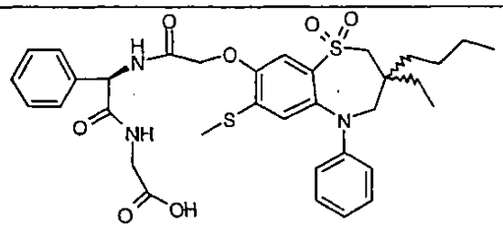
Example 92

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-[*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine sodium salt

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine sodium salt (WO 01/66533; 120 mg, 0.278 mmol) dissolved in DCM (4 ml) was added to a solution of α-[*N*-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 86; 90%, 150 mg, 0.511 mmol) in DCM (3 ml). 2,6-Dimethylpyridine (65 □l, 0.559 mmol) and TBTU (137 mg, 0.427 mmol) were added and the reaction mixture was stirred at ambient temperature overnight. The solution was filtered over using DCM/EtOAc (8/2) as eluent. The solvent was evaporated. DCM (4 ml) and TFA (0.6 ml) were added and the mixture was stirred overnight. The solvent was evaporated and the crude product was purified by preparative HPLC on a Chromasil C_{18} column. An MeCN/ammonium acetate buffer gradient (50/50 to 100/0) was used as mobile phase. The MeCN was evaporated and lyophilisation gave the title compound in 36% yield (62 mg). NMR 0.73-0.82 (m, 6H), 1.00-1.23 (m, 4H), 1.30-1.65 (m, 4H), 3.05-3.18 (m, 2H), 3.65 (brs, 2H), 3.75 (ABdd, 2H), 4.46 (ABq, 2H), 5.70 (d, 1H), 6.79-7.24 (m, 10H), 7.36 (d, 2H), 7.46 (d, 1H), 7.83 (d, 1H), 8.00 (brs, 1H); m/z 622.

Example 93-94

The following compounds were synthesised by the procedure of Example 92 using the appropriate starting material except that the HPLC-chromatography was performed on a Chromasil C_8column and the eluent gradient was 45/55 to 60/40.

Ex	Compound	NMR (CD_3OD) and m/z	SM
93	 Enantiomer 1	0.75-0.84 (m, 6H) 1.00-1.27 (m, 4H), 1.38-1.66 (m, 4H) 2.15 (s, 3H), 3.22 (s, 2H), 3.75 (brs, 2H), 3.83 (ABdd, 2H), 4.69 (ABq, 2H), 5.60 (s, 1H), 6.71 (s, 1H), 6.96 (t, 1H), 7.09 (d, 2H), 7.23-7.37 (m, 5H), 7.39 (s, 1H), 7.46 (d, 2H); m/z 668	Meth 23; Meth 86
94	 Enantiomer 2	0.78-0.85 (m, 6H) 1.04-1.27 (m, 4H), 1.41-1.65 (m, 4H) 2.17 (s, 3H), 3.24 (s, 2H), 3.68 (brs, 2H), 3.89 (ABdd, 2H), 4.72 (ABq, 2H), 5.62 (s, 1H), 6.73 (s, 1H), 6.97 (t, 1H), 7.11 (d, 2H), 7.26-7.38 (m, 5H), 7.41 (s, 1H), 7.48 (d, 2H); m/z 668	Meth 24; Meth 86

Example 95

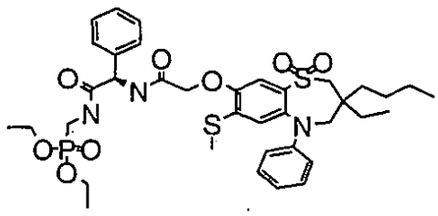
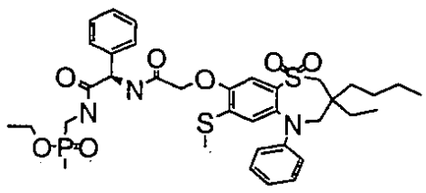
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(ethoxy)(methyl) phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 2-[(methyl)(ethyl)phosphoryl]ethylamine (Helv.Chim.Acta; GE; 75; 8; 1992; 2545-2552; 16 mg, 0.106 mmol) in DCM (2 ml) was added at 0 °C 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((*R*)-1'-phenyl-1'-carboxymethyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 38; 50 mg, 0.082 mmol) DIPEA (42 mg, 0.328 mmol) and TBTU (34 mg, 0.106 mmol) under argon. The reaction mixture was stirred at room temperature for 110 min and then DCM was added and the solution washed with $NaHCO_3$ (aq, sat) and brine. The organic layer was dried and the solvent evaporated under reduced pressure. The residue purified by chromatography and the product eluted with DCM/methanol (100:5). Yield 43 mg (71%). NMR (500 MHz) 0.78-0.85 (m, 6 H), 1.02-1.54 (m, 12H), 1.6-1.75 (br, 1H), 1.8-2.10 (m, 3H), 2.21 (s, 3H), 3.10-3.25 (m,

2H), 3.51-3.84 (m, 4 H), 3.9-3.99 (m, 1H), 4.01-4.09 (m, 1H), 4.54-4.69 (dd, 2H), 5.51 (d, 1H), 6.68 (s ,1 H), 6.96-7.02 (m, 1H), 7.03-7.18 (m, 3H), 7.25-7.42 (m, 6H), 7.43-7.48 (m, 2H), 8.05-8.15 (m, 1H).

Examples 96-97

The following compounds were synthesised by the procedure of Example 95 using the appropriate starting material.

Ex	Compound	NMR and m/z	SM
96		0.76-0.85 (m, 6H), 1.00-1.52 (m, 12H), 1.55-1.75 (m, 1H), 1.95-2.12 (br, 1H), 2.20 (s, 3H), 3.10-3.25 (m, 2H), 3.55-3.85 (m, 4H), 3.85-4.00 (m, 2H), 4.03-4.13 (m, 2H), 4.6 (q, 2H), 5.64 (d, 1H), 6.66 (s, 1H), 7.78 (br, 1H), 6.95-7.10 (m, 3H), 7.23-7.40 (m, 6H), 7.43-7.49 (m, 2H), 8.07 (d, 1H); m/z 760.3	Ex. 38
97[1]		(600 MHz) 0.75-0.82 (m, 6H), 1.0-1.42 (m, 13H), 1.64 (brs, 1H), 2.18 (s, 3H), 3.08-3.24 (m, 2H), 3.50-3.84 (m, 4H), 3.87-4.13 (m, 2H), 4.54-4.68 (m, 2H), 5.56-5.62 (m, 1H), 6.63 (s, 1H), 6.87-7.10 (m, 3H), 7.24-7.40 (m, 7H), 7.43-7.49 (m, 2H), 7.98-8.05 (m, 1H); m/z 730.5	Ex 38

[1] Amine: Tetrahedron; EN; 49; 47; 1993; 11055-11064

Example 98

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

To a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(ethoxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 95; 27 mg, 0.036 mmol) in ethanol (1.5 ml) was

added at 0°C 2 M aqueous NaOH (0.22 ml, 0.44 mmol). The reaction mixture was stirred at room temperature for 24 hours. Acetic acid (0.2 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The DCM layer was separated, washed with brine, dried and evaporated under reduced pressure. Recrystallization of the residue from DCM/ether/petroleum ether gave the title compound 23 mg (89%). NMR (600 MHz) 0.74-0.82 (m, 6H), 1.0-1.70 (m, 11H), 1.90-2.09 (m, 2H), 2.16 (s, 3H), 3.05-3.24 (m, 2H), 3.40-3.85 (m, 4H), 4.50-4.65 (dd, 2H), 5.55 (d, 1H), 6.63 (s, 1H), 6.93-7.07 (m, 3H), 7.20-7.50 (m, 9H), 8.10 (d, 1H); m/z 716.3.

Example 99

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

To a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[(diethoxy)phosphorylmethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 96; 13 mg, 0.017 mmol) in MeCN (0.5 ml) was added 1 M aqueous LiOH (0.171 ml, 0.171 mmol) dropwise. The reaction mixture was stirred at room temperature for 3 days. Acetic acid was added and the solvent evaporated under reduced pressure. The crude product was purified by preparative HPLC using MeCN and ammonium acetate buffer (45:55) as eluent to give the title compound 11 mg (88%). NMR (600 MHz, CD_3OD) 0.77-0.84 (m, 6H), 1.00-1.30 (m, 7H), 1.40-1.65 (m, 4H), 2.17 (s, 3H), 3.23 (brs, 2H), 3.51 (d, 2H), 3.6-3.85 (m, 4H), 4.70 (dd, 2H), 5.57 (s, 1H), 6.72 (s, 1H), 6.96 (t, 1H), 7.09 (d, 2H), 7.25-7.31 (m, 3H), 7.32-7.36 (m, 2H), 7.40 (s, 1H), 7.45 (d, 2H); m/z 732.4.

Example 100

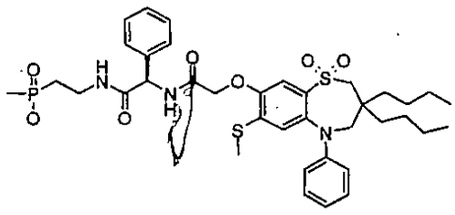
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[(hydroxy)(methyl) phosphorylmethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[(ethoxy)(methyl)phosphorylmethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 97; 85 mg, 0.12 mmol) in MeCN (2.4 ml) was added at 0°C 1 M aqueous LiOH (1.17 ml, 1.17 mmol) dropwise. The reaction mixture was stirred at room temperature for 20 hours. Acetic acid was added and the solvent evaporated

under reduced pressure. The crude product was purified by column chromatography using DCM/MeOH/Et_3N (100:15:0.2 and 100:30:0.2) as eluent to give the title compound 62 mg (76%). NMR (CD_3OD) 0.75-0.84 (m, 6H), 1.0-1.70 (m, 11H), 2.15 (s, 3H), 3.22 (brs, 2H), 3.35 (d, 2H), 3.60-3.90 (m, 2H), 4.70 (dd, 2H), 3.55 (s, 1H), 6.71 (s, 1H), 6.96 (t, 1 H), 7.09 (d, 2H), 7.23-7.38 (m, 5H), 7.40 (s, 1H), 7.46 (d, 2H); m/z 702.3

Example 101

The following compound was synthesised by the procedure of Example 100 using the appropriate starting material.

Ex	Compound	NMR (600 MHz, CD_3OD) and m/z	SM
101		0.76-0.83 (m, 6H), 1.05-1.55 (m, 15H), 1.91-1.99 (m, 2H), 2.15 (s, 3H), 3.24 (brs, 2H), 3.40-3.50 (m, 2H), 3.66-3.86 (m, 2H), 4.69 (dd, 2H), 5.42 (s, 1H), 6.70 (s, 1H), 6.92 (t, 1H), 7.11 (d, 2H), 7.25-7.39 (m, 6H), 7.43 (d, 2H); m/z 744.3	Ex 104

Example 102

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[di-(*t*-butoxy) phosphorylmethyl]carbamoyl}benzyl)carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 38; 80 mg, 0.131 mmol) and di-(*t*-butoxy)phosphorylmethyamine (Tet. Lett.; EN; 33; 1; 1992; 77-80; 37 mg, 0.164 mmol) in DCM (5 ml) was added 2,6-lutidine (28 mg, 0.262 mmol) and TBTU (53 mg, 0.164 mmol). The reaction mixture was stirred at room temperature for 2 hours and 50 min. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using DCM/MeOH (100:4) as eluent to give the title compound 92 mg (86%). NMR (500 MHz) 0.77-0.86 (m, 6H), 1.03-1.75 (m, 26H), 2.22 (s, 3H), 2.10-2.25 (m, 2H), 3.45-3.90 (m, 4H), 4.61 (dd, 2H), 5.52 (d, 1H), 5.94 (brs, 1H), 6.67 (s, 1H), 7.0 (t, 1H), 7.07 (d, 2H), 7.26-7.48 (m, 8H), 8.12 (d, 1H); m/z 704.22 [M-2(*t*-butyl)+2H].

Example 103

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

To a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[di-(*t*-butoxy) phosphorylmethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 102; 72 mg, 0.088 mmol) in DCM (4 ml) was added at 0°C TFA (1 ml). The reaction mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The organic layer was separated, washed with brine, dried and evaporated under reduced pressure. The residue was suspended in ether and the crystals filtered to give the title compound 60 mg (97%). NMR (500 MHz, DMSO-d_6) 0.70-0.80 (m, 6H), 0.99-1.61 (m, 8H), 2.18 (s, 3H), 2.80-4.0 (m, 6H), 4.80 (dd, 2H), 5.65 (d, 1H), 6.71 (s, 1H), 6.80-7.02 (m, 3H), 7.15-7.35 (m, 6H), 7.48 (d, 2H), 8.50-9.20 (m, 2H); m/z 704.3

Example 104

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

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 1; 60 mg, 0.094 mmol) and 2-[(methyl)(ethyl)phosphoryl]ethylamine (Helv.Chim.Acta; GE; 75; 8; 1992; 2545-2552;20 mg, 0.132 mmol) was added at 0°C 2,6-lutidine (20 mg, 0.19 mmol) and TBTU (39 mg, 0.121 mmol) under argon. The reaction mixture was stirred at room temperature for 70 min and then DCM was added and the solution washed with water and brine. The organic layer was dried and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using DCM/MeOH (100:5) as eluent to give the title compound 67 mg (92%). NMR (300 MHz) 0.74-86 (m, 6H), 1.0-1.60 (m, 18H), 1.80-2.05 (m, 2H), 2.20 (s, 3H), 2.17 (s, 2H), 3.47-3.80 (m, 4H), 3.88-4.10 (dd, 2H), 5.52 (d, 1H), 6.65 (s, 1H), 6.95-7.12 (m, 3H), 7.13-7.42 (m, 7H), 7.43-7.49 (m, 2H), 8.05-8.16 (m, 1H); m/z 772.4.

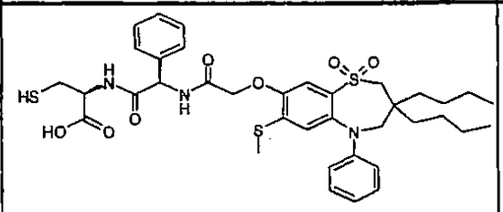
Example 105

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

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[2-(triphenylmethylsulphanyl)-1-(*t*-butoxycarbonyl)ethyl]carbamoyl}benzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 91; 37 mg, 0.036 mmol) in DCM (1 ml) was added at 0°C TFA (1 ml) under argon blanketing. The ice-bath was removed and triethylsilane (42 mg, 0.36 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours and then the solvent evaporated under reduced pressure. The crude product was purified by preparative HPLC using MeCN and ammonium acetate buffer (40:60 to 60:40) as eluent to give the title compound 16 mg (59%). NMR (500 MHz, CD_3OD) 0.76-0.85 (m, 6H), 1.05-1.60 (m, 12H), 2.17 (s, 3H), 2.77-2.92 (m, 2H), 3.24 (brs, 2H), 3.61-3.88 (m, 2H), 4.56 (t, 1H), 4.70 (dd, 2H), 5.65 (s, 1H), 6.71 (s, 1H), 6.98 (t, 1H), 7.12 (d, 2H), 7.25-7.43 (m, 6H), 7.50 (d, 2H); m/z 742.4.

Example 106

The following compound was synthesised by the procedure of Example 105 using the appropriate starting material.

Ex	Compound	NMR (500 MHz, CD_3OD) and m/z	SM
106		0.77-0.85 (m, 6H), 1.03-1.28 (m, 8H), 1.38-1.58 (m, 4H), 2.15 (s, 3H), 2.87-3.5 (m, 2H), 3.25 (s, 2H), 3.75 (brs, 2H), 4.55 (s, 1H), 4.71 (dd, 2H), 5.66 (s, 1H), 6.71 (s, 1H), 6.98 (t, 1H), 7.12 (d, 2H), 7.25-7.43 (m, 6H), 7.49 (d, 2H); m/z 742.28	Meth 93

Example 107

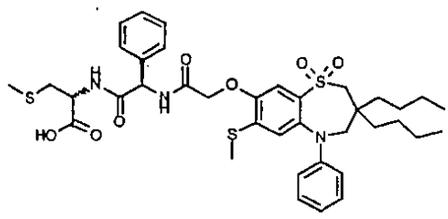
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-(2-{*N*-[(R)-α-(carboxy)benzyl] carbamoyl}ethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-(2-{*N*-[(R)-α-(*t*-butoxycarbonyl)benzyl] carbamoyl}ethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 90; 77 mg, 0.108 mmol) in DCM (3 ml) was added at 0°C TFA (0.75 ml). The reaction

mixture was stirred at room temperature for 2 h and 45 min. The solvent was evaporated under reduced pressure and the crude product was purified by preparative HPLC using MeCN and ammonium acetate buffer (40:60 to 50:50) as eluent to give the title compound 60 mg (82%). NMR (500MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.25 (m, 4H), 1.40-1.64 (m, 4H), 2.75-2.90 (m, 2H), 3.26 (s, 2H), 3.50-3.90 (m, 2H), 4.30-4.41 (m, 2H), 5.43 (s, 1H), 6.99 (t, 1H), 7.05-7.13 (m, 3H), 7.23-7.34 (m, 5H), 7.45 (d, 2H), 7.52 (s, 1H); m/z 658.

Example 108

The following compound was synthesised by the procedure of Example 107 using the appropriate starting material.

Ex	Compound	NMR (500 MHz, CD_3OD) and m/z	SM
108		0.78-0.85 (m, 6H), 1.02-1.30 (m, 8H), 1.38-1.58 (m, 4H), 1.87 (s, 3H), 2.15 (s, 3H), 2.77-2.83 (m, 1H), 2.87-2.94 (m, 1H), 3.24 (s, 2H), 3.74 (brs, 2H), 4.53-4.59 (m, 1H), 4.68 (dd, 2H), 5.66 (s, 1H), 6.71 (s, 1H), 6.98 (t, 1H), 7.12 (d, 2H), 7.25-7.31 (m, 3H), 7.32-7.36 (m, 2H), 7.40 (s, 1H), 7.49 (d, 2H); m/z 756.23	Meth 92

Example 109

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

To 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-1,5-benzothiazepine (Example 2; 80 mg, 0.122 mmol) and 2-[(methyl)(ethyl)phosphoryl]ethylamine (Helv.Chim.Acta; GE; 75; 8; 1992; 2545-2552;24 mg, 0.159 mmol) in DCM (2 ml) was added 2,6-lutidine (26 mg, 0.244 mmol) and TBTU (51 mg, 0.159 mmol) under argon. The reaction mixture was stirred at room temperature for 60 min, then diluted with DCM. The solution was washed with water, brine, dried and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using DCM/MeOH (100:7) as eluent to give the title compound

67 mg (92%). NMR (600 MHz), 0.74-0.80 (m, 6H), 1.0-1.55 (m, 18H), 1.82-1-98 (m, 2H), 2.15 (s, 3H), 3.14 (brs, 2H), 3.40-3.56 (m, 2H), 3.70 (brs, 2H), 3.89-4.02 (m, 2H), 4.51 (dd, 2H), 5.33 (t, 1H), 6.61 (s, 1H), 6.65-6.72 (m, 2H), 6.95 (t, 1H), 7.03 (d, 2H), 7.12-7.19 (m, 3H), 7.22-7.26 (m, 2H), 7.32 (s, 1H), 8.11 (t, 1H); m/z 788.56.

Example 110

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

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(ethyl)phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 104; 37 mg, 0.047 mmol) in MeCN/MeOH (4 ml, 1:1) was added 1 M aqueous LiOH (0.8 ml, 0.8 mmol). The reaction mixture was stirred at room temperature for 40 min. Acetic acid was added and the solvent evaporated under reduced pressure. The crude product was purified by preparative HPLC using MeCN and ammonium acetate buffer (40:60 and 45:55) as eluent to give the title compound 35 mg (96%). NMR (500 MHz, CD_3OD) 0.78-0.85 (m, 6H), 1.06-1.28 (m, 11H), 1.39-1.57 (m, 4H), 1.72-1.85 (m, 2H), 2.16 (s, 3H), 2.24 (s, 2H), 3.40-3.50 (m, 2H), 3.65-3.84 (m, 2H), 4.69 (dd, 2H), 5.36 (s, 1H), 6.71 (s, 1H), 6.76 (d, 2H), 6.99 (t, 1H), 7.13 (d, 2H), 7.22-7.33 (m, 4H), 7.39 (s, 1H); m/z 760.27

Example 111

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

The title compound was separated as by-product from the synthesis of Example 108. NMR (500 MHz, CD_3OD) 0.78-0.85 (m, 6H), 1.02-1.60 (m, 12H), 2.16 (d, 3H), 2.53 (d, 3H), 3.08-3.18 (m, 1H), 3.24 (s, 2H), 3.35 (v br, 1H), 3.75 (v br, 2H), 4.62 (v br, 1H), 4.71 (dd, 2H), 5.60 (d, 1H), 7.71 (s, 1H), 6.98 (t, 1H), 7.12 (d, 2H), 7.25-7.42 (m, 6H), 7.47 (d, 2H); m/z 772.25.

Example 112

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

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(S)-*N'*-(3-methylthio-2-methoxycarbonylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 94; 68 mg, 0.087 mmol) in ethanol (5 ml) was added NaOH (9 mg in 0.4 ml water) at 0°C. The reaction mixture was stirred at room temperature for 2.5 hours. Acetic acid was added and the solvent evaporated under reduced pressure. The crude product was purified by preparative HPLC using MeCN and ammonium acetate buffer (40:60 to 60:40) as eluent to give the title compound 52 mg (76%). NMR (500 MHz, CD_3OD) 0.79-0.86 (m, 6H), 1.05-1.29 (m, 8H), 1.40-1.58 (m, 4H), 1.84-1.93 (m, 4H), 2.01-2.21 (m, 5H), 2.26-2.34 (m, 1H), 3.26 (s, 2H), 3.76 (brs, 2H), 4.52-4.58 (m, 1H), 4.70 (dd, 2H), 5.61 (s, 1H), 6.73 (s, 1H), 7.0 (t, 1H), 7.14 (d, 2H), 7.27-7.43 (m, 6H), 7.49 (d, 2H); m/z 770.16.

Example 113

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

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(S)-*N'*-(2-mercapto-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 106; 15 mg, 0.02 mmol) in methanol (1.5 ml) was added sodium methoxide (0.104 mmol in 0.14 ml methanol) and methyl iodide (0.16 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 50 min. Acetic acid was added. The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The organic layer was separated, washed with brine, dried and evaporated under reduced pressure to give the title compound 4 mg (26%). NMR (500 MHz, CD_3OD) 0.75-8.30 (m, 6H), 1.03-1.57 (m, 12H), 2.10 (s, 3H), 2.17 (s, 3H), 2.83-2.30 (m, 1H), 3.0- 3.25 (m, 1H), 3.26 (s, 2H), 3.77 (brs, 2H), 4.58-4.63 (m, 1H), 4.72 (dd, 2H), 5.64 (s, 1H), 6.72 (s, 1H), 7.0 (t, 1H), 7.12 (d, 2H), 7.28-7.52 (m, 8H); m/z 756.25.

Example 114

1,1-Dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-[*N*-{(R)-α-[*N'*-(carboxymethyl) carbamoyl]benzyl}carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-[*N*-{(R)-α-[*N'*-(*t*-butoxycarbonylmethyl)carbamoyl]benzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 102; 129 mg, 0.164 mmol) in DCM (5 ml) was added at 0°C TFA (1.5 ml) under nitrogen. The reaction mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the crude product was purified by preparative HPLC using MeCN and ammonium acetate buffer (40:60 to 50:50) as eluent to give the title compound 77 mg (63%). NMR (500 MHz, CD_3OD) 0.84 (t, 6H), 1.10-1.22 (m, 8H), 1.35-1.45 (m, 4H), 2.34 (s, 3H), 3.19-3.27 (m, 2H), 3.55 (s, 2H), 3.87 (dd, 2H), 4.67 (dd, 2H), 5.61 (s, 1H), 7.09-7.15 (m, 3H), 7.27-7.37 (m, 6H), 7.47 (d, 2H); m/z 748.03 ($M+NH_3$).

Example 115

1,1-Dioxo-3,3-dipropyl-5-phenyl-7-methylthio-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3,3-dipropyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 118; 0.050 g, 0.105 mmol) in DMF (4 ml) was added 2-{[(2*R*)-2-amino-2-(4-hydroxyphenyl)ethanoyl]amino}ethanesulphonic acid (Method 80; 0.037 g, 0.135 mmol) and *N*-methylmorpholine (0.040 ml, 0.363 mmol). The mixture was stirred for 10 min and then was TBTU (0.044 g, 0.137 mmol) added. The reaction mixture was stirred for two days before the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a MeCN/ammonium acetate buffer to give the title compound in 0.042 g (55 %) as a white solid. NMR (DMSO-d_6) 0.60-0.80 (m, 6H), 1.05-1.50 (m, 8H), 2.15 (s, 3H), 2.45-2.55 (m, 2H), 3.05-3.80 (m, 6H), 4.70 (ABd, 1H), 4.80 (ABd, 1H), 5.25 (d, 1H), 6.65-6.75 (m, 3H), 6.80-7.05 (m, 3H), 7.10-7.25 (m, 4H), 7.30 (s, 1H), 8.20-8.30 (m, 1H). 8.45 (d, 1H).

Example 116

1,1-Dioxo-3,3-dipropyl-5-phenyl-7-methylthio-8-[*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3,3-dipropyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 118; 0.050 g, 0.105 mmol) in DCM (4 ml) was added (R)-α-[*N*-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 86; 0.036 g, 0.136 mmol) and *N*-methylmorpholine (0.040 ml, 0.363 mmol). The mixture was stirred for 5 min and then was TBTU (0.044 g, 0.137 mmol) added. The reaction mixture was stirred for two days and then was TFA (1.5 ml) added. After 1.5 h, the solution was diluted with toluene, before the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a MeCN/ammonium acetate buffer to give the title compound in 0.020 g (29 %) as a white solid. NMR (DMSO-d_6) 0.60-0.80 (m, 6H), 1.05-1.50 (m, 8H), 2.15 (s, 3H), 3.10-3.80 (m, 6H), 4.70 (ABd, 1H), 4.85 (ABd, 1H), 5.60 (d, 1H), 6.70 (s, 1H), 6.80-7.05 (m, 3H), 7.15-7.50 (m, 8H), 8.35 (brs, 1H), 8.55 (d, 1H).

Example 117

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 6; 0.020 g, $4.09*10^{-5}$ mol) in DMF (4 ml) was added 2-{[(2*R*)-2-amino-2-(4-hydroxyphenyl)ethanoyl]amino}ethanesulphonic acid (Method 80; 0.014 g, $5.10*10^{-5}$ mol) and *N*-methylmorpholine (0.020 ml, $1.81*10^{-4}$ mol). The mixture was stirred for 10 min and then was TBTU (0.016 g, $4.98*10^{-5}$ mol) added. The reaction mixture was stirred for 3 h and then the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a MeCN/ammonium acetate buffer to give the title compound in 0.023 g (75 %) as a white solid. NMR (500 MHz, DMSO-d_6) 0.65-0.80 (m, 6H), 0.80-1.50 (m, 12H), 2.40-2.60 (m, 2H), 3.15-3.45 (m, 4H), 3.60 (s, 3H), 3.65 (brs, 2H), 4.60 (ABd, 1H), 4.70 (ABd, 1H), 5.25 (d, 1H), 6.50 (s, 1H), 6.70-7.25 (m, 10H), 7.35 (s, 1H), 8.20-8.30 (m, 1H). 8.50 (d, 1H), 9.40 (brs, 1H).

Example 118

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxyl]-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 115; 0.020 g, $4.63*10^{-5}$ mol) in DMF (4 ml) was added 2-{[(2*R*)-2-amino-2-(4-hydroxyphenyl)ethanoyl]amino}ethanesulphonic acid (Method 80; 0.017 g, $6.20*10^{-5}$ mol) and *N*-methylmorpholine (0.016 ml, $1.46*10^{-4}$ mol). The mixture was stirred for 10 min and then TBTU (0.019 g, $5.92*10^{-5}$ mol) was added. The reaction mixture was stirred overnight and then the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a MeCN/ammonium acetate buffer to give the title compound in 0.008 g (24 %) as a white solid. NMR (500 MHz, DMSO-d_6) 0.65-0.80 (m, 6H), 0.80-1.60 (m, 8H), 2.40-2.55 (m, 2H), 3.20-3.40 (m, 4H), 3.65 (brs, 2H), 4.65 (ABd, 1H), 4.70 (ABd, 1H), 5.25 (d, 1H), 6.65-7.45 (m, 13H), 8.20-8.30 (m, 1H). 8.60 (d, 1H), 9.40 (brs, 1H).

Example 119

1,1-Dioxo-3,3-dibutyl-5-(4-*t*-butoxycarbonylaminophenyl)-8-[*N*-(α-(R)-carboxybenzyl)carbamoylmethoxyl]-2,3,4,5-tetrahydro-1,5-benzothiazepine

The title compound was synthesized from 1,1-dioxo-3,3-dibutyl-5-(4-*t*-butoxycarbonylaminophenyl)-8-[*N*-(α-(R)-methoxycarbonylbenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 45) by the procedure of Method 109. NMR (CD_3OD) 0.81 (brt, 6H), 1.03-1.3 (m, 8H), 1.32-1.59 (m, 13H), 3.24 (brs, 2H), 3.57-3.77 (m, 2H), 4.61 (brs, 2H), 5.51 (s, 1H), 6.83 (d, 1H), 7.0-7.1 (m, 3H), 7.26-7.43 (m, 7H), 7.49 (d, 1H); m/z 708.5.

Example 120

1,1-Dioxo-3,3-dibutyl-5-[4-(*N'*-*t*-butylureido)phenyl]-8-[*N*-(α-(R)-carboxybenzyl)carbamoylmethoxyl]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-(4-(*N'*-*t*-butylureido)phenyl)-8-[*N*-(α-(R)-methoxycarbonylbenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 111; 30 mg, 0.042 mmol) was dissolved in THF (1.5 ml), H_2O (0.5 ml) and LiOH (42 mg, 0.064 mmol, monohydrate) was added. The mixture was stirred for 2 hours. The compound was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95

to 100/0) as eluent to give the title product, 24 mg (82%). NMR (CD_3OD) 0.81 (brt, 6H), 1.05-1.26 (m, 8H), 1.35 (s, 9H), 1.38-1.57 (m, 4H), 3.25 (brs, 2H), 3.6-3.77 (m, 2H), 4.61 (ABq, 2H), 5.45 (s, 1H), 6.84 (d, 1H), 7.01-7.11 (m, 3H), 7.24 (d, 2H), 7.26-7.37 (m, 3H), 7.37-7.42 (m, 2H), 7.50 (d, 1H); m/z 707.5.

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-butyl-3-ethyl-5-phenyl-7-bromo-8-[1'-(ethoxycarbonyl)ethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

Sodium carbonate (0.30 g, 2.83 mmol), 2-bromopropanoic acid ethyl ester (0.145 g, 0.796 mmol) and tetrabutylammonium bromide (0.022 g, 0.07 mmol) was added to a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO 96/16051; 0.300 g, 0.663 mmol) in MeCN (10 ml). The suspension was heated under reflux overnight. The solvent was evaporated and the crude mixture was extracted (DCM/H_2O), dried ($MgSO_4$), evaporated and purified by flash chromatography (Hex:EtOAc - 5:1) to give the title compound 0.346 g (95 %) as a white solid. NMR 0.70-0.85 (m, 6H), 1.00-1.75 (m, 8H), 1.35 (t, 3H), 1.70 (d, 3H), 3.05-3.25 (m, 2H), 3.55-3.90 (m, 2H), 4.20-4.35 (m, 2H), 4.80 (q, 1H), 7.00-7.10 (m, 3H), 7.15 (s, 1H), 7.25-7.35 (m, 2H), 7.45 (s, 1H).

Method 2

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[1'-carboxyethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

Sodium hydroxide (0.045 g, 1.13 mmol) was added to a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[1-(ethoxycarbonyl)ethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 0.050 g, 0.090 mmol) in EtOH (4 ml, 95 %) and heated under reflux. After 1.5 hours AcOH (0.2 ml) was added and most of the solvent was removed under reduced pressure. The crude product was extracted (DCM/H_2O), dried ($MgSO_4$) and

acidic water three times. The organic layer was then concentrated and the residue was purified again as above to give the title compound 40 mg (41 %). NMR (300 MHz) 0.7-1.0 (m, 6H), 1.0-1.8 (m, 15H), 3.2 (q, 2H), 3.75 (m, 2H), 4.3 (m, 1H), 4.6 (s, 2H), 6.35 (s, 1H), 6.95-7.2 (m, 3H), 7.2-7.4 (m, 2H), 7.55 (s, 1H).

Method 16

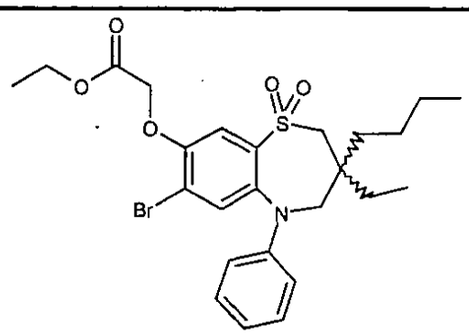
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 25; 500 mg, 1.2 mmol) was added MeCN (30 ml), tetrabutylammonium bromide (30 mg, 0.08 mmol), anhydrous sodium carbonate (500 mg, 4.7 mmol), ethyl bromoacetate (0.14 ml, 1.26 mmol) and caesium carbonate (20 mg, 0.06 mmol). This reaction mixture was then stirred overnight at 80°C. Then the solvent was removed under reduced pressure, water and DCM were added and the aqueous phase was extracted three times with DCM. The combined organic phases were then dried, concentrated and purified by flash chromatography [DCM : EtOAc, 1:0, 9:1] to give the title compound 600 mg (99%). NMR (300 MHz) 0.8-1.0 (m, 6H), 1.0-1.8 (m, 11H), 2.2 (s, 3H), 3.2 (q, 2H) 3.75 (brq, 2H), 4.3 (q, 2H), 4.75 (s, 1H), 6.7 (s, 1H), 6.95 (t, 1H), 7.05 (d, 2H), 7.25 (t, 2H), 7.3 (s, 1H).

Method 17

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 16; 478 mg, 0.95 mmol) was added THF (15 ml), water (3 ml) and LiOH (34 mg, 1.4 mmol). The reaction was then stirred for 1 hour. Then acetic acid (0.2 ml) was added along with water (10 ml) and DCM (10 ml) The aqueous layer were then extracted three times with DCM. The combined organic phases were then dried and concentrated to give the title compound 450 mg (99%). NMR 0.7-0.9 (m, 6H), 1.0-1.7 (m, 8H), 2.2 (s, 3H), 3.2 (q, 2H), 3.7 (m, 2H), 4.8 (s, 2H), 6.65 (s, 1H), 6.95 (t, 1H), 7.05 (d, 2H), 7.25 (t, 2H), 7.35 (s, 1H), 8.4 (brs, 1H).

13	 Enantiomer 2	538	Meth 84

Method 14

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 11; 2.2 g, 3.88 mmol) was dissolved in ethanol (15 ml). NaOH (0.8 g in 1.5 ml water) was added to the solution and the mixture was stirred for 30 min at room temperature. Acetic acid (2 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with EtOAc/water. The EtOAc layer was separated, dried and evaporated under reduced pressure to give the title compound 2.0 g (95%). NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.5 (m, 12H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.7 (s, 2H), 7.0-7.3 (m, 6H), 7.4 (s, 1H).

Method 15

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-isopropoxy-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To isopropyl alcohol (12 ml) was added sodium (115 mg, 5 mmol) and the temperature was then raised to 80°C to let the alcohol salt form. After all the sodium was dissolved 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 9; 100 mg, 0.2 mmol) was added in one portion. The reaction was then refluxed overnight, and then cooled to room temperature and quenched with acetic acid. The solvent was then removed under reduced pressure and the residue was dissolved in water and MeCN (70/30) and partially purified by HPLC. The residue was dissolved in ethylene glycol and NaOH (500 mg) was added. This reaction mixture was heated to 125°C overnight and then cooled to room temperature and quenched with acetic acid, and EtOAc (100 ml) was added. The ethylene glycol was removed by washing the organic layer with

evaporated to give the title compound 0.031 g (65 %) as white solid. NMR (500 MHz, CD_3OD) 0.70-0.85 (m, 6H), 0.95-1.25 (m, 4H), 1.35-1.70 (m, 4H), 2.65 (d, 3H), 3.10-3.35 (m, 2H), 3.45-3.95 (m, 2H), 4.70 (q, 1H), 6.90-7.35 (m, 6H), 7.45 (s, 1H).

Method 3

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[1'-phenyl-1'-ethoxycarbonylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

Ethyl α-bromophenylacetate (0.139 g), Na_2CO_3 (0.200 g) and tetrabutylammonium bromide (0.034 g) were added to a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO 96/16051; 0.200 g, 0.442 mmol) in MeCN (6 ml). The suspension was heated under reflux overnight before the solvent was removed under reduced pressure. The crude product was extracted (DCM/H_2O) and purified by flash chromatography (Hex:EtOAc-5:1) to give the title compound 0.256 g (94 %) as a white solid. NMR 0.65-0.85 (m, 6H), 0.95-1.65 (m, 8H), 3.00-3.15 (m, 2H), 3.50-3.80 (m, 2H), 3.70-3.80 (2s, 3H), 5.60 (s, 1H), 5.65 (d, 1H) 7.00-7.60 (m, 17H), 8.05-8.20 (2d, 1H).

Method 4

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[1'-phenyl-1'-carboxymethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

Lithium hydroxide (0.019 g) was added to a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[1'-phenyl-1'-ethoxycarbonylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 3; 0.244 g, 0.397 mmol) in THF/H_2O (2/1, 3 ml). After 2 days the solvent was removed under reduced pressure and the crude mixture was purified by HPLC to give the title compound 0.215 g (92 %) as a white solid. NMR (CD_3OD) 0.60-0.80 (m, 6H), 0.90-1.25 (m, 4H), 1.30-1.60 (m, 4H), 3.05-3.30 (m, 2H), 3.40-3.90 (m, 2H), 5.55 (s, 1H), 6.85-7.70 (m, 12H).

Method 5

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

Ethyl bromoacetate (0.13 ml), Na_2CO_3 (0.40 g) and tetrabutylammonium bromide (0.030 g) were added to a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (synthesised by the of WO9616051 for the

corresponding 3-butyl-3-ethyl analogue; 0.400 g, 0.927 mmol) in MeCN (10 ml). The suspension was heated under reflux overnight before most of the solvent was removed under reduced pressure. The crude product was extracted (DCM/H_2O) and filtered through a short silica-column (DCM:EtOAc-1:4) to give the title compound 0.476 g (99 %). NMR 0.65-0.85 (m, 6H), 0.95-1.65 (m, 8H), 3.00-3.15 (m, 2H), 3.50-3.80 (m, 2H), 3.70-3.80 (s, 3H), 5.60 (s, 1H), 5.65 (d, 1H) 7.00-7.60 (m, 17H), 8.05-8.20 (d, 1H).

Method 6

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

Lithium hydroxide (0.062 g) was added to a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 5; 0.448 g, 0.865 mmol) in THF/H_2O (2/1, 6 ml). After 1 hour AcOH (0.5 ml) was added and most of the solvent was removed under reduced pressure. The crude product was purified by HPLC (MeCN) to give the title compound 0.408 g (96 %) as a white solid. NMR (CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.65 (s, 3H), 3.70 (brs, 2H), 4.50 (s, 2H), 6.50 (s, 1H), 6.90-7.30 (m, 5H), 7.40 (s, 1H).

Method 7

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methoxy-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methoxy-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO 9616051; 1.0 g), ethyl bromoacetate (0,50 g), sodium carbonate (1,2 g) and tetrabutylammonium bromide (60 mg) in MeCN (15 ml) were refluxed overnight. The solvent was removed under reduced pressure and the residue was extracted (DCM/H_2O). The organic layer was separated and the solvent was removed under reduced pressure. The residue purified by chromatography (DCM/EtOAc (90:10)) to give the title compound 1.2 g (98%). NMR (CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.65 (s, 3H), 3.70 (brs, 2H), 4.50 (s, 2H), 6.50 (s, 1H), 6.90-7.30 (m, 5H), 7.40 (s, 1H).

Method 8

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

A mixture of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO 96/16051; 0.3 g), ethyl bromoacetate (0,14 g), sodium carbonate (0.3 g), tetrabutylammonium bromide (0.02 g) in MeCN (10 ml) were refluxed for 4 hours. The solvent was removed under reduced pressure. The residue was partitioned between DCM/H_2O and the organic layer was separated. The solvent was evaporated and the residue was purified by chromatography (DCM/EtOAc, 90:10) to give the title compound 0.34 g (95%). NMR (500 MHz) 0.7-0.9 (m, 6H), 1.0-1.8 (m, 11H), 3.2 (m, 2H), 3.6-3.8 (brs, 2H), 4.3 (q, 2H), 4.7 (s, 2H), 7.0-7.1 (m, 3H), 7.15 (s, 1H), 7.3 (m, 2H), 7.4 (s, 1H).

Method 9

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 8; 0.34 g) and sodium hydroxide (0.3 g) were dissolved in ethanol and the mixture was heated to reflux for 1 hour. Acetic acid (1 ml) was added and the solvent was removed at reduced pressure. The residue was partitioned between DCM/H_2O and the organic layer was separated and dried. Trituration of the residue with *n*-hexane gave the title compound 0.29 g (90%) as a solid. NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.7 (m, 8H), 3.1-3.2 (m, 2H), 3.6 (brs, 2H), 4.6 (s, 2H), 6.9-7.1 (m, 4H), 7.2 (m, 2H), 7.5 (s, 1H).

Method 10

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methoxy-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methoxy-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 7; 1.2 g) was dissolved in ethanol (20 ml). Sodium hydroxide (0.5) dissolved in H_2O (1 ml) was added and the reaction mixture was warmed to 40°C for 30 min. Acetic acid (1 ml) was added and the solvent was removed at reduced pressure. The residue was partitioned between DCM/H_2O and the organic layer was separated and dried. Trituration of the residue with *n*-hexane gave the title compound 1.1 g (97%) as a

solid. NMR 0.75-0.85 (m, 3H), 0.9 (t, 3H), 1.0-1.7 (m, 8H), 3.2 (q, 2H), 3.65 (s, 3H), 3.65-3.85 (m, 2H), 4.7 (s, 2H), 6.4 (s, 1H), 7.0 (t, 1H), 7.1 (d, 2H), 7.3 (t, 2H), 7.5 (s, 1H).

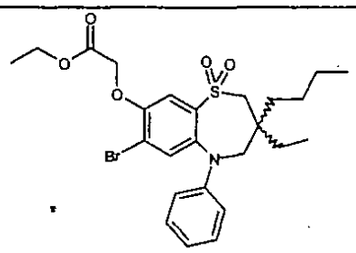
Method 11

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (synthesised by the of WO9616051 for the corresponding 3-butyl-3-ethyl analogue; 2.0 g, 4.16 mmol), ethyl bromoacetate (0.84 g, 5.03 mmol), sodium carbonate (2.0 g, 18.9 mmol) and tetrabutylammonium bromide (80 mg, 0.25 mmol) were added to MeCN (20 ml). The mixture was refluxed for 2 hours and then evaporated under reduced pressure. The residue was extracted with DCM/water. The DCM layer was separated and evaporated under reduced pressure. The residue was purified by column chromatography . The product was eluted with DCM / EtOAc (90:10) to give the title compound 2.2 g (93%). NMR 0.7-0.8 (m, 6H), 1.0-1.6 (m, 15H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.3 (q, 2H), 4.7 (s, 2H), 7.0-7.3 (m, 6H), 7.4 (s, 1H).

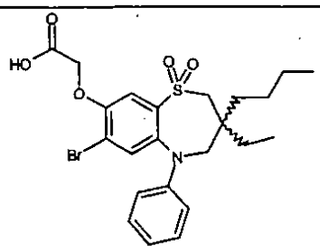
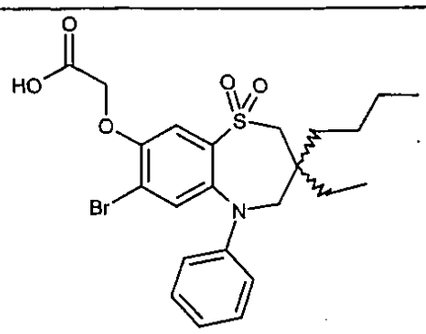
Methods 12-13

The following compounds were synthesised by the procedure of Method 11 using the appropriate acid and amine (source not indicated where commercially available).

Meth	Compound	M/z	SM
12	 Enantiomer 1	538	Meth 83

Method 18-19

The following compounds were synthesised by the procedure of Method 17 using the appropriate acid and amine (source not indicated where commercially available) except two equivalents of LiOH was used and the extraction was performed after 2 hours reaction time using EtOAc.

Meth	Compound	M/z	SM
18	 Enantiomer 1	510	Meth 12
19	 Enantiomer 2	510	Meth 13

Method 20

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-mesyl-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 16; 122 mg, 0.24 mmol) was added DCM (3 ml), water (3 ml) and potassium carbonate (120 mg, 0.87 mmol). The reaction mixture was then cooled to 0°C and m-chloroperoxybenzoic acid (160 mg, 0.51 mmol) was added in one portion. After 5 hours the reaction was quenched with DCM and saturated sodium hydrogen carbonate solution the aqueous phase were then extracted three times with DCM. The combined organic phases were dried, concentrated and purified by flash chromatography [DCM : EtOAc, 9:1] to give the title compound 46 mg (35%). NMR 0.7-0.8 (m, 6H), 1.0-1.65

(m, 11H), 3.2 (q, 2H), 3.3 (s, 3H), 3.7 (brs, 1H), 4.25 (q, 2H), 4.8 (s, 2H), 7.0-7.1 (m, 3H), 7.2-7.3 (m, 2H), 7.5 (s, 2H).

Method 21

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-mesyl-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-mesyl-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 20; 46 mg, 0.085 mmol) was added THF (5 ml), water (1 ml) and LiOH (10 mg, 0.4 mmol). The reaction was stirred for 1 hour and then excess acetic acid was added to quench the reaction. Water and DCM were added and the aqueous phase was extracted three times with DCM. The combined organic phases were dried and concentrated to give the title compound 40 mg (91%). NMR 0.7-0.85 (m, 6H), 1.0-1.7 (m, 8H), 3.2 (m, 2H), 3.3 (s, 3H), 3.8 (s, 2H), 4.9 (s, 2H), 5.0 (brs, 1H), 7.05-7.15 (m, 3H), 7.3-7.4 (t, 2H), 7.5 (s, 1H), 7.6 (s, 1H).

Method 22 (Preparation 1)

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

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 14; 500 mg, 0.93 mmol) was dissolved in DMF (10 ml). Sodium methanethiolate (200 mg, 2.85 mmol) was added and the mixture was stirred for 2 hours at 50°C. Acetic acid (0.4 ml) was added and the solvent was evaporated under reduced pressure. The residue was extracted with EtOAc/water. The EtOAc layer was separated, dried and evaporated under reduced pressure to give the title compound 450 mg (96%). NMR (300 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 2H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.8 (s, 2H), 6.6 (s, 1H), 6.9-7.1 (m, 3H), 7.2-7.4 (m, 3H).

Method 22 (Preparation 2)

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

A solution of NaOH (4.67 g, 116 mmol) in water (10 ml) was added to a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonyl-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 114; 15.45 g, 28.71 mmol) in EtOH (160 ml). The solution was

methanethiolate (450 mg, 6.42 mmol). The reaction was then heated to 60°C for 1 hour. The oil bath was then heated to 120°C for 4 hours. To quench the reaction, the temperature was lowered to room temperature and excess acetic acid was added quickly. The reaction was kept under a flow of nitrogen through sodium hypochlorite for 2 hours. Water and EtOAc were added and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with water, dried and concentrated under reduced pressure. The residue was then purified by flash chromatography [DCM : EtOAc, 9:1] to give the title compound 0.5 g (92%). NMR 0.65-0.8 (m, 6H), 0.95-1.6 (m, 8h), 3.1 (q, 2H), 3.6 (brq, 2H), 6.75 (s, 1H), 6.8 (t, 1H), 6.9 (d, 2H), 7.15 (t, 2H), 7.55 (s, 1H).

Method 26

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (synthesised by the of WO9616051 for the corresponding 3-butyl-3-ethyl analogue; 40 mg, 0.08 mmol) was added DMF (2 ml), sodium methanethiolate (60 mg, 0.85 mmol) and sodium borohydride (60 mg, 1.6 mmol). The reaction was run overnight at 60°C. Additional sodium borohydride (60 mg, 1.6 mmol) and sodium methanethiolate(60 mg, 0.85 mmol) was added and the temperature was raised to 120°C. The reaction heated at this temperature for 4 hours and then cooled to room temperature. Then acetic acid was added under a flow of nitrogen, through sodium hypochlorite overnight. Water and EtOAc was added and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with HCl (1M), dried and concentrated under reduced pressure. The residue was then purified by flash chromatography [EtOAc : heptane, 1:4] to give the title compound 0.34 g (93%). NMR 0.7-0.9 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 3H), 3.1 (s, 2H), 3.4 (s, 2H), 3.7 (brs, 2H), 6.7 (s, 1H), 6.85-7.05 (m, 2H), 7.2-7.4 (m, 2H).

Method 27

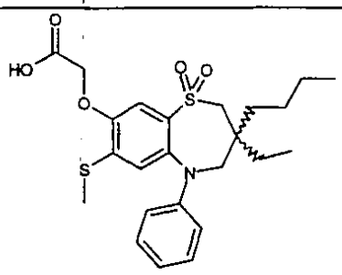
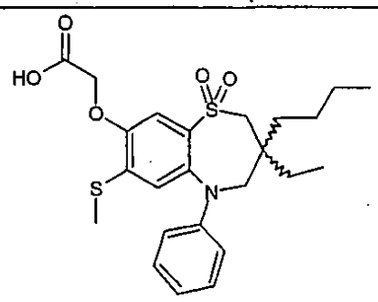
2-[(2'R)-2'-(*t*-Butoxycarbonylamino)-2'-phenylethanoylamino]ethanesulphonic acid ammonium salt

2-Aminoethanesulphonic acid (740 mg, 5.91 mmol) and (2R)-2-(*t*-butoxycarbonylamino)-2-phenylacetic acid (1.09 g, 4.34 mmol) were dissolved in DMF (20 ml). DIPEA (2.8 ml, 16.1 mmol) and TBTU (1.53 g, 4.78 mmol) were added and the mixture

stirred for 30 min at room temperature. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 1.0 M HCl. The aqueous layer was extracted twice more with EtOAc and the combined organic extracts were washed with brine and concentrated to give the title compound (14.28 g, 98 %) as a white powder. NMR (500 MHz, DMSO-d_6) 0.65-0.80 (m, 6H), 0.90-1.50 (m, 12H), 2.20 (s, 3H), 3.25 (s, 2H), 3.65 (bs, 2H), 4.80 (s, 2H), 6.70 (s, 1H), 6.80-7.30 (m, 6H), 13.20 (s, 1H).

Method 23-24

The following compounds were synthesised by the procedure of Method 22 (Preparation 1) using the appropriate acid and amine (source not indicated where commercially available) except that the reactions were performed at ambient temperature and in Method 24 for extended reaction time.

Meth	Compound	M/z	SM
23	 Enantiomer 1	478	Meth 18
24	 Enantiomer 2	478	Meth 19

Method 25

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO9616051; 600 mg, 1.29 mmol) were added DMF (5 ml) and sodium

was stirred for 2 hours at 60°C. The solvent was evaporated at reduced pressure. The residue was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound 589 mg (32%). NMR (CD_3OD) 1.43 (s, 9H), 2.85-3.0 (m, 2H), 3.53-3.68 (m, 2H), 5.1 (brs, 1H), 7.25-7.45 (m, 5H).

Method 28

2-((2'R)-2'-amino-2'-phenylethanoylamino)ethanesulphonic acid ammonium salt

2-[(2'R)-2'-(*t*-Butoxycarbonylamino)-2'-phenylethanoylamino]ethanesulphonic acid ammonium salt (Method 27; 589 mg, 1.57 mmol) was dissolved in EtOAc (20 ml) and the mixture was cooled in an ice bath. Hydrogen chloride gas was bubbled through the reaction, the ice bath was removed and the reaction was allowed to stand for 30 minutes at room temperature. The solvent was evaporated at reduced pressure. The residue was then redissolved in EtOAc (20 ml) and cooled in an ice bath. Hydrogen chloride gas was again bubbled through the reaction, the ice bath was removed and the reaction was allowed to stand for 30 minutes at room temperature. The solvent was evaporated at reduced pressure. DIPEA in DCM was added and the mixture was evaporated at reduced pressure. This was repeated twice. The mixture was lyophilised to give the title compound 563 mg (85%) containing 1 equivalent of di-isopropylethylammoniumchloride. NMR (D_2O) 1.35-1.38 (m, 15H), 2.96-3.12 (m, 2H), 3.21 (q, 2H), 3.50-3.80 (m, 4H), 5.11 (brs, 1H), 7.45-7.55 (m, 5H).

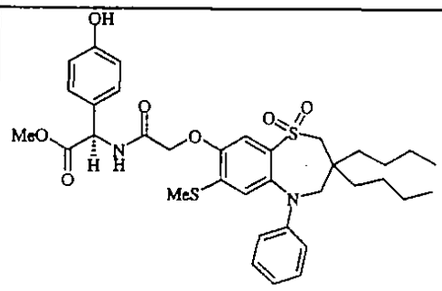
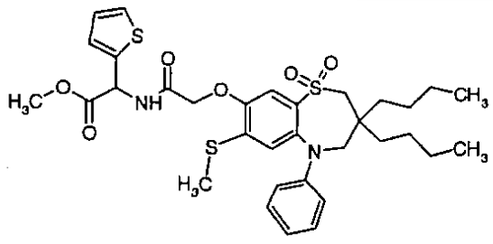
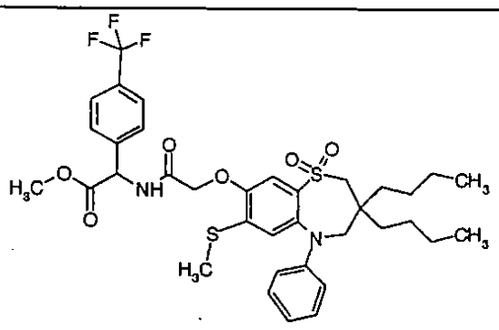
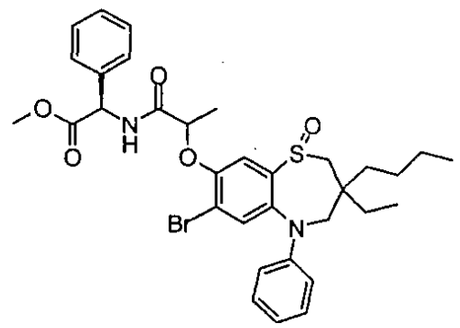
Method 29

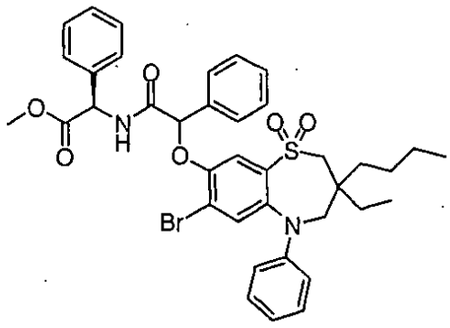
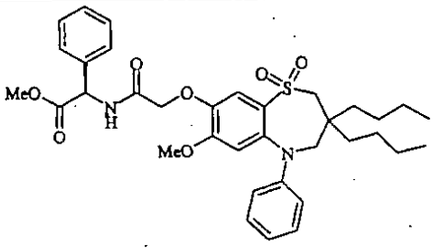
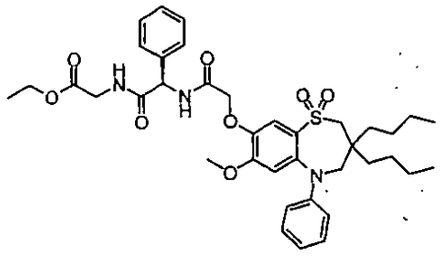
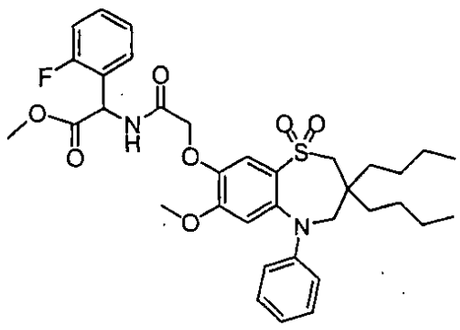
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-methoxycarbonylmethyl)carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

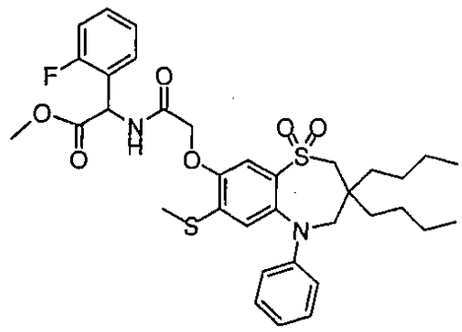
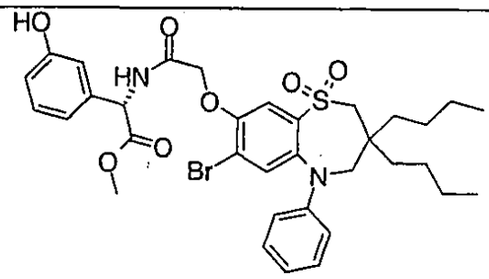
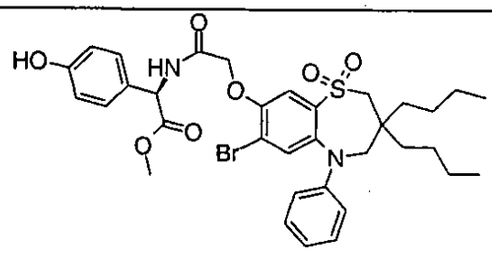
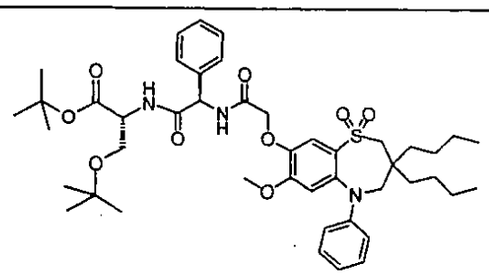
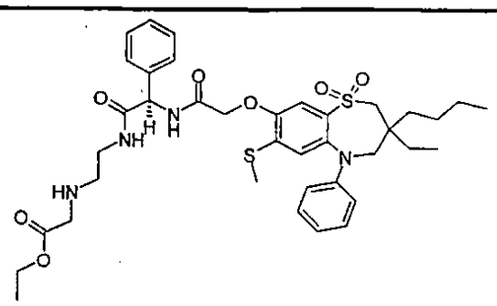
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 22; 250 mg, 0.49 mmol), (R)-2-phenylglycine methyl ester hydrochloride (120 mg, 0.60 mmol) and DIPEA (300 mg, 2.3 mmol) were dissolved in DCM (10 ml) and the mixture was stirred for 5 min in room temperature. TBTU (210 mg. 0.65 mmol) was added and the mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue was placed on a column and the product was eluted with DCM/EtOAc (90:10) to give the title compound 306 mg (95%). NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 brs, 2H), 3.6-3.8 (m, 5H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.9 (d, 1H).

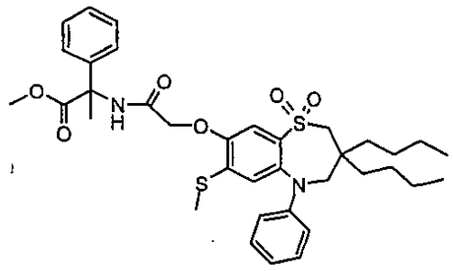
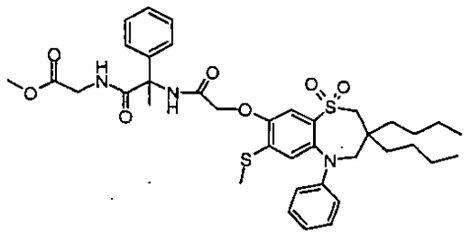
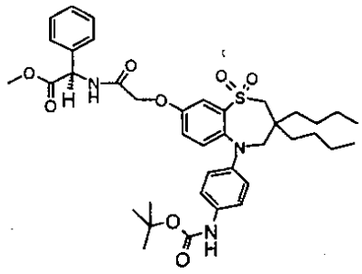
Methods 30-45

The following compounds were synthesised by the procedure of Method 29 using the appropriate acid and amine (source not indicated where commercially available) except that the reaction time was extended to 2 hours for some methods.

Meth	Compound	NMR or m/z	SM
30		(300 MHz, CD_3OD) 0.8-0.9 (m, 6H), 1.1-1.6 (m, 12H), 2.2 (s, 3H), 3.3 (s, 2H), 3.75 (brs, 5H), 4.7-4.8 (m, 2H), 5.45 (s, 1H), 6.7 (s, 1H), 6.8-7.3 (m, 9H), 7.45 (s, 1H)	Meth 22
31		(300 MHz, CD_3OD) 0.75-0.95 (m, 6H), 1.0-1-6 (m, 12H), 2.1 (s, 3H), 3.2 (s, 2H), 3.7 (s, 5H), 4.65 (s, 2H), 5.85 (s, 1H), 6.7 (s, 1H), 6.9-7.4 (m, 9H)	Meth 22
32		(300 MHz, CD_3OD) 0.75-0.9 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 3H), 3.2 (s, 2H), 3.75 (s, 5H), 4.7 (brs, 2H), 5.7 (s, 1H), 6.7 (s, 1H), 6.9-7.4 (m, 6H), 7.55-7.8 (m, 4H)	Meth 22 and Meth 71
33		0.70-0.85 (m, 6H), 0.95-1.75 (m, 8H), 1.55-1.75 (2d, 3H), 3.05-3.30 (m, 2H), 3.55-3.90 (m, 2H), 3.70-3.80 (2s, 3H) 4.75-4.90 (2q, 1H), 5.60 (d, 1H), 7.00-7.55 (m, 12H), 7.80-7.95 (m, 1H)	Meth 2

34		0.65-0.85 (m, 6H), 0.95-1.65 (m, 8H), 3.00-3.15 (m, 2H), 3.50-3.80 (m, 2H), 3.70-3.80 (2s, 3H), 5.60 (s, 1H), 5.65 (d, 1H) 7.00-7.60 (m, 17H), 8.05-8.20 (2d, 1H)	Meth 4
35		(CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.55 (s, 3H), 3.70 (s, 3H), 3.75 (brs, 2H), 4.60 (ABq, 2H), 5.55 (s, 1H), 6.50 (s, 1H), 6.95-7.40 (m, 10H), 7.50 (s, 1H)	Meth 6
36		707.4	Ex 12
37		0.75-0.85 (m, 6H), 1.00-1.60 (m, 12H), 3.20 (s, 2H), 3.60 (s, 3H), 3.75 (brs, 2H), 3.75 (s, 3H), 4.55 (ABq, 2H), 5.85 (d, 1H), 6.40 (s, 1H), 6.95-7.45 (m, 9H), 7.55 (s, 1H), 8.05 (d, 1H)	Meth 6

38		0.75-0.85 (m, 6H), 1.00-1.60 (m, 12H), 2.20 (s, 3H), 3.20 (s, 2H), 3.75 (brs, 2H), 3.80 (s, 3H), 4.60 (ABq, 2H), 5.90 (d, 1H), 6.65 (s, 1H), 6.95-7.45 (m, 10H), 7.95 (d, 1H)	Meth 22
39		(500 MHz) 0.7-0.8 (m, 6H), 1.0-1.5 (m, 12H), 3.2 (m, 2H), 3.7-3.8 (m, 5H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.8-7.4 (m, 10H), 7.5 (s, 1H)	Meth 14
40		(300 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 3.2 (brs, 2H), 3.7-3.8 (m, 5H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.8 (d, 2H), 7.0-7.4 (m, 8H), 7.9 (d, 1H)	Meth 14
41		766.4 (M-(*t*-butyl)+2H)	Ex 12
42		739.3	Ex 38

43		667	Meth 22
44		724	Ex 18
45		722.5	Meth 109

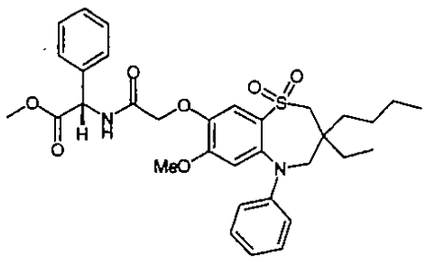
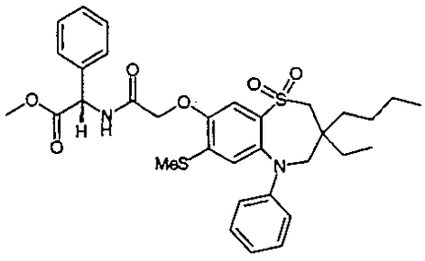
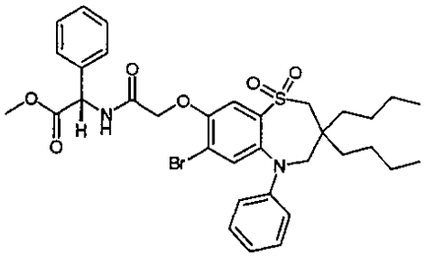
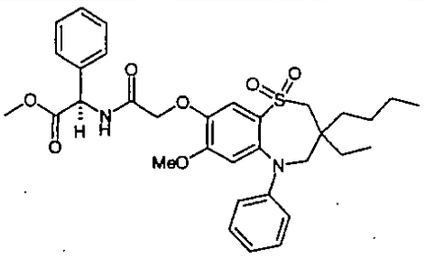
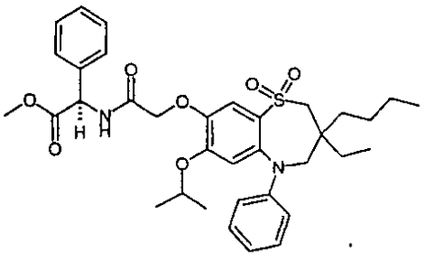
Method 46

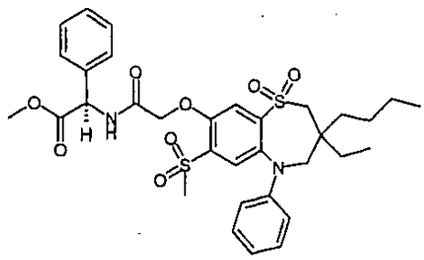
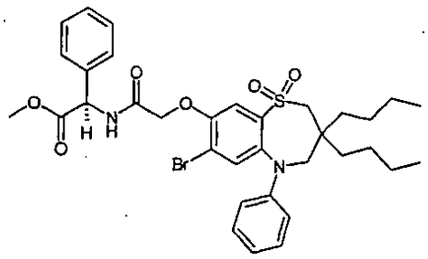
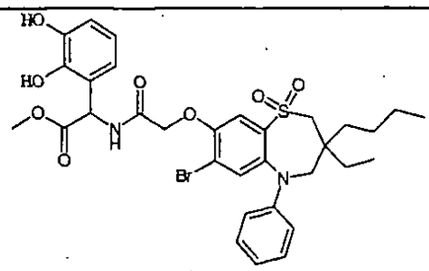
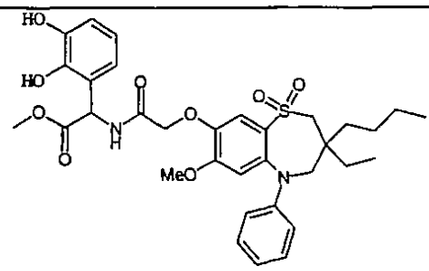
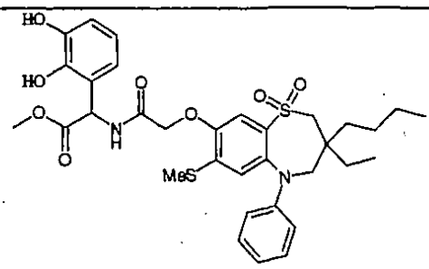
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-{*N*-((S)-1'-phenyl-1'-methoxycarbonylmethyl)carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

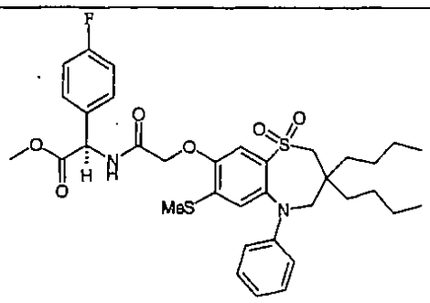
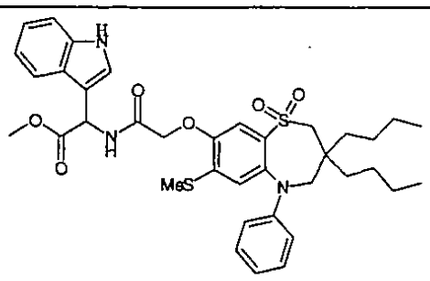
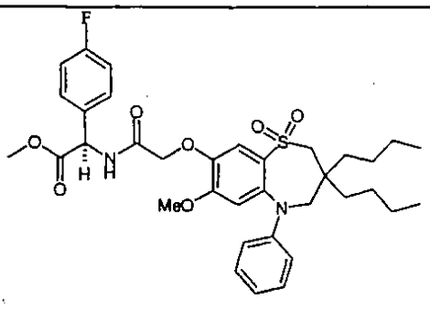
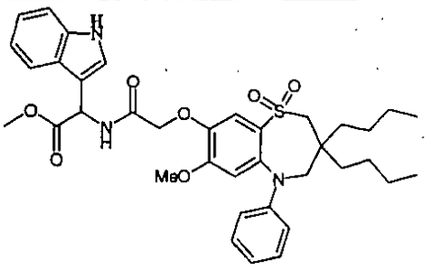
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 9; 50 mg, 0.098 mmol) was dissolved in DCM (2 ml). Methyl (2*S*)-amino(phenyl)acetate (19 mg, 0.12 mmol) and DIPEA (0.068 ml, 0.39 mmol) were added and the reaction was stirred for 2 minutes. TBTU (42 mg, 0.13 mmol) was added and the mixture was stirred for 1.5 hours at room temperature. The mixture was put on a pre-packed ISOLUTE column and eluted with 10 ml DCM/EtOAc 8/2 to give the title compound 60 mg (93%). M/z 657.5.

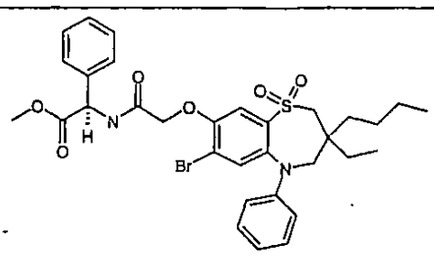
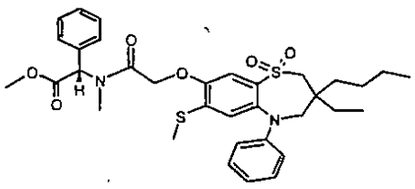
Methods 47-62

The following compounds were synthesised by the procedure of Method 46 (except that the reaction times were overnight) using the appropriate acid and amine (source not indicated where commercially available).

Meth	Compound	NMR or M/z	SM
47		609.4	Meth 10
48		625.4	Meth 17
49		685.3	Meth 14
50		609.4	Meth 10
51		637.4	Meth 15

52		657.4	Meth 21
53		685.3	Meth 14
54		0.73-0.95 (m, 6H), 0.98-1.78 (m, 8H), 3.12-3.28 (m, 2H), 3.6-4.0 (m, 5H), 4.60 (ABq, 2H), 5.79 (d, 1H), 6.0 (brs, 1H), 6.54 (dd, 1H), 6.83 (t, 1H), 6.95 (dd, 1H), 7.0-7.5 (m, 7H), 8.43 (d, NH), 9.32 (brs, 1H)	Meth 9 and Meth 74
55		0.75-0.9 (m, 6H), 1.0-1.78 (m, 8H), 3.10-3.26 (m, 2H), 3.63-3.87 (m, 8H), 4.56 (ABq, 2H), 5.76 (d, 1H), 5.99 (brs, 1H), 6.38 (s, 1H), 6.51 (dd, 1H), 6.81 (t, 1H), 6.93 (dd, 1H), 7.0-7.15 (m, 3H), 7.23-7.4 (m, 2H), 7.55 (s, 1H), 8.54 (d, NH), 9.45 (brs, 1H)	Meth 10 and Meth 74
56		0.76-0.87 (m, 6H), 1.0-1.8 (m, 8H), 2.23 (s, 3H), 3.1-3.25 (m, 2H), 3.6-3.95 (m, 5H), 4.61 (ABq, 2H), 5.79 (d, 1H), 6.0 (brs, 1H), 6.54 (dd, 1H), 6.65 (s, 1H), 6.83 (t, 1H), 6.92-7.1 (m, 4H), 7.23-7.4 (m, 3H), 8.37 (d, NH), 9.35 (brs, 1H)	Meth 17 and Meth 74

57		(CD_3OD) 0.76-0.85 (m, 6H), 1.02-1.3 (m, 8H), 1.36-1.56 (m, 4H), 2.16 (s, 3H), 3.24 (brs, 2H), 3.66-3.80 (m, 5H), 4.71 (ABq, 2H), 5.57 (s, 1H), 6.71 (s, 1H), 6.98 (t, 1H), 7.06-7.14 (m, 4H), 7.28 (brt, 2H), 7.37-7.45 (m, 3H)	Meth 22 and Meth 75
58		(CD_3OD) 0.76-0.85 (m, 6H), 1.02-1.28 (m, 8H), 1.36-1.56 (m, 4H), 1.96 (s, 3H), 3.24 (brs, 2H), 3.6-3.8 (m, 5H), 4.73 (ABq, 2H), 5.76 (s, 1H), 6.63 (s, 1H), 6.94-7.04 (m, 2H), 7.07-7.15 (m, 3H), 7.27 (t, 2H), 7.31 (s, 1H), 7.37 (d, 1H), 7.42 (s, 1H), 7.56 (d, 1H)	Meth 22
59		(CD_3OD) 0.80 (brt, 6H), 1.0-1.28 (m, 8H), 1.36-1.54 (m, 4H), 3.22 (brs, 2H), 3.61 (s, 3H), 3.69-3.8 (m, 5H), 4.62 (ABq, 2H), 5.56 (s, 1H), 6.49 (s, 1H), 6.99 (brt, 1H), 7.07-7.16 (m, 4H), 7.29 (brt, 2H), 7.37-7.43 (m, 2H), 7.52 (s, 1H)	Meth 6 and Meth 75
60		(CD_3OD) 0.75-0.84 (m, 6H), 1.0-1.29 (m, 8H), 1.35-1.54 (m, 4H), 3.20-3.23 (m, 5H), 3.65-3.8 (m, 5H), 4.64 (ABq, 2H), 5.74 (s, 1H), 6.34 (s, 1H), 6.95-7.04 (m, 2H), 7.09-7.15 (m, 3H), 7.24-7.31 (m, 3H), 7.37 (d, 1H), 7.50-7.54 (m, 2H)	Meth 6

61 [1]		0.74-0.83 (m, 6H), 0.98-1.7 (m, 8H), 3.18 (ABq, 2H), 3.60-3.90 (m, 5H), 4.59 (ABq, 2H), 5.67 (d, 1H), 7.0-7.2 (m, 4H), 7.2-7.55 (m, 8H), 7.91 (d, NH)	Meth 9
62		639.4	Meth 17 and Meth 76

[1] Eluent was DCM/EtOAc in a stepwise gradient from 100/0, 9/1, 8/2

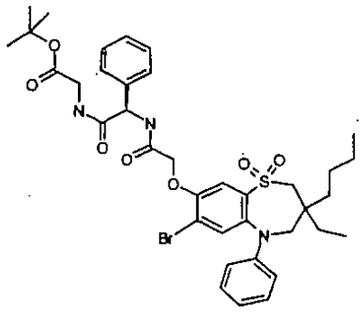
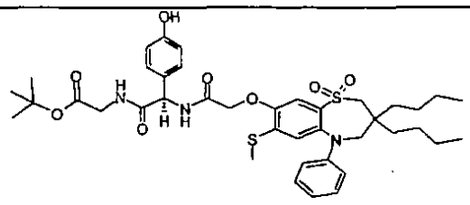
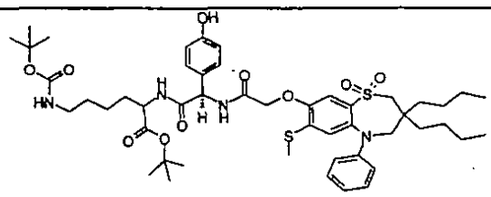
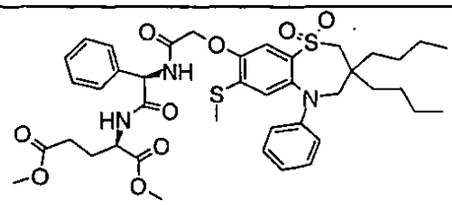
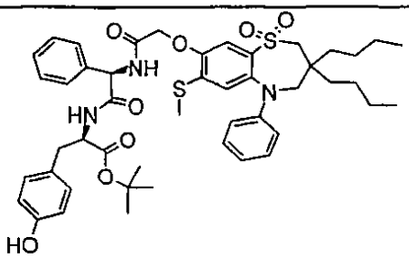
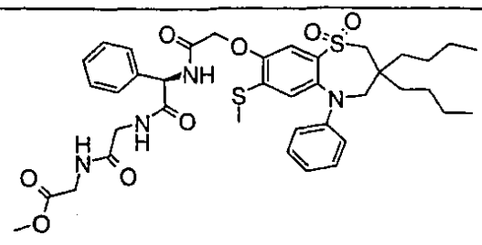
Method 63

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(*t*-butoxycarbonylmethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 1; 110 mg, 0.17 mmol), glycine tert-butyl ester (30 mg, 0.23 mmol) and DIPEA (120 mg, 0.93 mmol) were dissolved in DCM (2 ml). The mixture was stirred for 5 mins at room temperature. TBTU (72 mg, 0,22 mmol) was added and the mixture was stirred for 1 h at room temperature. The solvent was evaporated at reduced pressure and the residue was placed on a column and the product was eluted with DCM/EtOAc (90:10) to give the title compound 122 mg (94%). NMR (300 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 21H), 2.2 (s, 3H) 3.2 (s, 2H), 3.7-4.0 (m, 4H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.4 (t, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 8.1 (d, 1H).

Methods 64-69

The following compounds were synthesised by the procedure of Method 63 using the appropriate acid and amine (source not indicated where commercially available).

Meth	Compound	NMR or M/z	SM
64		756.1	Ex 22
65		(CD_3OD) 0.75-0.85 (m, 6H), 1.1-1.3 (m, 8H), 1.4 (s, 9H), 1.45-1.55 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.75 (brs, 1H), 3.85 (s, 2H), 4.7 (ABq, 2H), 5.5 (s, 1H), 6.7 (s, 1H), 6.75-7.35 (m, 9H), 7.4 (s, 1H)	Ex 2
66		937.9 $(M-H)^-$	Ex 2
67		796.4	Ex 1
68			Ex 1
69			Ex 1

65

Method 70

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-{*N*-[(S)-1'-phenyl-1'-(diethoxyphosphoryl)methyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine

The title compound was synthesised from 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 9) and diethyl (*S*)-amino(phenyl)methylphosphonate by the procedure of Example 33. NMR (600 MHz) 7.77-7.72 (1H, m), 7.47-7.42 (3H, m), 7.36-7.27 (5H, m), 7.14 (1H, s), 7.10-7.03 (2H, m), 5.55-5.48 (1H, m), 4.63-4.51 (2H, m), 4.14-4.02 (2H, m), 3.99-3.92 (1H, m), 3.81-3.60 (3H, m), 3.22-3.10 (2H, m), 1.65-1.25 (8H, m), 1.19-0.95 (6H, m), 0.78-0.73 (6H, m).

Method 71

4-Trifluoromethyl-α-methoxycarbonylbenzylamine

4-Trifluoromethyl-α-carboxybenzylamine (1.4 g, 1.83 mmol) and thionylchloride were added to methanol (8 ml) and the mixture was refluxed for 2 h. The solvent was evaporated under reduced pressure. The residue was suspended in diethyl ether and the product was filtered off, washed with ether and dried to give the title compound 0.34 g (69%). NMR (300 MHz, DMSO-d_6) 3.3 (s, 1H), 5.45 (s, 1H), 7.7-7.9 (m, 4H), 9.25 (brs, 3H).

Method 72

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

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 38; 52 mg, 0.082 mmol) and glycine ethyl ester hydrochloride (18 mg, 0.129 mmol) were dissolved in DCM (2 ml) and DIPEA (0.70 ml, 0.42 mmol) was added. After stirring at ambient temperature for 5 min TBTU (34 mg, 0.11 mmol) was added and the mixture was stirred for 2 hours. The solvent was evaporated and the residue was purified with flash chromatography (DCM:EtOAc 10:3) to give the title compound 50 mg (88%). NMR (500 MHz) 0.86 (m, 6H), 1.10-1.75 (m, 8H), 1.28 (m, 3H), 2.23 (s, 3H), 3.19 (q, 2H), 3.75 (m, 2H), 3.99-4.25 (m, 4H), 4.64 (q, 2H), 5.64 (m, 1H), 6.35 (brs, 1H), 6.69 (s, 1H), 7.03 (t, 1H), 7.09 (d, 1H), 7.29-7.52 (m, 7H), 8.10 (d, 1H).

Method 73

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

The title compound was synthesised by the procedure of Method 72 using 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-1'-phenyl-1'-carboxymethyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 38) and methyl (2R)-amino(phenyl)acetate hydrochloride.

Method 74

1-(1'-Methoxycarbonyl-1'-aminomethyl)-2,3-dihydroxyphenyl hydrochloride salt

1-(1'-Carboxy-1'-aminomethyl)-2,3-dihydroxyphenyl (40 g, 0.218 m mol) was mixed with methanol (230 ml). HCl gas was bubbled through. The mixture was refluxed for 2 hours. The solvent was evaporated under reduced pressure. The product was crystallised from methanol/EtOAc/diethyl ether to yield 35.5 g (70 %) of the title product. NMR (600 MHz, CD_3OD) 3.76 (s, 3H), 5.19 (s, 1H), 6.68-6-75 (m, 2H), 6.85 (dd, 1H)

Method 75

(R)-1-(1'-Methoxycarbonyl-1'-aminomethyl)-4-fluorophenyl hydrochloride salt

(2R)-amino(4-fluorophenyl)acetic acid (570 mg, 2.77 mmol) was dissolved in methanol (5 ml) and cooled in an ice-bath. Thionyl chloride (2 ml) was added dropwise and temperature was allowed to reach room temperature. After 5 hours the mixture was evaporated under reduced pressure. The procedure was repeated and the reaction was stirred overnight. The mixture was evaporated under reduced pressure to give the title product in a quantitative yield. NMR (500 MHz, CD_3OD) 3.84 (s, 3H), 5.26 (s, 1H), 7.26 (t, 2H), 7.53 (dd, 2H).

Methods 76-77

The following compounds were synthesised by the procedure of Method 75 using the appropriate acid and amine (source not indicated where commercially available).

Meth	Compound	NMR	SM
76	(S)-α-Methylamino-α-methoxycarbonylbenzyl	(CD_3OD) 2.63 (s, 3H), 3.81 (s, 3H), 5.15 (s, 1H), 7.45-7.55 (m, 5H)	(S)-α-Methylamino-α-carboxybenzyl
77 [1]	α-Methoxycarbonyl-*N*-methylbenzylamine hydrochloride	(D_2O) 2.65 (s, 3H), 3.81 (s, 3H), 5.15 (s, 1H), 7.45-7.48 (m, 2H), 7.52-7.59 (m, 3H)	(methylamino)(phenyl)acetic acid

[1] Total reaction time 5 days

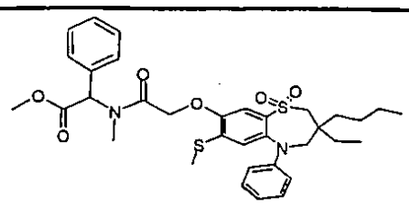
Method 78

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*t*-butoxycarbonyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine

tert-Butyl (2R)-amino(4-hydroxyphenyl)acetate (104 mg, 0.47 mmol) and 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 17; 185 mg, 0.39 mmol) were dissolved in DCM (5 ml) and lutidine (0.09 ml, 0.77 mmol) was added. After stirring at room temperature for 5 min o-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (208 mg, 0.55 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. Purification with flash chromatography (DCM:EtOAc 10:1→5:1) gave the title compound (175 mg, 66 %). NMR (300 MHz) 0.81 (m, 6H), 1.05-1.65 (m, 8H), 1.42 (s, 9H), 2.21 (s, 3H), 3.17 (ABq, 2H), 3.74 (m, 2H), 4.60 (ABq, 2H), 5.22 (brs, 1H), 5.49 (d, 1H), 6.67 (s, 1H), 6.79 (m, 2H), 7.00 (t, 1H), 7.07 (d, 2H), 7.23-7.30 (m, 3H), 7.40 (s, 1H), 7.82 (brd, 1H).

Method 79

The following compounds were synthesised by the procedure of Method 78 using the appropriate starting material.

Meth	Compound	M/z	SM
79		639.3	Meth 17 and Meth 77

Method 80

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

N-Boc-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 it was filtered and concentrated. TFA in DCM (20%, 20 ml) was added and the reaction mixture was stirred overnight. 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, 626 mg (71%). NMR (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).

Method 81

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-carboxymethylthio-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (113 mg, 0.24 mmol), Cs_2CO_3 (170 mg, 0.52 mmol) and ethyl thioglycolate (0.060 ml, 0.54 mmol) in DMF (4.0 ml) were subjected to microwave irradiation in a Smith Synthesiser at 80°C for 3 min and then at 90°C for 8 min. The reaction mixture was diluted with water (250 ml) and extracted with DCM (5 x 10 ml) and collected organic layers were dried ($MgSO_4$), concentrated and purified on a short column (petroleum ether : EtOAc 4:1 → 2:1). The resulting product was dissolved in THF (2 ml) and water (2 ml) and NaOH (aq., 0.5 ml, 1 M) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched with HCl (1 M) and the reaction mixture was diluted with water (10 ml) and extracted with DCM (3 x 3 ml). Purification with preparative HPLC yielded the title compound (58 mg, 59 %). NMR (300 MHz, CD_3OD) 0.81 (m, 6H), 1.00-1.70 (m, 8H), 3.21 (m, 2H), 3.42 (m, 2H), 3.71 (m, 2H), 3.92 (s, 3H), 6.88 (m, 2H), 7.02 (m, 2H), 7.23 (t, 2H), 7.40 (s, 1H).

purified with flash chromatography (DCM:EtOAc 7:1→5:1) to give the title compound (13 g, 94 %). NMR (500 MHz) 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).

Method 86

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

(R)-*N*-Benzyloxycarbonyl-α-[*N'*-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 85; 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 hours 30 min at room temperature. The reaction mixture was filtered through diatomaceous earth and the solvents were evaporated to give the title compound (8.4 g, 99 %). NMR (600 MHz) 1.45 (s, 9H), 3.93 (m, 2H), 4.54 (s, 1H), 7.31-7.42 (m, 5H), 7.51 (brs, 1H).

Method 87

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-(S)-(α-methoxycarbonylbenzyl) carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 22; 50 mg, 0.099 mmol) was dissolved in DCM (2 ml). (S)-Phenylglycine methyl ester hydrochloride (24.8 mg, 0.123 mmol) and diisopropyl ethyl amine (70 □l, 0.401 mmol) were added. The mixture was stirred for 15 min and then TBTU (38 mg, 0.118 mmol) was added. The reaction was completed after 1.5h (LC/MS). The crude product was purified by flash chromatography using chloroform/EtOAc (8/2) as the eluent (88.6%; 55.2 mg, 0.064 mmol). M/z 653.

Method 88

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(S)-α-[*N'*-(methoxycarbonylmethyl) carbamoyl]benzyl}carbamoylmethoxyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-(S)-(α-carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 88; 25 mg, 0.039 mmol) and glycine methyl ester (7.5 mg, 0.059 mmol) were dissolved in DCM (2 ml). Diisopropyl ethyl amine (27 □l, 0.158 mmol) and TBTU (15 mg, 0.047 mmol) were added successively and the mixture was stirred for 2 hours at ambient temperature. The crude

Method 82

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-ethoxycarbonylmethylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 9; 50 mg, 0.098 mmol) and Cs_2CO_3 (51 mg, 0.15 mmol) were added to DMF (2.0 ml) and ethyl thioglycolate (0.02 ml, 0.15 mmol) was added. The reaction mixture was subjected to microwave irradiation in a Smith Synthesiser at 150°C for 5 min. The reaction mixture was diluted with water (100 ml), made acidic with HCl (1 M), extracted with DCM (3 x 10 ml) and the collected organic layers were dried ($MgSO_4$) to give the crude title compound (54 mg). M/z 550.2.

Method 83 and Method 84

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Enantiomer 1); and

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Enantiomer 2)

The two enantiomers of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO 96/16051) were obtained by separation of the corresponding racemic mixture using preparative HPLC. The column used was a Chiralpak AD (20x250 mm i.d., 10□m) and the mobile phase was a heptane / IPA mixture in ratio 90/10. The injected racemate (17.3 mg in IPA (1 ml)) was eluted with a flow of 10 ml/min and the chromatogram was followed with UV-detection at 285nm. Totally 260 mg racemate was separated yielding 121 mg of the first eluting enantiomer (Enantiomer 1) and 115 mg of the second eluting enantiomer (Enantiomer 2). Total yield 91%. Each of the two enantiomers was obtained in 99.4% e.e.

Method 85

(R)-*N*-Benzyloxycarbonyl-α-[*N'*-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine

(R)-*N*-Benzyloxycarbonyl-α-carboxybenzylamine (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 added and stirring was continued 1 hour 30 min at 0°C and 3 hours 45 min at room temperature. The reaction mixture was washed with water (2 x 100 ml), dried ($MgSO_4$) and

product was purified by flash chromatography using DCM/EtOAc (8/2) as eluent 79% yield (22 mg). M/z 710.

Method 89

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-(2-carboxyethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

Sodium hydroxide (38 mg, 0.95 mmol) was dissolved in ethanol (2.5 ml) and then 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO 96/16051; 200 mg, 0.443 mmol) was added. After stirring at room temperature for 5 min, 3-bromopropionic acid (68 mg, 0.443 mmol) was added and the reaction mixture was refluxed for 20 hours. Acetic acid was added. The solvent was evaporated under reduced pressure and the residue was extracted with EtOAc/water. The organic layer was separated, washed with water, dried and evaporated under reduced pressure. The crude product was purified by column chromatography using DCM/MeOH (100:5) as eluent to give the title compound 89 mg (38%). NMR (CD_3OD) 0.75-0.83 (m, 6H), 1.0-1.25 (m, 4H), 1.38-1.65 (m, 4H), 2.82 (m, 2H), 3.26 (s, 2H), 3.50-3.90 (m, 2H), 4.33 (t, 2H), 6.99 (t, 1H), 7.07-7.13 (m, 3H), 7.28 (t, 2H), 7.53 (s, 1H).

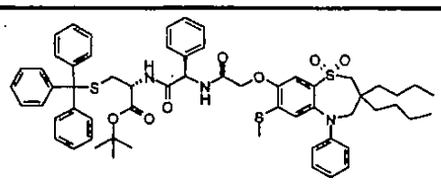
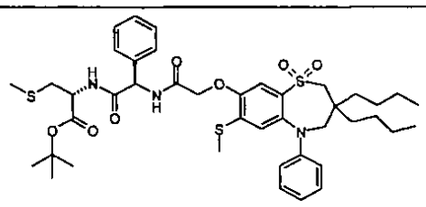
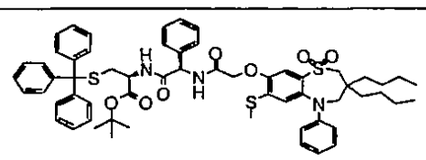
Method 90

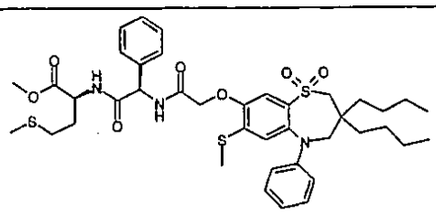
1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-(2-{*N*-[(R)-α-(*t*-butoxycarbonyl)benzyl] carbamoyl}ethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-(2-carboxyethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 89; 70 mg, 0.134 mmol) and (R)-α-(*t*-butoxycarbonyl)benzylamine (J.Amer.Chem.Soc.; EN; 117; 44; 1995; 10879-10888; 35 mg, 0.169 mmol) in DCM (2.5 ml) was added 2,6-lutidine (29 mg, 0.268 mmol) and TBTU (56 mg, 0.174 mmol). The reaction mixture was stirred at room temperature for 2.5 hours, then diluted with DCM. The solution was washed with $NaHCO_3$ (aq, sat), water, dried and the solvent was evaporated under reduced pressure. The residue was suspended in ether/petroleum ether and the crystals filtered to give the title compound 85 mg (89%). NMR (500 MHz) 0.79-0.86 (m, 6H), 1.04-1.28 (m, 4H), 1.35-1.56 (m, 11H), 1.60-1.77 (m, 2H), 2.82 (t, 2H), 3.13-3.25 (m, 2H), 3.72 (brs, 2H), 4.35-4.44 (m, 2H), 5.54 (d, 1H), 6.95 (d, 1H), 7.04 (t, 1H), 7.08 (d, 2H), 7.15 (s, 1H), 7.29-7.43 (m, 6H), 7.52 (s, 1H).

Methods 91-94

The following compounds were synthesised by the procedure of Example 104 using the appropriate starting material (source of amine indicated where not commercially available).

Meth	Compound	NMR (500 MHz) and m/z	SM
91		0.77-0.86 (m, 6H), 1.03-1.62 (m, 21H), 2.21 (s, 3H), 2.32 (dd, 1H), 2.54 (dd, 1H), 3.14 (s, 2H), 3.74 (brs, 2H), 4.48-4.53 (m, 1H), 4.60 (dd, 2H), 5.57 (d, 1H), 6.33 (d, 1H), 6.67 (s, 1H), 7.01 (t, 1H), 7.09 (d, 2 H), 7.17-7.40 (m, 21H), 7.50 (d, 2H), 8.10 (d, 1H); m/z 1040.83	Ex 1; [1]
92		0.78-0.86 (m, 6H), 1.05-1.27 (m, 8H), 1.36-1.58 (m, 13H), 1.78 (s, 3H), 2.23 (s, 3H), 2.77-2.92 (m, 2H), 3.19 (s, 2H), 7.75 (brs, 2H), 4.64 (dd, 2H), 4.72-4.77 (m, 1H), 6.68 (s, 1H), 6.81 (d, 1H), 7.01 (t, 1H), 7.09 (d, 2H), 7.27-7.42 (m, 6H), 7.50 (d, 2H), 8.16 (d, 1H); m/z 812.23	Ex 1; [2]
93		0.74-0.81 (m, 6H), 1.0-1.22 (m, 8H), 1.29-1.62 (m, 13H), 2.13 (s, 3H), 2.50-2.64 (m, 2H), 3.14 (s, 2H), 3.69 (brs, 2H), 4.42-4.48 (m, 1H), 4.58 (dd, 2H), 5.45 (d, 1H), 6.13 (d, 1H), 6.62 (s, 1H), 6.96 (t, 1H), 7.04 (d, 2H), 7.17-7.21 (m, 3H), 7.23-7.37 (m, 18H), 7.41 (d, 2H), 8.0 (d, 1H)	Ex 1; Meth 113

94		0.81-0.87 (m, 6H), 1.06-1.29 (m, 8H), 1.39-1.61 (m, 4H), 1.78 (brs, 2H), 1.94 (s, 3H), 2.07-2.17 (m, 1H), 2.20-2.27 (m, 4H), 3.31 (s, 2H), 3.77 (brs, 2H), 3.80 (s, 3H), 4.65 (dd, 2H), 4.76-4.82 (m, 1H), 5.65-5.70 (m, 1H), 6.69 (s, 1H), 7.04 (t, 1H), 7.12 (d, 2H), 7.29-7.44 (m, 7H), 7.52 (d, 2H), 8.16 (d, 1H)	Ex 1

[1] *t*-butyl L-(S-trityl)cysteinate hydrochloride: Org. Pre. Proced. Int.; 1999, 31:571-572

[2] S-methyl-L-cysteine tert-butyl ester: Pestic. Sci.; EN; 45; 4; 1995; 357-362

Method 95

3,3-Dibutyl-4-oxo-5-(4-chlorophenyl)-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

A mixture of 3,3-dibutyl-4-oxo-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO 95/04534; 1.0 g, 2.5 mmol), 4-bromochlorobenzene (4.78 g, 24.98 mmol), copper bromide (36 mg, 0.25 mmol) and potassium carbonate (0.35 g, 2.5 mmol) was refluxed for 20 hours. The reaction mixture was loaded onto a column and the product eluted with 5% EtOAc/petroleum ether (0.8 g, 63% yield). NMR (500 MHz) 0.86-0.92 (m, 6H), 1.16-1.35 (m, 8H), 1.45-1.65 (m, 4H), 3.16 (s, 2H), 3.96 (s, 3H), 7.06-7.10 (m, 2H), 7.19 (s, 1H), 7.29 (s, 1H), 7.33-7.38 (m, 2H). M/z 511.

Method 96

1,1-Dioxo-3,3-dibutyl-4-oxo-5-(4-chlorophenyl)-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a mixture of 3,3-dibutyl-4-oxo-5-(4-chlorophenyl)-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 95; 0.67 g, 1.304 mmol), DCM (34 ml), water (34 ml) and potassium carbonate (0.554 g, 4.0 mmol) was added at 0°C m-chloroperoxybenzoic acid (0.78 g, 3.2 mmol) in one portion. The reaction mixture was stirred at 0 °C for 10 h and then at room temperature for 14 hours. DCM (100 ml) and $NaHCO_3$ (aq, sat; 150 ml) were added. The organic layer was separated, washed with brine, dried and evaporated under reduced pressure to give the title compound 0.68 g (96%). NMR (600 MHz) 0.7-0.92 (m, 6H),

1.0-1.60 (m, 10H), 1.70-1.92 (m, 2H), 2.30-3.7 (m, 2H), 3.99 (s, 3H), 7.16-7.20 (m, 2H), 7.24 (s, 1H), 7.34-7.37 (m, 2H), 7.44 (s, 1H); m/z 543.

Method 97

1,1-Dioxo-3,3-dibutyl-4-oxo-5-(4-chlorophenyl)-7-methylthio-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

Sodium methanethiolate (0.43 g, 6.08 mmol) was added to a solution of 1,1-dioxo-3,3-dibutyl-4-oxo-5-(4-chlorophenyl)-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 96; 0.66 g, 1.22 mmol) in anhydrous DMF (11 ml) under nitrogen. The reaction mixture was stirred at room temperature for 72 hours. The solvent was evaporated under reduced pressure and the residue was extracted with trichloromethane/water. The organic layer was separated , washed with brine, dried and evaporated under reduced pressure. The crude product was purified by column chromatography using DCM as eluent to give the title compound 0.6 g (96%). NMR (500 MHz) 0.80-1.0 (m, 6H), 1.10-1.6 (m, 10H), 1.70-2.0 (m, 2H), 2.28 (s, 3H), 3.37-3.70 (m, 2H), 4.04 (s, 3H), 6.65 (s, 1H), 7.25-7.30 (m, 2H), 7.35-7.42 (m, 3H); m/z 510.4.

Method 98

1,1-Dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3,3-dibutyl-4-oxo-5-(4-chlorophenyl)-7-methylthio-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 97; 0.41 g, 0.79 mmol) in anhydrous ether (15 ml) was added $LiAlH_4$ (0.15 g, 3.97 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 2.5 hours. The reaction flask was cooled to 0°C and the excess $LiAlH_4$ was quenched by adding water (0.3 ml) and 2 M aqueous NaOH (0.3 ml). The mixture was filtered and the filtrate was dried and evaporated under reduced pressure. The crude product was purified by column chromatography using DCM as eluent to give the title compound 0.265 g (68%). NMR (300 MHz) 0.8-0.90 (m, 6H), 1.0-1.47 (m, 12H), 2.33 (s, 3H), 3.17 (s, 2H), 3.70 (s, 2H), 3.93 (s, 3H), 7.03-7.08 (m, 3H), 7.23-7.32 (m, 3H); m/z 496.

Method 99

1,1-Dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 98; 0.26 g 0.52 mmol) in anhydrous DCM (10 ml) was added boron tribromide (2.63 g, 10.48 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 2.5 h. The reaction flask was cooled to 0°C, water (20 ml) and hydrazine monohydrate (0.5 ml) was added. The organic layer was separated, dried and evaporated under reduced pressure. The crude product was purified by column chromatography using DCM/EtOAc (100:5 and 100:10) as eluent to give the title compound 0.20 g (80%). NMR (500 MHz) 0.85 (t, 6H), 1.03-1.28 (m, 8H), 1.35-1.46 (m, 4H), 2.39 (s, 3H), 3.21 (s, 2H), 3.73 (s, 2H), 7.04 (d, 2H), 7.29-7.34 (m, 3H), 7.44 (s, 1H); m/z 482.

Method 100

1,1-Dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

Ethyl bromoacetate (0.101 g, 0.604 mmol) was added to a mixture of 1,1-dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 99; 0.194 g, 0.402 mmol), anhydrous Na_2CO_3 (0.192 g, 1.81 mmol) and tetrabutylammonium bromide in MeCN (5 ml). The reaction mixture was refluxed for 3.5 hours. The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The organic layer was separated, dried and evaporated under reduced pressure. The crude product was purified by column chromatography using DCM/EtOAc (100:5 and 100:10) as eluent to give the title compound 0.197 g (86%). NMR (300 MHz) 0.80-0.89 (m, 6H), 1.0-1.45 (m, 15H), 2.34 (s, 3H), 3.16 (s, 2H), 3.68 (s, 2H), 4.30 (q, 2H), 4.71 (s, 2H), 7.05-7.11 (m, 3H), 7.19 (s, 1H), 7.29-7.35 (m, 2H).

Method 101

1,1-Dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 100; 0.195 g, 0.343 mmol) in ethanol (8 ml) was added NaOH (1.03 mmol in 0.5 ml water). The reaction mixture

was stirred at room temperature for 70 min and then quenched by adding acetic acid (0.3 ml). The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The organic layer was separated, washed with brine, dried and evaporated under reduced pressure to give the title compound 0.169 g (91%). NMR (500 MHz, CD_3OD) 0.86 (t, 6H), 1.11-1.28 (m, 8H), 1.37-1.44 (m, 4H), 2.33 (s, 3H), 3.25 (s, 2H), 3.55 (s, 2H), 4.73 (s, 2H), 7.10-7.15 (m, 3H), 7.26 (s, 1H), 7.28-7.32 (m, 2H).

Method 102

1,1-Dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-[*N*-{(R)-α-[*N'*-(*t*-butoxycarbonylmethyl)carbamoyl]benzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a solution of 1,1-dioxo-3,3-dibutyl-5-(4-chlorophenyl)-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 101; 100 mg, 0.185 mmol) and (R)-α-[*N*-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 86; 56 mg, 0.213 mmol) in DCM (4 ml) was added 2,6-lutidine (40 mg, 0.37 mmol) and TBTU (89 mg, 0.28 mmol). The reaction mixture was stirred at room temperature for 2 hours and then EtOAc was added and the solution washed with water. The organic layer was separated, dried and evaporated under reduced pressure. The crude product was purified by column chromatography using DCM/MeOH (100:3) as eluent to give the title compound 0.129 g (89%). NMR (600 MHz) 0.78-82 (m, 6H), 1.01-1.23 (m, 8H), 1.30-1.42 (m, 13H), 2.32 (s, 3H), 3.10-3.16 (m, 2H), 3.62-3.68 (m, 2H), 3.81-3.87 (m, 1H), 3.95-4.03 (m, 1H), 4.52 (dd, 2H), 5.57 (d, 1H), 6.27 (t, 1H), 7.01-7.07 (m, 3H), 7.20-7.43 (m, 8H), 8.02 (d, 1H).

Method 103

3,3-Dibutyl-4-oxo-5-(4-nitrophenyl)-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 3,3-dibutyl-4-oxo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (synthesised by the procedure of WO9616051 for the corresponding 3-butyl-3-ethyl analogue; 2.9 g, 9.0 mmol) was added p-nitrophenylbromide (24 g, 119 mmol), K_2CO_3 (1.6 g, 12 mmol) and CuI (180 mg, 0.95 mmol). The reaction mixture was heated to 200°C overnight. Then it was allowed to cool down to room temperature and the resulting solid was purified by chromatography using DCM as eluent. The fractions containing the product were concentrated under reduced pressure and EtOH (95%) was added and the insoluble p-nitrophenylbromide was then filtered off. The residue was purified again by flash

chromatography using DCM as eluent. The product was still not pure so the residue was then purified by flash chromatography using EtOAc:heptane, 1:9 as eluent to give the title compound 2.57 g (64%). NMR (600 MHz) 0.77-0.87 (m, 6H), 1.12-1.31 (m, 8H), 1.4-1.6 (m, 4H), 3.09 (brs, 2H), 3.79 (s, 3H), 6.72-6.83 (m, 2H), 7.18-7.27 (m, 3H), 8.3 (d, 2H).

Method 104

1,1-Dioxo-3,3-dibutyl-4-oxo-5-(4-nitrophenyl)-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 3,3-dibutyl-4-oxo-5-(4-nitrophenyl)-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 103; 2.57 g, 5.8 mmol) was added DCM (130 ml), water (130 ml) and K_2CO_3 (2.44 g, 17.6 mmol). The reaction mixture was cooled down to 0°C and m-chloroperoxybenzoic acid (3.42 g, 13.9 mmol) was added in one portion. The reaction was allowed to complete overnight with the temperature slowly rising to room temperature. Then $NaHCO_3$aq (sat) was added and the two layers were separated. The water layer was then extracted three times with DCM. The combined organic layers was dried, filtered and evaporated under reduced pressure. The product was purified by flash chromatography using DCM as eluent to give the title compound 2.4 g (87%). M/z 475.4.

Method 105

1,1-Dioxo-3,3-dibutyl-5-(4-aminophenyl)-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To $LiAlH_4$ (5.76 g, 151 mmol) were added THF (200 ml). The reaction mixture was cooled to 0 °C. and H_2SO_4 (4.06 ml, 76 mmol) were added slowly with a syringe. After the addition was completed the reaction was stirred for 10 minutes. Then 1,1-dioxo-3,3-dibutyl-4-oxo-5-(4-nitrophenyl)-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 104; 2.57 g, 5.06 mmol) dissolved in THF (50 ml) was added at 0°C. After vigorous stirring for 1hour the cooling bath was removed and the reaction was heated to 40°C overnight. Then $Na_2SO_4.10H_2O$ (3-4 teaspoons), water (8 ml), NaOH (15%, aq) (8 ml), water (25 ml) and MeOH (30 ml) were added in that order. The precipitate was removed by filtration and rinsed with DCM/MeOH. The solvent was dried, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using DCM:EtOAc, 9:1 then 3:1 as eluent to give the title compound 0.6 g (27%). M/z 431.3.

Method 106

1,1-Dioxo-3,3-dibutyl-5-(4-aminophenyl)-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-(4-aminophenyl)-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 105; 918 mg, 2.13 mmol) was dissolved in DMF (dry, 20 ml). Sodium thiomethoxide (810 mg, 11.6 mmol) was added. The reaction mixture was treated at 100-120°C for four hours then room temperature overnight. Acetic acid (3 ml) was added and the mixture was flushed with nitrogen (g) and the gas was lead through a flask containing sodium hypochlorite in order to destroy the methyl mercaptan formed. Water was added and the water layer was extracted two times with EtOAc. The combined organic layer was washed with brine, dried, filtered and evaporated under reduced pressure. The mixture contained DMF so toluene and brine was added (everything didn't dissolved). The water layer was extracted two times with toluene. The combined organic layers were washed once with brine. The separation funnel was washed with EtOAc in order to dissolve everything. The toluene and EtOAc solutions were combined, dried, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography using DCM:EtOAc, 7:3 as eluent to give the title compound 0.6 g (27%). M/z 417.4.

Method 107

1,1-Dioxo-3,3-dibutyl-5-(4-*t*-butoxycarbonylaminophenyl)-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-(4-aminophenyl)-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 106; 600 mg, 1.44 mmol was dissolved in THF (10 ml). Di-t-butyldicarbonate (314 mg, 1.44 mmol) was added and the mixture was stirred at 60°C for two hours and room temperature for 3 days. The solvent was evaporated under reduced pressure. EtOAc was added and the organic layer was washed once with $KHSO_4$-solution (0.3M, aq) and once with brine, dried, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography using DCM:EtOAc, 9:1 as eluent to give the title compound 0.597 g (80%). M/z 517.3.

Method 108

1,1-Dioxo-3,3-dibutyl-5-(4-*t*-butoxycarbonylaminophenyl)-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-(4-*t*-butoxycarbonylaminophenyl)-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 107; 597 mg, 1.16 mmol) was dissolved in MeCN (20 ml), K_2CO_3 (480 mg, 3.5 mmol), tetrabutylammoniumbromide (54 mg, 0.17 mmol) and ethyl bromoacetate (167µl, 1.5 mmol) was added. The mixture was heated to 60°C overnight. The solvent was evaporated under reduced pressure. EtOAc and water was added and the water layer was extracted two times with EtOAc. The combined organic layer was washed once with brine, dried, filtered and evaporated under reduced pressure to give the title compound 0.617 g (89%). M/z 603.3.

Method 109

1,1-Dioxo-3,3-dibutyl-5-(4-*t*-butoxycarbonylaminophenyl)-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-(4-*t*-butoxycarbonylaminophenyl)-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 108; 607 mg, 1.0 mmol) was dissolved in THF (6 ml), H_2O (6 ml) and LiOH (127 mg, 3.02 mmol, monohydrate) was added. The mixture was stirred for 1 hour. The mixture was poured into water and the solution was acidified using HCl-solution (aq, 1M). The water layer was extracted two times with EtOAc. The combined organic layer was wash once with brine, dried, filtered and evaporated under reduced pressure to give the title compound 0.571 g (99%). M/z 575.4.

Method 110

1,1-Dioxo-3,3-dibutyl-5-(4-aminophenyl)-8-[*N*-(α-(R)-methoxycarbonylbenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-(4-*t*-butoxycarbonylaminophenyl)-8-[*N*-(α-(R)-methoxycarbonylbenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 45; 562 mg, 0.78 mmol) was dissolved in DCM (18 ml). TFA (4 ml) was added and the reactions mixture was stirred for 3 hours. The solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and NaOH solution (1M, aq). The aqueous phase was extracted one more time with EtOAc. The combined organic layer was wash with brine,

dried, filtered and evaporated under reduced pressure to give the title compound 440 mg (91%). M/z 622.5.

Method 111

1,1-Dioxo-3,3-dibutyl-5-[4-(*N'*-*t*-butylureido)phenyl]-8-[*N*-(α-(R)-methoxycarbonylbenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-(4-aminophenyl)-8-[*N*-(α-(R)-methoxycarbonylbenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 110; 40 mg, 0.064 mmole) was dissolved in DMF (1 ml). *t*-Butyl isocyanate (8.3µl, 0.071 mmol) was added. The reaction mixture was stirred at 60-80°C overnight. Tert-butyl isocyanate (20µl, 0.171 mmol) was added. The reaction mixture was stirred at 60-80°C for 2 days and then room temperature for a few days. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title product, 30 mg (65%). M/z 721.6.

Method 112

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-(α-methoxycarbonylmethyl-benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

The title compound was synthesized from 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 17) and methyl 3-amino-3-phenylpropanoate (Helv.Chim.Acta; EN; 83; 6; 2000; 1256 – 1267) by the procedure of Example 56. M/z 639.4.

Method 113

t-Butyl D-(S-trityl)cysteinate hydrochloride

To a vigorously stirred suspension of S-trityl-D-cysteine (2.0 g, 5.5 mmol) in *t*-butyl acetate (35 ml), 70% $HClO_4$ (1.6 ml) was added dropwise. The reaction mixture was stirred at room temperature for 70 min and EtOAc (50 ml) and $NaHCO_3$ (aq, sat) to pH 8.0 were added. The precipitate, unreacted S-trityl-D-cysteine was filtered off. The organic layer was separated, washed with 0.5 M HCl (2 x 75 ml) and brine, dried and evaporated to give the title compound 2.02 g (81%). NMR (500 MHz): 1.43 (s, 9H), 2.83-2.95 (m, 2H), 3.41-3.48 (m, 1H), 7.21-7.37 (m, 9H), 7.46 (d, 6H).

product was eluted with DCM/EtOAc (90:10). 0.480 g (97%) of the title compound was obtained. NMR (300 MHz) 0.7-0.85 (m, 6H), 1.0-1.7 (m, 11H), 3.1-3.3 (m, 2H), 3.6-3.8 (m, 2H), 4.3 (q, 2H), 4.6 (s, 2H), 6.9-7.3 (m, 7H), 7.5 (d, 1H).

Method 117

1,1-Dioxo-3,3-dipropyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a suspension of 1,1-dioxo-3,3-dipropyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (prepared according to WO 96/16051 using identical synthetic steps except that the starting material was chosen to give the dipropyl compound instead of the butyl/ethyl compound; 0.756 g, 1.62 mmol) in DMF (40 ml) was added NaSMe (0.605 g, 8,20 mmol, 95 %), and the mixture was stirred over night 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 ($MgSO_4$) and concentrated. The title compound was obtained in 0.665 g (98 %). NMR (500 MHz, DMSO-d_6) 0.60-0.80 (m, 6H), 1.05-1.50 (m, 8H), 2.15 (s, 3H), 3.20 (s, 2H), 3.65 (brs, 2H), 6.65 (s, 1H), 6.75-6.95 (m, 3H), 7.10-7.25 (m, 2H), 7.30 (s, 1H), 10.5 (s, 1H).

Method 118

1,1-Dioxo-3,3-dipropyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a suspension of 1,1-dioxo-3,3-dipropyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 117; 0.665 g, 1.58 mmol) in MeCN (10 ml) was added ethyl bromoacetate (0.262 ml, 2.35 mmol), tetrabutylammonium bromide (0.051 g, 0.158 mmol) and sodium carbonate (0.870 g, 8.21 mmol). 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 ($MgSO_4$) and concentrated. The residue was filtered through a short silica column (DCM:EtOAc-9:1), concentrated and dissolved in EtOH (10 ml). A solution of NaOH (0.25 g, 6.25 mmol) in water (1 ml) was added and the solution was stirred over night at room temperature. 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 washed with brine and concentrated. The crude product was purified by

Method 114

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

To a suspension of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 26; 12.85 g, 28.71 mmol) in MeCN (150 ml) was added ethyl bromoacetate (3.85 ml, 34.6 mmol), tetrabutylammonium bromide (0.925 g, 2.869 mmol) and sodium carbonate (12.85 g, 121.2 mmol). The mixture was heated under reflux for 5 hours. The solvent was removed under reduced pressure and the residue was partitioned between DCM and 0.5 M HCl. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. Chromatography using DCM/EtOAc (9:1) as eluent gave the desired product (15.45 g) as a tan oil. NMR 0.70-0.85 (m, 6H), 1.00-1.55 (m, 15H), 2.15 (s, 3H), 3.10 (s, 2H), 3.70 (bs, 2H), 4.25 (q, 2H), 4.70 (s, 2H), 6.65 (s, 1H), 6.90-7.30 (m, 6H).

Method 115

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 116; 0.48 g, 1.04 mmol) was dissolved in ethanol (10 ml). NaOH (0.30 g, 7.5 mmol) was added and the mixture was refluxed for 30 min. Acetic acid (1 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The DCM layer was separated, dried and evaporated. 0.44 g (97%) of the title compound was obtained. NMR (300 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 8H), 3.1-3.3 (m, 2H), 3.5-3.8 (m, 2H), 4.6 (s, 3H), 6.8-7.3 (m, 7H), 7.5 (s, 1H).

Method 116

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepin (WO9616051; 0.40 g, 1.07 mmol), ethyl bromoacetate (0.23 g, 1.38 mmol), sodium carbonate (0.50 g, 4.7 mmol) and tetrabutylammonium bromide (30 mg, 0.093 mmol) were added to MeCN (10 ml). The mixture was refluxed for 18 hours and then evaporated under reduced pressure. The residue was extracted with DCM/water. The DCM layer was separated and evaporated under reduced pressure. The residue was purified by column chromatography. The

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	10 mg/ml
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

(g): Injection III	(1 mg/ml, buffered to pH 6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for Example to provide a coating of cellulose acetate phthalate.

preparative HPLC using a MeCN/ammonium acetate buffer to give the title compound in 0.441 g (58 %) as a white solid. NMR (DMSO-d_6) 0.55-0.75 (m, 6H), 1.05-1.50 (m, 8H), 2.15 (s, 3H), 3.20 (s, 2H), 3.65 (brs, 2H), 4.50 (s, 2H), 6.65 (s, 1H), 6.80-7.00 (m, 3H), 7.15 (s, 1H), 7.15-7.25 (m, 2H).

Example 121

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	**mg/tablet**
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	**mg/tablet**
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	**mg/tablet**
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

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)$_2$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^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};

D is -O-, -N(R^a)-, -S(O)$_b$- or -CH(R^a)-; wherein R^a 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};

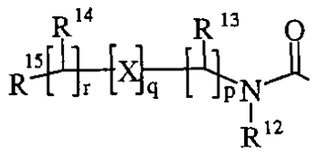
R^7 is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{18};

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, sulpho, sulphino, phosphono, tetrazolyl, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) or -P(O)(OR^c)(R^d) wherein R^c and R^d are independently selected from C_{1-6}alkyl; or R^{11} is a group of formula (**IB**):



(IB)

wherein:

X is –N(R^q)-, -N(R^q)C(O)-, -O-, and -S(O)$_a$-; wherein a is 0-2 and R^q is hydrogen or C_{1-4}alkyl;

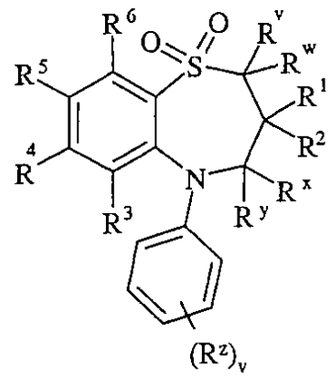
R^{12} is hydrogen or C_{1-4}alkyl;

R^{13} and R^{14} are independently selected from hydrogen, C_{1-4}alkyl, carbocyclyl, heterocyclyl or R^{23}; wherein said C_{1-4}alkyl, carbocyclyl or heterocyclyl may be independently optionally substituted by one or more substituents selected from R^{20};

Claims

What we claim is:

1. A compound of formula (I):



(I)

wherein:

$\mathbf{R^v}$ and $\mathbf{R^w}$ are independently selected from hydrogen or C_{1-6}alkyl;

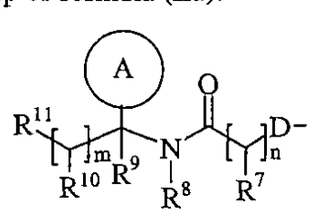
$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from C_{1-6}alkyl;

$\mathbf{R^x}$ and $\mathbf{R^y}$ are independently selected from hydrogen or C_{1-6}alkyl, or one of R^x and R^y is hydrogen or C_{1-6}alkyl and the other is hydroxy or C_{1-6}alkoxy;

$\mathbf{R^z}$ 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)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, ureido, *N'*-(C_{1-6}alkyl)ureido, *N*-(C_{1-6}alkyl)ureido, *N',N'*-(C_{1-6}alkyl)$_2$ureido, *N'*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkyl)ureido, *N',N'*-(C_{1-6}alkyl)$_2$-*N*-(C_{1-6}alkyl)ureido, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl;

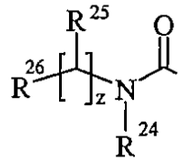
v is 0-5;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula (IA):



(IA)

R^{15} is carboxy, sulpho, sulphino, phosphono, tetrazolyl, -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 C_{1-6}alkyl; or R^{15} is a group of formula (IC):



(IC)

wherein:

R^{24} is selected from hydrogen or C_{1-4}alkyl;

R^{25} is selected from hydrogen, C_{1-4}alkyl, carbocyclyl, heterocyclyl or R^{27}; wherein said C_{1-4}alkyl, carbocyclyl or heterocyclyl may be independently optionally substituted by one or more substituents selected from R^{28};

R^{26} is selected from carboxy, sulpho, sulphino, phosphono, tetrazolyl, -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;

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;

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

z is 0-3; wherein the values of R^{25} may be the same or different;

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)$_2$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};

R^{19}, R^{20}, R^{23}, R^{27} and R^{28} 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_{1-6}alkyl; wherein R^{19}, R^{20}, R^{23}, R^{27} and R^{28} 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, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl;

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

2. A compound of formula (I) according to claim 1 wherein R^v and R^w are both hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

3. A compound of formula (I) according to either of claims 1 or 2 wherein R^1 and R^2 are independently selected from ethyl, propyl or butyl or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

4. A compound of formula (I) according to any one of claims 1 to 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) according to any one of claims 1 to 4 wherein R^z is selected from halo, amino, C_{1-6}alkyl, C_{1-6}alkoxycarbonylamino or *N'*-(C_{1-6}alkyl)ureido or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

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

7. A compound of formula (I) according to any one of claims 1 to 6 wherein R^3 is hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

8. A compound of formula (I) according to any one of claims 1 to 7 wherein the R^4 or R^5 that is not the group of formula (IA) is selected from hydrogen, halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that R^4 or R^5 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy, carboxy and *N,N*-(C_{1-4}alkyl)$_2$amino or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

9. A compound of formula (I) according to any one of claims 1 to 8 wherein R^5 is a group of formula (IA) (as depicted in claim 1) and R^4 is methylthio or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

10. A compound of formula (I) according to any one of claims 1 to 9 wherein R^6 is hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

11. A compound of formula (I) according to any one of claims 1 to 10 wherein in the group of formula (IA):

D is -O- or -S-;

Ring A is phenyl, thienyl or indolyl; wherein Ring A is optionally substituted by one or more substituents selected from halo, hydroxy, methoxy or trifluoromethyl;

R^7 is hydrogen, methyl or phenyl;

R^8 is hydrogen or methyl;

R^9 is hydrogen or methyl;

R^{10} is hydrogen;

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

R^{11} is carboxy, -P(O)(OH)(OEt) or a group of formula (IB) (as depicted in claim 1); or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

12. A compound of formula (I) according to any one of claims 1 to 11 wherein in the group of formula (IB):

R^{12} is hydrogen or methyl;

R^{13} is hydrogen, methyl, ethyl, butyl or phenyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; R^{20} is hydroxy, methylthio, methoxy, amino, imidazolyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more hydroxy; R^{23} is carboxy;

X is –NH- or –NHC(O)-;

R^{14} is selected from hydrogen, methyl or phenyl; wherein said methyl or phenyl may be optionally substituted by one or more substituents selected from hydroxy;

R^{15} is carboxy, sulpho, 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 methyl or ethyl or R^{15} is a group of formula (**IC**) (as depicted in claim 1);

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

q is 0-1; and

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

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

13. A compound of formula (**I**) according to any one of claims 1 to 12 wherein in the group of formula (**IC**):

R^{24} is hydrogen;

R^{25} is hydrogen;

R^{26} is carboxy; and

z is 1;

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

14. A compound of formula (**I**) (as depicted in claim 1) wherein:

R^v and R^w are both hydrogen;

R^1 and R^2 are independently selected from C_{1-4}alkyl;

R^x and R^y are both hydrogen;

R^z is selected from halo, amino, C_{1-6}alkyl, C_{1-6}alkoxycarbonylamino or *N'*-(C_{1-6}alkyl)ureido;

v is 0 or 1;

R^3 and R^6 are hydrogen;

one of R^4 and R^5 is a group of formula (**IA**) (as depicted in claim 1) and the other is selected from hydrogen, halo, C_{1-4}alkoxy or C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2; wherein that

R^4 or R^5 may be optionally substituted on carbon by one or more R^{16}; wherein R^{16} is independently selected from hydroxy, carboxy and *N,N*-(C_{1-4}alkyl)$_2$amino;

D is -O- or -S-;

$\mathbf{R^7}$ is hydrogen, methyl or phenyl;

$\mathbf{R^8}$ is hydrogen or methyl;

Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from R^{17}; wherein R^{17} is selected from halo, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy; wherein R^{17} may be optionally substituted on carbon by one or more R^{21}; wherein R^{21} is selected from halo;

$\mathbf{R^9}$ is hydrogen or methyl;

$\mathbf{R^{10}}$ is hydrogen;

$\mathbf{R^{11}}$ is carboxy, -P(O)(OH)(OR^c) wherein R^c is selected from C_{1-4}alkyl or a group of formula **(IB)** (as depicted in claim 1);

$\mathbf{R^{12}}$ is hydrogen or methyl;

X is –NH- or –NHC(O)-;

$\mathbf{R^{13}}$ is hydrogen, C_{1-4}alkyl, carbocyclyl or R^{23}; wherein R^{13} is optionally substituted by one or more substituents selected from R^{20}; wherein R^{20} is hydroxy, C_{1-4}alkyl$S(O)_a$ wherein a is 0, C_{1-4}alkoxy, amino, carbocyclyl, heterocyclyl or mercapto; wherein R^{20} may be independently optionally substituted on carbon by one or more R^{22}; R^{22} is selected from hydroxy; and R^{23} is carboxy;

$\mathbf{R^{14}}$ is selected from hydrogen, C_{1-4}alkyl or carbocyclyl; wherein said C_{1-4}alkyl or carbocyclyl may be optionally substituted by one or more substituents selected from R^{20}; and R^{20} is hydroxy;

$\mathbf{R^{15}}$ is carboxy, sulpho, 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 C_{1-4}alkyl or R^{15} is a group of formula **(IC)** (as depicted in claim 1);

$\mathbf{R^{24}}$ is hydrogen;

$\mathbf{R^{25}}$ is hydrogen;

$\mathbf{R^{26}}$ is carboxy;

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;

n is 1-2; wherein the values of R^7 may be the same or different;

z is 0-1; wherein the values of R^{25} may be the same or different;

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

15. A compound of formula (I) (as depicted in claim 1) selected from:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

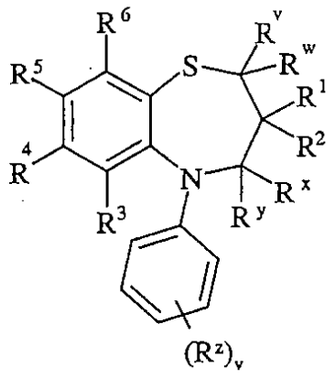
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; and

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

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

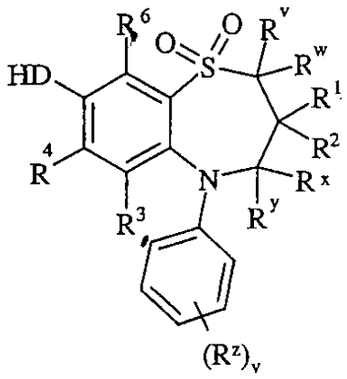
16. A process for preparing a compound of the formula **(I)** as claimed in any one of claims 1 to 15 which comprises of:-

Process 1): oxidising a benzothiazepine of formula **(II)**:

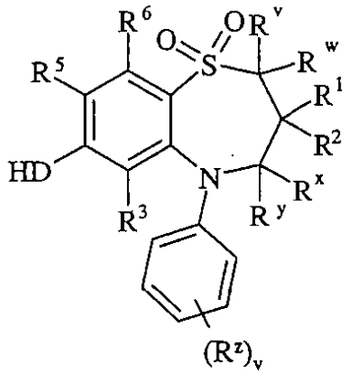


(II);

Process 2): for compounds of formula (I) wherein D is -O-,-NR^a or -S-; reacting a compound of formula **(IIIa)** or **(IIIb)**:

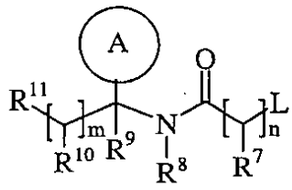


(IIIa)



(IIIb)

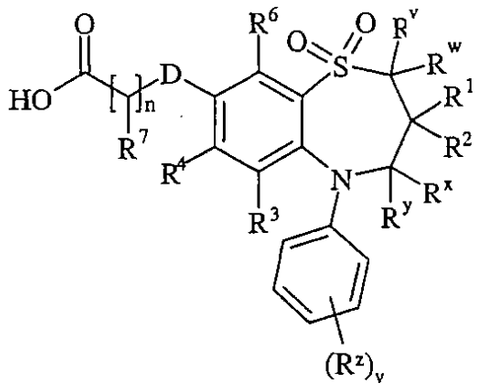
with a compound of formula **(IV)**:



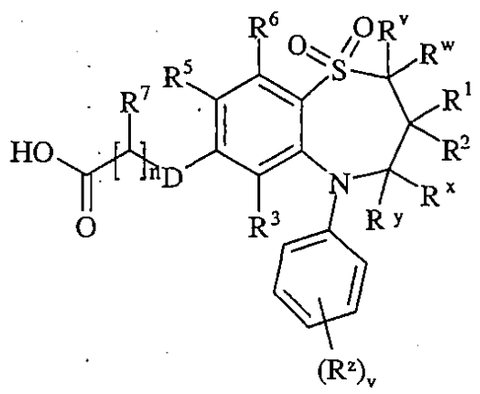
(IV)

wherein L is a displaceable group;

Process 3): reacting an acid of formula **(Va)** or **(Vb)**:

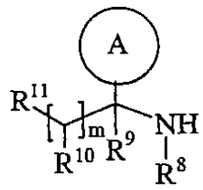


(Va)



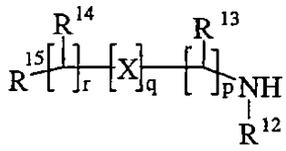
(Vb)

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



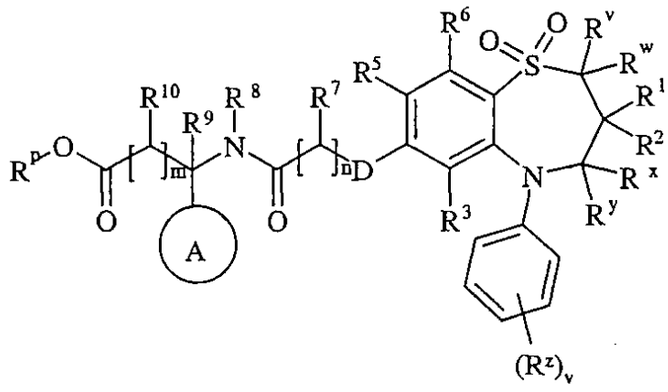
(VI);

Process 4): 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 (VII):



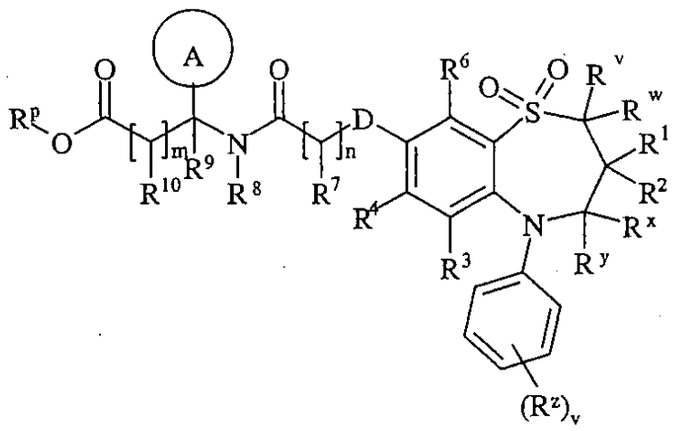
(VII)

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



(VIIIa)

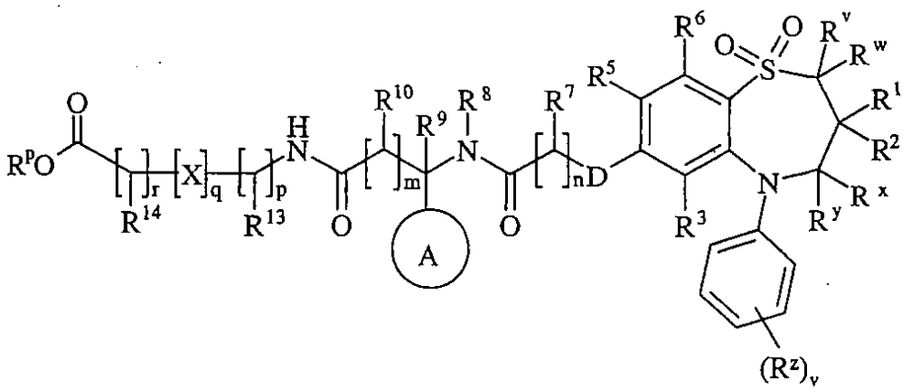
or (VIIIb):



(VIIIb)

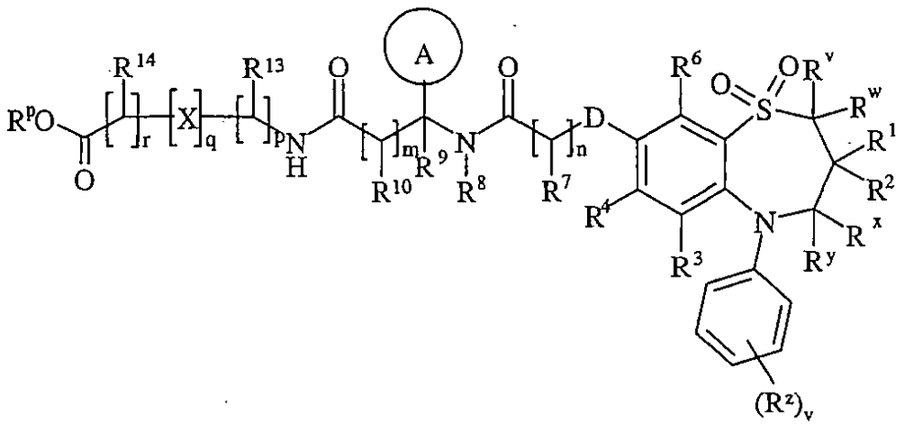
wherein R^p is C_{1-4}alkyl;

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 (**IXa**):



(IXa)

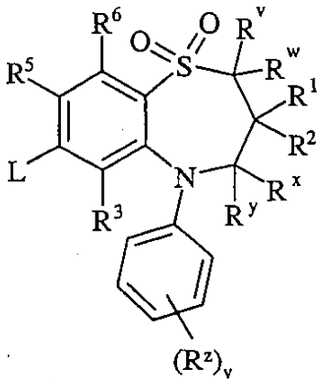
or (**IXb**):



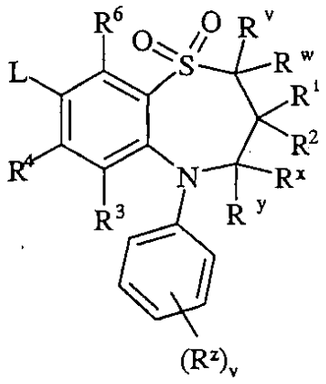
(IXb)

wherein R^p is C_{1-4}alkyl;

Process 7) for compounds of formula **(I)** wherein one of R^4 and R^5 are independently selected from C_{1-4}alkylthio optionally substituted on carbon by one or more R^{16}; reacting a compound of formula **(Xa)** or **(Xb)**:



(Xa)



(Xb)

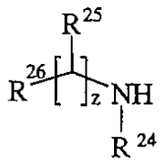
wherein L is a displaceable group; with a thiol of formula **(XI)**:

R^y-H

(XI)

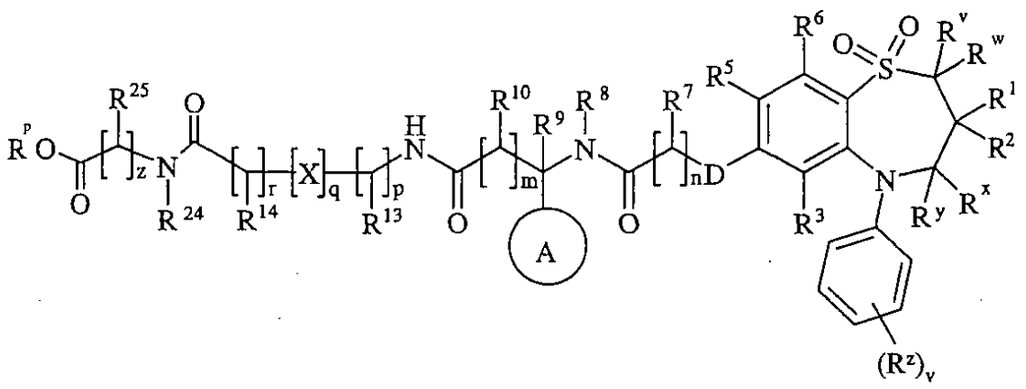
wherein R^y is C_{1-4}alkylthio optionally substituted on carbon by one or more R^{16};

Process 8) for compounds of formula **(I)** wherein R^{15} is a group of formula **(IC)** reacting a compound of formula **(IXa)** or **(IXb)** wherein R^p is hydrogen with a compound of formula **(XII)**:



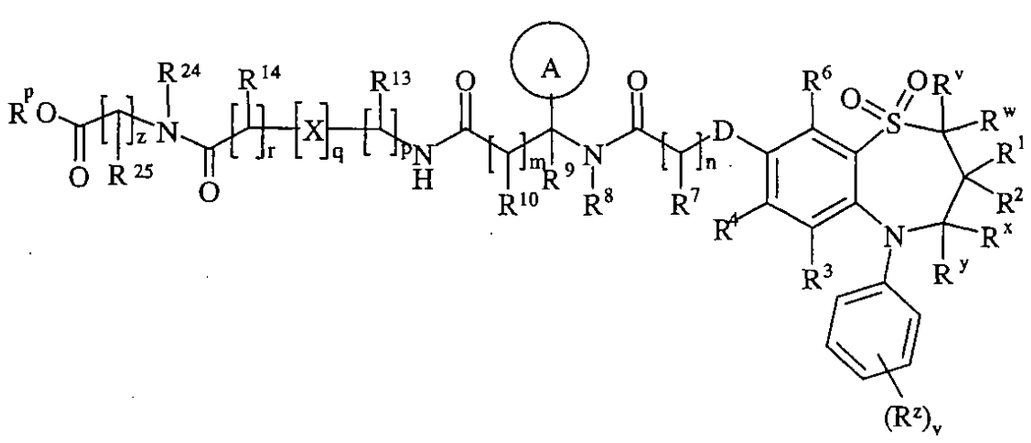
(XII)

Process 9): for compounds of formula **(I)** wherein R^{11} is a group of formula **(IB)** and R^{15} is a group of formula **(IC)** and R^{26} is carboxy; deprotecting a compound of formula **(XIIIa)**:



(XIIIa)

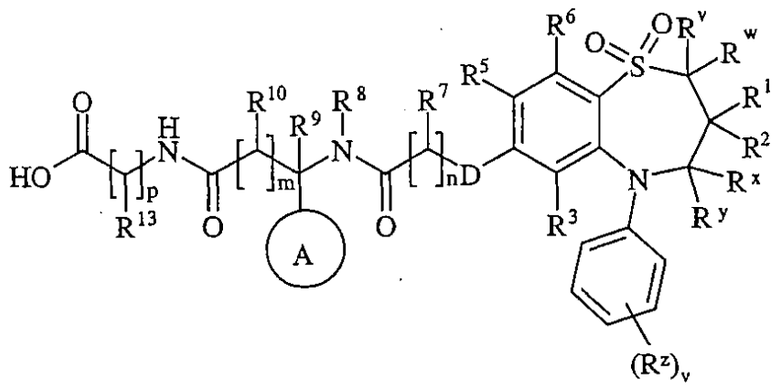
or **(XIIIb)**:



(XIIIb)

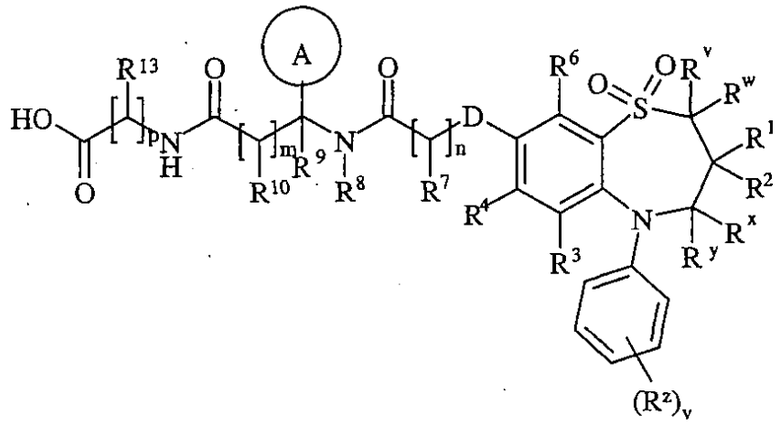
and R^p is C_{1-4}alkyl;

Process 10): for compounds of formula **(I)** wherein X is $-N(R^q)C(O)-$; reacting a compound of formula **(XIVa)**:



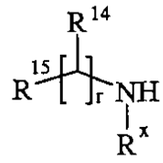
(XIVa)

or **(XIVb)**:



(XIVb)

with a compound of formula **(XV)**:



(XV)

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.

17. 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 15 for use as a medicament.

18. 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 15 for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

19. 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 claimed in any one of claims 1 to 15 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

20. 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, as claimed in any one of claims 1 to 15.

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 15, in association with a pharmaceutically-acceptable diluent or carrier.

22. 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 15, 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.

23. 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 15, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.

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 15, 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.

25. A composition according to claim 22 or claim 24 wherein the HMG Co-A reductase inhibitor is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

26. A composition according to claim 22 or claim 24 wherein the HMG Co-A reductase inhibitor is rosuvastatin, or a pharmaceutically acceptable salt thereof.

27. 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 15 and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

28. A composition according to claim 27 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.

29. A compound of formula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** or **(XIIIb)** (as depicted in claim 16) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. 51

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 100248/WO

Box No. I TITLE OF INVENTION

CHEMICAL COMPOUNDS

Box No. II APPLICANT ☐ This person is also inventor

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ASTRAZENECA AB
151 85 Sodertalje
SWEDEN

Telephone No. +44-1625-516485

Facsimile No. +44-1625-510752

Teleprinter No. 669095/669388

Applicant's registration No. with the Office

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London
W1Y 6LN
United Kingdom

This person is:
☒ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV 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 ☐ common representative

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.)*

BRYANT, Tracey et al
ASTRAZENECA
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire, SK10 4TG, United Kingdom

Telephone No. (01625) 513228

Facsimile No. (01625) 510752

Teleprinter No. 669095/669388

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.

85

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

STARKE, Ingemar
S-431 83 Molndal
SWEDEN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DAHLSTROM, Mikael
S-431 83 Molndal
SWEDEN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: FI

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BLOMBERG, David
S-431 83 Molndal
SWEDEN

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Box No.V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AG** Antigua and Barbuda
☒ **AL** Albania
☒ **AM** Armenia
☒ **AT** Austria
☒ **AU** Australia
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina
☒ **BB** Barbados
☒ **BG** Bulgaria
☒ **BR** Brazil
☒ **BY** Belarus
☒ **BZ** Belize
☒ **CA** Canada
☒ **CH** & LI Switzerland and Liechtenstein
☒ **CN** China
☒ **CO** Colombia
☒ **CR** Costa Rica
☒ **CU** Cuba
☒ **CZ** Czech Republic
☒ **DE** Germany
☒ **DK** Denmark
☒ **DM** Dominica
☒ **DZ** Algeria
☒ **EE** Estonia
☒ **ES** Spain
☒ **FI** Finland
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia
☒ **GH** Ghana
☒ **GM** Gambia
☒ **HR** Croatia
☒ **HU** Hungary
☒ **ID** Indonesia
☒ **IL** Israel
☒ **IN** India
☒ **IS** Iceland
☒ **JP** Japan
☒ **KE** Kenya
☒ **KG** Kyrgyzstan
☒ **KP** Democratic People's Republic of Korea
☒ **KR** Republic of Korea
☒ **KZ** Kazakhstan
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco
☒ **MD** Republic of Moldova
☒ **MG** Madagascar
☒ **MK** The former Yugoslav Republic of Macedonia
☒ **MN** Mongolia
☒ **MW** Malawi
☒ **MX** Mexico
☒ **MZ** Mozambique
☒ **NO** Norway
☒ **NZ** New Zealand
☒ **PL** Poland
☒ **PT** Portugal
☒ **RO** Romania
☒ **RU** Russian Federation
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia
☒ **SK** Slovakia
☒ **SL** Sierra Leone
☒ **TJ** Tajikistan
☒ **TM** Turkmenistan
☒ **TR** Turkey
☒ **TT** Trinidad and Tobago
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine
☒ **UG** Uganda
☒ **US** United States of America
☒ **UZ** Uzbekistan
☒ **VN** Viet Nam
☒ **YU** Yugoslavia
☒ **ZA** South Africa
☒ **ZW** Zimbabwe

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ ....EC Ecuador ☒ ..OM Oman ☒ ..TN Tunisia
☒ ....PH Philippines ☒ ..ZM Zambia ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. 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. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

   (i) *if **more than two persons are to be indicated as applicants and/or inventors** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

   (ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

   (iii) *if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America**: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III," (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

   (iv) *if, in addition to the agent(s) indicated in Box No. IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

   (v) *if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication **"patent of addition,"** or **"certificate of addition,"** or if, in Box No. V, the name of the United States of America is accompanied by an indication **"continuation"** or **"continuation-in-part"**: in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

   (vi) *if, in Box No. VI, there are **more than five earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

2. *If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

Continuation of Box II:

ASTRAZENECA AB is applicant for the purposes of:

All designated states except MG, Madagascar and US, United States of America

Continuation of Box III:

ASTRAZENECA UK LIMITED is applicant for the purpose of:

MG, Madagascar

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Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 21 December 2000 (21/12/2000)	0004811-6	SE		
item (2) 24 May 2001 (24/05/01)	0112592.1	GB		
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* . . . .

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EPO

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No, VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i) Declaration as to the identity of the inventor :

☐ Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :

☐ Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :

☐ Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America) :

☐ Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :

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Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application **contains**:

(a) the following number of **sheets in paper form**:

request (including declaration sheets)	:	06
description (excluding sequence listing part)	:	140
claims	:	17
abstract	:	01
drawings	:	00
Sub-total number of sheets	:	164
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	164

(b) sequence listing part of description filed in **computer readable form**

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☒ original separate power of attorney	:	1
3. ☐ original general power of attorney	:	
4. ☐ copy of general power of attorney; reference number, if any:	:	
5. ☐ statement explaining lack of signature	:	
6. ☒ priority document(s) identified in Box No. VI as item(s): 1 & 2	:	2
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:	
10. ☐ other *(specify)*:	:	

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X 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 request).

T. Bryant

BRYANT, Tracey et al, Agent for the Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

90

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: 100248/WO

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/GB01/05554	17 December 2001 (17.12.01)	21 December 2000 (21.12.00)

Title of invention

1,5 BENZOTHIAZEPINES AND THEIR USE AS ANTIHYPERLIPIDEMICS

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
151 85 Södertälje
Sweden

Telephone No.: +44 1625 516485
Facsimile No.: +44 1625 510752
Teleprinter No.: 669095/669388
Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
SE	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
W1Y 6LN
United Kingdom

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
GB	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
S-431 83 Molndal
SWEDEN

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
SE	SE

☒ Further applicants are indicated on a continuation sheet.

International application No.
PCT/GB01/05554

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
S-431 83 Molndal
SWEDEN

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
FI	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
S-431 83 Molndal
SWEDEN

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
SE	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:

☐ Further applicants are indicated on another continuation sheet.

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International application No.
PCT/GB01/05554

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ 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 earlier.

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.)*

BRYANT, Tracey et al
ASTRAZENECA
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire, SK10 4TG
United Kingdom

Telephone No.
(01625) 513228

Facsimile No.
(01625) 510752

Teleprinter No.
669095/669388

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 filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ 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:**

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Sheet No. 4.

International application No.
PCT/GB01/05554

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:			For International Preliminary Examining Authority use only: received	not received
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	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(specify)*:

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, Agent for the Applicants

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:

PATENT COOPERATION TREATY

LCP
94

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

11 JUL 2002

CODE	DATE	NTD

To:
Bryant, Tracey
ASTRAZENECA
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
GRANDE BRETAGNE

ANKOM 09 JUL 2002
DATA ENTERED
FINAL CHECK

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	05/07/2002

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
~~200248/WO~~ 100248	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 01/05554	17/12/2001	21/12/2000

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.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27 (5), 33 (5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	SMITH K M Tel. (+49-89) 2399 2828

EUROPÄISCHES PATENTAMT · EUROPEAN PATENT OFFICE · OFFICE EUROPÉEN DES BREVETS

Form PCT/IPEA/416 (28/06/2002) P20473

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
200248/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 01/05554	17/12/2001	21/12/2000
International Patent Classification (IPC) or national classification and IPC		
C07D281/10		
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

Date of submission of the demand	Date of completion of this report
11/06/2002	02/07/2002
Name and mailing address of the IPEA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	VERHULST W Tel. (+49-89) 2399 2828

EUROPÄISCHES PATENTAMT - EUROPEAN PATENT OFFICE - OFFICE EUROPÉEN DES BREVETS

Form PCT/IPEA/409 (cover sheet) (July 1998)

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.

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

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha Internacional de Publicación
27 de Junio de 2002 (27.06.2002)

(10) Número Internacional de Publicación

PCT

WO 02/50051 A1

(51) Clasificación Internacional de Patentes[7]: C07D 281/10, 417/12, C07F 9/6536, C07K 5/065, 5/087, A61K 31/554, 31/675, 38/05, 38/06, A61P 3/06

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(22) Fecha de Presentación Internacional:
17 de Diciembre de 2001 (17.12.2001)

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0112592.1 24 de Mayo de 2001 (24.05.2001) GB

(71) Solicitante *(para todos los países destinatarios con excepción de MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(71) Solicitante *(para MG únicamente)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London WIY 6LN (GB)

(72) Inventores, e
(75) Inventores/Solicitantes (para *US únicamente)*: **STARKE, Ingemar** [SE/SE]; S-431 83 Molndal (SE). **DAHLSTROM, Mikael** [FI/SE]; S-431 83 Moindal (SE). **BLOMBERG, David** [SE/SE]; Pepparedsleden 1, S-431 83 Molndal (SE)

(74) Agentes: **BRIANT, Tracey**; AstraZeneca, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire, SK 10 4TG (GB)

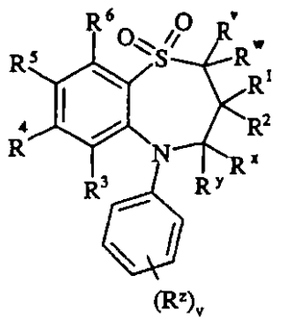
(81) Países destinatarios *(nacional)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT,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

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

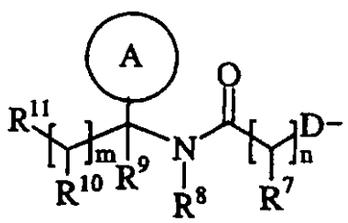
publicada:
- *con informe internacional de búsqueda*

Para códigos de dos letras y otras abreviaturas, remítase a la "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.

(54) Título: COMPUESTOS QUÍMICOS



(I)



(IA)

(57) Extracto: La presente invención se relaciona con compuestos de la fórmula (I): (en donde grupos variables son como se definen en ella) sus sales, solvatos, solvatos de dichas sales y profármacos de aceptación farmacéutica, y su uso como inhibidores de transporte de ácido biliar ileal (IBAT) en el tratamiento de hiperlipidemia. Asimismo se describen procesos para su manufactura y composiciones farmacéuticas que los contienen.

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1,5 BENZOTIAZEPINAS Y SU USO COMO ANTIHIPERLIPIDÉMICOS

Esta invención se relaciona con derivados de benzotiazepina, o sus sales de aceptación farmacéutica, solvatos, solvatos de dichas sales y profármacos. Estas benzotiazepinas poseen actividad inhibidora de transporte de ácido biliar ileal (IBAT) y, por consiguiente, tienen utilidad en el tratamiento de estados patológicos asociados con condiciones hiperlipidémicas 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, 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 hiperlipidémicas 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 ligadores de ácido biliar, tales como resinas. Ligadores de ácido biliar de uso frecuente 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 inhibidor de 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 hypocholeslerolaemic properties", Biochemica 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 hiperlipidémicas.

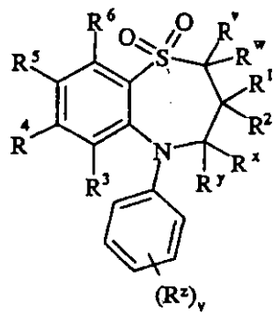
Compuestos que poseen dicha actividad inhibidora IBAT se han descrito, véase por ejemplo compuestos descritos en WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/OS484, WO 96/16051, WO 97/33882, WO 98/38182, WO 99/35135, WO 9S/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, 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 0 864 582.

Un aspecto adicional de esta invención se relaciona con el uso de los compuestos de la invención en el tratamiento de condiciones dislipidémicas 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, falla cardiaca, enfermedades cardiacas coronarias, enfermedades cardiovasculares, infarto del miocardio, angina pectoris, enfermedades vasculares periféricas, inflamación de tejidos cardiovasculares tales como corazón, válvulas, vasculatura, arterias y venas, aneurismas, estenosis, restenosis, placas vasculares, estrías adiposas

vasculares, leucocito, monocitos y/o infiltrado de macrófago, engrosamiento intimal, adelgazamiento medial, trauma infeccioso y quirúrgico y trombosis vascular, apoplejía y ataques isquémicos transitorios.

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

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



(I)

en donde:

$\mathbf{R^v}$ y $\mathbf{R^w}$ se seleccionan independientemente de hidrógeno o C_{1-6}alquilo;

$\mathbf{R^1}$ y $\mathbf{R^2}$ se seleccionan independientemente de hidrógeno o C_{1-6}alquilo;

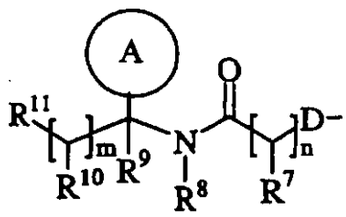
$\mathbf{R^x}$ y $\mathbf{R^y}$ se seleccionan independientemente de hidrógeno o C_{1-6}alquilo, o uno de R^x y R^y es hidrógeno o C_{1-6}alquilo y el otro es hidroxi o C_{1-8}alcoxi;

$\mathbf{R^z}$ se selecciona de halo, nitro, ciano, hidroxi, amino, carboxi, 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}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, ureido, *N'*-(C_{1-6}alquil)ureido, *N*-(C_{1-6}alquil)ureido, *N',N'*-(C_{1-6}alquil)$_2$ureido, *N'*-(C_{1-6}alquil)-*N*-(C_{1-}

$_{6}$alquil)ureido, *N',N'*-(C_{1-6}alquil)$_2$-*N*-(C_{1-6}alquil)ureido, *N'*-(C_{1-6}alquil)sulfamoilo y *N,N*-(C_{1-6}alquil)$_2$sulfamoilo;

v es 0-5;

uno de $\mathbf{R^4}$ y $\mathbf{R^5}$ es un grupo de fórmula **(IA)**:



(IA)

$\mathbf{R^3}$ y $\mathbf{R^6}$ y los demás de $\mathbf{R^4}$ y $\mathbf{R^5}$ se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, 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}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N,N*-(C_{1-4}alquil)$_2$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 más R^{16};

D es -O-, -N(R^a)-, -S(O)$_b$- o -CH(R^3)-; 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};

$\mathbf{R^7}$ 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};

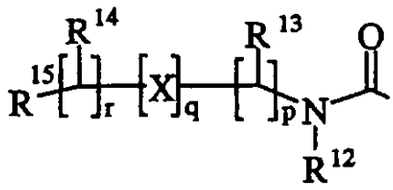
$\mathbf{R^8}$ es hidrógeno o C_{1-4}alquilo;

$\mathbf{R^9}$ es hidrógeno o C_{1-4}alquilo;

$\mathbf{R^{10}}$ 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};

$\mathbf{R^{11}}$ es carboxi, sulfo, sulfino, fosfono, tetrazolilo, -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 fórmula **(IB):**



(IB)

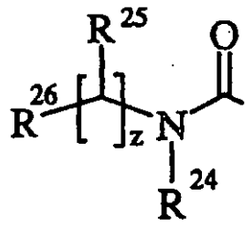
en donde:

X es $-N(R^q)-$, $-N(R^q)C(O)-$, $-O-$, y $-S(O)_a-$; en donde a es 0-2 y $\mathbf{R^q}$ es hidrógeno o C_{1-4}alquilo;

$\mathbf{R^{12}}$ es hidrógeno o C_{1-4}alquilo;

$\mathbf{R^{13}}$ y $\mathbf{R^{14}}$ se seleccionan independientemente de hidrógeno, C_{1-4}alquilo, carbociclilo, heterociclilo o R^{23}; en donde dicho C_{1-4}alquilo, carbociclilo o heterociclilo puede sustituirse opcionalmente en forma independiente por uno o más sustituyentes seleccionados de R^{20} ;

$\mathbf{R^{15}}$ es carboxi, sulfo, sulfino, fosfono, tetrazolilo, $-P-(O)(OR^e)(OR^f)$, $-P-(O)(OH)(OR^e)$, $-P(O)(OH)(R^e)$, o $-P(O)(OR^e)(R^f)$ en donde R^e y R^f se seleccionan independientemente de C_{1-6}alquilo; o R^{15} es un grupo de fórmula **(IC):**



(IC)

en donde:

$\mathbf{R^{24}}$ se selecciona de hidrógeno o C_{1-4}alquilo;

$\mathbf{R^{25}}$ se selecciona de hidrógeno, C_{1-4}alquilo, carbociclilo, heterociclilo o R^{27}; en donde dicho C_{1-4}alquilo, carbociclilo o heterociclilo puede sustituirse opcionalmente en forma independiente por uno o más sustituyentes seleccionados de R^{28};

$\mathbf{R^{26}}$ se selecciona de carboxi, sulfo, sulfino, fosfono, tetrazolilo, $-P(O)(OR^g)(OR^h)$, $-P(O)(OH)(OR^g)$, $-P(O)(OH)(R^g)$ o $-P(O)(OR^g)(R^h)$ en donde R^g y R^h se seleccionan independientemente de C_{1-6}alquilo;

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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;

z es 0-3; en donde los valores de R^{25} pueden ser los mismos o diferentes;

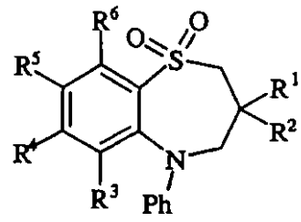
R^{16}, **R^{17}** y **R^{18}** se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N,N*-(C_{1-4}alquil)$_2$amino, 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}alcoxicarbonilo, *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 opcionalmente en forma independiente en carbono por uno o más R^{21};

R^{19}, **R^{20}**, **R^{23}**, **R^{27}** y **R^{28}** se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, 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}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo, *N,N*-(C_{1-4}alquil)$_2$sulfamoilo, carbociclilo, heterociclilo, sulfo, sulfino, amidino, fosfono, -P(O)(OR^a)(OR^b),-P(O)(OH)(OR^a),-P(O)(OH)(OR^a) 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}, R^{20}, R^{23}, R^{27} y R^{28} pueden sustituirse opcionalmente en forma independiente en carbono por uno o más R^{22};

R^{21} y **R^{22}** se seleccionan independientemente de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carboxi, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxicarbonilo, 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 profármaco.

De acuerdo con un aspecto adicional de la presente invención se provee un compuesto de fórmula **(I')**:

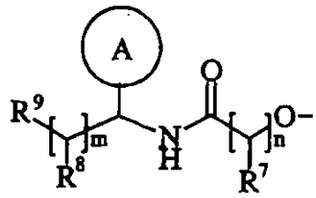


(I')

en donde:

R^1 y **R^2** se seleccionan independientemente de C_{1-6}alquilo;

uno de **R^4** y **R^5** es un grupo de fórmula **(IA')**:



(IA')

R^3 y **R^6** y los demás de **R^6** y **R^5** se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, 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}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)$_2$sulfamoilo y *N,N*-(C_{1-4}alquil)$_2$sulfamoilo; en donde R^3 y R^6 y los

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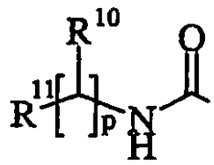
demás de R^4 y R^5 pueden sustituirse opcionalmente en carbono por uno o más R^{12};

Anillo A es arilo o heteroarilo; en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{13};

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^{14};

R^8 es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo; en donde R^8 se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{15};

R^9 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^9 es un grupo de fórmula **(IB')**:



(IB')

en donde:

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^{16};

R^{11} es carboxi, sulfo, sulfino, fosfono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) o -P(O)(OR^e)(Rf) 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^{10} pueden ser los mismos o diferentes;

m es 0-2; en donde los valores de R^8 pueden ser los mismos o diferentes;

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

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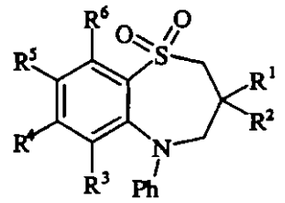
R^{12}, R^{13} y **R^{14}** se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N,N*-(C_{1-4}alquil)$_2$amino, C_{1-4}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N,N*-(C_{1-4}alquil)$_2$sulfamoilo; en donde R^{12}, R^{13} y R^{14} pueden sustituirse opcionalmente en forma independiente en carbono por uno o más R^{17};

R^{15} y R^{16} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, 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}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N,N*-(C_{1-4}alquil)$_2$sulfamoilo, 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_{1-6}alquilo; en donde R^{15} y R^{16} pueden sustituirse opcionalmente en forma independiente en carbono por uno o más R^{18};

R^{17} y R^{18} se seleccionan independientemente de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carboxi, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxicarbonilo, 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 profármaco.

De acuerdo con un aspecto adicional de la presente invención se provee un compuesto de fórmula **(I")**:

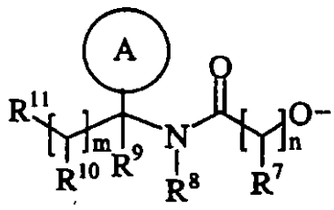


(I")

en donde:

R^1 y **R^2** se seleccionan independientemente de C_{1-6}alquilo;

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 hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, $_{C1-4}$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}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N,N*-(C_{1-4}alquil)$_2$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 más R^{16};

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

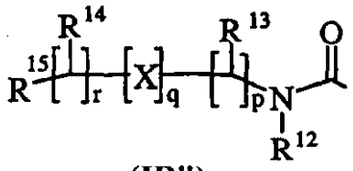
R^7 es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo; en donde R^7 se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{18};

R^8 es hidrógeno 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 más sustituyentes seleccionados de R^{19};

$\mathbf{R^{11}}$ 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 $\mathbf{R^{11}}$ es un grupo de fórmula **(IB")**:



(IB")

en donde;

X es -N(R^q)-, -N(R^q)(O)-, -O-, y -S(O)$_a$-; en donde a es 0-2 y R^q es hidrógeno o C_{1-4}alquilo;

$\mathbf{R^{12}}$ es hidrógeno o C_{1-4}alquilo;

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

$\mathbf{R^{15}}$ es carboxi, 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;

$\mathbf{R^{16}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, 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}alcoxicarbonilo, *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 opcionalmente en forma independiente en carbono por uno o más R^{21};

R^{19} y **R^{20}** se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{1-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)$_2$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}alcoxicarbonilo, *N*,(C_{1-4}alquil)$_2$sulfamoilo, *N,N*-(C_{1-4}alquil)$_2$sulfamoilo, 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_{1-6}alquilo; en donde R^{19} y R^{20} pueden sustituirse opcionalmente en forma independiente en carbono por uno o más R^{22};

R^{21} y **R^{22}** se seleccionan independientemente de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carboxi, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxicarbonilo, 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 profármaco.

En los siguientes parágrafos de la descripción, y en las reivindicaciones, donde se hace mención a un compuesto de fórmula **(I)**, hay que entender que este aspecto se relaciona también con compuestos de fórmula **(I')** y compuestos de fórmula **(I'')**.

Adicionalmente, la persona experta apreciará que el sistema de numeración diferencia entre compuestos de fórmula **(I)** y compuestos de fórmula **(I')**. El sistema de numeración usado aquí en lo sucesivo se refiere

a compuestos de fórmula **(I)**, pero tiene que entenderse que estas afirmaciones se aplican igualmente a los valores correspondientes en fórmula **(I')**.

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 únicamente. Por ejemplo, "C_{1-6}alquilo" incluye C_{1-4}alquilo, C_{1-3}alquilo, propilo, isopropilo y *t*-butilo. Sin embargo, referencias a grupos alquilo individuales tales como 'propilo' son específicos de la versión de cadena recta únicamente y referencias a grupos alquilo individuales de cadena ramificada tales como 'isopropilo' son específicos de la versión de cadena ramificada únicamente. Una convención similar se aplica a otros radicales, por ejemplo "fenilC_{1-6}alquilo" incluiría fenilC_{1-4}alquilo, 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 ó 6 átomos o un anillo bicíclico que contiene 9 ó 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 ser carbono o nitrógeno. En otro aspecto de la invención, "heteroarilo" se refiere a un anillo monocíclico totalmente insaturado, que contiene 5 ó 6 átomos o un anillo bicíclico que contiene 8, 9 ó 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, tiadizolilo, isotiazolilo, triazolilo, piranilo, indolilo, pirimidilo, pirazinilo, piridazinilo, piridilo, y quinolilo. Preferiblemente el término "heteroarilo" se refiere a tienilo o indolilo.

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

Preferiblemente "arilo" es un anillo monocíclico que contiene 5 ó 6 átomos o un anillo bicíclico que contiene 9 ó 10 átomos. Valores apropiados para "arilo" incluyen febilo 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 nitrógeno, 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 ó 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-azabiciclo[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-trilazolilo, piranilo, indolilo,

pirimidilo, tiazolilo, pirazinilo, piridazinilo, piridilo, 4-piridonilo, quinolilo y 1-isoquinolonilo.

Un "carbociclilo" es un anillo carbono mono o bicíclico saturado, parcialmente saturado o insaturado, que contiene 3-12 átomos; en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un -C(O)-. Preferiblemente "carbociclilo" es un anillo monocíclico que contiene 5 ó 6 átomos o un anillo bicíclico que contiene 9 ó 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 "C_{1-6}alcanoiloxi" y "C_{1-4}alcanoiloxi" es acetoxi. Ejemplos de "C_{1-6}alcoxicarbonilo" y "C_{1-4}alcoxicarbonilo" incluyen metoxicarbonilo, etoxicarbonilo, *n*- y *t*-butoxicarbonilo. Ejemplos de "C_{1-6}alcoxi" y "C_{1-4}alcoxi" incluyen metoxi, etoxi y propoxi. Ejemplos de "C_{1-6}alcanoilamino" y "C_{1-4}alcanoilamino" incluyen formamido, acetamido y propionilamino. Ejemplos de "C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2" y "C_{1-4}alquilS(O)a en donde a es 0 a 2" incluyen metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo y etilsulfonilo. Ejemplos de "C_{1-6} alcanoilo" y "C_{1-4}alcanoilo" incluyen C_{1-3}alcanoilo, propionilo y acetilo. Ejemplos de "*N*-(C_{1-6}alquil)amino" y "*N*,(C_{1-4}alquil)amino" incluyen metilamino y etilamino. Ejemplos de "*N*,*N*,(C_{1-6}alquil)$_2$amino" y "*N*,*N*(C_{1-4}alquil)$_2$amino" incluyen di-*N*-metilamino, di-(*N*-etil)amino y *N*-etil-*N*-metilamino. Ejemplos de "C_{2-6}alquenilo" y "C_{2-4}alquenilo" son vinilo, alilo y 1-propenilo. Ejemplos de "C_{2-6}alquinilo" y "C_{2-4}alquinilo" son etinilo, 1-propinilo y 2-propinilo. Ejemplos de *N*-(C_{1-6}alquil)sulfamoilo" y "*N*-(C_{1-4}alquil)sulfamoilo" son *N*-(C_{1-3}alquil)sulfamoilo, *N*-(metil)sulfamoilo y *N*-(etil)sulfamoilo. Ejemplos de "*N*-(C_{1-6}alquil)$_2$sulfamoilo" y "*N*-(C_{1-4}alquil)$_2$sulfamoilo" son *N*,*N*-(dimetil)sulfamoilo y *N*-(metil)-*N*-(etil)sulfamoilo. Ejemplos de "*N*-(C_{1-6}alquil)carbamoilo" y "*N*-(C_{1-4}alquil)carbamoilo" son metilaminocarbonilo y etilaminocarbonilo. Ejemplos de "*N*,*N*-(C_{1-6}alquil)$_2$carbamoilo" y "*N*,*N*-

$(C_{1-4}alquil)_2carbamoilo$" son dimetilaminocarbonilo y metiletilaminocarbonilo. Ejemplos de "C_{1-6}alcoxicarbonilamino" son etoxicarbonilamino y *t*-butoxicarbonilamino. Ejemplos de "*N'*-(C_{1-6}alquil)ureido" son *N'*-metilureido y *N'*-etilureido. Ejemplos de "*N'*-*N'*-(C_{1-6}alquil)$_2$ureido son *N'*,*N'*-metilureido y *N'*-metil-*N'*-etilureido. Ejemplos de "*N'*-(C_{1-6}alquil)-*N*-(C_{1-6}alquil)ureido son *N'*-metil-*N*-metilureido y *N*-propil-*N*-metilureido. Ejemplos de *N'*,*N'*-(C_{1-6}alquil)$_2$-*N*-(C_{1-6}alquil)ureido son *N*-dimetil-*N*-metilureido y *N'*-metil-*N'*-etil-*N*-propilureido.

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, fosfórico, trifluoroacético, cítrico o maleico. Además, una sal apropiada de aceptación farmacéutica de un compuesto de la invención que es suficientemente acídica es una sal de metal alcalino, por ejemplo, una sal de sodio o potasio, una sal de metal alcalinotérreo, por ejemplo, una sal de calcio o magnesio, una sal de amonio o una sal con una base orgánica que 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 hidrolizables *in vivo* de un compuesto de la fórmula **(I)** que contiene un grupo carboxi o hidroxi 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}alcoximetilo, por ejemplo, ésteres de metoximetilo, C_{1-6}alcanoiloximetilo, por ejemplo, ésteres de pivaloiloximetilo, ftaalidilo, ésteres de C_{3-8}cicloalcoxicarboniloxiC_{1-}

$_{6}$alquilo, por ejemplo, 1-ciclohexilcarboniloxietilo; ésteres de 1,3-dioxolen-2-onilmetilo, por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo; u ésteres de C_{1-6}alcoxicarboniloxietilo, por ejemplo 1-metoxicarboniloxietilo y pueden formarse en cualquier grupo carboxi en los compuestos de esta invención.

Un ester hidrolizable *in vivo* de un compuesto de la fórmula **(I)** que contiene un grupo hidroxi 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 hidroxi principal. Ejemplos de éteres de α-aciloxialquilo incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi. Una selección de grupos que forman éster hidrolizable *in vivo* para hidroxi incluyen alcanoilo, benzoilo, fenilacetilo y benzoilo sustituido y fenilacetilo, alcoxicarbonilo (para producir ésteres de alquil carbonato), dialquilcarbamoilo y *N*-(dialquilaminoetil)-*N*-alquilcarbamoilo (para producir carbamatos), dialquilaminoacetilo y carboxiacetilo. Ejemplos de sustituyentes en benzoilo incluyen morfolino y piperazino enlazados desde un átomo de 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 fórmula **(I)** que contiene un grupo carboxi es, por ejemplo, una *N*-C_{1-6}alquil o *N,N*-di-C_{1-6}alquil amida tal como *N*-metil, *N*-etil, *N*-propil, *N*-dimetil, *N*-etil-*N*-metil o *N,N*-dietil amida.

Algunos compuestos de la fórmula **(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 fórmula **(I)** pueden existir en formas solvatadas así como no solvatadas tales como, por ejemplo, formas hidratadas. Hay que entender que invención

comprende todas aquellas formas solvatadas que poseen actividad inhibidora IBAT.

Valores preferidos de R^1, R^2, R^3, R^4, R^5 y R^6 son como sigue. Dichos valores pueden usarse donde se considere apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas más arriba o más abajo en el texto.

Preferiblemente R^v y R^w son ambos hidrógeno.

Preferiblemente R^1 y R^2 se seleccionan independientemente de C_{1-4}alquil.

Más preferiblemente R^1 y R^2 se seleccionan independientemente de etilo o butilo.

Más preferiblemente R^1 y R^2 se seleccionan independientemente de etilo, propilo o butilo.

En un aspecto de la invención particularmente R^1 y R^2 son ambos butilo.

En un aspecto más de la invención particularmente R^1 y R^2 son ambos propilo.

En otro aspecto de la invención particularmente uno de R^1 y R^2 es etilo y el otro es butilo.

Preferiblemente R^x y R^y se seleccionan independientemente de hidrógeno o C_{1-6}alquilo.

Más preferiblemente R^x y R^y son ambos hidrógeno.

Preferiblemente R^z se selecciona de halo, amino, C_{1-6}alquilo, C_{1-6}alcoxicarbonilamino o *N'*-(C_{1-6}alquil)ureido.

Más preferiblemente R^z se selecciona de cloro, amino, *t*-butilo, *t*-butoxicarbonilamino o *N'*-(*t*-butil)ureido.

Preferiblemente v es 0 ó 1.

En un aspecto de la invención, más preferiblemente v es 0.

En un aspecto de la invención, más preferiblemente v es 1.

En un aspecto de la invención preferiblemente R^4 es un grupo de fórmula **(IA)** (como se describe más arriba).

En otro aspecto de la invención preferiblemente R^5 es un grupo de fórmula **(IA)** (como se describe más arriba).

Preferiblemente R^3 y R^6 son hidrógeno.

Preferiblemente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** se selecciona de halo, C_{1-4}alcoxi o C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2; en donde ese R^4 o R^5 pueden sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{16} se selecciona independientemente de hidroxi y *N,N*-(C_{1-4}alquil)$_2$amino.

Más preferiblemente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** se selecciona de bromo, metoxi, isopropoxi, metiltio, etiltio, isopropiltio o mesilo; en donde ese R^4 o R^5 pueden sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{16} se selecciona independientemente de hidroxi y *N,N*-dimetilamino.

Particularmente el otro de R^4 y R que no es el grupo de fórmula **(IA)** se selecciona de bromo, metoxi, isopropoxi, metiltio, etiltio, isopropiltio, 2-hidroxietiltio, 2-(*N,N*-dimetilamino)etiltio o mesilo.

Más particularmente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** es metiltio.

Preferiblemente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** se selecciona de hidrógeno, halo, C_{1-4}alcoxi o C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2; en donde ese R^4 o R^5 pueden sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{16} se selecciona independientemente de hidroxi, carboxi y *N,N*(C_{1-4}alquil)$_2$amino.

Más preferiblemente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** se selecciona de hidrógeno, bromo, metoxi, isopropoxi, metiltio, etiltio, isopropiltio o mesilo; en donde ese R^4 o R^5 pueden sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{16} se selecciona independientemente de hidroxi, carboxi y *N,N*-dimetilamino.

Particularmente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** se selecciona de hidrógeno, bromo, metoxi, isopropoxi, metiltio, carboximetiltio, etiltio, isopropiltio, 2-hidroxietiltio, 2-(*N,N*-dimetilamino)etiltio o mesilo.

En otro aspecto de la invención, más preferiblemente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** se selecciona de hidrógeno, cloro, bromo, metoxi, isopropoxi, metiltio, etiltio o isopropiltio; en donde ese R^4 o R^5 pueden sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{10} se selecciona independientemente de hidroxi, carboxi y *N,N*-dimetilamino.

En otro aspecto de la invención, particularmente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** se selecciona de hidrógeno, cloro, bromo, metoxi, isopropoxi, metiltio, carboximetiltio, etiltio, isopropiltio, 2-hidroxietiltio o 2-(*N,N*-dimetilamino)etiltio.

En otro aspecto de la invención, más particularmente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** es bromo o cloro.

En otro aspecto de la invención, más particularmente el otro de R^4 y R^5 que no es el grupo de fórmula **(IA)** es metoxi.

En un aspecto de la invención, preferiblemente Anillo A es arilo.

En otro aspecto de la invención, preferiblemente Anillo A es heteroarilo.

Cuando Anillo A es arilo, preferiblemente Anillo A es fenilo.

CuandoAnillo A es heteroarilo, preferiblemente Anillo A es tienilo o indolilo.

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

R^{17} se selecciona de halo, hidroxi o C_{1-4}alquilo; en donde R^{17} puede sustituirse opcionalmente en carbono por uno o más R^{21}; en donde

R^{21} se selecciona de halo.

Preferiblemente D es -O- o -S-.

En un aspecto de la invención, más preferiblemente D es -O-.

En un aspecto de la invención, más preferiblemente D es -S-.

Más preferiblemente Anillo A es fenilo, tienilo o indolilo; en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, hidroxi o trifluorometilo.

Particularmente Anillo A se selecciona de fenilo, 4-hidroxifenilo, tien-2-ilo, 4-trifluorometilfenilo, 3-hidroxifenilo, 2-fluorofenilo, 2,3-dihidroxifenilo o indol-3-ilo.

Más particularmente Anillo A es fenilo.

En otro aspecto de la invención, preferiblemente Anillo A es arilo o heteroarilo; en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{17}; en donde

R^{17} se selecciona de halo, hidroxi, C_{1-4}alquilo o C_{1-4}alcoxi; en donde R^{17} puede sustituirse opcionalmente en carbono por uno o más R^{21}; en donde

R^{21} se selecciona de halo.

En otro aspecto de la invención, más preferiblemente Anillo A es fenilo, tienilo o indolilo; en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, hidroxi, metoxi o trifluorometilo.

En otro aspecto de la invención, particularmente Anillo A se selecciona de fenilo, 4-hidroxifenilo, 4-metoxifenilo, tien-2-ilo, 4-trifluorometilfenilo, 3-hidroxifenilo, 2-fluorofenilo, 2,3-dihidroxifenilo o indol-3-ilo.

En un aspecto adicional de la invención, particularmente Anillo A se selecciona de fenilo, 4-hidroxifenilo, 4-metoxifenilo, tien-2-ilo, 4-trifluorometilfenilo, 3-hidroxifenilo, 2-fluorofenilo, 4-fluorofenilo, 2,3-dihidroxifenilo o indol-3-ilo.

Preferiblemente R^7 es hidrógeno, C_{1-4}alquilo o carbociclilo.

Más preferiblemente R^7 es hidrógeno, metilo o fenilo.

Particularmente R^7 es hidrógeno.

En un aspecto de la invención, preferiblemente R^8 es hidrógeno.

En otro aspecto de la invención, preferiblemente R^8 es C_{1-4}alquilo.

En otro aspecto de la invención, más preferiblemente R^8 es hidrógeno o metilo.

En un aspecto de la invención, preferiblemente R^9 es hidrógeno.

En otro aspecto de la invención, preferiblemente R^9 es C_{1-4}alquilo.

En otro aspecto de la invención, más preferiblemente R^9 es hidrógeno o metilo.

Preferiblemente R^{10} es hidrógeno.

En un aspecto de la invención, preferiblemente 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,

En otro aspecto de la invención, preferiblemente R^{11} es un grupo de fórmula **(IB)** (como se describe más arriba).

Preferiblemente R^{11} es carboxi, P(O)(OH)(OR^c) ó un grupo de fórmula **(IB)** (como se describe más arriba).

Más preferiblemente R^{11} es carboxi, -P(O)(OH)(OEt) o un grupo de fórmula **(IB)** (como se describe más arriba).

En otro aspecto de la invención, preferiblemente R^{11} es carboxi, sulfo, -P(O)(OH)(OR^c) en donde R^c se selecciona de C_{1-4}alquilo o un grupo de fórmula **(IB)** (como se describe más arriba).

Preferiblemente X es -NH- o -NHC(O)-.

Más preferiblemente X es -NHC(O)-.

En un aspecto de la invención, preferiblemente R^{12} es hidrógeno.

En otro aspecto de la invención, preferiblemente R^{12} es C_{1-4}alquilo.

En otro aspecto de la invención, más preferiblemente R^{12} es hidrógeno o metilo.

Preferiblemente R^{13} es hidrógeno, C_{1-4}alquilo o carbociclilo; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde

R^{20} es hidroxi.

Más preferiblemente R^{13} es hidrógeno, metilo o fenilo; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde

R^{20} es hidroxi.

Particularmente R^{13} es hidrógeno, hidroximetilo o fenilo.

Más particularmente R^{13} es hidrógeno o hidroximetilo.

En otro aspecto de la invención, preferiblemente R^{13} es hidrógeno, C_{1-4}alquilo o carbociclilo; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde

R^{20} es hidroxi, carboxi, carbociclilo o amino; en donde R^{20} puede sustituirse opcionalmente en carbono por uno o más R^{22};

R^{22} es hidroxi.

En otro aspecto de la invención, más preferiblemente R^{13} es hidrógeno, metilo, etilo, butilo o fenilo; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde

R^{20} es hidroxi, carboxi, fenilo o amino; en donde R^{20} puede sustituirse opcionalmente en carbono por uno o más R^{22};

R^{22} es hidroxi.

En otro aspecto de la invención, particularmente R^{13} es hidrógeno, hidroximetilo, 4-aminobutilo, 2-carboxietilo, 4-hidroxibencilo o fenilo.

En un aspecto adicional de la invención, preferiblemente R^{13} es hidrógeno, C_{1-4}alquilo o carbociclilo; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde

R^{20} es hidroxi, carboxi, carbociclilo, heterociclilo o amino; en donde R^{20} puede sustituirse opcionalmente en carbono por uno o más R^{22};

R^{22} es hidroxi.

En un aspecto adicional de la invención, más preferiblemente R^{13} es hidrógeno, metilo, etilo, butilo o fenilo; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde

R^{20} es hidroxi, carboxi, fenilo, imidazolilo o amino; en donde R^{20} puede sustituirse opcionalmente en carbono por uno o más R^{22} ;

R^{22} es hidroxi.

En un aspecto adicional de la invención, particularmente R^{13} es hidrógeno, hidroximetilo, 4-aminobutilo, 2-carboxietilo, 4-hidroxibenzilo, imidazol-5-ilmetilo o fenilo.

En otro aspecto más de la invención, preferiblemente R^{13} es hidrógeno, C_{1-4}alquilo, carbociclilo o R^{23}; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20} ; en donde

R^{20} es hidroxi. C_{1-4}alquilS$(O)_a$ en donde a es 0, C_{1-4}alcoxi, amino, carbociclil, heterociclilo o mercapto; en donde R^{20} pueden sustituirse opcionalmente en forma independiente en carbono por uno o más R^{22};

R^{22} se selecciona de hidroxi; y

R^{23} es carboxi.

En otro aspecto más de la invención, más preferiblemente R^{13} es hidrógeno, metilo, etilo, butilo o fenilo o R^{23}; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde

R^{20} es hidroxi, metiltio, metoxi, amino, imidazolilo o mercapto; en donde R^{20} puede sustituirse opcionalmente en forma independiente en carbono por uno o más R^{22};

R^{22} se selecciona de hidroxi; y

R^{23} es carboxi.

En otro aspecto más de la invención, particularmente R^{13} es hidrógeno, carboxi, hidroximetilo, mercaptometilo, metoximetilo, metiltiometilo, 2-metiltioetilo, 4-aminobutilo, 4-hidroxibenzilo, imidazol-5-ilmetilo o fenilo.

En otro aspecto más particularmente R^{13} es metiltiometilo, metilsulfinilmetilo o metilsulfonilmetilo.

Preferiblemente R^{14} es hidrógeno.

En otro aspecto de la invención, preferiblemente R^{14} se selecciona de hidrógeno, C_{1-4}alquilo o carbociclilo; en donde dicho C_{1-4}alquilo o carbociclilo puede sustituirse opcionalmente por uno o más sustituyentes seleccionados de R^{20}; y

R^{20} es hidroxi.

En otro aspecto de la invención, más preferiblemente R^{14} se selecciona de hidrógeno, metilo o fenilo; en donde dicho metilo o fenilo puede sustituirse opcionalmente por uno o más sustituyentes seleccionados de R^{20}; y

R^{20} es hidroxi.

En otro aspecto de la invención, particularmente R^{14} es hidrógeno, fenilo o hidroximetilo.

Particularmente R^{15} es carboxi o sulfo.

En un aspecto de la invención, más particularmente R^{15} es carboxi.

En otro aspecto de la invención, más particularmente R^{15} es sulfo.

Preferiblemente R^{15} es carboxi, sulfo, -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_{1-4}alquilo.

Más preferiblemente R^{15} es carboxi, sulfo, -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 Re y R^f se seleccionan independientemente de metilo o etilo.

Preferiblemente R^{15} es carboxi, sulfo, -P(O)(OEt)(OEt), -P(O)(OH)(OEt), -P(O)(OH)(Me) o -P(O)(OEt)(Me).

Preferiblemente R^{15} es carboxi, sulfo, 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_{1-4}alquilo o R^{15} es un grupo de fórmula **(IC)** (como se describe más arriba).

Más preferiblemente R^{15} es carboxi, sulfo, 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 metilo o etilo o R^{15} es un grupo de fórmula (**IC**) (como se describe más arriba).

Preferiblemente R^{15} es carboxi, sulfo, fosfono, -P(O)(OEt)(OEt), -P(O)(O*t*-Bu)(O*t*- Bu), -P(O)(OH)(OEt), -P(O)(OH)(Me) o -P(O)(OEt)(Me) o R^{15} es un grupo de fórmula **(IC)** (como se describe más arriba).

En un aspecto de la invención, preferiblemente R^{15} es un grupo de fórmula **(IC)** (como se describe más arriba).

En otro aspecto de la invención, preferiblemente R^{15} no es un grupo de fórmula **(IC)** (como se describe más arriba).

En un aspecto de la invención, preferiblemente R^{15} es carboxi.

En otro aspecto de la invención, preferiblemente R^{15} es sulfo.

En otro aspecto de la invención, preferiblemente R^{15} es -P(O)(OH)(OEt).

En otro aspecto de la invención, preferiblemente R^{15} es -P(O)(OH)(Me).

En otro aspecto de la invención, preferiblemente R^{15} es -P(O)(OEt)(Me).

En un aspecto de la invención, preferiblemente R^{24} es hidrógeno.

En otro aspecto de la invención, preferiblemente R^{24} es C_{1-4}alquilo.

Preferiblemente R^{25} es hidrógeno.

Preferiblemente R^{26} es carboxi.

Preferiblemente p es 1 ó 2; en donde los valores de R^{13} pueden ser los mismos o diferentes.

En un aspecto de la invención, más preferiblemente p es 1.

En otro aspecto de la invención, más preferiblemente p es 2; en donde los valores de R^{13} pueden ser los mismos o diferentes.

En un aspecto adicional de la invención, más preferiblemente p es 3; en donde los valores de R^{13} pueden ser los mismos o diferentes.

En un aspecto de la invención, preferiblemente q es 0.

En un aspecto adicional de la invención, preferiblemente q es 1.

En un aspecto de la invención, preferiblemente r es 0.

En un aspecto de la invención, más preferiblemente r es 1.

En otro aspecto de la invención, más preferiblemente r es 2; en donde los valores de R^{14} pueden ser los mismos o diferentes.

En un aspecto adicional de la invención, más preferiblemente r es 3; en donde los valores de R^{14} pueden ser los mismos o diferentes.

Preferiblemente m es 0.

En otro aspecto de la invención, preferiblemente m es 0 ó 1.

Preferiblemente n es 1.

En otro aspecto de la invención, preferiblemente n es 1 ó 2.

Preferiblemente z es 1.

El grupo de fórmula **(IA')** en donde R^7 es hidrógeno, metilo o fenilo, n es 1, Anillo A es fenilo, tienilo o indolilo; en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, hidroxi o trifluorometilo, m es 0 y R^9 es carboxi, -P(O)(OH)(OR^c) o un grupo de fórmula **(IB).**

El grupo de fórmula **(IA)** en donde:

D es -O- o -S-;

Anillo A es fenilo, tienilo o indolilo; en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, hidroxi, metoxi o trifluorometil;

R^7 es hidrógeno, metilo o fenilo;

R^8 es hidrógeno o metilo;

R^9 es hidrógeno o metilo;

R^{10} es hidrógeno;

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

R^{11} es carboxi, -P(O)(OH)(OEt) o un grupo de fórmula **(IB)** (como se describe en Reivindicación 1);

El grupo de fórmula **(IB')** en donde R^{10} es hidrógeno, hidroximetilo o fenilo, p es 1 ó 2; en donde los valores de R^{10} pueden ser los mismos o diferentes y R^{11} es carboxi o sulfo.

El grupo de fórmula **(IB)** en donde:

R^{12} es hidrógeno o metilo;

R^{13} es hidrógeno, metilo, etilo, butilo o fenilo o R^{23}; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; R^{20} es hidroxi, metiltio, metoxi, amino, imidazolilo o mercapto; en donde R^{20} puede sustituirse opcionalmente en forma independiente en carbono por uno o más hidroxi; R^{23} es carboxi;

X es-NH- o -NHC(O)-;

R^{14} se selecciona de hidrógeno, metilo o fenilo; en donde dicho metilo o fenilo puede sustituirse opcionalmente por uno o más sustituyentes seleccionados de hidroxi;

R^{15} es carboxi, sulfo, 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 metilo o etilo o R^{15} es un grupo de fórmula **(IC)** (como se describe en Reivindicación 1);

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

q es 0-1; y

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

El grupo de fórmula **(IC)** en donde

R^{24} es hidrógeno;

R^{25} es hidrógeno;

R^{26} es carboxi; y

z es 1;

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

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

R^1 y **R^2** se seleccionan independientemente de etilo o butilo;

R^3 y **R^6** son hidrógeno;

R^4 se selecciona de halo, C_{1-4}alcoxi o C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2; en donde ese R^4 puede sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{16} se selecciona independientemente de hidroxi y *N,N*-(C_{1-4}alquil)$_2$amino;

R^5 es un grupo de fórmula **(IA')**;

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

R^{17} se selecciona de halo, hidroxi o C_{1-4}alquilo; en donde R^{17} puede sustituirse opcionalmente en carbono por uno o más R^{21}; en donde

R^{21} se selecciona de halo;

R^7 es hidrógeno, C_{1-4}alquilo o carbociclilo;

R^{11} es carboxi, P(O)(OH)(OR^c) o un grupo de fórmula **(IB')** (como se describe más arriba);

R^{13} es hidrógeno, C_{1-4}alquilo o carbociclilo; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde

R^{20} es hidroxi;

R^{15} es carboxi o sulfo;

p es 1 ó 2; en donde los valores de R^{13} pueden ser los mismos o diferentes;

m es 0; y

n es 1;

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

Por consiguiente en un aspecto adicional de la invención, se provee un compuesto de fórmula **(I')** como se describe más arriba en donde:

$\mathbf{R^1}$ y $\mathbf{R^2}$ son ambos butilo o uno de R^1 y R^2 es etilo y el otro es butilo;

$\mathbf{R^4}$ es metiltio;

$\mathbf{R^5}$ es un grupo de fórmula **(IA')** (como se describe más arriba);

$\mathbf{R^3}$ y $\mathbf{R^6}$ son hidrógeno;

Anillo A es fenilo;

$\mathbf{R^7}$ es hidrógeno;

$\mathbf{R^{11}}$ es un grupo de fórmula **(IB')** (como se describe más arriba);

$\mathbf{R^{13}}$ es hidrógeno o hidroximetilo;

$\mathbf{R^{15}}$ es carboxi o sulfo;

p es 1 ó 2; en donde los valores de R^{13} pueden ser los mismos o diferentes;

m es 0;

n es 1;

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

Por consiguiente, en un aspecto adicional de la invención, se provee un compuesto de fórmula **(I")** como se describe más arriba en donde:

$\mathbf{R^1}$ y $\mathbf{R^2}$ se seleccionan independientemente de etilo o butilo;

$\mathbf{R^3}$ y $\mathbf{R^6}$ son hidrógeno;

$\mathbf{R^4}$ se selecciona de halo, C_{1-4}alcoxi o C_{1-4}alquilS$(O)_a$ en donde a es 0 a 2; en donde ese R^4 puede sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{16} se selecciona independientemente de hidroxi y *N,N*$(C_{1-4}$alquil$)_2$amino;

$\mathbf{R^5}$ es un grupo de fórmula **(IA")**;

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** o carbociclilo;

R^8 es hidrógeno o metilo;

R^9 es hidrógeno o metilo;

R^{11} es carboxi, -P(O)(OH)(OR^c) o un grupo de fórmula (**IB''**) (como se describe más arriba);

X es-NH- o -NHC(O)-;

R^{12} es hidrógeno o metilo;

R^{13} es hidrógeno, C_{1-4}alquilo o carbociclilo; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20};

R^{14} es hidrógeno;

R^{15} es carboxi o sulfo;

R^{17} se selecciona de halo, hidroxi, C_{1-4}alquilo o C_{1-4}alcoxi; en donde R^{17} puede sustituirse opcionalmente en carbono por uno o más R^{21};

R^{20} es hidroxi, carboxi, carbociclilo o amino; en donde R^{20} puede sustituirse opcionalmente en carbono por uno o más R^{22};

R^{21} se selecciona de halo;

R^{22} es hidroxi;

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; y en donde si q es 1, r no es 0;

m es 0 - 2; y

n es 1 -3;

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

Por consiguiente en otro aspecto más de la invención, se provee un compuesto de fórmula **(I)** como se describe más arriba en donde:

R^v y **R^w** son ambos hidrógeno;

R^1 y **R^2** se seleccionan independientemente de C_{1-4}alquilo;

$\mathbf{R^x}$ y $\mathbf{R^y}$ son ambos hidrógeno;

$\mathbf{R^z}$ se selecciona de halo, amino, C_{1-6}alquilo, C_{1-6}alcoxicarbonilamino o
N'-(C_{1-6}alquil)ureido;

v es 0 ó 1;

$\mathbf{R^3}$ y $\mathbf{R^6}$ son hidrógeno;

uno de $\mathbf{R^4}$ y $\mathbf{R^5}$ es un grupo de fórmula **(IA)** (como se describe más arriba) y el otro se selecciona de hidrógeno, halo, C_{1-4}alcoxi o C_{1-4}alquil$S(O)_a$ en donde a es 0 a 2; en donde ese R^4 o R^5 puede sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{16} se selecciona independientemente de hidroxi, carboxi y *N*,*N*-(C_{1-4}alquil)$_2$amino;

D es -O- o -S-;

$\mathbf{R^7}$ es hidrógeno, metilo o fenilo;

$\mathbf{R^8}$ es hidrógeno o metilo;

Anillo A es arilo o heteroarilo; en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{17}; en donde R^{17} se selecciona de halo, hidroxi, C_{1-4}alquilo o C_{1-4}alcoxi; en donde R^{17} puede sustituirse opcionalmente en carbono por uno o más R^{21}; en donde R^{21} se selecciona de halo;

$\mathbf{R^9}$ es hidrógeno o metilo;

$\mathbf{R^{10}}$ es hidrógeno;

$\mathbf{R^{11}}$ es carboxi, -P(O)(OH)(OR^c) en donde R^c se selecciona de C_{1-4}alquil o un grupo de fórmula **(IB)** (como se describe más arriba);

$\mathbf{R^{12}}$ es hidrógeno o metilo;

X es -NH- o -NHC(O)-;

$\mathbf{R^{13}}$ es hidrógeno, C_{1-4}alquilo, carbociclilo o R^{23}; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde R^{20} es hidroxi, C_{1-4}alquil$S(O)_a$ en donde a es 0, C_{1-4}alcoxi, amino, carbociclilo, heterociclilo o mercapto; en donde R^{20} pueden sustituirse opcionalmente en forma independiente en carbono por uno o más R^{22}; R^{22} se selecciona de hidroxi; y R^{23} es carboxi;

R^{14} se selecciona de hidrógeno, C_{1-4}alquilo o carbociclilo; en donde dicho C_{1-4}alquilo o carbociclilo puede sustituirse opcionalmente por uno o más sustituyentes seleccionados de R^{20}; y R^{20} es hidroxi;

R^{15} es carboxi, sulfo, 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_{1-4}alquilo o R^{15} es un grupo de fórmula **(IC)** (como se describe más arriba);

R^{24} es hidrógeno;

R^{25} es hidrógeno;

R^{26} es carboxi;

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 1-2; en donde los valores de R^7 pueden ser los mismos o diferentes;

z es 0-1; en donde los valores de R^{25} pueden ser los mismos o diferentes;

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

En otro aspecto de la invención, compuestos preferidos de la invención son uno cualquiera de los Ejemplos o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

En un aspecto de la invención, se provee un compuesto de fórmula (I) seleccionado de Ejemplos 8, 9, 46, 56, 59, 60, 61, 62, 66 y 69 o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

En otro aspecto de la invención, se provee un compuesto de fórmula **(I)** que es Ejemplo 73, 74, 95, 96, 97, 98, 99 y 100 o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

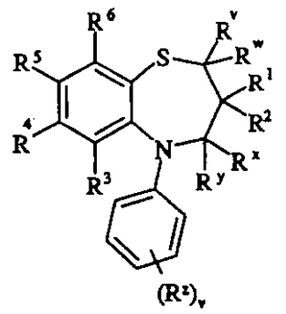
En otro aspecto de la invención, compuestos preferidos de la invención son uno cualquiera de Ejemplos 43, 50, 51 y 52 o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

En otro aspecto adicional de la invención, compuestos preferidos de la invención son uno cualquiera de Ejemplos 43, 46, 50, 51, 56, 58, 59, 61, 62, 63, 69, 81, 83, 85, 94, 97, 98, 108, 109, 110, 111 ó 117.

Aspectos preferidos de la invención son aquellos que se relacionan con el compuesto de fórmula **(I)** o su sal de aceptación farmacéutica.

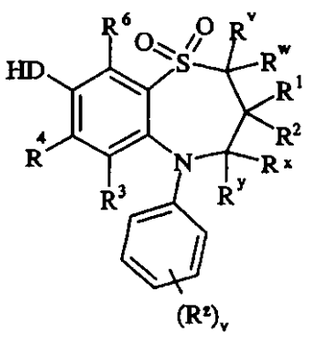
Otro aspecto de la presente invención provee un proceso para preparar un compuesto de fórmula **(I)** o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, el cual proceso (en donde grupos variables son, a menos que se especifique lo contrario, como se define en fórmula (**I**)) comprende:

Proceso 1): oxidar una benzotiazepina de fórmula **(II):**

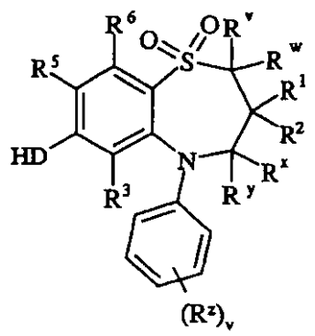


(II)

Proceso 2): para compuestos de fórmula **(I)** en donde D es -O-.-NR^a o -S-; hacer reaccionar un compuesto de fórmula **(IIIa)** o **(IIIb):**

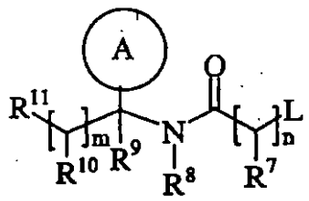


(IIIa)



(IIIb)

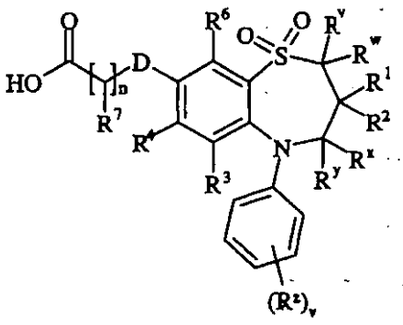
con un compuesto de fórmula (IV):



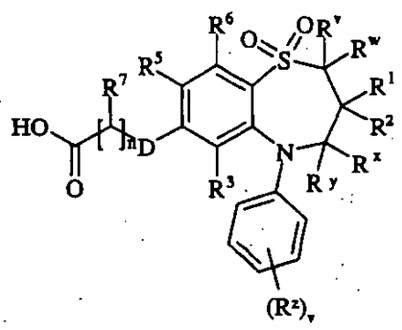
(IV)

en donde L es un grupo desplazable;

Proceso 3): hacer reaccionar un ácido de **(Va)** o **(Vb):**

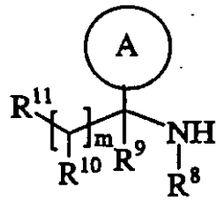


(Va)



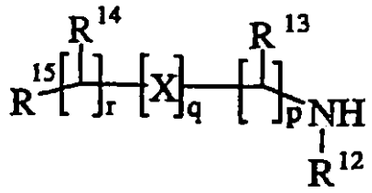
(Vb)

o su derivado activado; con una amina de fórmula **(VI)**:



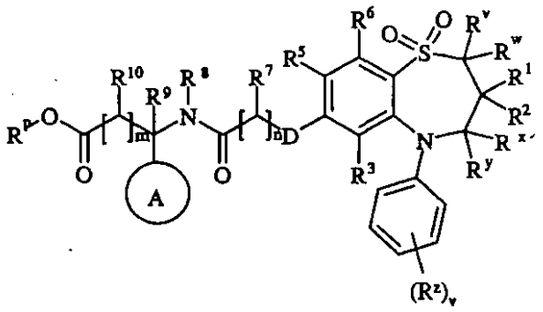
(VI)

Proceso 4): 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 fórmula **(VII)**;



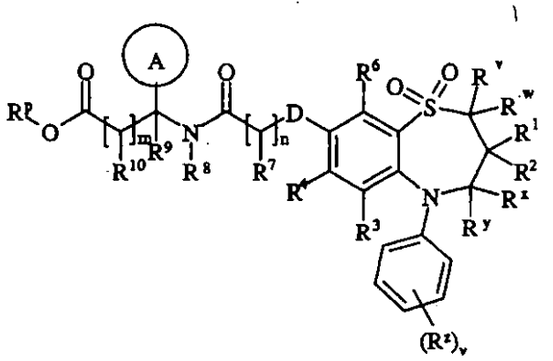
(VII)

Proceso 5): para compuestos de fórmula **(I)** en donde R^{11} es carboxi; desproteger un compuesto de fórmula **(VIIIa)**:



(VIIIa)

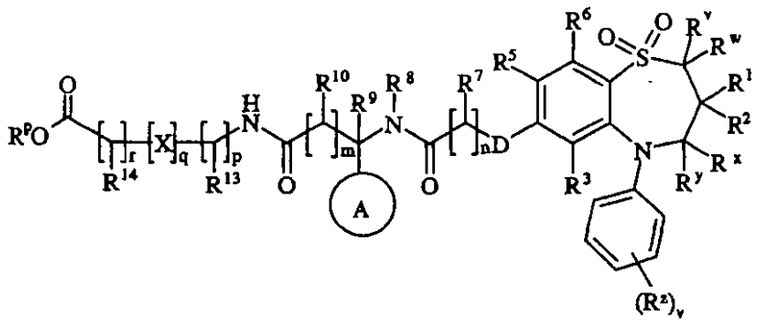
o **(VIIIb)**



(VIIIb)

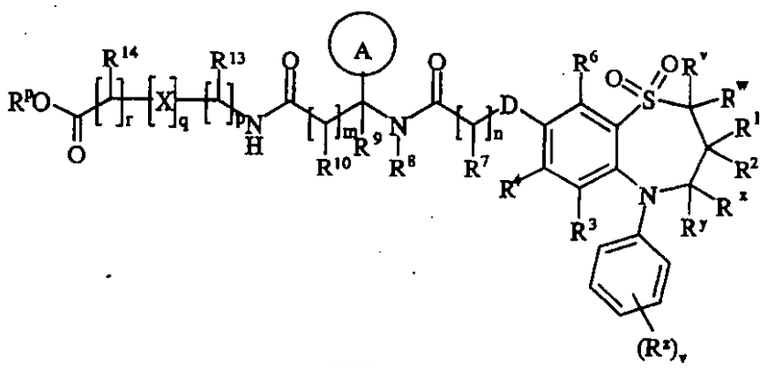
en donde R^p es C_{1-4}alquilo;

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 (**IXa**):



(IXa)

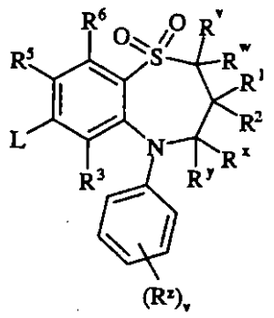
o **(IXb)**



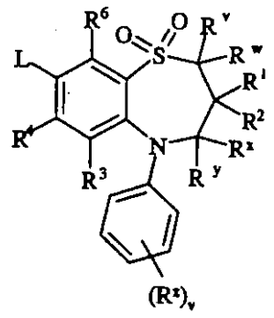
(IXb)

en donde R^p es C_{1-4}alquilo;

Proceso 7) para compuestos de fórmula (**I**) en donde uno de R^4 y R^5 se seleccionan independientemente de C_{1-4}alquiltio sustituido opcionalmente en carbono por uno o más R^{16}; hacer reaccionar un compuesto de fórmula (**Xa**) o (**Xb**):



(**Xa**)



(**Xb**)

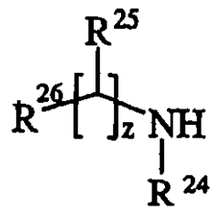
en donde L es un grupo desplazable; con un tiol de fórmula (**XI**):

R^y-H

(**XI**)

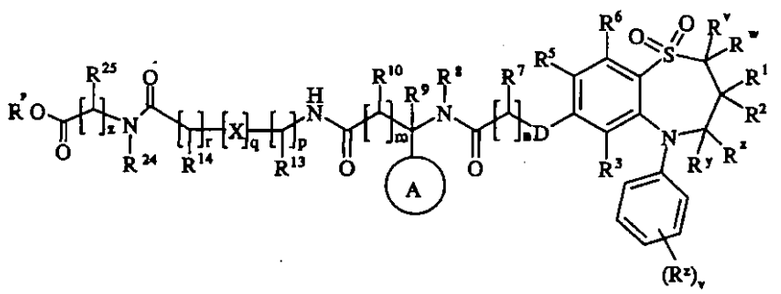
en donde R^y es C_{1-4}alquiltio sustituido opcionalmente en carbono por uno o más R^{16};

Proceso 8) para compuestos de fórmula (**I**) en donde R^{15} es un grupo de fórmula (**IC**) hacer reaccionar un compuesto de fórmula (**IXa**) o (**IXb**) en donde R^p es hidrógeno con un compuesto de fórmula (**XII**):



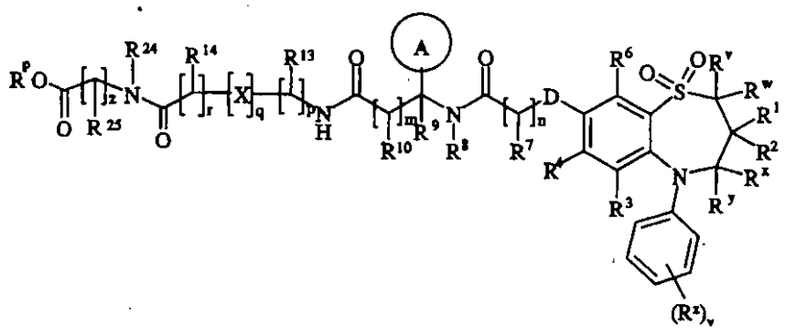
(**XII**)

Proceso 9): para compuestos de fórmula (**I**) en donde R^{11} es un grupo de fórmula (**IB**) y R^{15} es un grupo de fórmula (**IC**) y R^{26} es carboxi; desproteger un compuesto de fórmula (**XIIIa**):



(XIIIa)

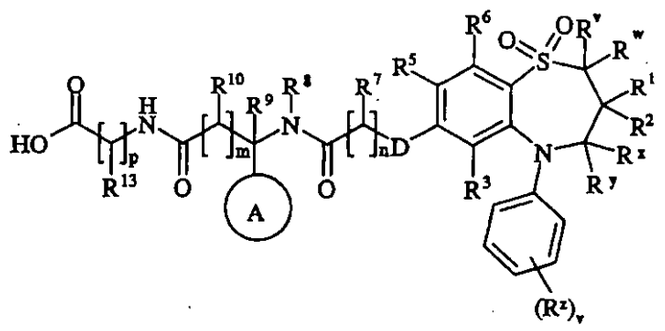
o **(XIIIb):**



(XIIIb)

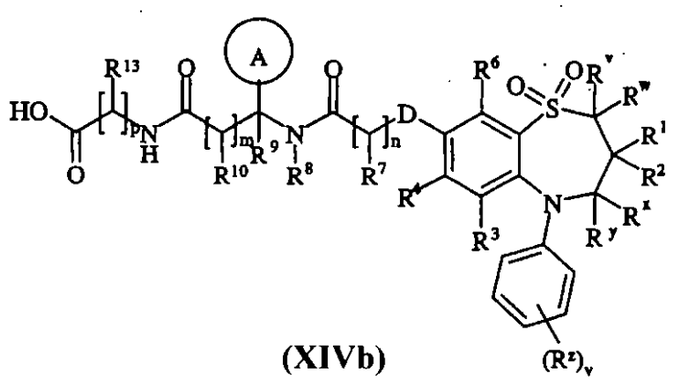
y R^p es C_{1-4}alquilo;

Proceso 10): para compuestos de fórmula **(I)** en donde X es $-N(R^q)C(O)-$; hacer reaccionar un compuesto de fórmula **(XIVa)**:



(XIVa)

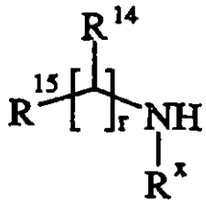
o **(XIVb)**



(XIVb)

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con un compuesto de fórmula (**XV**):



(XV)

y, posteriormente, si es necesario o deseable:

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

ii) retirar cualesquiera grupos protectores;

iii) formar una sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

La persona experta apreciará igualmente que proceso similares correspondientes a los procesos anteriores pueden usarse asimismo para preparar compuestos de fórmula (**I'**) y compuestos de fórmula (**I''**) en donde las definiciones de los grupos variables pueden diferir.

L es un grupo desplazable, valore apropiados para L son, por ejemplo, un grupo halógeno o sulfoniloxi, por ejemplo, un grupo cloro, bromo, metanosulfoniloxi o tolueno-4-sulfoniloxi.

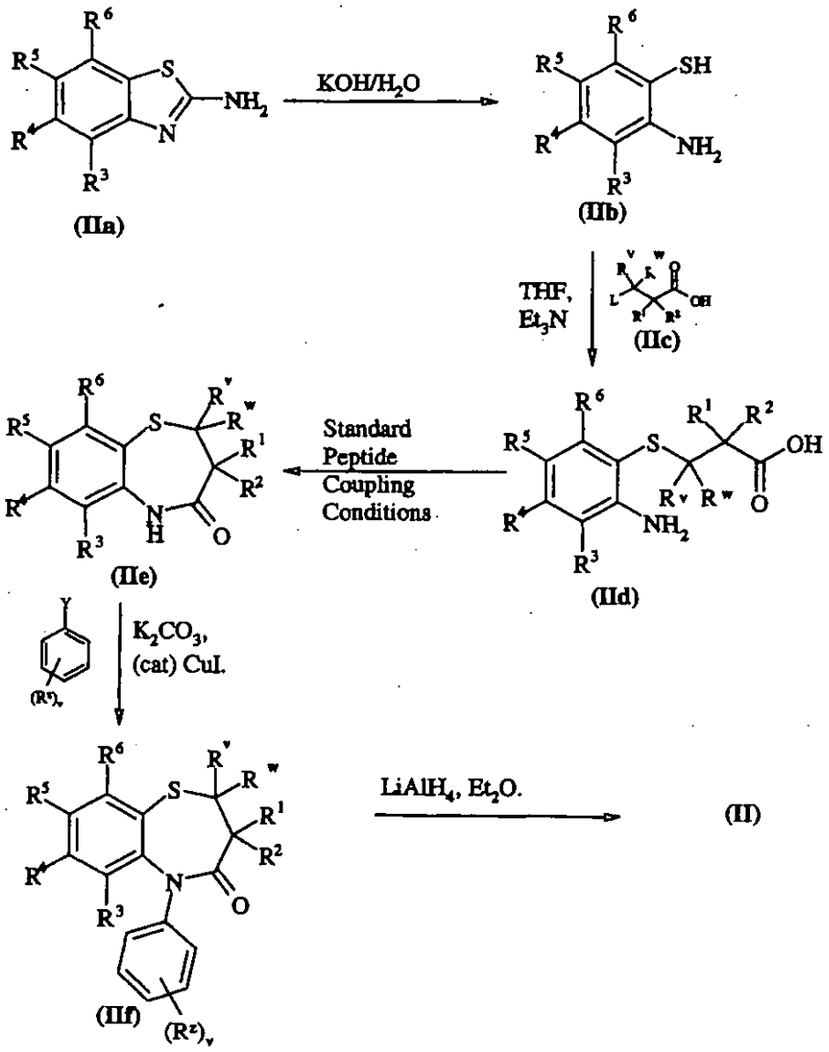
R^p es C_{1-4}alquilo. Preferiblemente R^p es metilo o etilo. Más preferiblemente R^p es metilo.

Condiciones de reacción específicas para las reacciones anteriores son como sigue.

Proceso 1): Benzotiazepinas de fórmula **(II)** pueden oxidarse bajo condiciones estándar de oxidación de azufre; por ejemplo, usando peróxido de hidrógeno y ácido trifluoroacético a una temperatura en el rango de 0°C a reflujo, preferiblemente a temperatura ambiente o cercana a ella.

Compuestos de fórmula (**II**) pueden prepararse de acuerdo con Esquema I para compuestos de fórmula **(I)** en donde R^x y R^y son hidrógeno. El experto apreciará que donde R^x y R^y no son ambos hidrógeno necesita

manipularse la siguiente ruta sintética usando procedimientos conocidos por la persona experta.



Esquema 1

en donde L es un grupo desplazable como se define más arriba, y Y es un grupo desplazable, por ejemplo halo.

Compuestos de fórmula **(IIa)** y **(IIc)** son compuestos obtenibles en el comercio, o son conocidos en la literatura, o se preparan por procesos estándar conocidos en el arte.

Proceso 2): Alcoholes de fórmula **(IIa)** o **(IIIb)** pueden hacerse reaccionar con compuestos de fórmula **(IV)** en la presencia de una base por ejemplo una base inorgánica tal como carbonato de sodio, o una base orgánica tal como base de Hunigs, en la presencia de un solvente apropiado tal como acetonitrilo, diclorometano o tetrahidrofurano a una temperatura en el rango de 0°C a reflujo, preferiblemente a reflujo, o cerca de él.

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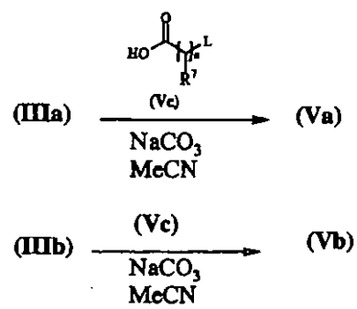
Compuestos de fórmula **(IIa)** o **(IIIb)** pueden prepararse en una manera similar a compuestos de fórmula (II) (pero en donde R^4 ó R^5 es hidroxi) seguida por el paso de oxidación de Proceso 1).

Compuestos de fórmula **(IV)** son obtenibles en el comercio, o son conocidos en la literatura, o se preparan por procesos estándar conocidos en el arte.

Proceso 3), Proceso 4, Proceso 8) y *Proceso 10):* Ácidos y aminas pueden acoplarse juntos en la presencia de un reactivo apropiado de acoplamiento. Reactivos estándar de acoplamiento de péptidos conocidos en el arte pueden emplearse como reactivos adecuados, o por ejemplo carbonildiimidazol y diciclohexil-carbodiimida, 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 tal como 2,6-lutidina o 2,6-di-*tert*-butilpiridina. Solventes apropiados incluyen dimetilacetamida, diclorometano, benceno, tetrahidrofurano y dimetilformamida. La reacción de acoplamiento puede realizarse convenientemente a una temperatura en el rango de -40 a 40°C.

Derivados 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 descritas más arriba, y en un solvente apropiado, tal como los descritos anteriormente. La reacción puede realizarse convenientemente a una temperatura en el rango de -40 a 40°C.

Compuestos de fórmula **(Va)** o **(Vb)** en donde D es -O-,-NR^a- o -S- pueden prepararse de acuerdo con Esquema 2:

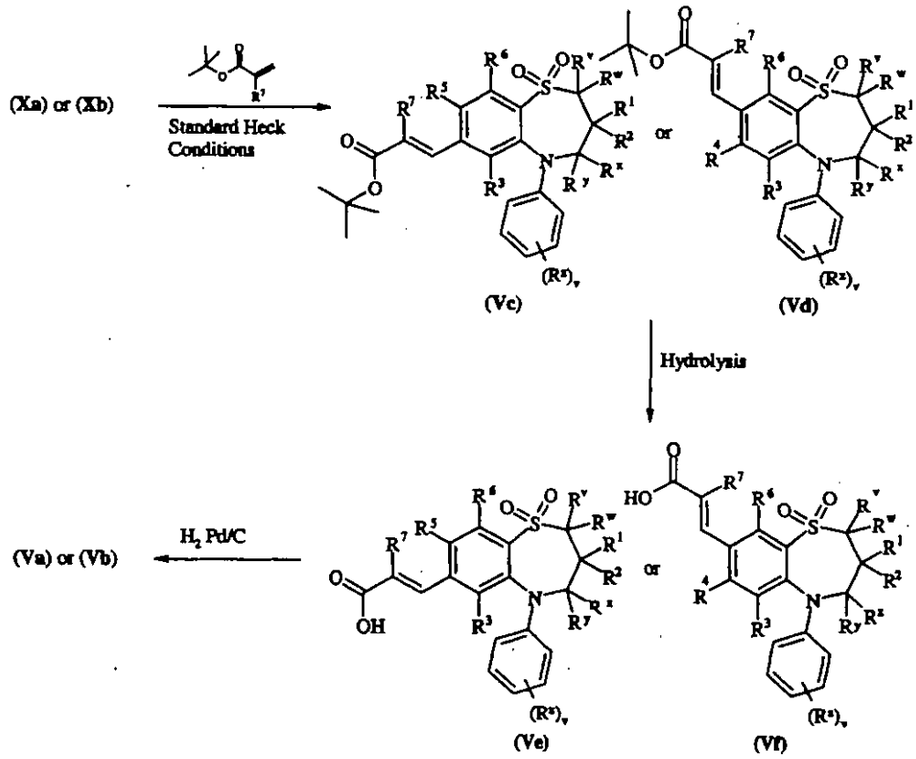


Esquema 2

en donde L es un grupo desplazable como se define más arriba.

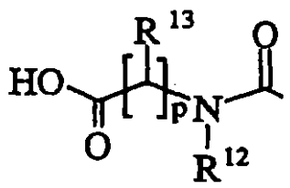
Compuestos de fórmula **(Va)** y **(Vb)** donde D es -SO- o $-SO_2-$ pueden prepararse oxidando los compuestos resultantes de fórmula **(Va)** y **(Vb)** de *Esquema 2* donde D es -S-.

Compuestos de fórmula **(Va)** o **(Vb)** en donde D es $-CH_2-$ pueden prepararse de acuerdo con *Esquema 3.*



Esquema 3

Compuestos de fórmula **(XIVa)** o **(XIVa)** pueden prepararse por cualquiera de los procesos descritos aquí donde R^{11} es un grupo de fórmula **(IB)** pero en donde **(IB)** es un grupo de fórmula) **(XVI)**:



(XVI)

Compuestos de fórmula **(Vc)**, **(VI)**, **(VII)**, **(XII)**, **(XV)** y **(XVI)** son compuestos obtenibles en el comercio, o son conocidos en la literatura, o se preparan por procesos estándar conocidos en el arte.

Proceso 5), Proceso 6) y *Proceso 9):* Ésteres de fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)** **(XIIIa)** y **(XIIIb)** pueden desprotegerse bajo condiciones estándar tal como las descritas más adelante, por ejemplo, pueden desprotegerse con hidróxido de sodio en metanol a temperatura ambiente.

Ésteres de fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)** **(XIIIa)** y **(XIIIb)** pueden prepararse por cualquiera de los procedimientos anteriores para la preparación de compuestos de fórmula **(I)**, pero en donde R^{11}, R^{15} o R^{26} es C_{1-4}alcoxicarbonilo.

Proceso 7): Compuestos de fórmula **(Xa)** y **(Xb)** pueden hacerse reaccionar con tiols de fórmula **(XI)** en la presencia de una base, por ejemplo, una base orgánica tal como carbonato de sodio o una base orgánica como base de Hunigs base, en la presencia de un solvente apropiado tal como DMF o THF a una temperatura en el rango de 0°C a reflujo.

Compuestos de fórmula **(Xa)** y **(Xb)** 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 fórmula **(XI)** son compuestos obtenibles en el comercio, o son conocidos en la literatura, o se preparan por procesos estándar conocidos en el arte.

Se apreciará que algunos de los diferentes sustituyentes de anillo en los compuestos de la presente invención pueden introducirse por reacciones estándar de sustitución aromática o generarse por modificaciones convencionales de grupo funcional antes o inmediatamente después de los procesos arriba mencionados, y como tales se incluyen en el aspecto de procesos de la invención. Dichas reacciones y modificaciones incluyen, por ejemplo, introducción de un sustituyente por medio de una reacción de sustitución aromática, reducción de sustituyentes, alquilación de sustituyentes y oxidación de sustituyentes. Los reactivos y condiciones de reacción para dichos procedimientos son bien conocidos en el arte químico.

Ejemplos particulares de reacciones de sustitución aromática incluyen la introducción de un grupo nitro usando ácido nítrico concentrado, la introducción de un grupo acilo usando, por ejemplo, un halogenuro de acilo y ácido de Lewis (tal como un tricloruro de aluminio) bajo condiciones de Friedel Crafts; la introducción de un grupo alquilo usando una halogenuro de alquilo y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; y la introducción de un grupo halógeno. Ejemplos particulares de modificaciones incluyen la reducción de un grupo nitro en un grupo amino, por ejemplo, mediante hidrogenación catalítica con un catalizador de níquel o tratamiento con hierro en la presencia de ácido clorhídrico con calentamiento; oxidación de alquiltio a 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. Las instancias donde es necesaria o deseable la protección y métodos adecuados para protección son conocidos por los expertos en el arte. Grupos protectores convencionales pueden usarse de acuerdo con la práctica estándar (para ilustración véase T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Así pues, si los reactivos incluyen grupos tales como amino, carboxi o hidroxi, puede ser deseable proteger el grupo en algunas de las reacciones mencionadas aquí.

Un grupo protector adecuado para un grupo amino o alquilamino es, por ejemplo, un grupo acilo, por ejemplo, un grupo alcanoilo tal como acetilo, un grupo alcoxicarbonilo, por ejemplo, un grupo metoxicarbonilo, etoxicarbonilo o *t*-butoxicarbonilo, un grupo arilmetoxicarbonilo, por ejemplo, benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo. Las condiciones de desprotección para los grupos protectores anteriores varían necesariamente con la elección del grupo protector. Así, por ejemplo, un grupo acilo tal como un grupo alcanoilo o alcoxicarbonilo o un grupo aroilo puede retirarse, por ejemplo, mediante hidrólisis con una base apropiada tal como un hidróxido de metal alcalino, por ejemplo, hidróxido de sodio o

litio. Alternativamente un grupo acilo tal como un grupo *t*-butoxicarbonilo puede retirarse, por ejemplo, mediante tratamiento con un ácido adecuado como ácido clorhídrico, sulfúrico o fosfórico o ácido trifluoroacético y un grupo arilmetoxicarbonilo tal como un grupo benciloxicarbonilo puede retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio-en-carbono, o mediante tratamiento con un ácido de Lewis, por ejemplo, tris(trifluoroacetato) de boro. Un grupo protector alternativo apropiado para un grupo amino primario es, por ejemplo, un grupo ftaloilo el cual puede retirarse mediante tratamiento con una alquilamina, por ejemplo, dimetilaminopropilamina, o con hidrazina.

Un grupo protector adecuado para un grupo hidroxi es, por ejemplo, un grupo acilo, por ejemplo, un grupo alcanoilo tal como acetilo, un grupo aroilo, por ejemplo benzoilo, o un grupo arilmetilo, por ejemplo, bencilo. Las condiciones de desprotección para los grupos protectores anteriores variarán necesariamente con la elección del grupo protector. Así, por ejemplo, un grupo acilo tal como alcanoilo o un grupo aroilo pueden retirarse, por ejemplo, mediante hidrólisis con una base apropiada tal como un hidróxido de metal alcalino, por ejemplo, hidróxido de sodio o litio. Alternativamente un grupo arilmetilo tal como un grupo bencilo puede retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio-en-carbono.

Un grupo protector adecuado para un grupo carboxi es, por ejemplo, un grupo esterificante, por ejemplo, un grupo metilo o etilo el cual puede retirarse, por ejemplo, mediante hidrólisis con una base tal como hidróxido de sodio, o, por ejemplo, un grupo *t*-butilo el cual puede retirarse, por ejemplo, mediante tratamiento con un ácido, por ejemplo, un ácido orgánico tal como ácido trifluoroacético, o, por ejemplo, un grupo bencilo el cual puede retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio-en-carbono.

Los grupos protectores pueden retirarse en cualquier etapa conveniente en la síntesis usando técnicas convencionales bien conocidas en el arte químico.

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

De acuerdo con un aspecto más de la invención se provee una composición farmacéutica la cual comprende un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se define más arriba en el texto en asociación con un transportador o diluyente de aceptación farmacéutica.

La composición puede ser en una forma adecuada para administración oral, por ejemplo, como una tableta o cápsula, para inyección parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o infusión) como una solución estéril, suspensión o emulsión, para administración tópica como un ungüento 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 su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, se administrará normalmente a un animal de sangre caliente en una dosis unitaria en el rango 5-5000 mg por área corporal en metros cuadrados del animal, es decir, aproximadamente 0.1-100 mg/kg o 0.01-50 mg/kg, y ésta normalmente provee una dosis de efecto terapéutico. Una forma de dosis unitaria tal como una tableta o cápsula contendrá usualmente, por ejemplo, 1-250 mg de ingrediente activo. Preferiblemente se emplea una dosis diaria en el rango de 1-50 mg/kg. En otro aspecto, se emplea una dosis diaria en el rango de 0.02-20 mg/kg. Sin embargo, la dosis diaria se variará

necesariamente dependiendo de el anfitrión tratado, la ruta 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 cualquier paciente particular.

De acuerdo con un aspecto adicional de la presente invención se provee un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se define anteriormente para uso en un método de tratamiento terapéutico o profiláctico de un animal de sangre caliente, como el hombre.

Hemos encontrado que los compuestos definidos en la presente invención, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, son inhibidores efectivos de IBAT y, en consecuencia, poseen utilidad en el tratamiento de estados patológicos asociados con condiciones hiperlipidémicas.

Así, de acuerdo con este aspecto de la invención se provee un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se define anteriormente para uso como un medicamento.

De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se define anteriormente en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre.

De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se define anteriormente en la manufactura de un medicamento para uso en el tratamiento de condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre.

De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se define anteriormente en

la manufactura de un medicamento para uso en el tratamiento de condiciones dislipidémicas y trastornos tales como hiperlipidemia, hipertrigliceridemia, hiperbetalipoproteinemia (LDL alta), hiperprebetalipoproteinemia (VLDL alta), hiperquilomicronemia, hipolipoproteinemia, hipercolesterolemia, hiperlipoproteinemia e hipoalfalipoproteinemia (HDL baja) en un animal de sangre caliente, como el hombre.

De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se define anteriormente en la manufactura de un medicamento para uso en el tratamiento de diferentes condiciones clínicas tales como aterosclerosis, arteriosclerosis, arritmia, condiciones hiper-trombóticas, disfunción vascular, disfunción endotelial, falla cardiaca, enfermedades cardiacas coronarias, enfermedades cardiovasculares, infarto del miocardio, angina pectoris, enfermedades vasculares periféricas, inflamación de tejidos cardiovasculares tales como corazón, válvulas, vasculatura, arterias y venas, aneurismas, estenosis, restenosis, placas vasculares, estrías adiposas vasculares, leucocito, monocitos y/o infiltrado de macrófagos, engrosamiento intimal, adelgazamiento medial, trauma infeccioso y quirúrgico y trombosis vascular, apoplejía y ataques isquémicos transitorios en un animal de sangre caliente, como el hombre.

De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se define anteriormente, en la manufactura de un medicamento para uso en el tratamiento de aterosclerosis, enfermedades cardiacas coronarias, infarto del miocardio, angina pectoris, enfermedades vasculares periféricas, apoplejía y ataques isquémicos transitorios en un animal de sangre caliente, como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para producir un efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre, necesitado de dicho

tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

De acuerdo con una característica más de este aspecto de la invención se provee un método de tratar condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

De acuerdo con una característica más de este aspecto de la invención se provee un método de tratar condiciones y trastornos dislipidémicos tales como hiperlipidemia, hipertrigliceridemia, hiperbetalipoproteinemia (LDL alta), hiperprebetalipoproteinemia (VLDL alta), hiperquilomicronemia, hipolipoproteinemia, hipercolesterolemia, hiperlipoproteinemia e hipoalfalipoproteinemia (HDL baja) en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

De acuerdo con una característica más de este aspecto de la invención se provee un método de tratar diferentes condiciones clínicas tales como aterosclerosis, arteriosclerosis arritmia, condiciones hiper-trombóticas, disfunción vascular, disfunción endotelial, falla cardiaca, enfermedades cardiacas coronarias, enfermedades cardiovasculares, infarto del miocardio, angina pectoris, enfermedades vasculares periféricas, inflamación de tejidos cardiovasculares tales como corazón, válvulas, vasculatura, arterias y venas, aneurismas, estenosis, restenosis, placas vasculares, estrías adiposas vasculares, leucocito, monocitos y/o infiltrado de macrófagos, engrosamiento intimal, adelgazamiento medial, trauma quirúrgico e infeccioso y trombosis vascular, apoplejía y ataques isquémicos transitorios, en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad

efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

De acuerdo con una característica más de este aspecto de la invención se provee un método de tratar aterosclerosis, enfermedades cardiacas coronarias, infarto del miocardio, angina pectoris, enfermedades vasculares periféricas, apoplejía y ataques isquémicos transitorios en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

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

El tamaño de la dosis requerida para el tratamiento terapéutico o profiláctico se variará necesariamente dependiendo del anfitrión tratado, la ruta de administración y la gravedad de la afección que se está tratando. Se contempla una dosis unitaria en el rango, por ejemplo, 1-100 mg/kg, preferiblemente 1-50 mg/kg.

La actividad inhibidora IBAT definida anteriormente puede aplicarse como terapia única o puede implicar, además de un compuesto de la invención, una o más otras sustancias y/o tratamientos. Dicho tratamiento conjunto puede lograrse mediante administración simultánea, secuencial o separada de los componentes individuales del tratamiento. De acuerdo con este aspecto de la invención se provee un producto farmacéutico que comprende un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se define anteriormente y un sustancia adiciona inhibidora de IBAT como se define

anteriormente y un agente hipolipidémico adicional para el tratamiento conjunto de hiperlipidemia.

En otro aspecto de la invención, el compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, puede administrarse en asociación con un inhibidor de HMG Co-A reductasa, o sales de aceptación farmacéutica, solvatos, solvatos de dichas sales o sus profármacos. Inhibidores apropiados de HMG Co-A reductasa, sales de aceptación farmacéutica, solvatos, solvatos de dichas sales o sus profármacos 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(metilsulfonil)amino]pirimidin-5-il](3R,5S)-3,5-dihidroxihept-6-enoico (rosuvastatina), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco. Una estatina particular es atorvastatina, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco. Una estatina más particular es sal de calcio de atorvastatina. Una estatina particular adicional es ácido (E)-7-[4-(4-fluorofenil)-6-isopropil-2-[metil(metilsulfonil)amino]pirimidin-5-il](3R,5S)-3,5-dihidroxihept-6-enoico (rosuvastatina), o su sal de aceptación farmacéutica, solvato, solvato dicha sal o su profármaco. Una estatina particular preferible es sal de calcio de rosuvastatina.

En un aspecto adicional de la invención, el compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco puede administrarse en asociación con un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y/o un ligador 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 ácido biliar ileal. Un exceso de ácidos biliares en los contenidos viscerales puede causar diarrea. Así pues, la presente invención provee además un tratamiento de un posible efecto colateral tal como diarrea en pacientes durante la terapia que comprende el

compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

Un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, por su acción, disminuirá el colesterol endógeno disponible para la síntesis de ácido biliar y tendrá un efecto aditivo en combinación con el compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco en reducir lípido.

Ligadores adecuados de ácido biliar para dicha terapia de combinación son resinas, tales como colestiramina y colestipol. Una ventaja es que la dosis del ligador de ácido biliar podría mantenerse más baja que la dosis terapéutica para tratamiento de colesterolemia en un solo tratamiento que comprenda únicamente un ligador de ácido biliar. Mediante una dosis baja de ligador de ácido biliar podrían evitarse igualmente cualesquiera efectos colaterales posibles causados por una baja tolerancia del paciente a la dosis terapéutica.

Por lo tanto, en una característica adicional de la invención, se provee un método para producir efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco en administración simultánea, secuencial o separada con una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

Por consiguiente en una característica adicional de la invención, se provee un método para producir efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco en administración simultánea, secuencial o separada con un ligador de ácido biliar.

Por consiguiente, en una característica adicional de la invención, se provee un método para producir un efecto inhibidor de IBAT en un animal de sangre caliente, 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 de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco en administración simultánea, secuencial o separada con una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en administración simultánea, secuencial o separada con un ligador de ácido biliar.

Por consiguiente en una característica adicional de la invención, se provee un método de tratar condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco en administración simultánea, secuencial o separada con una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

Por consiguiente en una característica adicional de la invención, se provee un método de tratar condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco en administración simultánea, secuencial o separada con una cantidad efectiva de un ligador de ácido biliar.

Por consiguiente en una característica adicional de la invención, se provee un método de tratar condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco en administración simultánea, secuencial

o separada con una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en administración simultánea, secuencial o separada con un ligador de ácido biliar.

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

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un ligador de ácido biliar, en asociación con un transportador o diluyente de aceptación farmacéutica.

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un inhibidor de HMG Co-A reductasa, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un ligador de ácido biliar en asociación con un transportador o diluyente de aceptación farmacéutica.

De acuerdo con un aspecto adicional de la presente invención se provee un kit que comprende un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

De acuerdo con un aspecto adicional de la presente invención se provee un kit que comprende un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un ligador de ácido biliar.

De acuerdo con un aspecto adicional de la presente invención se provee un kit que comprende un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco y un ligador de ácido biliar.

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

a) un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en una primera forma de dosis unitaria;

b) un inhibidor de HMG Co-A reductasa, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco; en una segunda forma de dosis unitaria; y

c) medios de envase para contener dichas formas de dosis primera y segunda.

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

a) un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en una primera forma de dosis unitaria;

b) un ligador de ácido biliar; en una segunda forma de dosis unitaria; y

c) medios de envase para contener dichas formas de dosis primera y segunda.

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

a) un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en una primera forma de dosis unitaria;

b) un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco; en una segunda forma de dosis unitaria;

c) un ligador de ácido biliar; en una tercera forma de dosis unitaria; y

d) medios de envase para contener dichas formas de dosis primera, segunda y tercera.

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

a) un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, junto con un transportador o diluyente de aceptación farmacéutica, en una primera forma de dosis unitaria;

b) un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en una segunda forma de dosis unitaria; y

c) medios de envase para contener dichas formas primera y segunda.

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

a) un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, junto con un transportador o diluyente de aceptación farmacéutica, en una primera forma de dosis unitaria;

b) un ligador de ácido biliar, en una segunda forma de dosis unitaria; y

c) medios de envase para contener dichas formas de dosis primera y segunda.

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

a) un compuesto de fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, junto con un transportador o diluyente de aceptación farmacéutica, en una primera forma de dosis unitaria;

b) un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en una segunda forma de dosis unitaria; y

c) un ligador de ácido biliar; en una tercera forma de dosis unitaria; y

d) medios de envase para contener dichas formas de dosis primera, segunda y tercera.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre. De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, y un ligador de ácido biliar, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre.

De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un ligador de ácido biliar, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre.

De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en la manufactura de un medicamento para uso en el tratamiento de condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre.

De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, un ligador de ácido biliar, en la

manufactura de un medicamento para uso en el tratamiento de condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre.

De acuerdo con otra característica de la invención se contempla el uso de un compuesto de la fórmula (**I**), o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un ligador de ácido biliar, en la manufactura de un medicamento para uso en el tratamiento de condiciones hiperlipidémicas en un animal de sangre caliente, 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 su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica, con la administración simultánea, secuencial o separada de una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica a un animal de sangre caliente 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 su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica, con la administración simultánea, secuencial o separada de una cantidad efectiva de un ligador de ácido biliar, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica a un animal de sangre caliente 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 su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica, con la administración simultánea, secuencial o separada de una cantidad efectiva de un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, opcionalmente junto con un excipiente de aceptación farmacéutica, con la administración simultánea, secuencial o separada de una cantidad efectiva de un ligador de ácido biliar, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica a un animal de sangre caliente como el hombre, necesitado de dicho tratamiento terapéutico.

De acuerdo con un aspecto adicional más 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 su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica, con la administración simultánea, secuencial o separada de uno o más de los siguientes agentes seleccionados de:

- un inhibidor de CETP (proteína de transferencia de éster colesterílico), por ejemplo aquellos referenciados y descritos en WO 00/38725 página 7 renglón 22 - página 10, renglón 17 los cuales se incorporan aquí por referencia;
- un antagonista de absorción de colesterol por ejemplo azetidinonas tales como SCH 58235 y aquellas descritas en US 5,767,115 las cuales se incorporan aquí por referencia;
- un inhibidor MTP (proteína de transferencia microsomal) por ejemplo aquellos descritos en Science, 282, 751-54, 1998 los cuales se incorporan aquí por referencia;
- un derivado de ácido fíbrico; por ejemplo clofibrato, gemfibrozil, fenofibrato, ciprofibrato y bezafibrato;
- un derivado de ácido nicotínico, por ejemplo, ácido nicotínico (niacina), acipimox y niceritrol;

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- un compuesto de fitosterol por ejemplo stanols;
- probucol;
- un compuesto anti-obesidad por ejemplo orlistat (EP 129,748) y sibutramina (GB 2,184,122 y US 4,929,629);
- un compuesto anti-hipertensivo por ejemplo un inhibidor de enzima convertidora de angiotensina (ACE), un antagonista de receptor de angiotensina, un bloqueador andrenérgico, un bloqueador alfa andrenérgico, un bloqueador beta andrenérgico, un bloqueador mixto alfa/beta andrenérgico, un estimulante andrenérgico, bloqueador de canal de calcio, un diurético o un vasodilator;
- insulina;
- sulfonilureas incluyendo glibenclamida, tolbutamida;
- metformina; y/o
- acarbosa;

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica a un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento terapéutico.

Inhibidores ACE particulares o sales de aceptación farmacéutica, solvatos, solvato de dichas sales o sus profármacos, incluyendo metabolitos activos, que pueden usarse en combinación con un compuesto de fórmula **(I)** incluyen pero no se limitan a, los siguientes compuestos: alacepril, alatriopril, altiopril calcio, ancovenin, benazepril, clorhidrato de benazepril, benazeprilat, benzoilcaptopril, captopril, captopril-cisteína, captopril-glutatión, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diácido, enalapril, enalaprilat, enapril, epicaptopril, foroximitina, fosfenopril, fosenopril, fosenopril sodio, fosinopril, fosinopril sodio, fosinoprilat, ácido fosinoprílico, glicopril, hemorfin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, liciumina A, liciumina B, mixanpril, moexipril, moexiprilat, moveltipril, muraceína A, muraceína B, muraceína C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, clorhidrato de quinapril, quinaprilat, ramipril, ramiprilat,

spirapril, clorhidrato de spirapril, spiraprilat, spiropril, clorhidrato de spiropril, temocapril, clorhidrato de temocapril, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril y zofenoprilat. Inhibidores ACE preferidos para uso en la presente invención son ramipril, ramiprilat, lisinopril, enalapril enalaprilat. Inhibidores de ACE más preferidos para usos en la presente invención son ramipril y ramiprilat.

Antagonistas preferidos de angiotensina II, sales de aceptación farmacéutica, solvatos, solvato de dichas sales o sus profármacos 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, telmisaran y eprosartan. Antagonistas particularmente preferidos de angiotensina II o sus derivados de aceptación farmacéutica 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 de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, puede administrarse en asociación con un agonista PPAR alfa y/o gamma, o sales de aceptación farmacéutica, solvatos, solvatos de dichas sales o sus profármacos. Agonistas apropiados PPAR alfa y/o gamma, sales de aceptación farmacéutica, solvatos, solvatos de dichas sales o sus profármacos son bien conocidos en el arte. Éstos incluyen los compuestos descritos en WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, 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 listadas en la página 634) y J Med Chem, 2000, 43, 527 todos los cuales se incorporan aquí por referencia. Particularmente un agonista PPAR alfa y/o gamma se refiere a WY-14643, clofibrato, fenofibrato, bezafibrato, GW 9578, troglitazona, pioglitazona, rosiglitazona, eglitazona, proglitazona, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 y GW 2433. Particularmente un agonista alfa y/o gamma se refiere a ácido (S)-2-etoxi-3-[4-(2-{4-

metanosulfoniloxifenil}etoxi)fenil]propanoico y sus sales de aceptación farmacéutica.

Por consiguiente, en una característica adicional de la invención, se provee un método para producir un efecto inhibidor IBAT en un animal de sangre caliente, 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 de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco en administración simultánea, secuencial o separada con una cantidad efectiva de un agonista PPAR alfa y/o gamma, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco.

Por consiguiente, en una característica adicional de la invención, se provee un método de tratar condiciones hiperlipidémicas en un animal de sangre caliente, 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 de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco en administración simultánea, secuencial o separada con una cantidad efectiva de un agonista PPAR alfa y/o gamma, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco.

De acuerdo con un aspecto más de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula **(I)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, y un agonista PPAR alfa y/o gamma, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, en asociación con un transportador o diluyente de aceptación farmacéutica.

De acuerdo con un aspecto más de la presente invención se provee un kit que comprende un compuesto de fórmula **(I)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, y un agonista PPAR alfa y/o gamma, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco.

De acuerdo con un aspecto más de la presente invención se provee un kit que comprende:

a) un compuesto de fórmula **(I)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, en una primera forma de dosis unitaria;

b) un agonista PPAR alfa y/o gamma, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco; en una segunda forma de dosis unitaria; y

c) medios de envase para contener dichas formas de dosis primera y segunda.

De acuerdo con un aspecto más de la presente invención se provee un kit que comprende:

a) un compuesto de fórmula **(I)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, junto con un transportador o diluyente de aceptación farmacéutica, en una primera forma de dosis unitaria;

b) un agonista PPAR alfa y/o gamma, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, en una segunda forma de dosis unitaria; y

c) medios de envase para contener dichas formas de dosis primera y segunda.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula **(I)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, y un agonista PPAR alfa y/o gamma, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de IBAT en un animal de sangre caliente, 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 de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, un agonista PPAR alfa y/o gamma, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal

o su profármaco, en la manufactura de un medicamento para uso en el tratamiento de condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre.

De acuerdo con un aspecto más 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 de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica, con la administración simultánea, secuencial o separada de una cantidad efectiva de un agonista PPAR alfa y/o gamma, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, opcionalmente junto con un transportador o diluyente de aceptación farmacéutica a un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento terapéutico.

Además de su uso en medicina terapéutica, los compuestos de fórmula **(I)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, son también útiles como herramientas farmacológicas en el desarrollo y estandarización de sistemas de prueba in vitro e *in vivo* para la evaluación de efectos inhibidores de IBAT en animales de laboratorio tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la investigación de nuevos agentes terapéuticos.

Muchos de los intermedios descritos aquí son novedosos y, por lo tanto, se proveen como una característica adicional de la invención. Por ejemplo, compuestos de fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** y **(XIIIb)** muestran actividad inhibidora de IBAT cuando se analizan en el ensayo de prueba *in vitro* referenciado más arriba y, por consiguiente, se reivindican como una característica más de la invención.

Así, en una característica más de la invención, se provee un compuesto de fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** o **(XIIIb)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco.

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Por consiguiente, de acuerdo con un aspecto más de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** o **(XIIIb)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, como se define más arriba en el texto en asociación con un transportador o diluyente de aceptación farmacéutica.

De acuerdo con una aspecto adicional de la presente invención se provee un compuesto de la fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** o **(XIIIb)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, como se define más arriba en el texto para uso en un método de tratamiento terapéutico o profiláctico de un animal de sangre caliente, como el hombre.

Así, de acuerdo con este aspecto de la invención se provee un compuesto de la fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** o **(XIIIb)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco, como se define más arriba en el texto para uso como medicamento.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** o **(XIIIb)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco como se define más arriba en el texto en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** o **(XIIIb)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco como se define más arriba en el texto en la manufactura de un medicamento para uso en el tratamiento de condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre.

De acuerdo con una característica más de este aspecto de la invención se provee un método para producir un efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento

que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** o **(XIIIb)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco.

De acuerdo con una característica más de este aspecto de la invención se provee un método de tratar condiciones hiperlipidémicas en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** o **(XIIIb)**, o una sal de aceptación farmacéutica, solvato, solvato de dicha sal o su profármaco.

En la otra composición farmacéutica, proceso, método, uso y características de manufactura de medicamentos mencionados, se aplican igualmente las incorporaciones alternativas y preferidas de los compuestos de la invención descritos aquí.

Ejemplos

La invención se ilustrará ahora en los siguientes Ejemplos no limitantes, en los cuales, donde sea apropiado, pueden emplearse técnicas estándar conocidas por el químico experto y técnicas análogas a las descritas es estos Ejemplos, y en los cuales, a menos que se indique lo contrario:

(i) evaporaciones se llevaron a cabo mediante evaporación rotatoria in vacuo y procedimientos de preparación se realizaron después del retiro de sólidos residuales tales como agentes de secado 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 de grado HPLC bajo condiciones anhidras, salvo que se indique lo contrario;

(iii) cromatografía de columna (mediante el método de destello) se realizó en gel de sílice 40-63 μm (Merck);

(iv) rendimientos de dan con fines de ilustración únicamente y no son necesariamente el máximo alcanzable;

(v) las estructuras de los productos finales de la fórmula **(I)** se confirmaron generalmente por técnicas de resonancia magnética (generalmente protón) nuclear (NMR) y técnicas de espectro de masa; valores de conversión química de resonancia magnética se midieron en $CDCl_3$ deuterado (a menos que se indique lo contrario) en la escala delta (ppm campo abajo de tetrametilsilano); los datos de protones se citan a menos que se indique lo contrario; los espectros se registraron en un espectómetro Varian Mercury-300 MHz, Varian Unity plus- 400 MHz, Varian Unity plus-600 MHz o en Varian Inova-500 MHz; a menos que se indique lo contrario los datos se registraron a 400MHz; y las multiplicidades de picos se muestran como sigue: s, singlete; d, doblete; dd, doble doblete; t, triplete; tt, triple triplete; q, cuartete; tq, triple cuartete; m, multiplete; br, amplio; ABq, cuartete AB; ABd, doblete AB, ABdd, doblete de dobletes AB; dABq, doblete de cuartetes AB; LCMS se registraron en una Aguas ZMD, LC column x Terra MS C_8(Aguas), detección con un detector equipado con arreglo de diodos HP 1100 MS espectros de masa (MS) (lazo) se registraron en VG Platform II (Fisons Instruments) con un detector equipado con arreglo de diodos HP-1100 MS; a menos que se indique lo contrario, el ión de masa citado es (MH^+); a menos que se especifiquen más detalles en el texto, cromatografía analítica líquida de alto rendimiento (HPLC) se llevó a cabo en Prep LC 2000 (Aguas), Cromasil C_8, 7 µm, (Akzo Nobel); MeCN y agua deionizada 10 mM acetato de amonio como fases móviles, con composición adecuada;

(vii) intermedios por lo general no se caracterizaron completamente y la pureza se evaluó mediante cromatografía de capa delgada (TLC), HPLC, infra-rojo (IR), MS o análisis NMR;

(viii) donde se secaron soluciones, sulfato de sodio fue el agente de secado;

(ix) donde se menciona una columna "ISOLUTE", esto significa una columna que contiene 2 g de sílice, estando el sílice contenido en una jeringa desechable de 6 ml y soportada por un disco poroso de 54Å tamaño

de poro, obtenida de International Sorbent Technology bajo el nombre "ISOLUTE"; "ISOLUTE" es una marca registrada;

(x) las siguientes abreviaturas pueden emplearse más arriba o más adelante en el texto:-

DCM	diclorometano;
DMF	*N*, *N*-dimetilformamida;
TBTU	o-Benzotriazol-1-il-*N*, *N*, *N'*, *N'*-tetrametiluronio tetrafluoroborato;
EtOAc	EtOAC;
MeCN	acetonitrilo;
TFA	ácido trifluoroacético;
IPA	isopropanol;
DIPEA	di-isopropiletilamina; y
THF	tetrahidrofurano.

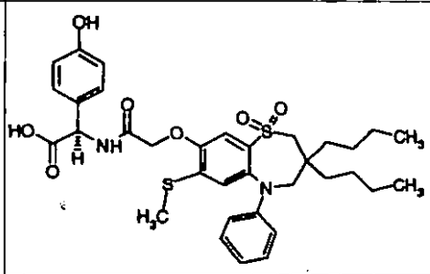
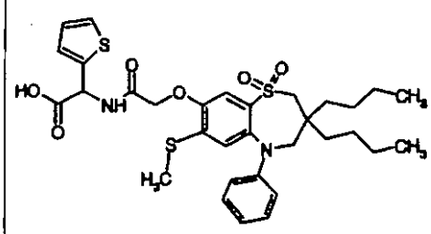
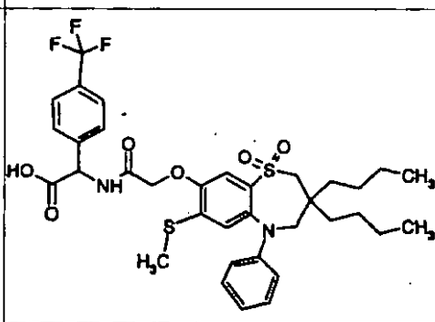
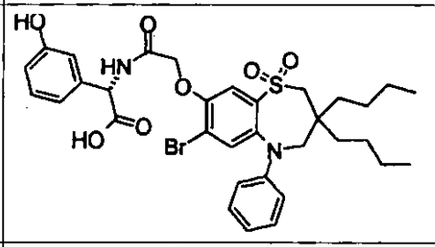
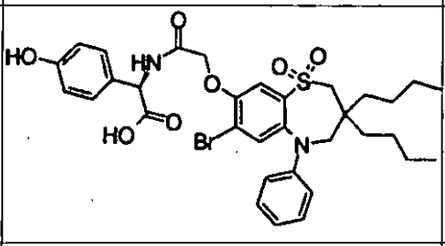
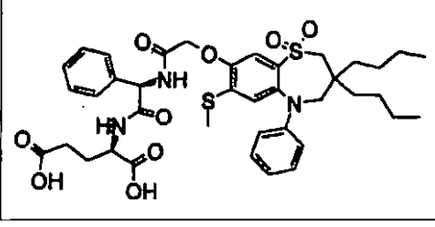
Ejemplo 1

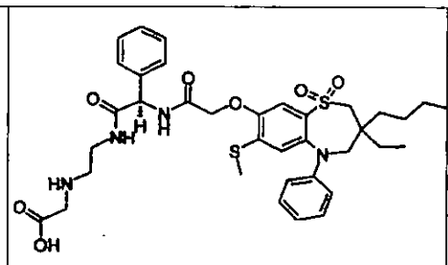
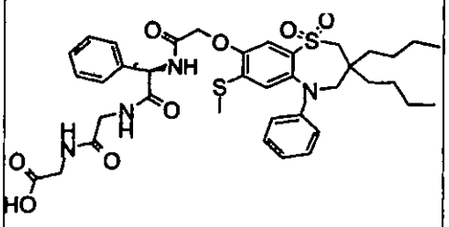
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-((R)-1'-fenil-1'-carboximetil) carbamoilmetoxi]-2, 3, 4, 5-tetrahidro-l, 5-benzotiazepina

1, 1-Dioxo-3, 3-dibutil-5-fenil-7-metiltio-8-[*N*-((R)-1'-fenil-1'-metoxicarbonilmetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 29; 300 mg, 0.46 mmol) se disolvió en metanol (5 ml). Se agregó NaOH (100 mg, en 0.2 ml agua) a la solución y la mezcla se agitó a temperatura ambiente durante 1 hora. Se agregó ácido acético (0.3 ml). El solvente se evaporó bajo presión reducida y el residuo se extrajo con DCM/agua. Se separó la capa DCM, se secó y se evaporó bajo presión reducida para producir el compuesto del título 270 mg (92%). NMR, 500 MHz, 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 (brs, 2H), 3.6-3.8 (m, 2H), 4.6 (s, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.8 (d, 1H).

Ejemplos 2-9

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 1 usando el material base apropiado.

Ej.	Compuesto	NMR	SM
2		(300 MHz, CD_3OD) 0.9-0.95 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.2 (s, 3H), 3.25 (s, 2H), 3.75 (brs, 2H), 4.65 (dd, 2H), 5.2 (s, 1H), 6.7-7.3 (m, 10H), 7.4 (s, 1H)	Mét. 30
3		(300 MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 3H), 3.75 (brs, 2H), 3.25 (s, 2H), 4.6-4.7 (m, 2H), 5.7 (s, 1H), 6.7 (s, 1H), 6.9-7.3 (m, 8H), 7.4 (s, 1H)	Mét. 31
4		(300 MHz, CD_3OD) 0.75-0.9 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 3H), 3.25 (s, 2H), 3, 75 (brs, 2H), 4.6-4.8 (m, 2H), 5.45 (s, 1H), 6.7 (s, 1H), 6.95-7.3 (m, 5H), 7.4 (s, 1H), 7.6 (s, 4H)	Mét. 32
5		(500 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 3.2 (brs, 2H), 3.6 (brs, 2H), 4.48 (m, 2H), 5.0 (s, 1H), 6.5 (d, 1H), 6.7-7.4 (m, 10H), 7.9 (s, 1H)	Mét. 39
6		(DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.6 (m, 12H), 3.2(brs, 2H), 3.7 (brs, 2H), 4.6-4.8 (m, 3H), 6.6 (d, 2H), 6.9-7.3 (m, 8H), 7.4 (s, 1H), 8.3 (d, 1H)	Mét. 40
7		M/z = 768.9	Mét. 67

8[1]		(300 MHz, CD_3OD) 0.75-0.9 (m, 6H), 1.0-1.25 (m, 4H), 1.4-1.6 (m, 4H), 2.15 (s, 3H), 3, 1- 3.3 (m, 4H), 3.5-3.8 (m, 5H), 4.75 (ABq, 2H), 5.45 (s, 2H), 6.75 (s, 1H), 6.95-7.5 (11H); m/z 711.3	Mét. 42
9		(500 MHz, DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.6 (m, 12H), 2.2 (s, 3H) 3, 2-3.8 (m, 8H), 4.8 (ABq, 2H), 5.6 (d, 1H), 6.7 (s, 1H), 6.8-7.5 (m, 11H), 7.8 (brs, 1H), 8.6 (d, 1H), 8.8 (t, 1H)	Mét. 69

[1] Etanol en lugar de metanol, purificado por HPLC preparativa usando MeCN y tampón de acetato de amonio (55:45) como eluyente.

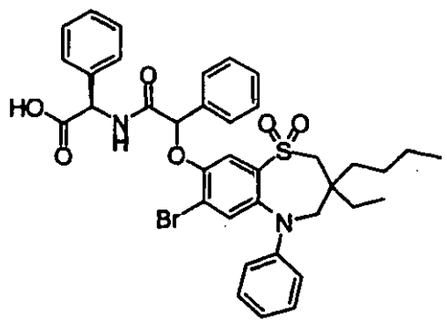
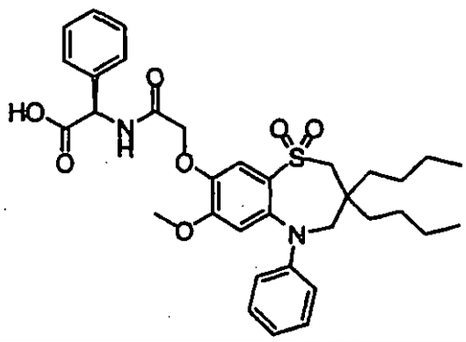
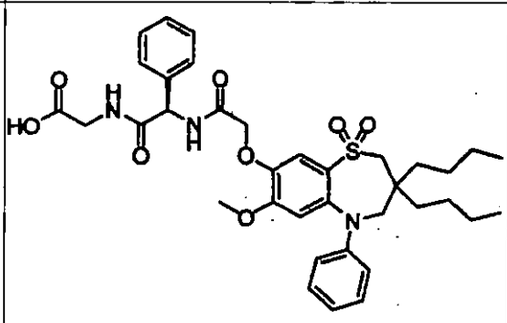
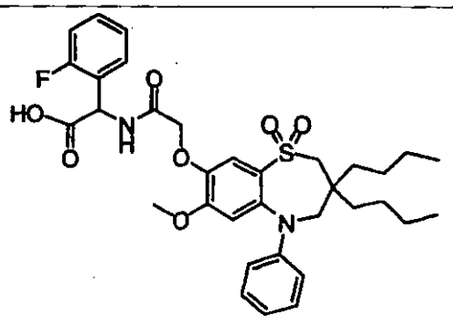
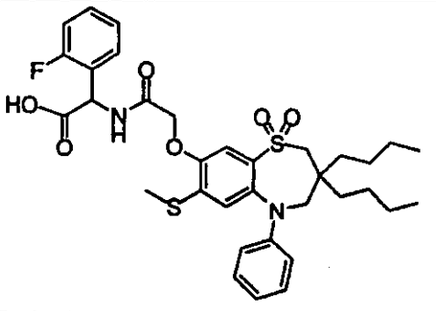
Ejemplo 10

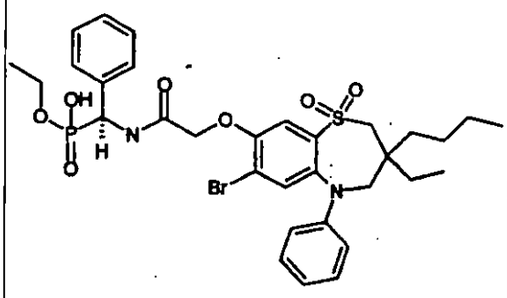
1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-{1-[*N*-((R)-1'-fenil-1'-carboximetil) carbamoil]etoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-{1-[*N*-((R)-1'-fenil-1'-metoxicarbonilmetil)carbamoil]etoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 33; 103 mg, 0.15 mmol) se disolvió en una mezcla de THF y H_2O (2:1, 3 ml). Se agregó LiOH(7 mg, 0.3 mmol) y la mezcla se agitó durante 7 horas a temperatura ambiente. La mayor parte del solvente se retiró bajo presión reducida y el producto crudo se purificó mediante HPLC preparativa usando MeCN y tampón de acetato de amonio (45:55) como eluyente para producir el compuesto del título 97 mg (96 %). NMR (DMSO-d_6) 0.60-0.80 (m, 6H), 0.90-1.60 (m, 11H), 3.15-3.45 (m, 2H), 3.50-3.90 (m, 2H), 4.95-5.25 (m, 2H), 6.85-7.55 (m, 12H), 8.55-8.95 (m, 15 1H).

Ejemplos 11-16

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 10 usando el material base apropiado.

Ej.	Compuesto	NMR	SM
11		($(CD_3)_2CO$) 0.70-0.90 (m, 6H), 0.95-1.35 (m, 4H), 1.40-1.75 (m, 4H), 3.15-3.35 (m, 2H), 3.80 (brs, 2H), 5.40 (d, 1H), 5.90-6.15 (2s, 1H), 6.95-7.75 (m, 18H)	Mét. 34
12		(CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.60 (s, 3H), 3.75 (brs, 2H), 4.60 (ABq, 2H), 5.40 (s, 1H), 6.50 (s, 1H), 6.95-7.45 (m, 10H), 7.55 (s, 1H)	Mét. 35
13		(CD_3OD) 0.75-0.85 (m, 6H), 1.00- 1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.55 (s, 3H), 3.75 (brs, 2H), 3.90 (ABq, 2H), 4.60 (ABq, 2H), 5.60 (s, 1H), 6.50 (s, 1H), 6.95-7.45 (m, 10H), 7.55 (s, 1H)	Mét. 36
14		(CD_3OD) 0.75-0.85 (m, 6H), 1.00- 1.30 (m, 8H), 1.35-1.60 (m, 4H), 3.20 (s, 2H), 3.60 (s, 3H), 3.75 (brs, 2H), 4.55 (ABq, 2H), 5.55 (s, 1H), 6.50 (s, 1H), 6.95-7.45 (m, 9H), 7.50 (s, 1H)	Mét. 37
15		(CD_3OD) 0.75-0.85 (m, 6H), 1.00- 1.30 (m, 8H), 1.35-1.60 (m, 4H), 2.15 (s, 3H), 3.25.(s, 2H), 3.75 (brs, 2H), 4.65 (ABq, 2H), 5.60 (s, 1H), 6.70 (s, 1H), 6, 90-7.45 (m, 10H)	Mét. 38

16		(CD_3OD) 7.55-7.41 (3H, m), 7.35- 7.20 (5H, m), 7.15-7.08 (3H, m), 7.04-6.98 (1H, m), 5.48-5.32 (1H, m), 4.80-4.60 (2H, m), 4.00-3.56 (4H, m), 3.27-3.22 (2H, m), 1.61-1.00 (11H, m), 0.83-0.74 (6H, m)	Mét. 70

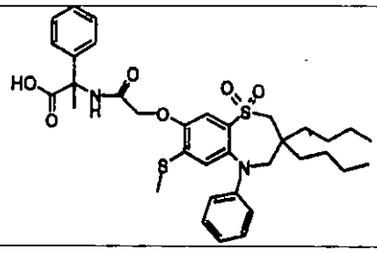
Ejemplo 17

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((S)-1'-fenil-1'-carboximetil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

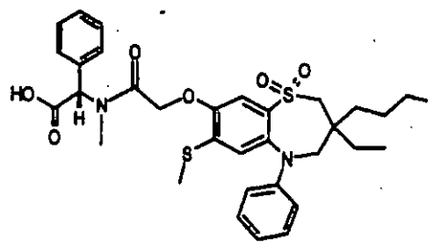
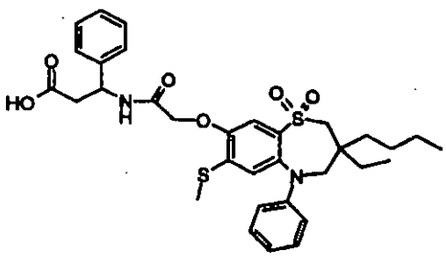
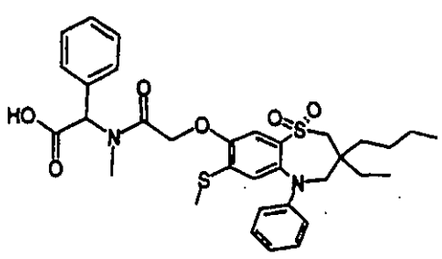
1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((S)-1'-fenil-1'-metoxicarbonilmetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 46; 60 mg, 0.091 mmol) se disolvió en THF (1 ml) y se agregó a una solución monohidrato hidróxido de litio (12.6 mg, 0.29 mmol) en agua (1 ml). La mezcla se agitó ocasionalmente durante 30 minutos. Se agregó 2M HCl solución (0.3 ml) y la capa de agua se extrajo con DCM. La capa orgánica se lavó una vez con salmuera, se secó, se filtró y se evaporó a presión reducida para producir el compuesto del título 48 mg (82%). NMR (CD_3OD) 0.73-0.84 (m, 6H), 1.0-1.6 (m, 8H), 3.27 (brs, 2H), 3.60-3-90 (m, 2H), 4.71 (ABq, 2H), 5.47- 5.55 (m, 1H), 7.02 (brt, 1H), 7.08-7.17 (m, 3H), 7.25-7.46 (m, 7H), 7.52 (s, 1H), 8.43 (d, NH); m/z 643.5.

Ejemplos 18-21

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 17 usando el material base apropiado.

Ej.	Compuesto	NMR	SM
18[1]		M/z 670 ($M+NH_4^+$)	Mét. 43

169

19[2]		(CD_3OD) 0.70-0.90 (m, 6H), 1.0-1.32 (m, 4H), 1.32-1.70 (m, 4H), 2.15 (s, 3H), 2.85 (brs, 3H), 3.23 (brs, 2H), 3.53-3.93 (m, 2H), 4.99 (ABq, 2H), 6.27 (s, 1H), 6.71 (s, 1H), 6.94 (t, 1H), 7.07 (d, 2H), 7.25 (t, 2H), 7.3-7.47 (m, 6H); m/z 625.3	Mét. 62
20		(CD_3OD) 0.75-0.84 (m, 6H), 1.0-1.29 (m, 4H), 1.36-1.65 (m, 4H), 2.15 (s, 3H), 2.82-2.97 (m, 2H), 3.22 (brs, 2H), 3.6-3.85 (m, 2H), 4.66 (ABq, 2H), 5.43 (t, 1H), 6.71 (s, 1H), 6.96 (t, 1H), 7.09 (d, 2H), 7.2-7.38 (m, 7H), 7.40 (s, 1H); m/z 625.4	Mét. 112
21		(600 MHz, CD_3OD) 0.77-0.88 (m, 6H), 1.0-1.32 (m, 4H), 1.39-1.70 (m, 4H), 2.16 (s, 3H), 2.88 (brs, 3H), 3.25 (brs, 2H), 3.52-3.93 (m, 2H), 5.03 (ABq, 2H), 6.28 (s, 1H), 6.73 (s, 1H), 6.96 (t, 1H), 7.09 (brd, 2H), 7.27 (t. 2H), 7.32-7.46 (m, 6H)	Mét. 79

[1] 2.2 equivalentes de LiOH en THF/agua (4/1)

[2] Purificado por HPLC preparativa usando una gradiente MeCN/tampón acetato de amonio (5/95 a 100/0) como eluyente.

Ejemplo 22

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((R)-1'-fenil-1'-carboximetil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

El compuesto del título se sintetizó de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-*N*-((R)-1'-fenil-1'-metoxicarbonilmetil)-carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 61) mediante el procedimiento de Ejemplo 17, salvo que la capa de agua se extrajo con EtOAc. El producto se purificó mediante HPLC preparativa usando una gradiente tampón MeCN/acetato de amonio (5/95 a 100/0) como eluyente.

NMR 0.75-0.83 (m, 6H), 1.0-1.25 (m, 4H), 1.32-1.52 (m, 3H), 1.55-1.70 (m, 1H), 3.20 (ABq, 2H), 3.65-3.83 (m, 2H), 4.62 (ABq, 2H), 5.68 (d. 1H), 7.04-7.15 (m, 4H), 7, 3-7.5 (m, 8H), 7.87 (brd, 1H); m/z 643.1.

Ejemplo23

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-(*N*-{(S)-1'-fenil-1'-[*N*'-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina sal de amonio

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((S)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 17; 48 mg, 0.075 mmol) y ácido 2-aminoetanosulfónico (17 mg, 0.14 mmol) se disolvió en DMF (2 ml) y DIPEA (0.052 ml, 0.30 mmol). La mezcla se agitó durante 15 minutos a 60°C. Se agregó TBTU (31 mg, 0.097 mmol) y la mezcla se agitó durante 2 horas a 60°C. El solvente se evaporó a presión reducida. El residuo se purificó mediante HPLC preparativa usando una gradiente tampón MeCN/acetato de amonio (5/95 a 100/0) como eluyente. Liofilización arrojó el compuesto del título 4 mg (7%). NMR (CD_3OD) 0.75-0.83 (m, 6H), 0.95-1.65 (m, 8H), 2.85-3.0 (m, 2H), 3.27 (brs, 2H), 3.5-3.9 (m, 4H), 4.72 (ABq, 2H), 5.48 (s, 1H), 7.02 (brt, 1H), 7.09-7.15 (m, 3H), 7.25-7.52 (m, 8H); m/z 750.3.

Ejemplos 24-37

Los siguientes compuestos se prepararon por el mismo procedimiento. El ácido (1 equivalente) se disolvió en THF (1 ml) y se agregó a una solución de monohidrato de hidróxido de litio (12.6 mg, 2.9-6.6 equivalentes) en agua (1 ml). La mezcla se agitó ocasionalmente y después de 1.5-6 horas se concluyó la desprotección (de acuerdo con LC-MS). Se agregó 2M solución HCl (0.3 ml).

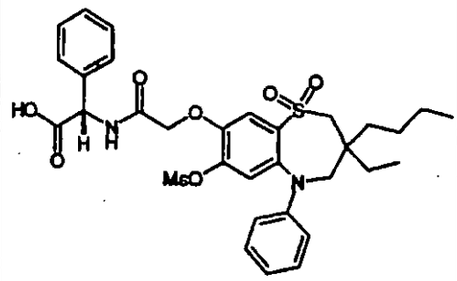
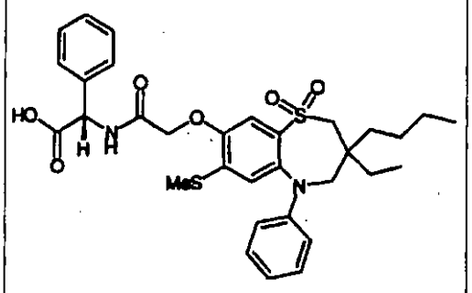
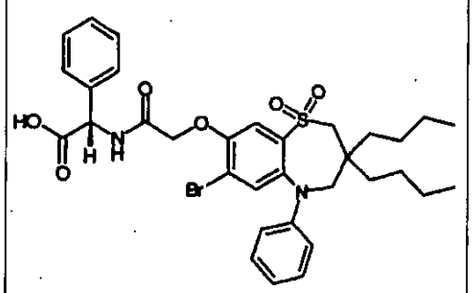
Ejemplos 24-33

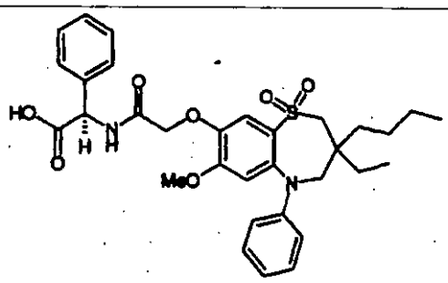
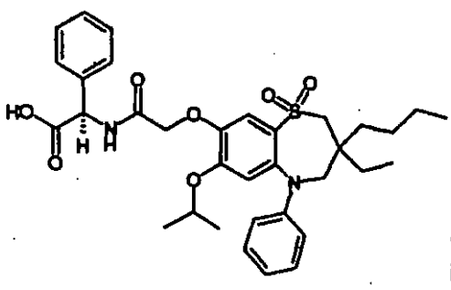
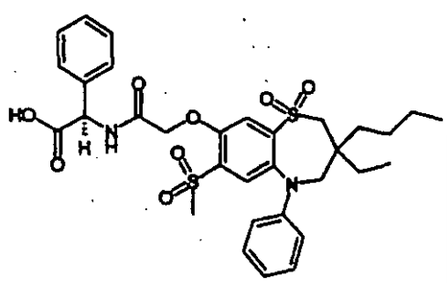
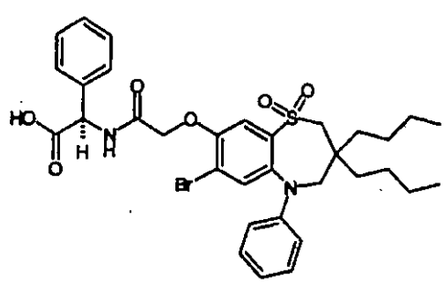
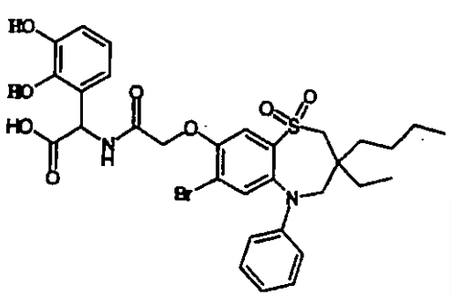
La mezcla de reacción se puso en una jeringa llenada con hydramatrix®. El producto se eluyó con DCM. El DCM se secó, se filtró y

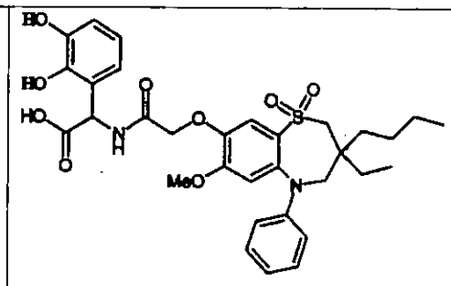
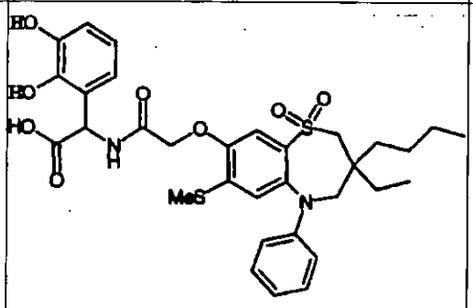
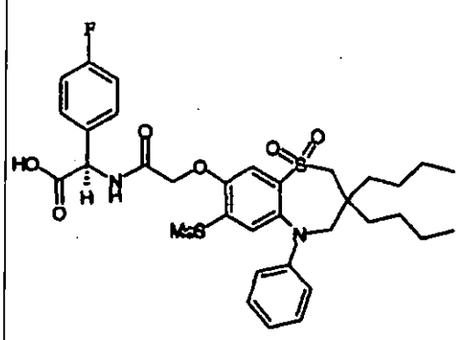
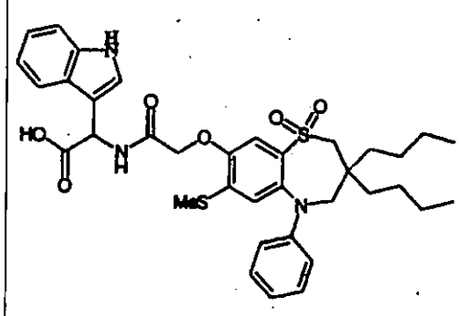
se evaporó a presión reducida. El producto se purificó mediante HPLC preparativa usando una gradiente tampón MeCN/acetato de amonio (5/95 a 100/0) como eluyente.

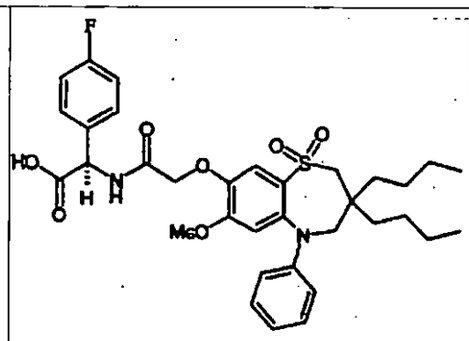
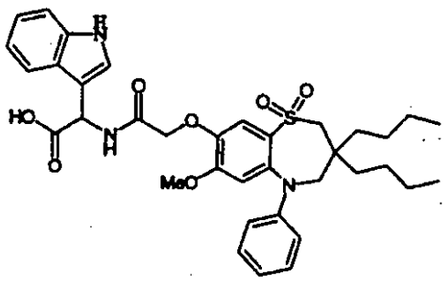
Ejemplos 34-37

La capa de agua se extrajo dos veces con DCM. La capa orgánica se secó, se filtró y se evaporó a presión reducida.

Ej.	Compuesto	NMR (CD_3OD)	m/z	SM
24		0.75-0.84 (m, 6H), 1.0-1.25 (m, 4H), 1.37-1.65 (m, 4H), 3.20 (brs, 2H), 3.55-3.90 (m, 5H), 4.58 (ABq, 2H), 5.33 (s, 1H), 6-51 (s, 1H), 6.97 (brt, 1H), 7.12 (brd, 2H), 7.2-7.33 (m. 5H), 7.41 (brd, 2H), 7.54 (s, 1H)	595.4	Mét. 47
25		0.73-0.85 (m, 6H), 1.0-1.3 (m, 4H), 1.35-1.65 (m, 4H), 2.17 (s, 3H), 3.23 (brs, 2H), 3.55-3.90 (m, 2H), 4.71 (ABq, 2H), 5.49-5.52 (m, 1H), 6.73 (s, 1H), 6.96 (brt, 1H), 7.10 (brd, 2H), 7.23- 7.45 (m, 8H), 8.36 (brd, NH)	611.2	Mét. 48
26		0.74-0.84 (m, 6H), 1.0-1.3 (m, 8H), 1.37-1.54 (m, 4H), 3.28 (brs, 2H), 3.65-3.85 (m, 2H), 4.72 (ABq, 2H), 5.49-5.52 (m, 1H), 7.04 (brt, 1H), 7.09-7, 18 (m, 3H), 7.28-7.46 (m, 7H), 7.52 (s, 1H), 8.45 (brd, NH)	671.2	Mét. 49

27		0.74-0.84 (m, 6H), 1.0-1.3 (m, 4H), 1.35-1.65 (m, 4H), 3.21 (brs, 2H), 3.59 (s, 3H), 3.62-3.90 (m, 2H), 4.62 (ABq, 2H), 5.49 (s, 1H), 6.50 (s, 1H) 6.98 (brt, 1H), 7.12 (brd, 2H), 7.24-7, 43 (m, 7H), 7.54 (s, 1H)	595.3	Mét. 50
28		0.74-0.85 (m, 6H), 0.85-1.65 (m, 14H), 3.21 (brs, 2H), 3.6-3.9 (m, 2H), 4.25-4.36 (m, 1H), 4.53- 4.66 (m, 2H), 5, 49 (s, 1H), 6.47 (s, 1H) 6.91-7.0(m, 1H), 7.04- 7.16 (m, 2H), 7.22-7, 46 (m, 7H), 7.51 (s, 1H)	623.3	Mét. 51
29		0.73-0.85 (m, 6H), 0.85-1.65 (m, 8H), 3.24 (brs, 3H), 3.34 (brs, 2H), 3.6-3.95 (m, 2H), 4.8-4.95 (m, 2H), 5.52 (s, 1H), 7.06 (brt, 1H), 7.17 (brd, 2H), 7.27-7.40 (m, 5H), 7.40-7.50 (m, 3H), 7.69 (s, 1H)	643.3	Mét. 52
30		0.74-0.84 (m, 6H), 0.85-1.55 (m, 12H), 3.24-3.33 (m, 2H), 3.65-3.85 (m, 2H), 4, 65-4.78 (m, 2H), 5.50 (brs, 1H), 6.99-7.2 (m, 4H), 7.25-7.48 (m, 7H), 7.51 (s, 1H)	671.2	Mét. 53
31		0.72-0.84 (m, 6H), 0.85-1.65 (m, 8H), 3.27 (brs, 2H), 3.54-3.9 (m, 2H), 4.70 (ABq, 2H), 5.70 (s, 1H), 6.63-6.69 (m, 1H), 6.71-6.77 (m, 2H), 7.02 (brt, 1H), 7.08-7.17 (m, 3H), 7.30 (brt, 2H), 7.52 (s, 1H)	675.4	Mét. 54

32		0.72-0.84 (m, 6H), 0.98-1.67 (m, 8H), 3.21 (brs, 2H), 3.54-3.9 (m, 5H), 4.62 (ABq, 2H), 5.57 (s, 1H), 6.51(s, 1H), 6.59-6.73 (m, 3H), 6.97 (brt, 1H), 7.12 (brd, 2H), 7.28 (brt, 2H), 7.56 (s, 1H)	627.5	Mét. 55
33		0.73-0.86 (m, 6H), 1.0-1.68 (m, 8H), 2.19 (s, 3H), 3.24 (brs, 2H), 3.55-3.9 (m, 2H), 4.71 (ABq, 2H), 5.53 (s, 1H), 6.60-6.73 (m, 3H), 6.75 (s, 1H), 6.96 (brt, 1H), 7.10 (brd, 2H), 7.27 (brt, 2H), 7.44 (s, 1H)	643.4	Mét. 56
34		0.74-0.86 (m, 6H), 1.0-1.3 (m, 8H), 1.35-1.57 (m, 4H), 2.19 (s, 3H), 3.23 (brs, 2H), 3.62-3.85 (m, 2H), 4.65 (ABq, 2H), 5.28 (s, 1H), 6.72 (s, 1H), 6.94-7.05 (m, 3H), 7.12 (brd, 2H), 7.28 (brt, 2H), 7.39 (s, 1H), 7.43 (dd, 2H)	657.3	Mét. 57
35		0.75-0.86 (m, 6H), 1.0-1.3 (m, 8H), 1.35-1.55 (m, 4H), 2.01 (s, 3H), 3.11-3.26 (ABq, 2H), 3.6- 3.8 (m, 2H), 4.58 (d, 1H), 4.70 (d, 1H), 5.64 (s, 1H), 6.62 (s, 1H), 6.91-7.0 (m, 2H), 7.01-7.12 (m, 3H), 7.23-7.33 (m, 4H), 7.37 (s, 1H), 7.69 (brd, 1H)	678.4	Mét. 58

36		0.76-0.84 (m, 6H), 1.0-1.3 (m, 8H), 1.36-1.53 (m, 4H), 3.21 (brs, 2H), 3.64 (s, 3H), 3.67-3.87 (m, 2H), 4.57 (ABq, 2H), 5.31 (s, 1H), 6.50 (s, 1H), 6.95-7.06 (m, 3H), 7.14 (brd, 2H), 7.28 (brt, 2H), 7.38-7.46 (m, 2H), 7.51 (s, 1H)	641.4	Mét. 59
37		0.75-0.87 (m, 6H), 1.0-1.3 (m, 8H), 1.34-1.53 (m, 4H), 3.18 (ABq, 2H), 3.27 (s, 3H), 3.65-3.85 (m, 2H), 4.52 (d, 1H), 4.65 (d, 1H), 5.66 (s, 1H), 6.30 (s, 1H), 6.90-7.02 (m, 2H), 7.03- 7.16 (m, 3H), 7.23-7.34 (m, 4H), 7.50 (s, 1H), 7.59 (brd, 1H)	662.4	Mét. 60

Ejemplo 38

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-1'-fenil-1'-carboximetil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 22; 50 mg, 0.078 mmol) se disolvió en DMF (1.5 ml). Se agregó metanotiolato de sodio (20 mg, 0.29 mmol) y la mezcla se agitó durante 1.5 horas a 50°C. Se agregó ácido acético (40 mg) y el solvente se evaporó bajo presión reducida. El residuo se purificó mediante HPLC preparativa usando tampón MeCN/acetato de amonio (45:55) como eluyente para producir el compuesto del título 29 mg (61%). NMR (DMSO-d_6): 0.7-0.8 (m, 6H), 0.9-1.6 (m, 8H), 2.2 (s, 3H), 3.1-3.7 (m, 4H), 4.6-4.8 (m, 3H), 6.7 (s, 1H), 6.8-7.4 (m, 11H), 8.3 (d, 1H).

Ejemplo 39

1,1-Dioxo-3-butil-3-etil-5-fenil-7-etiltio-8-[N-((R)-1'-fenil-1'-carboximetil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 22; 50 mg, 0.078 mmol), etanotiol (99 mg, 1.59 mmol) y carbonato de cesio (253 mg, 0.78 mmol) se agregaron a DMF (5 ml) y la mezcla se agitó durante 30 horas a 44°C. El solvente se filtró, se evaporó bajo presión reducida. El residuo se purificó mediante HPLC preparativa usando tampón MeCN/acetato de amonio (45:55) como eluyente. El residuo se purificó mediante cromatografía de columna usando DCM: metanol (100:15) para producir el compuesto del título 15 mg (31%). NMR (300 MHz, CD_3OD) 0.7-0.85 (m, 6H), 1.0-1.6 (m, 11H), 2.65 (q, 2H), 3.2 (s, 2H), 3.7 (brs, 2H), 4.6 (q, 2H), 5.3 (s, 1H), 6.75 (s, 1H), 6.9-7.5 (m, 11H).

Ejemplo 40

1,1-Dioxo-3-butil-3-etil-5-fenil-7-(2-hidroxietiltio)-8-[*N*-(R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 22; 50 mg, 0.078 mmol), 2-mercaptoetanol (281 mg, 3.59 mmol) y carbonato de cesio (228 mg, 0.7 mmol) se agregaron a DMF (5 ml) y la mezcla se agitó durante 9 horas a 70°C. El solvente se evaporó bajo presión reducida. El residuo se purificó mediante HPLC preparativa usando tampón MeCN/acetato de amonio (45:55) como eluyente. Las fracciones recogidas se liofilizaron para producir el compuesto del título 20 mg (40%). NMR (300 MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.6 (m, 8H), 2.9 (t, 2H), 3.2 (s, 2H), 3.55 (t, 2H), 3.7 (brs, 2H), 4.65 (q, 2H), 5.3 (s, 1H), 6.9 (s, 1H), 6.95-7.5 (m, 11H).

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Ejemplo 41

1,1-Dioxo-3-butil-3-etil-5-fenil-7-(2-*N'*,*N'*-dimetilaminoetiltio)-8-[*N*-((R)-1'-fenil-1'-carboximetil]carbamoilmetoxi]-2,3,4,5-tetrahidro-1.5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 22; 50 mg, 0.078 mmol), dimetilaminoetanotiol clorhidrato (99 mg, 0.94 mmol), carbonato de potasio (129 mg, 0.94 mmol), DIPEA (100 mg, 0.77 mmol) y borohidruro de sodio (35 mg, 0.93 mmol) se agregaron a DMF (10 ml) y la mezcla se agitó durante 24 horas a 85°C.

El solvente se filtró y se evaporó bajo presión reducida. El residuo se purificó dos veces mediante HPLC preparativa usando tampón MeCN/acetato de amonio (40:60) como eluyente. Las fracciones recogidas se liofilizaron para producir el compuesto del título 15 mg (30%). NMR (300 MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.65 (m, 8H), 2.65 (s, 6H), 3.05 (t, 2H), 3.2 (t, 2H), 3.3 (s, 2H), 3.75 (brs, 2H), 4.75 (s, 2H), 5.2 (s, 1H), 6.95-7.4 (m, 11), 7.5 (s, 1H).

Ejemplo 42

1,1-Dioxo-3-butil-3-etil-5-fenil-7-isopropiltio-8-[*N*-((R)-1'-fenil-1'-carboximetil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 22; 50 mg, 0.078 mmol), 2-propanotiol (126 mg, 1.65 mmol), carbonato de cesio (152 mg, 0.47 mmol), borohidruro de sodio (25 mg, 0.66 mmol) se agregaron a DMF (5 ml) y la mezcla se agitó durante 5 minutos a 100°C. El solvente se evaporó bajo presión reducida. El residuo se purificó mediante HPLC preparativa usando tampón MeCN/acetato de amonio (45:55) como eluyente. Las fracciones recogidas se liofilizaron para producir el compuesto del título 15 mg (30%).

NMR (300 MHz, DMSO-d_6) 0.7-0.85 (m, 6H), 0.95-1.65 (m, 14H), 3.3 (s, 2H), 3.7 (brs, 2H), 4.75 (dd, 2H), 5.05 (brs, 1H), 6.75-7.4 (m, 12H), 8.5 (brs, 1H).

Ejemplo-43

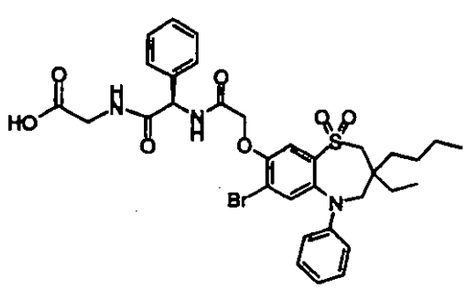
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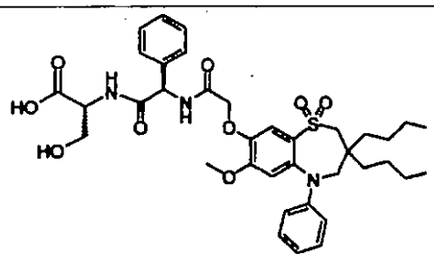
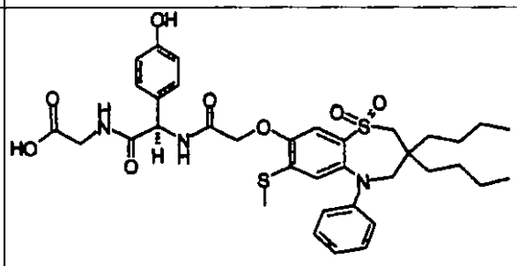
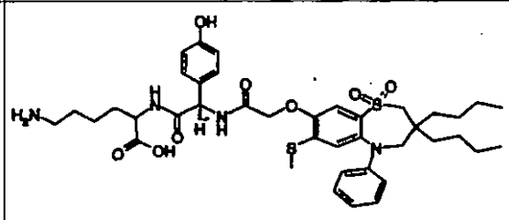
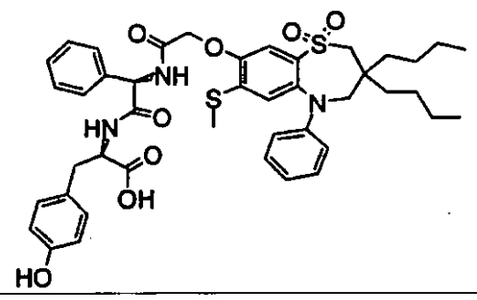
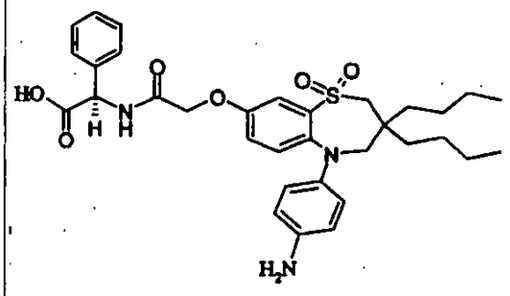
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*'-(*t*-butoxicarbonilmetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5- benzotiazepina (Método 63; 120 mg, 0.17 mmol) se disolvió en DCM (2 ml). Se agregó TFA (0.7 ml) y la mezcla se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se evaporó bajo presión reducida. El residuo se purificó mediante HPLC preparativa usando tampón MeCN/acetato de amonio (50:50) como eluyente para producir el compuesto del título 95 mg (85%).

NMR (300 MHz, DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.6 (m, 12H), 2.2 (s, 3H) 3.2-3.3 (m, 2H), 3.5-3.8 (m, 4H), 4.8 (ABq, 2H), 5.6 (d; 1H), 6.7 (s, 1H), 6.8-7.5 (m, 11H), 8.5-8.7 (m, 2H).

Ejemplos 44-49

Los siguientes compuestos se sintetizaron mediante el procedimiento de Ejemplo 43 usando el material base apropiado.

Ej.	Compuesto	NMR o m/z	SM
44		(300 MHz) 0.7-0.9 (m, 6H), 1.0-1.7 (m. 8H), 3.2 (m, 2H), 3.75 (brs, 2H), 3.9-4.0 (m, 1H), 4.15-4.25 (m, 1H), 4.5-4, 7 (m, 2H), 5.75-5.9 (m, 1H), 7.05-7.2 (m, 4H), 7.25-7.4 (m, 5H), 7.45-7.55 (m, 3H), 8.2 (d, 1H)	Mét. 64

45		(CD_3OD) 0.70-0, 90 (m, 6H), 1.00- 1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H) 3.55 (s, 3H), 3.75 (brs, 2H), 3.80-4.00 (m, 2H), 4.40-4.70 (m, 3H), 5.65 (s, 1H), 6.50 (s, 1H), 6.95-7.50 (m, 10H), 7.55 (s, 1H)	Mét. 41
46		(300 MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.2 (s, 3H), 3.25 (2H), 3.7- 3.95 (m, 4H), 4.7 (ABq, 2H), 5.5 (s, 1H), 6.7 (s, 1H), 6.75-7.35 (m, 9H), 7.4 (s, 1H)	Mét. 65
47		783.5	Mét. 66
48		802.7	Mét. 68
49		(500 MHz, CD_3OD) 0.82 (brt, 6H), 1.05-1.26 (m, 8H), 1.42-1.56 (m, 4H), 3.27 (brs, 2H), 3.6-3.75 (m, 2H), 4.58 (ABq, 2H), 5.41 (s, 1H), 6.73-6.82 (m, 3H), 7.0 (d, 2H), 7.05 (dd, 1H), 7.25-7.36 (m, 3H), 7.41 (brd, 2H), 7.48 (d, 1H); m/z 608.3	Ej. 119

Ejemplo 50

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*'-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina sal de amonio

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1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 22; 150 mg, 0.30 mmol) y ácido 2-((2'R)-2'-amino-2'-feniletanoilamino)etanosulfónico (Método 28; que contenía DIPEA clorhidrato, 150 mg, 0.36 mmol) se disolvió en DMF (6 ml). Se agregaron DIPEA (0.2 ml, 1.15 mmol) y TBTU (114 mg, 0.36 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente.

El solvente se evaporó a presión reducida. El residuo se purificó mediante HPLC preparativa usando una gradiente tampón MeCN/acetato de amonio (5/95 a 100/0) como eluyente para producir el compuesto del título 73 mg (32%). NMR (CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.3 (m, 8H), 1.3-1.6 (m, 4H), 2.16 (s, 3H), 2.85-3.0 (m, 2H), 3.24 (brs, 2H) 3.5-3.85 (m, 4H), 4.70 (ABq, 2H), 5.47 (s, 1H), 6.71 (s, 1H), 6.97 (brt, 1H), 7.11 (brd, 2H), 7.23-7.45 (m, 8H); m/z 746.2.

Ejemplo 51

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[N'-(2-sulfoetil)carbamoil]metil)carbamoilmetoxi)-2,3,4,5-tetrahidro-1.5-benzotiazepina sal de amonio

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 17; 49 mg, 0.10 mmol) y ácido 2-((2'R)-2'-amino-2'-feniletanoilamino)etanosulfónico (Método 28; que contenía DIPEA clorhidrato; 52 mg, 0, 12 mmol) se disolvió en DMF (2 ml). Se agregaron DIPEA (0.071 ml, 0.41 mmol) y TBTU (39 mg, 0.12 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente. El solvente se evaporó a presión reducida. El residuo se purificó mediante HPLC preparativa usando una gradiente tampón MeCN/acetato de amonio (5/95 a 100/0) como eluyente para producir el compuesto del título 59 mg (78%). NMR (CD_3OD) 0.74-0.90 (m, 6H), 0.98-1.3 (m, 4H), 1.35-1.67 (m, 4H), 2.16 (s, 3H), 2.85-3.02 (m, 2H), 3.23 (brs, 2H) 3.52-3.90 (m, 4H), 4.70 (ABq, 2H), 5.47 (s, 1H), 6.71 (s, 1H), 6.96 (brt, 1H), 7.09 (brd, 2H), 7.21-7.48 (m, 8H); m/z 718.4.

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Ejemplo 52

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*-(carboximetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-(R)-1'-fenil-1'-[-*N*-(etoxicarbonilmetil)carbamoil]metil)carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 72; 44 mg, 0.063 mmol) se disolvió en THF; H_2O, 1:1, (2 ml) y se agregó NaOH (l M, 0.126 mmol). La mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se acidificó con HCl (1 M), se diluyó a 10 ml y se extrajo con DCM (3 x 10 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$) y el solvente se evaporó para producir el compuesto del título 33 mg (78%). NMR (300 MHz) 0.78-0.85 (m, 6H), 1.02- 1.70 (m, 8H), 2.20 (s, 3H), 3.15/3.21 (ABq, 2H), 3.78 (m, 2H), 3.94/4.20 (dABq, 2H), 4.64 (q, 2H), 5.91 (d, 1H), 6.65 (s, 1H), 6.98-7.52 (m, 11H), 8.17 (d, 1H).

Ejemplo 53

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*-(1"-carboxi-1"-fenilmetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1-5-benzotiazepina

El compuesto del título se sintetizó de 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[N-(1"-metoxicarbonil-1"-fenilmetil) carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 73) mediante el procedimiento de Ejemplo 52. NMR (500 MHz) 0.76-0.84 (m, 6H), 1.05-1.73 (m, 8H), 2.14 (s, 3H), 3.16 (m, 2H), 3.74 (m, 2H), 4.48 (m, 2H), 5.53 (d, 2H), 5-96 (d, 2H), 6.63 (s, 1H), 6.97- 7.48 (m, 13H), 7.86 (m, 1H), 8.17 (m, 1H).

Ejemplo 54

1,1-Dioxo-3-etil-3-butil-5-fenil-7-metiltio-8-{1-[*N*-((R')-α-carboxibencil) carbamoil]etoxi}-2,3,4,5-tetrahidro-1.5-benzotiazepina

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A una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-{1-*N*-((R)-1'-fenil-1'-carboximetil)carbamoil]etoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 10, 0.050 g, $7.6x10^{-5}$ mol) en DMF (4 ml) se agregó tiometilato de sodio (0.021 g, $3.0x10^{-4}$ mol) y la solución se agitó durante 4 horas a temperatura ambiente. La mezcla se concentró y el residuo se dividió en porciones entre agua y éter. La fase acuosa se extrajo dos veces más con éter y los extractos orgánicos combinados se secaron ($MgSO_4$), se concentraron y purificaron por HPLC. El compuesto del título se obtuvo en 0.030 g (63 %) como un sólido blanco. NMR (CD_3OD) 0.75-0.90 (m, 6H), 1.00-1.30 (m, 4H), 1.40-1.70 (m, 7H), 2.15 (d, 3H), 3.10-3.30 (m, 2H), 3.55-3.95 (m, 2H), 4.80-4.95 (m, 2H), 5.30 (d, 1H), 6.70-7.50 (m, 12H); m/z 625.3.

Ejemplo 55

1,1-Dioxo-3-etil-3-butil-5-fenil-7-metiltio-8-{α-[*N*-((R)-α-carboxibencil)-carbamoil]benciloxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3-etil-3-butil-5-fenil-7-metiltio-8-{α-[*N*-((R)-α-carboxibencil)carbamoil]benciloxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 11; 3.018 g, $2.5x10^{-5}$ mol) en DMF (3 ml) se agregó tiometilato de sodio (0.007 g, $1.0x10^{-4}$ mol) y la solución se agitó durante 4 horas a temperatura ambiente. La mezcla se concentró y el residuo se dividió en porciones entre agua y éter. La fase acuosa se extrajo dos veces más con éter y los extractos orgánicos combinados se secaron ($MgSO_4$), se concentraron y purificaron mediante HPLC. El compuesto del título se obtuvo en 0.015 g (89 %) como un sólido blanco. NMR (CD_3OD) 0.70-0.85 (m, 6H), 1.00-1.25 (m, 4H), 1.35-1.65 (m, 4H), 2.20 (d, 3H), 3.10-3.20 (m, 2H), 3.50-3.85 (m, 2H), 5.30 (d, 1H), 5.80 (d, 1H), 6.70 (s, 1H), 6.90- 7.65 (m, 16H).

Ejemplo 56

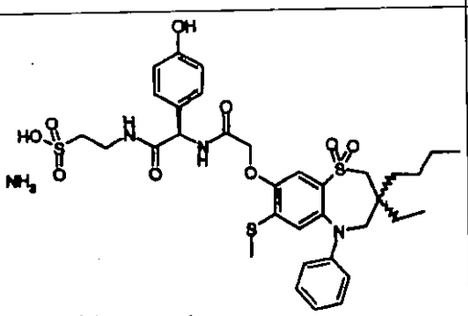
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*'-(2-sulfoetil)

carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

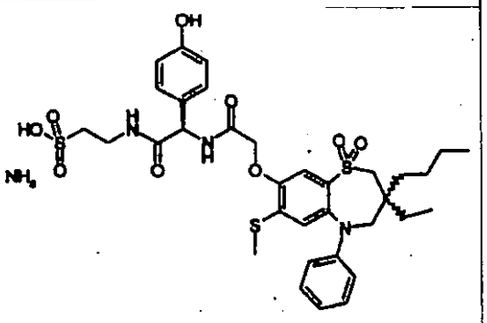
Ácido 2-{[(2R)-2-amino-2-(4-hidroxifenil)etanoil]amino} etanosulfónico (Método 80; 32.5 mg, 0.119 mmol) se mezcló con DMF (4 ml) y N-metilmorfolina (30 µl, 0.272 mmol). Se obtuvo una solución clara y 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 22; 50 mg, 0.099 mmol) y TBTU (38 mg, 0.119 mmol) se agregaron sucesivamente. La reacción se agitó a temperatura ambiente durante 30 minutos y se retiró el DMF. El producto crudo se purificó mediante HPLC preparativa usando un tampón MeCN/acetato de amonio (1:1). La liofilización arrojó 55 mg del compuesto del título (71%). NMR (500 MHz, MeOD) 0.78-0.86 (m, 6H), 1.0- 1.3 (m, 8H), 1.4-1.6 (m. 4H), 2.15 (s, 3H), 2.85-3.00 (m, 2H), 3.25 (s, 2H), 3.55-3.68 (m, 2H), 3.75 (brs, 2H), 4.65 (ABq, 2H), 5.36 (s, 1H), 6, 70 (s, 1H), 6.75 (d, 2H), 6, 98 (t, 1H), 7.12 (d, 2H), 7.22 (d, 2H) 7.28 (t, 2H), 7.4 (s, 1H); m/z 762.

Ejemplos 57-58

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 56 usando el material base apropiado, salvo que la reacción se dejó continuar durante 64 horas (Ejemplo 57) o 2 horas (Ejemplo 58) y el producto se purificó mediante HPLC preparativa usando una gradiente tampón MeCN/acetato de amonio (45/55 a 60/40) como eluyente.

Ej.	Compuesto	NMR (CD_3OD) y m/z	SM
57	 Enantiómero 1	0.75-0.84 (m, 6H) 1.00-1.27 (m, 4H), 1.37-1.64 (m, 4H) 2.14 (s, 3H), 2.86-3.00 (m, 2H), 3.22 (s, 2H), 3.53-3.68 (m, 2H), 3.85 brd, 2H), 4.68 (ABq, 2H), 5.35 (s, 1H), 6.70 (s, 1H), 6.75 (d, 2H), 6.95 (t, 1H), 7.08 (d, 2H), 7.20-7.29 (m, 4H), 7.37 (s,	Mét. 23

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		1H); m/z 751 ($M+NH_4^+$)	
58	 Enantiómero 2	0.77-0.85 (m, 6H) 1.06-1.27 (m, 4H), 1.40-1.62 (m, 4H) 2.17 (s, 3H), 2.87-3.00 (m, 2H), 3.24 (s, 2H), 3.56-3.68 (m, 2H), 3.75 (brd, 2H), 4.71 (ABq, 2H), 5.37 (s, 1H), 6-72 (s, 1H), 6.77 (d. 2H), 6.97 (t, 1H), 7.10 (d, 2H), 7.23 (d, 2H), 7.28 (t, 2H), 7.40 (s, 1H); m/z 751 ($M+NH_4^+$)	Mét. 24

Ejemplo 59

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α[*N'*-(2-carboxietil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

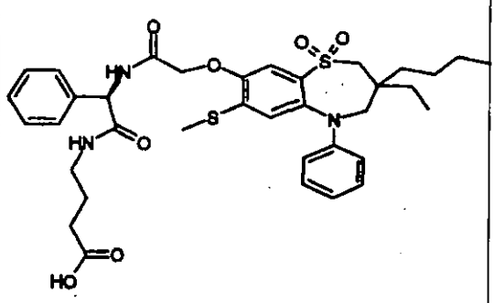
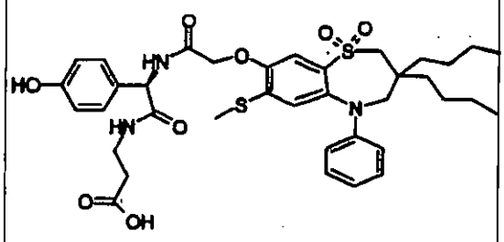
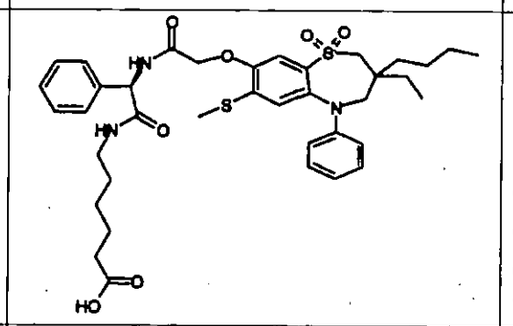
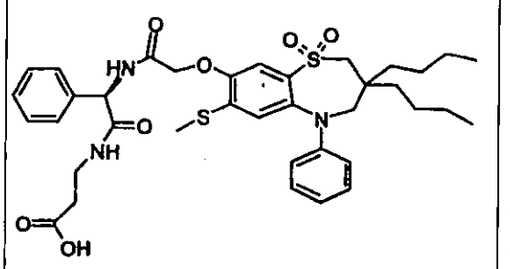
1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-carboxibencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 38; 66.8 mg, 0.109 mmol) y β-alanina etiléster clorhidrato (23.0 mg, 0.15 mmol) se disolvió en DCM (2.5 ml) y se agregó *N*-metil morfolina (0.07 ml, 0.64 mmol). Luego de agitar a temperatura ambiente durante 5 minutos se agregó TBTU (45.6 mg, 0.142 mmol) seguido por agitación durante 2 horas. La mezcla de reacción se filtró a través de una columna corta y se concentró. El éster crudo se disolvió en THF (1.5 ml) y agua (1.5 ml) y se agregó NaOH (1 M, 0.20 mmol). Luego de agitar a temperatura ambiente durante 1 hora la reacción se extinguió con 1 M HCl. La mezcla de reacción se diluyó con agua (10 ml) y se extrajo con DCM (3 x 5 ml).

Las capas orgánicas se concentraron y purificaron con HPLC preparativa para producir el compuesto del título (60 mg, 81%). NMR (300 MHz) 0.80 (m, 6H), 1.00-1.70 (m, 8H), 2.17 (s, 3H), 2.48 (m, 2H), 3.17 (ABq, 2H), 3.35 (m, 1H), 3.57 (m, 1H), 3.70 (m, 2H), 4.62 (ABq, 2H), 5.77 (d, 1H), 6.64 (s, 1H), 6.98 (t, 1H), 7.06 (d, 2H), 7.28 (m, 4H), 7.42 (m, 3H), 7.56 (m, 1H).8.10(m, 1H).

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Ejemplos 60-63

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 59 usando el material base apropiado.

Ej.	Compuesto	NMR	SM
60		0.81 (m, 6H), 1.00-1.95 (m, 10H), 2.22 (s, 3H), 3.37 (m, 2H), 3.18 (ABq, 2H), 3.48 (m, 2H), 3.75 (m, 2H), 4.66 (q, 2H), 5.75 (d, 1H), 6.67 (s, 1H), 7.00 (t, 1H), 7.09 (m, 2H), 7.20 (m, 1H), 7.30 (m, 4H), 7.44 (m, 2H), 8.25 (m, 1H)	Ej. 38
61		(300 MHz, DMSO-d_6) 0.74 (m, 6H), 0.95-1.50 (m, 12H), 2.16 (s, 3H), 2.28 (t, 2H), 3.24 (m, 2H), 4.74 (q, 2H), 5.33 (d, 1H), 6.69 (m, 2H), 6.85 (t, 1H), 6-99 (m, 2H), 7.16 (m, 4H), 8.33-8.45 (m, 2H)	Ej. 2
62		(300 MHz) 0.81 (m, 6H), 1.00-1.74 (m, 14H), 2.22 (s, 3H), 2.31 (m, 2H), 3.10-3.35 (m, 4H), 3.73 (m, 2H), 4.62 (ABq, 2H), 5.64 (d. 1H), 6.39 (brs, 1H), 6.67 (s, 1H), 6.96-7.10 (m, 3H), 7.25-7.48 (m, 7H), 8.21 (d, 1H)	Ej. 38
63		0.81 (m, 6H), 1.03-1.55 (m, 12H), 2.19 (s, 3H), 2.55 (m, 2H), 3.18 (m, 2H), 3.46 (m, 1H), 3.58 (m, 1H), 3.74 (m, 2H), 4.64 (ABq, 2H), 5.80 (m, 1H), 6.64 (s, 1H), 7.01 (t, 1H), 7.08 (d, 2H), 7.30 (m, 5H), 7.44 (m, 3H), 8.11(m, 1H)	Ej. 1

Ejemplo 64

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-carboxi-4-metoxibencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1.5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*t*-butoxicarbonil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5)-tetrahidro-1,5-benzotiazepina (Método 78; 48 mg, 0.070 mmol), bromoetil(trimetilamoniobromuro) (57 mg, 0.230 mmol), tetrabutilamonio bromuro (3 mg, 0.009 mmol) y Cs_2CO_3 (71 mg, 0.22 mmol) se agregaron a CH_3CN (1.0 ml) y la mezcla de reacción se calentó a reflujo durante la noche. El solvente se evaporó y el residuo se agregó a agua (10 ml), se extrajo con DCM (3x5 ml) y se secó ($MgSO_4$). El éster crudo se disolvió en DCM (2.5 ml), se agregó TFA (0.3 ml) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Los solventes se evaporaron y el producto crudo se purificó con HPLC preparativa para producir el compuesto del título (23 mg, 51 %). NMR (DMSO-d_6) 0.74 (m, 6H), 0.94-1.60 (m, 8H), 2.17 (s, 3H), 3.25 (m, 2H), 3.69 (s, 3H), 4.70 (ABq, 2H), 4.95 (brs, 1H), 6.71 (s, 1H), 6.83 (m, 3H), 6.97 (d, 2H), 7.20 (m, 4H), 7.27 (s, 1H), 8.37 (brs, 1H).

Ejemplo 65

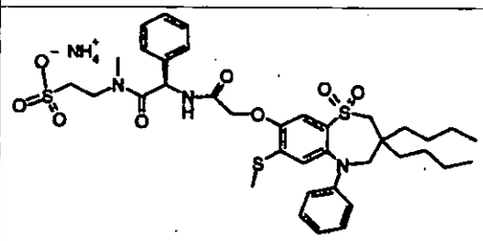
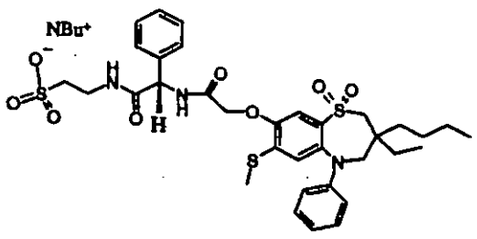
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(α-[*N'*-(2-sulfoetil)carbamoil]-α-metilbencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1.5-benzotiazepina sal de amonio

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-(α-carboxi-α-metilbencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 18; 27 mg, 0.041 mmol) se disolvió en DCM (2 ml). Se agregaron sal de taurina tetrabutilamonio (45 mg, 0.123 mmol) y TBTU (16 mg, 0.050 mmol) sucesivamente y la mezcla se agitó durante 5 horas a temperatura ambiente. El solvente se evaporó y el producto se purificó mediante HPLC preparativa usando un tampón MeCN/acetato de amonio (50/50) como eluyente. La liofilización arrojó el compuesto del título en un rendimiento del 62% (20 mg). NMR mostró que 16% del producto

permaneció como una sal de tetrabutilamonio. NMR (500 MHz) 0.75-0.9 (m, 6H), 1.0-1.3 (m, 8H), 1.3-1.6 (m, 4H), 1.95 (s, 3H), 2.1 (s, 3H), 2.9 (brs, 2H), 3.05 (brs, 2H), 3.55 (ABd, 2H), 3.75 (brs, 2H), 4.55 (ABq, 2H), 6.6 (s, 1H), 6.9-7.6 (m, 12H), 8.2-8.3 (brs, 1H); m/z 777 ($M+NH4^+$).

Ejemplos 66-67

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 65 usando el material base apropiado.

Ej.	Compuesto	NMR (CD_3OD) y M/z	SM
66		777 ($M+NH_4^+$)	Ej. 1
67		0.75-0.85 (m, 6H), 1.02 (t, 12H), 1.05-1.3 (m, 4H), 1.3-1.7 (m, 20H), 2.17 (s, 3H), 2.85-2.99 (m, 2H), 3.19-3.26 (m, 10H), 3.52-3.92 (m, 4H), 4.71 (ABq, 2H), 5.47 (s, 1H), 6.72 (s, 1H), 6.96 (1, 1H), 7.09 (brd, 2H), 7.23-7.44 (m, 8H); m/z 735.2 ($M+NH_4^+$)	Ej. 25

Ejemplo 68

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-(carboximetil)carbamoil]-α-metilbencil)carbamoilmetoxi)-2,3,4,5-tetrahidro-1.5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{α-[*N*-(metoxicarbonilmetil)carbamoil]-α-metilbencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina; (Método 44; 20 mg, 0.028 mmol) se disolvió en 2.5 ml de una mezcla THF/agua (4/1). Se agregó LiOH (2 mg, 0.084 mmol) y la mezcla se agitó durante 1 hora a temperatura ambiente. El

compuesto del título se purificó con HPLC preparativa usando un tampón MeCN/acetato de amonio (50/50) como eluyente. El MeCN se evaporó y el tampón remanente se acidificó con ácido acético. La liofilización arrojó 10 mg de producto (51%). NMR 0.7-0.9 (m, 6H), 1.0-1.35 (m, 8H), 1.35-1.6 (m, 4H), 2.0 (s, 3H), 2.2 (s, 3H), 3.2 (brs, 2H), 3.65-3.85 (brs, 2H), 3.9-4.1 (d, 2H), 4.5-4.7 (ABq, 2H), 6.6 (s, 1H), 6.8 (brs, 1H), 6.9- 7.5(m, 11H), 8.1(s, 1H);m/z 727($M+NH_4^+$).

Ejemplo 69

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{α(*N'*-2-sulfoetil)carbamoil]-2-fluorobencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{α-carboxi-2-fluorobencil] carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 15; 20 mg, 0.030 mmol), sal de taurina tetrabutilamonio (20 mg, 0.054 mmol) y DIPEA (25 mg, 0.19 mmol) se disolvieron en DMF (0.4 ml). Se agregó TBTU (15 mg, 0.047 mmol) y la mezcla se agitó durante 30 minutos a temperatura ambiente. El producto se separó de la mezcla de reacción mediante HPLC preparativa usando tampón MeCN/acetato de amonio (50:50) como eluyente. Se obtuvieron 7 mg (29%) del compuesto del título. M/z = 764.5.

Ejemplo 70

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

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N'*-(carboximetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 43; 35 mg, 0.050 mmol) y (R)-α-[*N*-(*t*-butoxicarbonilmetil)carbamoil]bencilamina (Método 86; 20 mg, 0.076 mmol) se disolvieron en DCM (2 ml) y se agregó 2,6-lutidina (0.03 ml, 0.26 mmol). Luego de agitar a temperatura ambiente durante 5 minutos, se agregó TBTU (20mg, 0.062 mmol) y la agitación se continuó durante 3

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horas. La mezcla de reacción se filtró a través de una columna usando DCM ; EtOAc; 3 : 1 como eluyente. El éster t-butílico se disolvió entonces en DCM (6 ml) y se agregó TFA (1 ml). Luego de agitar a temperatura ambiente durante la noche los solventes se evaporaron. Se agregó tolueno y se evaporó dos veces. No fue necesaria más purificación para producir el compuesto del título (40 mg, 93 %). NMR (500 MHz, DMSO-d_6) 0.75 (m. 6H), 0.95-1.50 (m, 12H), 2.16 (s, 3H), 3.25 (m, 2H), 3.75 (m, 2H), 3.90 (dd, 1H), 4.73/4.84 (ABq, 2H), 5.54 (m, 2H), 5.58 (d, 1H), 6.68 (s, 1H), 6.85 (t, 1H), 6.99 (d, 2H), 7.18-7.46 (m, 13H), 8.51-8.73 (m, 4H).

Ejemplo 71

1,1-Dioxo-3.3-dibutil-5-fenil-7-metiltio-8-[*N*-(S)-(α-carboxi-4-hydroybencil)carbamoilmetoxi]2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro- 1,5-benzotiazepina (Método 22; 61 mg, 0.12 mmol) y clorhidrato de metil (2S)-amino(4-hidroxifenil)acetato (31 mg, 0.14 mmol) se disolvieron en DCM (4 ml) y se agregó 2,6-lutidina (0.04 ml, 0.34 mmol). Luego de agitar a temperatura ambiente durante 5 minutos se agregó TBTU (53 mg, 0.17 mmol) y la agitación se continuó durante 2 horas. La mezcla de reacción se filtró a través de una columna corta. El éster metílico crudo se disolvió en THF (1.5 ml) y se agregó agua (1.0 ml) y NaOH (aq., 1 M, 0.39 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 8 horas, se extinguió con HCl (1 M) y se extrajo con DCM (3 x 5 ml). Las capas orgánicas recogidas se concentraron y purificaron con HPLC preparativa usando tampón MeCN/acetato de amonio (50:50) para producir el compuesto del título (57 mg, 72 %). NMR (500 MHz, CD_3OD) 0.81 (m, 6H), 1.05-1.26 (m, 8H), 1.40-1.55 (m, 4H), 2.17 (s, 3H), 3.24 (brs, 2H), 3.74 (brs, 1H), 4.66 (ABq, 2H), 6.70-6.75 (m, 3H), 6.99 (t, 1H), 7.11 (d, 2H), 7.22-7.30 (m, 4H), 7.40 (s, 1H).

Ejemplo 72

1,1-Dioxo-3.3-dibutil-5-fenil-7-metiltio-8-(*N*-(S)-(α-{*N*'-(2-sulfoetil)

carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina sal de amonio

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-(S)-(α-carboxi-4-hidroxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 71; 31 mg, 0.047 mmol) y taurina de tetrabutilamonio (57 mg, 0.155 mmol) se disolvieron en DCM (2 ml). Luego de agitar a temperatura ambiente durante 5 minutos se agregó TBTU (24 mg, 0.075 mmol) y la agitación se continuó durante 6 horas. El solvente se evaporó y el residuo se purificó con HPLC preparativa (dos veces para retirar toda la sal de tetrabutilamonio) usando tampón MeCN/acetato de amonio para producir el compuesto del título 6 mg (16%). M/z 762.2.

Ejemplo 73 y Ejemplo 74

1,1-Dioxo-3-R/S)-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-(R)-{α-[*N'*-(R)-(2-imidazol-5-il-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1.5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 38; 56.4 mg, 0.092 mmol) y diclorhidrato de metil D-histidinato (25.2 mg, 0.104 mmol) se agregaron a DCM (3 ml). Se agregó N-metil morfolina (0.05 ml, 0.41 mmol) seguida por TBTU (40 mg, 0.12 mmol). La mezcla de reacción se agitó a 4°C durantel hora 30 minutos y a temperatura ambiente durante 3 horas. Se agregaron más TBTU (15 mg, 0.047 mmol) y DIPEA (0.025 ml, 0.14 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante otros 30 minutos. El solvente se evaporó y el residuo se filtró a través de una columna corta MeOH como eluyente. El éster metílico crudo se disolvió en THF (1.0 ml) y se agregó agua (1.0 ml) y NaOH (aq., 1 M, 0.15 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas y se extinguió con HCl (1 M). Los solventes se evaporaron y el residuo se purificó con HPLC preparativa usando tampón MeCN/acetato de amonio. El compuesto se eluyó como dos picos, que se asumió que eran los dos diastereómeros. Primer pico (10 mg,

14%). Segundo pico (16.8 mg, 24%). Primer pico: NMR (DMSO-d_6) 0.74 (m, 6H), 0.95-1.60 (m, 8H), 2.17 (s, 3H), 2.82 (m, 2H), 3.23 (m, 2H), 4.27 (m, 1H), 4.80 (ABq, 2H), 5.60 (d, l 1H), 6.55 (brs, 1H), 6.70 (s, 1H), 6.84 (t, 1H), 6.96 (d, 2H), 7.14-7.28 (m, 6H), 7.33 (s, 1H), 7.44 (brs, 1H), 8.54 (d, 1H), 8.60 (brs, 1H); m/z 748.4. Segundo pico: NMR (DMSO-d_6) 0.74 (m, 6H), 0.95-1.60 (m, 8H), 2.17 (s, 3H), 2.92 (dABq, 2H), 3.23 (m, 2H), 4.41 (m, 1H), 4.79 (ABq, 2H), 5.60 (d, 1H), 6.70 (s, 1H), 6.78 (s, 1H), 6.84 (t, 1H), 6.96 (d, 2H), 7.16-7.34 (m, 6H), 7.40 (m, 2H), 7.55 (s, 1H), 8.55 (d, 1H), 8.71 (d, 1H); m/z 748.4.

Ejemplo 75

1,1-Dioxo-3,3-dibutil-5-(4-*t*-butilfenil)-7-metiltio-8-(*N*-{(R)-α-{*N'*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

El compuesto del título se aisló como un sub-producto en síntesis de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'[*N'*-(carboximetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 43). Aproximadamente 1 g de este compuesto se purificó con HPLC preparativa (tampón MeCN/acetato de amonio (50:50)) para producir el compuesto del título (32 mg). NMR (500 MHz, DMSO-d_6) 0.73 (m, 6H), 0.90-1.40 (m, 12H), 1.24 (s, 9H), 2.16 (s, 3H), 3.23 (m, 2H), 3.65/3.75 (dABq, 2H), 4.72/4.82 (ABq, 2H), 5.60 (d, 1H), 6.65 (s, 1H), 6.97 (d, 2H), 7.23-7.35 (m, 6H), 7.45 (d, 2H), 8.58 (d, 1H), 8.62 (t, 1H).

Ejemplo 76

1,1-Dioxo-3-butil-3-etil-5-fenil-7-(*N*-((R)-α-carboxibencil)carbamoil] metiltio)-8-metoxi-2,3,4,5-tetrahidro-1.5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-carboximetiltio-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 81; 38 mg, 0.080 mmol) y D-fenilglicina metil éster clorhidrato (24 mg, 0.12 mmol) se disolvieron en DCM (2 ml) y se agregó N-metil morfolina (0.05 ml, 0.42 mmol). Luego

de agitar a temperatura ambiente durante 5 minutos se agregó TBTU (44 mg, 0.14 mmol) y la agitación se continuó durante 2 horas. La mezcla de reacción se filtró a través de una columna corta. El producto resultante se disolvió en THF (1 ml) y agua (1 ml) y se agregó NaOH (aq., 0.2 ml, 1 M) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La reacción se extinguió con HCl (1 M), se diluyò con agua (10 ml) y se extrajo con DCM (3 x 3 ml). Purificación con HPLC preparativa produjo el compuesto del título (40 mg, 82 %). NMR (DMSO-d_6) 0.75 (m, 6H), 0.96-1.60 (m, 8H), 3.22 (m, 2H), 3.56 (ABq, 2H), 3.89 (s, 3H), 4.81 (d, 1H), 6.78 (t, 1H), 6.83 (d, 2H), 6.89 (s, 1H), 7.11-7.23 (m, 7H), 7.31 (s, 1H), 8.37 (m, 1H).

Ejemplo 77

1,1-Dioxo-3-butil-3-etil-5-fenil-7-carboximetiltio-8-[*N*-(α-carboxibencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-etoxicarbonilmetiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 82; 21 mg, 0.038 mmol) y fenil glicina metil éster clorhidrato (12 mg, 0.061 mmol) se disolvieron en DCM (1.5 ml) y se agregó N-metil morfolina (0.02 ml, 0.19 mmol). Luego de agitar a temperatura ambiente durante 5 minutos se agregó TBTU (18 mg, 0.056 mmol) y la agitación se continuó durante 2 horas. La mezcla de reacción se filtró a través de una columna corta. El diéster crudo se disolvió en THF (1 ml) y agua (1 ml) y se agregó NaOH (aq., 0.1 ml, 1 M). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, se extinguió con HCl (1 M), se diluyó con agua (10 ml) y se extrajo con DCM (3x3 ml). Las capas orgánicas recogidas se concentraron y se purificaron con HPLC preparativa usando tampón MeCN/acetato de amonio (30:70→40:60) para producir el compuesto del título (20 mg, 80%). NMR (CD_3OD) 0.80 (m, 6H), 1.03-1.26 (m, 4H), 1.38-1.65 (m, 4H), 1.96 (s, 3H), 3.20 (s, 2H), 3.44 (s, 2H), 3.67 (brs, 1H), 3.76 (brs, 1H), 4.67 (ABq, 2H), 5.29 (s, 1H), 6.89 (s, 1H), 6.92 (t, 1H), 7.05 (d, 2H), 7.19-7.32 (m, 5H), 7.41 (s, 1H), 7.45 (d, 2H).

Ejemplo 78

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-(R)-(α-{*N'*-{(S)-*N''*-(2-hidroxi-1-carboxietil)carbamoilmetil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*-(carboximetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 43; 50 mg, 0.072 mmol), *tert*-butil o-(*tert*-butil)-D-serinato clorhidrato (22 mg, 0.087 mmol) y N-metilmorfolina (40 mg, 0.40 mmol) se disolvieron en DCM (1 ml). Se agregó TBTU (29 mg, 0.090 mmol) y la mezcla se agitó durante 1 hora a temperatura ambiente. La mezcla de reacción se evaporó y el residuo se filtró a través de una columna corta (DCM: EtOAc, 1:4). La sustancia obtenida (ca. 60 mg) se disolvió en DCM (1 ml). Se agregó TFA (0.59 g, 5.2 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente. El solvente se evaporó y el residuo se purificó mediante HPLC preparativa usando tampón MeCN/acetato de amonio (50:50) como eluyente. Se obtuvieron 38 mg (72%) del compuesto del título. NMR (300 MHz, DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.5 (m, 12H), 2.2 (s, 3H), 3.2-3.9 (m, 10H), 4.2 (brs, 1H), 4.8 (ABq, 2H), 5.6 (d, 1H), 6.7 (s, 1H), 6.8- 7.5 (m, 11H), 8.0 (d, 1H), 8.6 (d, 1H), 8.7 (t, 1H).

Ejemplo 79

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-(R)-(α-{*N'*-[(S)-*N''*-(2-hidroxi-1-carboxietil)carbamoilmetil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N''*-(carboximetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 43; 50 mg, 0.072 mmol), *tert*-butil *O*-(*tert*-butil)-L-serinato clorhidrato (22 mg, 0.087 mmol) y N-metilmorfolina (40 mg, 0.40 mmol) se disolvieron en DCM (1 ml). Se agregó TBTU (29 mg, 0.090 mmol) y la mezcla se agitó durante 1 hora a temperatura ambiente. La mezcla de reacción se evaporó y el residuo se filtró a través de una columna

corta (DCM: EtOAc, 1:4). La sustancia obtenida (ca. 60 mg) se disolvió en DCM (1 ml). TFA (0.44 g, 3.9 mmol) se agregó y la mezcla se agitó durante 18 horas a temperatura ambiente. El solvente se evaporó y el residuo se purificó mediante HPLC preparativa usando tampón MeCN/acetato de amonio (50:50) como eluyente. Se obtuvieron 33 mg (63%) del compuesto del título. NMR (300 MHz, DMSO-d_6) 0.7-0.8 (m, 6H), 0.9-1.5 (m, 12H), 2.2 (s, 3H), 3.2-3.9 (m, 10H), 4.2 (m, 1H), 4.8 (ABq, 2H), 5.6 (d, 1H), 6.7 (s, 1H), 6.8- 7.5 (m, 11H), 7.9 (d, 1H), 8.6 (d, 1H), 8.7 (t, 1H).

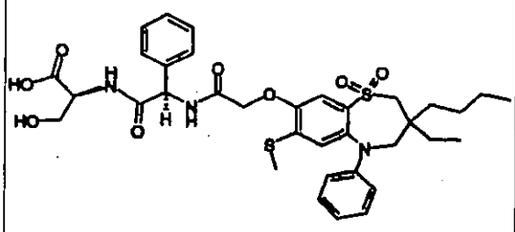
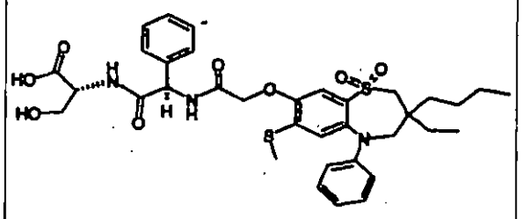
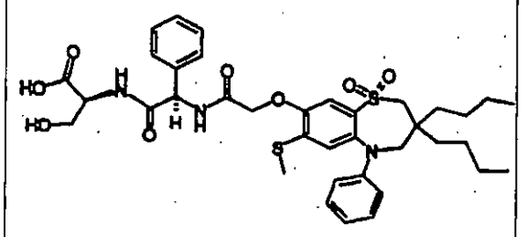
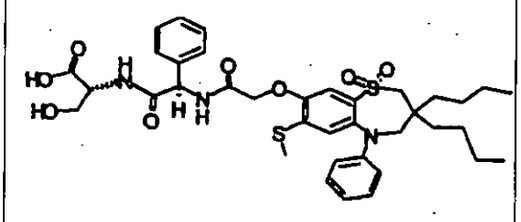
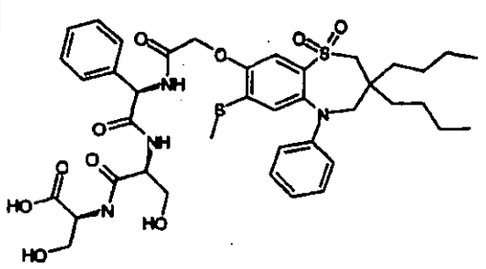
Ejemplo 80

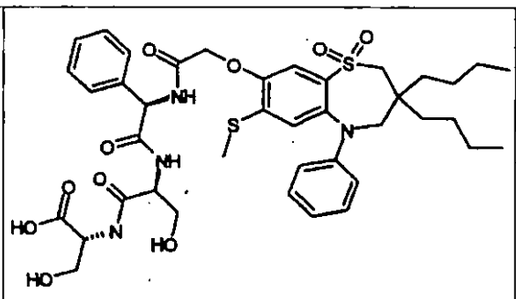
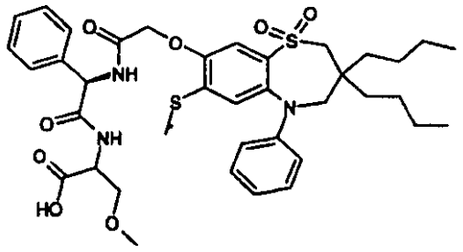
1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(1,1-dicarboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 38; 50 mg, 0.082 mmol), dimetilaminomalonato (60 mg, 0.13 mmol) y N-metilmorfolina (55 µl, 0.5 mmol) se disolvieron en DCM (3 ml), se agregó TBTU (42 mg, 0.13 mmol) y la mezcla se agitó durante 15 minutos. El solvente se evaporó bajo presión reducida. El residuo se disolvió en etanol (95%) (2 ml) y se agregó una solución de NaOH (80 mg, 2 mmol) en agua (80 µl). La mezcla de reacción se agitó durante 4 horas. La mezcla se neutralizó con ácido acético. El solvente se evaporó bajo presión reducida y el residuo se purificó mediante HPLC preparativa usando tampón MeCN/acetato de amonio (40:60) como eluyente. Las fracciones recogidas se liofilizaron para obtener 4 mg (7%) del compuesto del título. NMR (300 MHz, CD_3OD) 0.75-0.9 (m, 6H), 1.0-1.3 (m, 4H), 1.4-1.65 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.7 (brs, 2H), 4.65-4.8 (m, 2H), 5.75 (s, 1H), 6.75 (s, 1H), 6.9-7.55 (m, 11H).

Ejemplos 81-87

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 80 usando el material base apropiado salvo que se empleó 2,6-lutedina en vez de *N*-metilmorfolina y la proporción de eluyente fue tampón MeCN/acetato de amonio (45:55). El tiempo de reacción en cada etapa varió levemente.

Ej.	Compuesto	NMR (300 MHz, CD_3OD)	SM
81		(500 MHz) 0.8-0.95 (m, 6H), 1.05-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 3H), 3.25 (s, 2H), 3.7-3.9 (m, 4H), 4.4-4.45 (m, 1H), 4.7-4.8 (m, 2H), 5.7 (s, 1H), 6.75 (s, 1H), 6.95-7.6 (m, 11H)	Ej. 38
82		0.75-0.9 (m, 6H), 1.05-1.3 (m, 4H), 1.4-1.6 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.7-3.95 (m, 4H), 4.25-4.3 (m, 1H), 4.75 (ABq, 2H), 5.65 (s, 1H), 6.75 (s, 1H), 7.95-7.55 (m, 11H)	Ej. 38
83		0.75-0.9 (m, 6H), 1.05-1.35 (m, 8H), 1.4-1.6 (m, 4H), 2.15 (s. 3H), 3.25 (s, 2H), 3.7-3.9 (m, 4H), 4.35-4.45 (m, 1H), 4.7 (ABq, 2H), 5.7 (s, 1H), 6.75(s, 1H), 6.95-7.55 (m, 11H)	Ej. 1
84[1]		0.75-0.9 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2-15 (s, 3H), 3.25 (s, 2H), 3.7-3.9 (m, 4H), 3.3-3.4 (m, 1H), 4.7 (ABq, 2H), 5.65 (s, 1H), 6.7(s, 1H), 6.95-7.55 (m, 11H)	Ej. 1
85[2]		0.75-0.9 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 3.25 (s, 3H), 3.6-3.9 (m, 6H), 4.3-4.5 (m, 2H), 4.7 (ABq, 2H), 5.65 (s, 1H), 6.7 (s, 1H), 6.95- 7.5 (m, 11H)	Ej. 83

86[3]		0, 75-0.9 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.6-3.9 (m, 6H), 4.35-4.5 (m, 2H), 4.7 (ABq, 2H), 5.6 (s, 1H), 6.7(s, 1H), 6.95-7.55 (m, 11H)	Ej. 83
87[4]		0.75-0.9 (m, 6H), 1.05-1.3 (m, 8H), 1.4-1.6 (m, 4H), 2.2 (d, 3H), 3.15-3.35 (m, 5H), 3.5-3, 85 (4H), 4.4-4.5 (m, 1H), 4.6-4, 7 (m, 2H), 5.6 (s, 1H), 6.7 (s, 1H), 6.95-7.55 (m, 11H)	Ej. 1

[1] Proporción de eluyente (55:45); [2] Proporción de eluyente – gradiente variable; [3] Proporción de eluyente (50:50); [4] Proporción de eluyente (60:40)

Ejemplo 88

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-((S)-(α-carboxibencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-(S)-(α(-metoxicarbonilbencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 87; 55.2 mg, 0.064 mmol) se disolvió en THP (2 ml) y 0.5 ml agua. Se agregó LiOH (3.1 mg, 0.127 mmol) y la mezcla se agitó durante hora. Se agregó agua (1 ml) y la mezcla se acidificó con 0.1M HCl y se extrajo con DCM (3 x 2 ml). La fase DCM se secó y se concentró. El producto sólido se co-evaporó con éter dietílico y se disolvió en HPLC grado agua. La liofilización arrojó el compuesto del título como un sólido blanco en un rendimiento del 68% (28 mg). NMR 0.77-0.85 (m, 6H), 1.03-1.25 (m, 8H), 1.34-1.57 (m, 4H), 2.16 (s, 3H), 3.18 (brs, 2H), 3.75 (brs, 2H), 4.65 (ABq, 2H), 5.7 (d, 1H), 6.63 (s, 1H), 7.0 (t, 1H), 7.1 (d. 2H), 7.26-7.48 (m, 8H), 7.85 (d, 1H); m/z 639.

Ejemplo 89

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-{(S)-α-[*N'*-(carboximetil]

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carbamoil]bencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-{(S)-α-[*N*'-(metoxicarbonilmetil)carbamoil]bencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5- benzotiazepina (Método 88; 19 mg, 0.027 mmol) se hidrolizó mediante LiOH (1.3 mg, 0-054 mmol) en THF (1 ml) y agua (0.3 nil). Después de 1 hora se agregó agua (3 ml) y la mezcla se acidificó usando 0.1M HCl y se extrajo con DCM (3x3 ml). La capa orgánica se secó y se evaporó produciendo 16 mg (rendimiento del 82%) del compuesto del título. NMR 0.77-0.85 (m, 6H), 1.0-1.3 (m, 8H), 1.34-1.57 (m, 4H), 2.17 (s, 3H), 3.18 (s, 2H), 3.75 (brs, 2H), 3.90-4.20 (m, 2H), 4.65 (ABq, 2H), 5.87 (m, 1H), 6.63 (s, 1H), 6.98-7.50 (m, 12H), 8.12-8.20 (m, 1H); m/z 696.

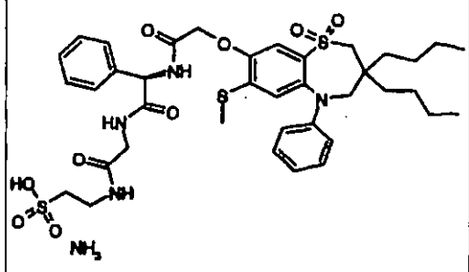
Ejemplo 90

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-{(S)-α-[*N*'-(2-sulfoetil) carbamoil]bencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina sal de sodio

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-(S)-(α-carboxibencil)carbarmoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 88; 41 mg, 0.064 mmol) se disolvió en 3 ml DCM. Se agregaron sucesivamente taurina tetrabutil sal de amonio (70 mg, 0.191 mmol) y TBTU (25 mg, 0.078 mmol) y la mezcla se agitó durante la noche a temperatura ambiente. El solvente se evaporó y el producto se purificó mediante HPLC preparativa usando una gradiente tampón MeCN/acetato de amonio (45/55 a 55/45) como eluyente. La liofilización de las fracciones recogidas y luego la cromatografía de intercambio de iones sobre 4 g Amberlite CG 120, Na^+-forma, produjeron el compuesto del título en un rendimiento del 85% (42 mg). NMR 0.7-0.8 (m, 6H), 0.9-1.2 (m, 8H), 1.3-1.5 (m, 4H), 2.0 (s, 3H), 2.9-3.2 (m, 2H+2H), 3.3-3.8 (m, 2H+2H), 4.4-4.7 (m, 2H), 5.6 (m, 1H), 6.57 (s, 1H), 6.9-7.5 (m, 11H), 7.8-8.1 (m, 2H); m/z 746.

Ejemplo 91

El siguiente compuesto se sintetizó mediante el procedimiento de Ejemplo 90 usando el material base apropiado salvo que el producto se purificó usando una gradiente tampón de 40/60 a 70/30 y luego se liofilizó para producir la sal de amonio.

Ej.	Compuesto	NMR (CD_3OD) y m/z	SM
91		0.76-0.84 (m, 6H), 1.03-1.27 (m, 8H), 1.38-1.55 (m, 4H), .15 (s, 3H), 2.95 (l, 2H), 3.24 (s,2H), 3.58 (dt, 2H), 3.75 (brs, 2H), 3.85 (ABdd, 2H), 4.72 (ABq, 2H), 5.51 (s, 1H), 6.70 (s, 1H), 6.97 (t, 1H), 7.11 (d, 2H), 7.25-7.40 (m, 6H), 7.46 (d, 2H); m/z 803	

Ejemplo 92

1,1-Dioxo-3-butil-3-etil-5-fenil-7-[*N*-{(R)-α-[*N'*-(carboximetil)carbamoil]bencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina sal de sodio

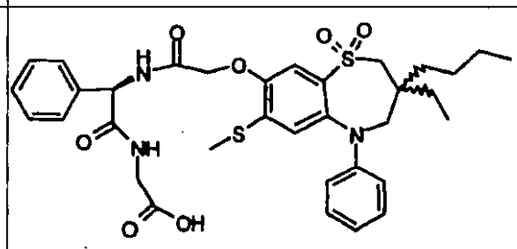
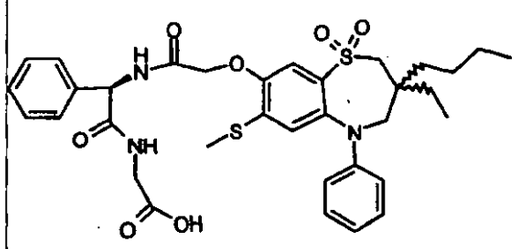
1,1-Dioxo-3-butil-3-etil-5-fenil-7-carboximetoxi-2,3,4,5-tetrahidro-1, 5-benzotiazepina sal de sodio (WO 01/66533; 120 mg, 0.278 mmol) disuelta en DCM (4 ml) se agregó a una solución de α-[*N*-(*t*-butoxicarbonilmetil-carbamoil-bencilamina (Método 86; 90%, 150 mg, 0.511 mmol) en DCM (3 ml). 2,6-Dimetilpiridina (65 ml, 0.559 mmol) y TBTU (137 mg, 0.427 mmol) se agregaron y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La solución se filtró sobre (sic) usando DCM/EtOAc (8/2) como eluyente. El solvente se evaporó. Se agregaron DCM (4 ml) y TFA (0.6 ml) y la mezcla se agitó durante la noche. El solvente se evaporó y el producto crudo se purificó mediante HPLC preparativa en una columna Chromasil C_{18}. Se empleó una gradiente tampón MeCN/acetato de amonio (50/50 a 100/0) como fase

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móvil. El MeCN se evaporó y la liofilización arrojó el compuesto del título en un rendimiento del 36% (62 mg). NMR 0.73-0.82 (m, 6H), 1.00-1.23 (m, 4H), 1.30-1.65 (m, 4H), 3.05-3.18 (m, 2H), 3.65 (brs, 2H), 3.75 (ABdd, 2H), 4.46 (ABq, 2H), 5.70 (d, 1H), 6.79-7.24 (m, 10H), 7, 36 (d, 2H), 7.46 (d, 1H), 7.83 (d, 1H), 8.00 (brs, 1H); m/z 622.

Ejemplo 93-94

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 92 usando el material base apropiado salvo que la cromatografía HPLC se llevó a cabo en una columna Chromasil C_8 y la gradiente de eluyente fue de 45/55 a 60/40.

Ej.	Compuesto	NMR (CD_3OD) y m/z	SM
93	 Enantiómero 1	0.75-0.84 (m, 6H) 1.00-1.27 (m, 4H), 1,38-1.66 (m, 4H) 2.15(s, 3H), 3.22 (s, 2H), 3.75 (brs, 2H), 3.83 (ABdd, 2H), 4.69 (ABq, 2H), 5.60 (s, 1H), 6.71(s, 1H), 6.96(t, 1H), 7.09 (d, 2H), 7.23-7.37 (m, 5H), 7.39 (s, 1H), 7.46 (d, 2H); m/z 668	Mét. 23; Mét. 86
94	 Enantiómero 2	0.78-0.85 (m, 6H) 1.04-1.27 (m, 4H), 1.41-1.65 (m, 4H) 2.17 (s, 3H), 3.24 (s, 2H), 3.68 (brs, 2H), 3.89 (ABdd, 2H), 4.72 (ABq, 2H), 5.62 (s, 1H), 6.73 (s, 1H), 6.97 (t, 1H), 7.11 (d, 2H), 7.26-7.38 (m. 5H), 7.41 (s, 1H), 7.48 (d, 2H); m/z 668	Mét. 24; Mét. 86

Ejemplo 95

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-{*N*-[(R)-α-*N'*-{2-(etoxi)(metil)

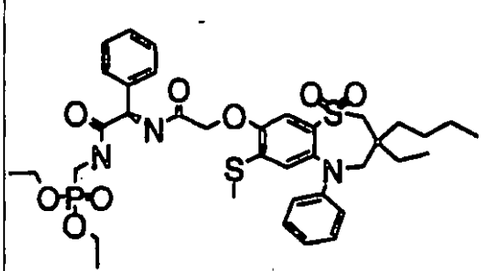
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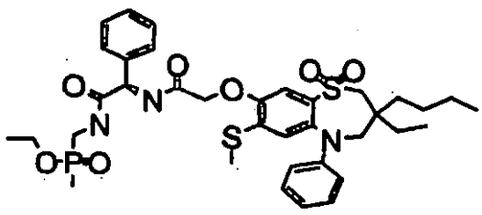
fosforil]etil}carbamoil)bencil]carbamoilmetoxil-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 2-[(metil)(etil)fosforil]etilamina (Helv.Chim.Acta; GE; 75; 8; 1992; 2545-2552; 16 mg, 0.106 mmol) en DCM (2 ml) se agregó a 0 °C 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 38; 50 mg, 0.082 mmol) DIPEA (42 mg, 0.328 mmol) y TBTU (34 mg, 0.106 mmol) bajo argón. La mezcla de reacción se agitó a temperatura ambiente durante 110 minutos y luego se agregó DCM y la solución se lavó con $NaHCO_3$ (aq, sat) y salmuera. La capa orgánica se secó y el solvente se evaporó bajo presión reducida. El residuo se purificó mediante cromatografía y el producto se eluyó con DCM/metanol (100:5). Rendimiento 43 mg (71%). NMR (500 MHz) 0-78-0.85 (m, 6 H), 1.02-1.54 (m, 12H), 1.6-1.75 (br, 1H), 1.8-2.10 (m, 3H), 2.21 (s, 3H), 3.10-3.25 (m, 2H), 3.51-3.84 (m, 4 H), 3.9-3.99 (m, 1H), 4.01-4.09 (m, 1H), 4.54-4.69 (dd, 2H), 5.51 (d, 1H), 6.68 (s , 1 H), 6.96-7.02 (m, 1H), 7.03-7.18 (m, 3H), 7.25-7.42 (m, 6H), 7.43-7.48 (m, 2H), 8.05-8.15 (m, 1H).

Ejemplos 96-97

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 95 usando el material base apropiado.

Ej.	Compuesto	NMR y m/z	SM
96		0.76-0.85 (m, 6H), 1.00-1.52 (m, 12H), 1.55-1.75 (m, 1H), 1.95-2.12 (br, 1H), 2.20 (s, 3H), 3.10-3.25 (m, 2H), 3.55- 3.85 (m, 4H), 3.85-4.00 (m, 2H), 4.03-4.13 (m, 2H), 4.6 (q, 2H), 5.64 (d, 1H), 6.66 (s. 1H), 7.78 (br, 1H), 6.95-7.10 (m, 3H), 7.23-7.40 (m, 6H), 7.43-7.49	Ej. 38

		(m, 2H), 8.07 (d, 1H); m/z 760.3	
97		(600 MHz) 0.75-0.82 (m, 6H), 1.0-1.42(m, 13H), 1.64 (brs, 1H), 2.18 (s, 3H), 3.08-3.24 (m, 2H), 3.50-3.84 (m, 4H), 3.87-4.13 (m, 2H), 4.54-4.68 (m, 2H), 5.56-5.62 (m, 1H), 6.63 (s, 1H), 6.87-7.10 (m, 3H), 7.24-7.40 (m, 7H), 7.43-7.49 (m, 2H), 7.98-8.05 (m, 1H); m/z 730.5	Ej. 38

[1]Amina: Tetrahedron; EN; 49; 47, 1993; 11055-11064

Ejemplo 98

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-{*N*-(R)-α-(*N'*-(2-[(hidroxi)(metil)fosforil]etil}carbamoil)bencil]carbamoilmetoxil-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{2-[(etoxi)(metil)fosforil]etil}carbamoil)bencil] carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 95; 27 mg, 0.036 mmol) en etanol (1.5 ml) se agregó a 0°C 2 M NaOH acuoso (0.22 ml, 0.44 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 24 horas. Se agregó ácido acético (0.2 ml). El solvente se evaporó bajo presión reducida y el residuo se extrajo con DCM/agua. La capa DCM se separó, se lavó con salmuera, se secó y se evaporó bajo presión reducida. La recristalización del residuo a partir de DCM/éter/éter de petróleo produjo el compuesto del título 23 mg (89%). NMR (600 MHz) 0.74-0.82 (m, 6H), 1.0-1.70 (m, 11H), 1.90-2.09 (m, 2H), 2.16 (s, 3H), 3.05-3.24 (m, 2H), 3.40-3.85 (m, 4H), 4.50-4.65 (dd, 2H), 5.55 (d, 1H), 6.63 (s, 1H), 6.93-7.07 (m, 3H), 7.20-7.50 (m, 9H), 8.10 (d, 1H); m/z 716.3.

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Ejemplo 99

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-(*N'*-[(hidroxi)(etoxi) fosforilmetil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N'*-[(dietoxi)fosforilmetil[]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 96; 13 mg, 0.017 mmol) en MeCN (0.5 ml) se agregó 1 M LiOH acuoso (0.171 ml, 0.171 mmol) gota a gota. La mezcla de reacción se agitó a temperatura ambiente durante 3 días. Se agregó ácido acético y el solvente se evaporó bajo presión reducida. El producto crudo se purificó mediante HPLC preparativa usando MeCN y tampón de acetato de amonio (45:55) como eluyente para producir el compuesto del título 11 mg (88%). NMR (600 MHz, CD_3OD) 0.77-0.84 (m, 6H), 1.00-1.30 (m, 7H), 1.40-1.65 (m, 4H), 2.17 (s, 3H), 3.23 (brs, 2H), 3.51 (d, 2H), 3.6-3.85 (m, 4H), 4.70 (dd, 2H), 5.57 (s, 1H), 6.72 (s, 1H), 6.96 (t, 1H), 7.09 (d, 2H), 7.25-7.31 (m, 3H), 7.32-7.36 (m, 2H), 7.40 (s, 1H), 7.45 (d, 2H); m/z 732.4.

Ejemplo 100

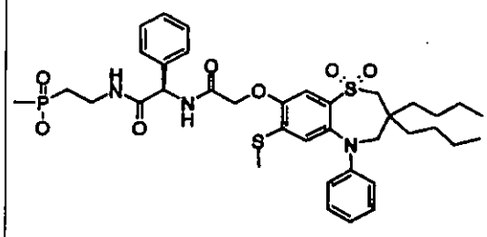
1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N'*-[(hidroxi)(metil) fosforilmetil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N'*-[(etoxi)(metil)fosforilmetil]carbamoil}bencil) carbamoilmetoxi]-2,3,4,5- tetrahidro-1,5-benzotiazepina (Ejemplo 97; 85 mg, 0.12 mmol) en MeCN (2.4 ml) se agregó a 0°C 1 M LiOH acuoso (1.17 ml, 1.17 mmol) gota a gota. La mezcla de reacción se agitó a temperatura ambiente durante 20 horas. Se agregó ácido acético y el solvente se evaporó bajo presión reducida. El producto crudo se purificó por cromatografía de columna usando DCM/MeOH/Et_3N (100:15:0.2 y 100:30:0.2) como eluyente para producir el compuesto del título 62 mg (76%). NMR (CD_3OD) 0.75-0.84 (m, 6H), 1.0-1.70 (m, 11H), 2.15 (s, 3H),

3.22 (brs, 2H), 3.35 (d, 2H), 3.60-3.90 (m, 2H), 4.70 (dd, 2H), 3.55 (s, 1H), 6.71 (s, 1H), 6.96 (t, 1 H), 7.09 (d, 2H), 7.23-7.38 (m, 5H), 7.40 (s, 1H), 7.46 (d, 2H); m/z 702.3

Ejemplo 101

El siguiente compuesto se sintetizó mediante el procedimiento de Ejemplo 100 usando el material base apropiado.

Ej.	Compuesto	NMR (600 MHz, CD_3OD) y m/z	SM
101		0.76-0.83 (m, 6H), 1.05-1.55 (m, 15H), 1.91-1.99 (m, 2H), 2.15 (s, 3H), 3.24 (brs, 2H), 3.40-3.50 (m, 2H), 3.66-3.86 (m, 2H), 4.69 (dd, 2H), 5.42 (s, 1H), 6.70 (s, 1H), 6.92 (t, 1H), 7.11 (d, 2H), 7.25- 7.39 (m, 6H), 7.43 (d, 2H); m/z 744.3	Ej.104

Ejemplo 102

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N*'-[di(*t*-butoxi)fosforilmetil]carbamoil}bencil)carbamoilmetoxi]-2.3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 38; 80 mg, 0.131 mmol) y di-(*t*-butoxi)fosforilmetilamina (Tet. Lett.; EN; 33; 1; 1992; 77-80; 37 mg, 0.164 mmol) en DCM (5 ml) se agregó 2,6-lutidina (28 mg, 0.262 mmol) y TBTU (53 mg, 0.164 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas y 50 minutos. El solvente se evaporó bajo presión reducida y el producto crudo se purificó cromatografía de columna usando DCM/MeOH (100:4) como eluyente para producir el compuesto del título 92 mg (86%). NMR (500 MHz) 0.77-0.86 (m, 6H), 1.03- 1.75 (m, 26H), 2.22 (s, 3H), 2.10-2.25 (m, 2H), 3.45-3.90 (m, 4H), 4.61 (dd, 2H), 5.52 (d,

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1H), 5.94 (brs, 1H), 6.67 (s, 1H), 7.0 (t, 1H), 7.07 (d, 2H), 7.26-7.48 (m, 8H), 8.12 (d, 1H); m/z 704.22 [M-2(*t*-butil)+2H].

Ejemplo 103

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[N-((R)-α-{N'-[di-(hidroxi)fosforilmetil]carbamoil}bencil)carbamoilmetoxi]2,3,4,5-tetrahidro-1.5-benzotiazepina

A una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N*'-[di-(*t*-butoxi)fosforilmetil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 102; 72 mg, 0.088 mmol) en DCM (4 ml) se agregó a 0°C TFA (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. El solvente se evaporó bajo presión reducida y el residuo se extrajo con DCM/agua. La capa orgánica se separó, se lavó con salmuera, se secó y se evaporó bajo presión reducida. El residuo se suspendió en éter y los cristales se filtraron para producir el compuesto del título 60 mg (97%). NMR (500 MHz, DMSO-d_6) 0.70-0.80 (m, 6H), 0.99-1.61 (m, 8H), 2.18 (s, 3H), 2.80- 4.0 (m, 6H), 4.80 (dd, 2H), 5.65 (d, 1H), 6.71 (s, 1H), 6.80-7.02 (m, 3H), 7.15-7.35 (m, 6H), 7.48 (d, 2H), 8.50-9.20 (m, 2H); m/z 704.3

Ejemplo 104

1,1-Dioxo-3, 3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N*'-{2-[(metil)(etil) fosforil]etil}carbamoil)bencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 1; 60 mg, 0.094 mmol) y 2-[(metil)(etil)fosforil] etilamina (Helv.Chim.Acta; GE; 75; 8; 1992; 2545-2552;20 mg, 0.132 mmol) se agregó a 0°C 2,6-lutidina (20 mg, 0.19 mmol) y TBTU (39 mg, 0.121 mmol) bajo argón. La mezcla de reacción se agitó a temperatura ambiente durante 70 minutos y luego se agregó DCM y la solución se lavó

con agua y salmuera. La capa orgánica se secó y el solvente se evaporó bajo presión reducida. El residuo se purificó mediante cromatografía de columna usando DCM/MeOH (100:5) como eluyente para producir el compuesto del título 67 mg (92%). NMR (300 MHz) 0.74-86 (m, 6H), 1.0-1.60 (m, 18H), 1.80- 2.05 (m, 2H), 2.20 (s, 3H), 2.17 (s, 2H), 3.47-3.80 (m, 4H), 3.88-4.10 (dd, 2H), 5.52 (d, 1H), 6.65 (s, 1H), 6.95-7.12 (m, 3H), 7.13-7.42 (m, 7H), 7.43-7.49 (m, 2H), 8.05-8.16 (m, 1H); m/z 772.4.

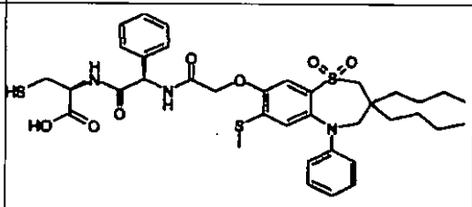
Ejemplo 105

1,1-Dioxo-3.3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-mercapto-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[N-((R)-α-{*N'*-[2-(trifenilmetilsulfanil)-1-(*t*-butoxicarbonil)etil]carbamoil}bencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 91; 37 mg, 0.036 mmol) en DCM (1 ml) se agregó a 0°C TFA (1 ml) bajo una capa protectora de argón. Se retiró el baño de hielo y se agregó trietilsilano (42 mg, 0.36 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas y luego el solvente se evaporó bajo presión reducida. El producto crudo se purificó mediante HPLC preparativa usando MeCN y tampón de acetato de amonio (40:60 a 60:40) como eluyente para producir el compuesto del título 16 mg (59%). NMR (500 MHz, CD_3OD) 0.76-0.85 (m. 6H), 1.05-1.60 (m, 12H), 2.17 (s, 3H), 2.77-2.92 (m, 2H), 3.24 (brs, 2H), 3.61-3.88 (m, 2H), 4.56 (t, 1H), 4.70 (dd, 2H), 5.65 (s, 1H), 6.71 (s, 1H), 6.98 (t, 1H), 7.12 (d, 2H), 7.25-7.43 (m, 6H), 7.50 (d, 2H); m/z 742.4.

Ejemplo 106

El siguiente compuesto se sintetizó mediante el procedimiento de Ejemplo 105 usando el material base adecuado.

Ej.	Compuesto	NMR (500 MHz, CD_3OD) y m/z	SM
106		0.77-0.85 (m, 6H), 1.03-1.28 (m, 8H), 1.38-1.58 (m, 4H), 2.15 (s, 3H), 2.87-3.5 (m, 2H), 3.25 (s, 2H), 3.75 (brs, 2H), 4.55 (s, 1H), 4.71 (dd, 2H), 5.66 (s, 1H), 6.71 (s, 1H), 6.98 (t, 1H), 7.12(d, 2H), 7.25-7.43 (m, 6H), 7.49 (d, 2H); m/z 742.28	Mét. 93

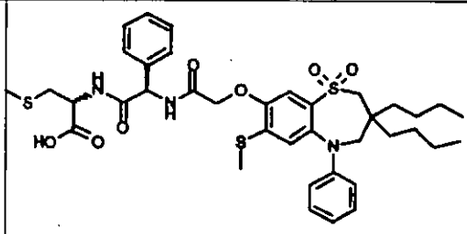
Ejemplo 107

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-(2-{*N*-[(R)-α-(carboxi)bencil] carbamoil1etoxi)-2.3-4, 5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-(2-{*N*-[(R)-α-(*t*-butoxicarbonil)bencil]carbamoil}etoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 90; 77 mg, 0.108 mmol) en DCM (3 ml) se agregó a 0°C TFA (0.75ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas y 45 minutos. El solvente se evaporó bajo presión reducida y el producto crudo se purificó mediante HPLC preparativa usando MeCN y tampón de acetato de amonio (40:60 a 50:50) como eluyente para producir el compuesto del título 60 mg (82%). NMR (500MHz, CD_3OD) 0.75-0.85 (m, 6H), 1.0-1.25 (m. 4H), 1.40-1.64 (m, 4H), 2.75-2.90 (m, 2H), 3.26 (s, 2H), 3.50-3.90 (m, 2H), 4.30-4.41 (m, 2H), 5.43 (s, 1H), 6.99 (t, 1H), 7.05-7.13 (m, 3H), 7.23-7.34 (m, 5H), 7.45 (d, 2H), 7.52 (s, 1H); m/z 658.

Ejemplo 108

El siguiente compuesto se sintetizó mediante el procedimiento de Ejemplo 107 usando el material base adecuado.

Ej.	Compuesto	NMR (500 MHz, CD_3OD) y m/z	SM
108		0.78-0.85 (m, 6H), 1.02-1.30 (m, 8H), 1.38-1.58 (m, 4H), 1.87 (s, 3H), 2.15 (s, 3H), 2.77-2.83 (m, 1H), 2.87-2.94 (m, 1H), 3.24 (s, 2H), 3.74 (brs, 2H), 4.53-4.59 (m, 1H), 4.68 (dd, 2H), 5.66 (s, 1H), 6.71 (s, 1H), 6.98 (t, 1H), 7.12 (d, 2H), 7.25-7.31 (m, 3H), 7.32-7.36 (m, 2H), 7.40 (s, 1H), 7.49 (d, 2H); m/z 756.23	Mét. 92

Ejemplo 109

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N*'-{2-[(metil)(etil) fosforil]etil}carbamoil)-4-hidroxibencil]carbamoilmetoxi}-2,3,5-tetrahidro-1,5-benzotiazepina

A 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-1,5-benzotiazepina (Ejemplo 2; 80 mg, 0.122 mmol) y 2-[(metil)(etil)fosforil]etilamina (Helv. Chim. Acta; GE; 75; 8; 1992; 2545-2552: 24 mg, 0.159 mmol) en DCM (2 ml) se agregó 2,6-lutidina (26 mg, 0.244 mmol) y TBTU (51 mg, 0.159 mmol) bajo argón. La mezcla de reacción se agitó a temperatura ambiente durante 60 minutos, luego se diluyó con DCM. La solución se lavó con agua, salmuera, se secó y el solvente se evaporó bajo presión reducida. El residuo se purificó mediante cromatografía de columna usando DCM/MeOH (100:7) como eluyente para producir el compuesto del título 67 mg (92%). NMR (600 MHz), 0.74-0.80 (m, 6H), 1.0-1.55 (m, 18H), 1.82-1-98 (m, 2H), 2.15 (s, 3H), 3.14 (brs, 2H), 3.40-3.56 (m, 2H), 3.70 (brs, 2H), 3.89-4.02 (m, 2H), 4.51 (dd, 2H), 5.33 (t, 1H), 6.61 (s, 1H), 6.65-6.72 (m, 2H), 6.95 (t, 1H), 7.03 (d, 2H),

7.12-7.19 (m, 3H), 7.22-7.26 (m, 2H), 7.32 (s, 1H), 8.11 (t, 1H); m/z 788.56.

Ejemplo 110

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N*'-{2-(metil-hidroxi)fosforil]etil}carbamoil)-4-hidroxibencil]carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N*'-{2-[(metil)(etil)fosforil]etil}carbamoil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 104; 37 mg, 0.047 mmol) en MeCN/MeOH (4 ml, 1:1) se agregó 1 M LiOH acuoso (0.8 ml, 0.8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 40 minutos. Se agregó ácido acético y el solvente se evaporó bajo presión reducida. El producto crudo se purificó mediante HPLC preparativa usando MeCN y tampón de acetato de amonio (40:60 y 45:55) como eluyente para producir el compuesto del título 35 mg (96%). NMR (500 MHz, CD_3OD) 0.78-0.85 (m, 6H), 1.06-1.28 (m, 11H), 1.39-1.57 (m, 4H), 1.72-1.85 (m, 2H), 2.16 (s, 3H), 2.24 (s, 2H), 3.40-3.50 (m, 2H), 3.65-3.84 (m, 2H), 4.69 (dd, 2H), 5.36 (s, 1H), 6.71 (s, 1H), 6.76 (d, 2H), 6.99 (t, 1H), 7.13 (d, 2H), 7.22-7.33 (m, 4H), 7.39 (s, 1H); m/z 760.27

Ejemplo 111

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N*'-{2-metilsulfinil-1-carboxietil)carbamoil[bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

El compuesto del título se separó como sub-producto de la síntesis de Ejemplo 108. NMR (500 MHz, CD_3OD) 0.78-0.85 (m, 6H), 1.02-1.60 (m, 12H), 2.16 (d, 3H), 2.53 (d, 3H), 3.08-3.18 (m, 1H), 3.24 (s, 2H), 3.35 (v br, 1H), 3.75 (v br, 2H), 4.62 (v br, 1H), 4.71 (dd, 2H), 5.60 (d, 1H), 7.71 (s, 1H), 6.98 (t, 1H), 7.12 (d, 2H), 7.25-7.42 (m, 6H), 7.47 (d, 2H); m/z 772.25.

Ejemplo 112

1,1-Dioxo-3,3-dibutil--fenil-7-metiltio-8-{*N*-[(R)-α-[(S)-*N'*-(3-metiltio-2-carboxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8{*N*-[(R)-α-[(S)-*N'*-(3-metiltio-2-metoxicarbonilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 94; 68 mg, 0.087 mmol) en etanol (5 ml) se agregó NaOH (9 mg en 0.4 ml agua) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 2.5 horas. Se agregó ácido acético y el solvente se evaporó bajo presión reducida. El producto crudo se purificó mediante HPLC preparativa usando MeCN y tampón de acetato de amonio (40:60 a 60:40) como eluyente para producir el compuesto del título 52 mg (76%). NMR (500 MHz, CD_3OD) 0.79-0.86 (m, 6H), 1.05-1.29 (m, 8H), 1.40-1.58 (m, 4H), 1.84-1.93 (m, 4H), 2.01-2.21 (m, 5H), 2.26-2.34 (m, 1H), 3.26 (s, 2H), 3.76 (brs, 2H), 4.52-4.58 (m, 1H), 4.70 (dd, 2H), 5.61 (s, 1H), 6.73 (s, 1H), 7.0 (t, 1H), 7.14 (d, 2H), 7.27-7.43 (m, 6H), 7.49 (d, 2H); m/z 770.16.

Ejemplo 113

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-[(S)-*N'*-(3-metiltio-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-[(S)-*N'*-(2-mercapto-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 106; 15 mg, 0.02 mmol) en metanol (1.5 ml) se agregó metóxido de sodio (0.104 mmol en 0.14 ml metanol) y yoduro de metilo (0.16 mmol) bajo nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 50 minutos. Se agregó ácido acético. El solvente se evaporó bajo presión reducida y el residuo se extrajo con DCM/agua. La capa orgánica se separó, se lavó con salmuera, se secó y se evaporó bajo presión reducida para producir el compuesto del

título 4 mg (26%). NMR (500 MHz, CD_3OD) 0.75-8.30 (m, 6H), 1.03-1.57 (m, 12H), 2.10 (s, 3H), 2.17 (s, 3H), 2.83-2.30 (m, 1H), 3.0- 3.25 (m, 1H), 3.26 (s, 2H), 3.77 (brs, 2H), 4.58-4.63 (m, 1H), 4.72 (dd, 2H), 5.64 (s, 1H), 6.72 (s, 1H), 7.0 (t, 1H), 7.12 (d, 2H), 7.28-7.52 (m, 8H); m/z 756.25.

Ejemplo 114

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

A una solución de 1,1-dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-[*N*-{(R)-α-[*N*'-(*t*-butoxicarbonilmetil)carbamoil]bencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 102; 129 mg, 0.164 mmol) en DCM (5 ml) se agregó a 0° C TFA (1.5 ml) bajo nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. El solvente se evaporó bajo presión reducida y el producto crudo se purificó mediante HPLC preparativa usando MeCN y tampón de acetato de amonio (40:60 a 50:50) como eluyente para producir el compuesto del título 77 mg (63%). NMR (500 MHz, CD_3OD) 0.84 (t, 6H), 1.10-1.22 (m, 8H), 1.35-1.45 (m. 4H), 2.34 (s, 3H), 3.19-3.27 (m, 2H), 3.55 (s, 2H), 3.87 (dd, 2H), 4.67 (dd, 2H), 5.61 (s, 1H), 7.09-7.15 (m, 3H), 7.27-7.37 (m. 6H), 7.47 (d, 2H); m/z 748.03 ($M+NH_3$).

Ejemplo 115

1,1-Dioxo-3,3-dipropil-5-fenil-7-metiltio-8-[*N*-{(R)-α-[*N*'-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dipropil-5-fenil-7-metiltio-8-carboximetoxi- 2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 118; 0.050 g, 0.105 mmol) en DMF (4 ml) se agregó ácido 2-{[(2*R*)-2-amino-2-(4-hidroxifenil)etanoil]amino}etanosulfónico (Método 80; 0.037 g, 0.135 mmol) y *N*-metilmorfolina (0.040 ml, 0.363 mmol). La mezcla se agitó durante 10 minutos y luego se agregó TBTU (0.044 g, 0.137 mmol). La

mezcla de reacción se agitó durante dos días antes de retirar el solvente bajo presión reducida. El residuo se purificó mediante HPLC preparativa usando un tampón MeCN/acetato de amonio para producir el compuesto del título en 0.042 g (55 %) como un sólido blanco. NMR (DMSO-d_6) 0.60- 0-80 (m, 6H), 1.05-1.50 (m, 8H), 2.15 (s, 3H), 2.45-2.55 (m, 2H), 3.05-3.80 (m, 6H), 4.70 (ABd, 1H), 4.80 (ABd, 1H), 5.25 (d, 1H), 6.65-6.75 (m, 3H), 6.80-7.05 (m, 3H), 7.10-7.25 (m, 4H), 7.30 (s, 1H), 8.20-8.30 (m, 1H), 8.45 (d, 1H).

Ejemplo 116

1,1-Dioxo-3,3-dipropil-5-fenil-7-metiltio-8[*N*-{(R)α-[*N*'-(carboximetil)-carbamoil]-4-hidroxibencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dipropil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 118; 0.050 g, 0.105 mmol) en DCM (4 ml) se agregó (R)-α-[*N*-(*t*-butoxicarbonilmetil)carbamoil]bencilamina (Método 86; 0.036 g, 0.136 mmol) y *N*-metilmorfolina (0.040 ml, 0.363 mmol). La mezcla se agitó durante 5 minutos y luego se agregó TBTU (0.044 g, 0.137 mmol). La mezcla de reacción se agitó durante dos días y luego se agregó TFA (1.5 ml). Luego de 1.5 horas, la solución se diluyó con tolueno, antes de retirar el solvente bajo presión reducida. El residuo se purificó mediante HPLC preparativa usando un tampón MeCN/acetato de amonio para producir el compuesto del título en 0.020 g (29 %) como un sólido blanco. NMR (DMSO-d_6) 0.60-0.80 (m, 6H), 1.05-1.50 (m, 8H), 2.15 (s, 3H), 3.10-3.80 (m, 6H), 4.70 (ABd, 1H), 4.85 (ABd, 1H), 5.60 (d, 1H), 6.70 (s, 1H), 6.80-7.05 (m, 3H), 7.15-7.50 (m, 8H), 8.35 (brs, 1H), 8.55 (d, 1H).

Ejemplo 117

1,1-Dioxo-3.3-dibutil-5-fenil-7-metoxi-8-[*N*-{(R)α-[*N*'-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metoxi-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 6; 0.020 g, $4.09*10^{-5}$ mol) en DMF (4 ml) se agregó ácido 2-{[(2*R*)-2-amino-2-(4-hidroxifenil)etanoil]amino}etanosulfónico (Método 80; 0.014 g, $5.10^{*}10^{-5}$ mol) y *N*-metilmorfolina (0.020 ml, $1.81*10^{-4}$ mol). La mezcla se agitó durante 10 minutos y luego se agregó TBTU (0.016 g, $4.98^{*}10^{-5}$ mol). La mezcla de reacción se agitó durante 3 horas y entonces el solvente se retiró bajo presión reducida. El residuo se purificó mediante HPLC preparativa usando un tampón MeCN/acetato de amonio para producir el compuesto del título en 0.023 g (75 %) como un sólido blanco. NMR (500 MHz, DMSO-d-) 0.65- 0.80 (m, 6H), 0.80-1.50 (m. 12H), 2.40-2.60 (m, 2H), 3.15-3.45 (m, 4H), 3.60 (s, 3H), 3.65 (brs, 2H), 4.60 (ABd, 1H), 4.70 (ABd, 1H), 5.25 (d, 1H), 6.50 (s, 1H), 6.70-7.25 (m, 10H), 7.35 (s, 1H), 8.20-8.30 (m, 1H), 8.50 (d, 1H), 9.40 (brs, 1H),

Ejemplo 118

1,1-Dioxo-3-butil-3-etil-5-fenil-8-[*N*-{(R)-α-[*N*'-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-8-carboximetoxi-2,3,4,5- tetrahidro-1,5-benzotiazepina (Método 115; 0.020 g, $4.63*10^{5}$ mol) en DMF (4 ml) se agregó ácido 2-{[(2*R*)-2-amino-2-(4-hidroxifenil)etanoil]amino)etanosulfónico (Método 80; 0.017 g, $6.20*10^{-5}$ mol) y *N*-metilmorfolina (0.016 ml, $1.46*10^{-4}$ mol). La mezcla se agitó durante 10 minutos y luego se agregó TBTU (0.019 g, $5.92*10^{-5}$ mol). La mezcla de reacción se agitó durante la noche y luego el solvente se retiró bajo presión reducida. El residuo se purificó mediante HPLC preparativa usando un tampón MeCN/acetato de amonio para producir el compuesto del título en 0.008 g (24 %) como un sólido blanco. NMR (500 MHz, DMSO-d_6) 0.65-0.80 (m, 6H), 0.80-1.60 (m, 8H), 2.40-2.55 (m, 2H), 3.20-3.40 (m, 4H), 3.65 (brs. 2H), 4.65 (ABd, 1H), 4.70 (ABd, 1H), 5.25 (d, 1H), 6.65-7.45 (m, 13H), 8.20-8.30 (m, 1H), 8.60 (d, 1H), 9.40 (brs, 1H).

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Ejemplo 119

1,1-Dioxo-3, 3-dibutil-5-(4-*t*-butoxicarbonilaminofenil)-8-[*N*-α-(R)-carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

El compuesto del título se sintetizó a partir de 1,1-dioxo-3,3-dibutil-5-(4-*t*- butoxicarbonilaminofenil)-8-[*N*-(α-(R)-metoxicarbonilbencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 45) mediante el procedimiento de Método 109. NMR (CD_3OD) 0.81 (brt, 6H), 1.03-1.3 (m, 8H), 1.32-1.59 (m, 13H), 3.24 (brs, 2H), 3.57-3.77 (m, 2H), 4.61 (brs, 2H), 5.51 (s, 1H), 6.83 (d, 1H), 7.0-7.1 (m, 3H), 7.26-7.43 (m, 7H), 7.49 (d, 1H); m/z 708.5.

Ejemplo 120

1,1-Dioxo-3,3-dibutil-5-(4-*t*-*N*'-butilureido)fenil-8-(*N*-(α-(R)-carboxibencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,.5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-(4-(*N*'-*t*-butilureido)fenil)-8-[*N*-(α-(R)-metoxicarbonilbencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 111; 30 mg, 0.042 mmol) se disolvió en THP (1.5 ml), H_2O (0.5 ml) y se agregó LiOH (42 mg, 0.064 mmol, monohidrato). La mezcla se agitó durante 2 horas. El compuesto se purificó mediante HPLC preparativa usando una gradiente tampón MeCN/acetato de amonio (5/95 a 100/0) como eluyente para producir el producto del título, 24 mg (82%). NMR (CD_3OD) 0.81 (brt, 6H), 1.05-1.26 (m, 8H), 1.35 (s, 9H), 1.38-1.57 (m, 4H), 3.25 (brs, 2H), 3.6-3.77 (m, 2H), 4.61 (ABq, 2H), 5.45 (s, 1H), 6.84 (d, 1H), 7.01-7.11 (m, 3H), 7.24 (d, 2H), 7.26-7.37 (m, 3H), 7.37-7.42 (m, 2H), 7.50 (d, 1H); m/z 707.5.

Preparación de Materiales Base

Los materiales base para los Ejemplos anteriores se encuentran 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 base usados en las reacciones de arriba.

Método 1

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[1'-(etoxicarbonil)etoxi]-2,3,4,5- tetrahidro-1,5-benzotiazepina

Carbonato de sodio (0.30 g, 2.83 mmol), ester etílico de ácido 2-bromopropanoico (0.145 g, 0.796 mmol) y bromuro de tetrabutilamonio (0.022 g, 0.07 mmol) se agregó a una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (WO 96/16051; 0.300 g, 0.663 mmol) en MeCN (10 ml). La suspensión se calentó bajo reflujo durante la noche. El solvente se evaporó y la mezcla cruda se extrajo (DCM/H_2O), se secó ($MgSO_4$), se evaporó y se purificó mediante cromatografía de destello (Hex:EtOAc - 5:1) para producir el compuesto del título 0.346 g (95 %) como un sólido blanco. NMR 0.70-0.85 (m, 6H), 1.00-1.75 (m, 8H), 1.35 (t, 3H), 1.70 (d, 3H), 3.05-3.25 (m, 2H), 3.55-3.90 (m, 2H), 4.20-.35 (m, 2H), 4.80 (q, 1H), 7.00-7.10 (m, 3H), 7.15 (s. 1H), 7.25-7.35 (m, 2H), 7.45 (s, 1H).

Método 2

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[1'-carboxietoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

Hidróxido de sodio (0.045 g, 1.13 mmol) se agregó a una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[1-(etoxicarbonil)etoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 1; 0.050 g, 0.090 mmol) en EtOH (4 ml, 95 %) y se calentó bajo reflujo. Después de 1.5 horas se agregó AcOH (0.2 ml) y la mayoría del solvente se retiró bajo presión reducida. El producto crudo se extrajo (DCM/H_2O), se secó ($MgSO_4$) y se evaporó para producir el compuesto del título 0.031 g (65 %) como un sólido blanco. NMR (500 MHz, CD_3OD) 0.70-0.85 (m, 6H), 0.95-1.25 (m, 4H), 1.35-1.70 (m, 4H), 2.65 (d, 3H), 3.10-3.35 (m, 2H), 3.45-3.95 (m, 2H), 4.70 (q, 1H), 6.90-7.35 (m, 6H), 7.45 (s, 1H).

Método 3

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[1'-fenil-1'-etoxicarbonilmetoxi] -2,3,4,5-tetrahidro-1,5-benzotiazepina

α-bromofenilacetato de etilo (0.139 g), Na_2CO_3 (0.200 g) y bromuro de tetrabutil amonio (0.034 g) se agregaron a una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (WO 96/16051; 0.200 g, 0.442 mmol) en MeCN (6 ml). La suspensión se calentó bajo reflujo durante la noche antes de retirar el solvente bajo presión reducida. El producto crudo se extrajo (DCM/H_2O) y se purificó mediante cromatografía de destello (Hex:EtOAc-5:1) para producir el compuesto del título 0.256 g (94 %) como un sólido blanco. NMR 0.65-0.85 (m, 6H), 0.95-1.65 (m, 8H), 3.00-3.15 (m, 2H), 3.50-3.80 (m, 2H), 3.70-3.80 (2s, 3H), 5.60 (s, 1H), 5.65 (d, 1H) 7.00-7.60 (m, 17H), 8.05-8.20 (2d, 1H).

Método 4

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[1'-fenil-1'-carboximetoxi]- 2,3,4,5-tetrahidro-1,5-benzotiazepina

Hidróxido de litio (0.019 g) se agregó a una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[1'-fenil-1'-etoxicarbonilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 3; 0.244 g, 0.397 mmol) en THP/H_2O (2/1, 3 ml). Después de 2 días el solvente se retiró bajo presión reducida y la mezcla cruda se purificó mediante HPLC para producir el compuesto del título 0.215 g (92 %) como un sólido blanco. NMR (CD_3OD) 0.60-0.80 (m, 6H), 0.90-1.25 (m, 4H), 1.30-1.60 (m, 4H), 3.05-3.30 (m. 2H), 3.40-3.90 (m, 2H), 5.55 (s, 1H), 6,85-7.70 (m, 12H).

Método 5

1,1-Dioxo-3.3-dibutil-5-fenil-7-metoxi-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

Bromoacetato de etilo (0.13 ml), Na_2CO_3 (0.40 g) y bromuro de tetrabutil amonio (0.030 g) se agregaron a una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metoxi-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

(sintetizada a la manera de W09616051 para el correspondiente 3-butil-3-etil análogo; 0.400 g, 0.927 mmol) en MeCN (10 ml). La suspensión se calentó bajo reflujo durante la noche antes de retirar la mayor parte del solvente bajo presión reducida. El producto crudo se extrajo (DCM/H_2O) y se filtró a través de una columna corta de sílice (DCM:EtOAc-1:4) para producir el compuesto del título 0.476 g (99 %). NMR 0.65-0.85 (m, 6H), 0.95-1.65 (m, 8H), 3.00-3.15 (m, 2H), 3.50-3.80 (m, 2H), 3.70-3.80 (s, 3H), 5.60 (s, 1H), 5.65 (d, 1H) 7.00-7.60 (m, 17H), 8.05-8.20 (d, 1H).

Método 6

1,1-Dioxo-3,3-dibutil-5-fenil-7-metoxi-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

Hidróxido de litio (0.062 g) se agregó a una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metoxi-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 5; 0.448 g, 0.865 mmol) en THF/H_2O (2/1, 6 ml). Después de 1 hora se agregó AcOH (0.5 ml) y la mayor parte del solvente se retiró bajo presión reducida. El producto crudo se purificó mediante HPLC (MeCN) para producir el compuesto del título 0.408 g (96 %) como un sólido blanco. NMR (CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.65 (s, 3H), 3.70 (brs, 2H), 4.50 (s, 2H), 6.50 (s, 1H), 6.90-7.30 (m, 5H), 7.40 (s, 1H).

Método 7

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metoxi-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metoxi-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (WO 9616051; 1.0 g), bromoacetato de etilo (0,50 g), carbonato de sodio (1,2 g) y bromuro de tetrabutil amonio (60 mg) en MeCN (15 ml) se hicieron refluir durante la noche. El solvente se retiró bajo presión reducida y el residuo se extrajo (DCM/H_2O). La capa orgánica se separó y el solvente se retiró bajo presión reducida. El residuo se purificó mediante cromatografía (DCM/EtOAc (90:10)) para producir el

compuesto del título 1.2 g (98%). NMR (CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s, 2H), 3.65 (s, 3H), 3.70 (brs, 2H), 4.50 (s, 2H), 6.50 (s, 1H), 6.90-7.30 (m, 5H), 7.40 (s, 1H).

Método 8

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

Una mezcla de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (WO 96/16051; 0.3 g), bromoacetato de etilo (0,14 g), carbonato de sodio (0.3 g), bromuro de tetrabutil amonio (0.02 g) en MeCN (10 ml) se hicieron refluir durante 4 horas. El solvente se retiró bajo presión reducida. El residuo se dividió en porciones entre DCM/H_2O y la capa orgánica se separó. El solvente se evaporó y el residuo se purificó mediante cromatografía (DCM/EtOAc, 90:10) para producir el compuesto del título 0.34 g (95%). NMR (500 MHz) 0.7-0.9 (m, 6H), 1.0-1.8 (m, 11H), 3.2 (m, 2H), 3.6-3.8 (brs, 2H), 4.3 (q, 2H), 4.7 (s, 2H), 7.0-7.1 (m, 3H), 7.15 (s, 1H), 7.3 (m, 2H), 7.4 (s, 1H).

Método 9

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método δ; 0.34 g) e hidróxido de sodio (0.3 g) se disolvieron en etanol y la mezcla se calentó a reflujo durante 1 hora. Se agregó ácido acético (1 ml) y el solvente se retiró a presión reducida. El residuo se dividió en porciones entre DCM/H_2O y la capa orgánica se separó y se secó. La trituración del residuo con *n*-hexano produjo el compuesto del título 0.29 g (90%) como un sólido. NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.7 (m, 8H), 3.1-3.2 (m, 2H), 3.6 (brs, 2H), 4.6 (s, 2H), 6.9-7.1 (m, 4H), 7.2 (m, 2H), 7.5 (s, 1H).

Método 10

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metoxi-8-carboximetoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metoxi-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 7; 1.2 g) se disolvió en etanol (20 ml). Se agregó hidróxido de sodio (0.5) disuelto en H_2O (1 ml) y la mezcla de reacción se calentó a 40°C durante 30 minutos. Se agregó ácido acético (1 ml) y el solvente se retiró a presión reducida. El residuo se dividió en porciones entre DCM/H_2O y la capa orgánica se separó y se secó. La trituración del residuo con *n*-hexano produjo el compuesto del título 1.1 g (97%) como un sólido. NMR 0.75-0.85 (m, 3H), 0.9 (t, 3H), 1.0-1.7 (m, 8H), 3.2 (q, 2H), 3.65 (s. 3H), 3.65-3.85 (m, 2H), 4.7 (s, 2H), 6.4 (s, 1H), 7.0 (t, 1H), 7.1 (d, 2H), 7.3 (t, 2H), 7.5 (s, 1H).

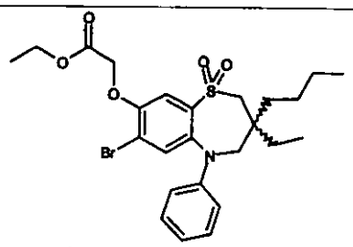
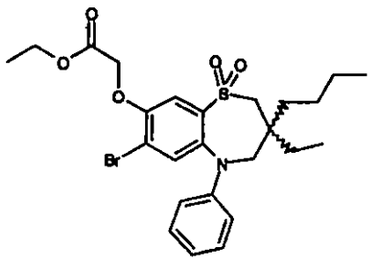
Método 11

1,1-Dioxo-3,3-dibutil-5-fenil-7-bromo-8-etoxicarbonilmetoxi-2.3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-bromo-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (sintetizada a la manera de WO9616051 para el correspondiente 3-butil-3-etil análogo; 2.0 g, 4.16 mmol), bromoacetato de etilo (0.84 g, 5.03 mmol), carbonato de sodio (2.0 g, 18.9 mmol) y bromuro de tetrabutil amonio (80 mg, 0.25 mmol) se agregaron a MeCN (20 ml). La mezcla se hizo refluir durante 2 horas y luego se evaporó bajo presión reducida. El residuo se extrajo con DCM/agua. La capa DCM se separó y se evaporó bajo presión reducida. El residuo se purificó mediante cromatografía de columna. El producto se eluyó con DCM / EtOAc (90:10) para producir el compuesto del título 2.2 g (93%). NMR 0.7-0.8 (m, 6H), 1.0-1.6 (m, 15H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.3 (q, 2H), 4.7 (s, 2H), 7.0-7.3 (m, 6H), 7.4 (s, 1H).

Métodos 12-13

Los siguientes compuestos se sintetizaron por el procedimiento de Método 11 usando el ácido y la amina apropiados (no se indica la fuente donde se obtiene en el comercio).

Mét.	Compuesto	M/z	SM
12	 Enantiómero 1	538	Mét. 83
13	 Enantiómero 2	538	Mét. 84

Método 14

1,1-Dioxo-3,3-dibutil-5-fenil-7-bromo-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-bromo-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 11; 2.2 g, 3-88 mmol) se disolvió en etanol (15 ml). NaOH (0.8 g in 1.5 ml agua) se agregó a la solución y la mezcla se agitó durante 30 minutos a temperatura ambiente. Se agregó ácido acético (2 ml). El solvente se evaporó bajo presión reducida y el residuo se extrajo con EtOAc/agua. La capa EtOAc se separó, se secó y se evaporó bajo presión reducida para producir el compuesto del título 2.0 g (95%). NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.5 (m, 12H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.7 (s, 2H), 7.0-7.3 (m, 6H), 7.4 (s, 1H).

Método 15

1,1-Dioxo-3-butil-3-etil-5-fenil-7-isopropoxi-8-carboximetoxi-2.3,4.5-tetrahidro-1,5- benzotiazepina

Se agregó sodio (115 mg, 5 mmol) a alcohol isopropílico (12 ml) y la temperatura se elevó entonces a 80°C para dejar que se formara la sal de alcohol. Después que todo el sodio se disolvió se agregó en una porción 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 9; 100 mg, 0.2 mmol). La reacción se hizo entonces refluir durante la noche, y luego se enfrió a temperatura ambiente y se extinguió con ácido acético. El solvente se retiró entonces bajo presión reducida y el residuo se disolvió en agua y MeCN (70/30) y se purificó parcialmente mediante HPLC. El residuo se disolvió en etilen glicol y se agregó NaOH (500 mg). Esta mezcla de reacción se calentó a 125°C durante la noche y luego se enfrió a temperatura ambiente y se extinguió con ácido acético, y se agregó EtOAc (100 ml). El etilen glicol se retiró lavando la capa orgánica con agua ácida tres veces. La capa orgánica se concentró entonces y el residuo se purificó nuevamente como antes para producir el compuesto del título 40 mg (41 %). NMR (300 MHz) 0.7-1.0 (m, 6H), 1.0-1.8 (m, 15H), 3.2 (q, 2H), 3.75 (m, 2H), 4.3 (m, 1H), 4.6 (s, 2H), 6.35 (s, 1H), 6.95-7.2 (m, 3H), 7.2-7.4 (m, 2H), 7.55 (s, 1H).

Método 16

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

A 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 25; 500 mg, 1.2 mmol) se agregó MeCN (30 ml), bromuro de tetrabutil amonio (30 mg, 0.08 mmol), carbonato de sodio anhidro (500 mg, 4.7 mmol), bromoacetato de etilo (0-14 ml, 1.26 mmol) y carbonato de cesio (20 mg, 0.06 mmol). Esta mezcla de reacción se agitó entonces durante la noche a 80°C. Luego el solvente se retiró bajo presión reducida, se agregaron agua y DCM y la fase acuosa se

extrajo tres veces con DCM. Las fases orgánicas combinadas se secaron entonces, se concentraron y se purificaron mediante cromatografía de destello [DCM: EtOAc, 1:0, 9:1] para producir el compuesto del título 600 mg (99%). NMR (300 MHz) 0.8-1.0 (m, 6H), 1.0-1.8 (m, 11H), 2.2 (s, 3H), 3.2 (q, 2H) 3.75 (brq, 2H), 4.3 (q, 2H), 4.75 (s, 1H), 6.7 (s, 1H), 6.95 (t, 1H), 7.05 (d, 2H), 7.25 (t, 2H), 7.3 (s, 1H).

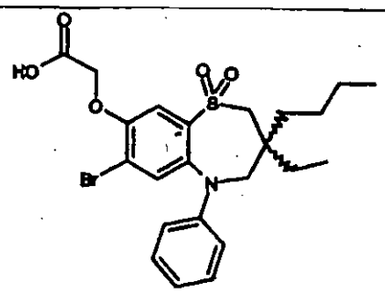
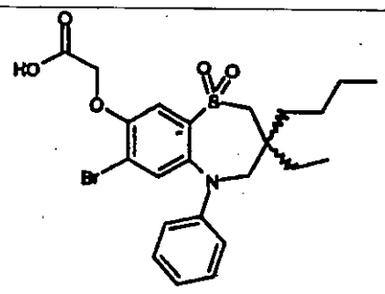
Método 17

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina

A 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 16; 478 mg, 0.95 mmol) se agregó THF (15 ml), agua (3 ml) y LiOH (34 mg, 1.4 mmol). La reacción se agitó entonces durante 1 hora. Luego se agregó ácido acético (0.2 ml) junto con agua (10 ml) y DCM (10 ml). La capa acuosa se extrajo entonces tres veces con DCM. Las fases orgánicas combinadas se secaron luego y se concentraron para producir el compuesto del título 450 mg (99%). NMR 0.7-0.9 (m, 6H), 1.0-1.7 (m, 8H), 2.2 (s, 3H), 3.2 (q, 2H), 3.7 (m, 2H), 4.8 (s, 2H), 6.65 (s, 1H), 6.95 (t, 1H), 7.05 (d, 2H), 7.25 (t, 2H), 7.35 (s, 1H), 8.4 (brs, 1H).

Método 18-19

Los siguientes compuestos se sintetizaron por el procedimiento de Método 17 usando el ácido y la amina apropiados (no se indica la fuente donde se obtiene en el comercio) salvo que se emplearon dos equivalentes de LiOH y la extracción se llevó a cabo después de 2 horas de tiempo de reacción usando EtOAc.

Mét.	Compuesto	M/z	SM
18	 Enantiómero 1	510	Mét. 12
19	 Enantiómero 2	510	Mét. 13

Método 20

1,1-Dioxo-3-butil-3-etil-5-fenil-7-mesil-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

A 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 16; 122 mg, 0.24 mmol) se agregó DCM (3 ml), agua (3 ml) y carbonato de potasio (120 mg, 0.87 mmol). La mezcla de reacción se enfrió entonces a 0°C y se agregó en una porción ácido m-cloroperoxibenzoico (160 mg, 0.51 mmol). Después de 5 horas la reacción se extinguió con DCM y solución de carbonato hidrogenado de sodio saturado, la fase acuosa se extrajo entonces tres veces con DCM. Las fases orgánicas combinadas se secaron, se concentraron y se purificaron mediante cromatografía de destello [DCM : EtOAc, 9:1] para producir el compuesto del título 46 mg (35%). NMR 0.7-0.8 (m, 6H), 1.0-1.65 (m, 11H), 3.2 (q, 2H), 3.3 (s, 3H), 3.7 (brs, 1H), 4.25 (q, 2H), 4.8 (s, 2H), 7.0-7.1 (m, 3H), 7.2-7.3 (m, 2H), 7.5 (s, 2H).

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Método 21

1,1-Dioxo-3-butil-3-etil-5-fenil-7-mesil-8-carboximetoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina

A 1,1-dioxo-3-butil-3-etil-5-fenil-7-mesil-8-etoxicarbonilmetoxi-2,3,4,5- tetrahidro-1,5-benzotiazepina (Método 20; 46 mg, 0.085 mmol) se agregó THF (5 ml), agua (1 ml) y LiOH (10 mg, 0.4 mmol). La reacción se agitó durante 1 hora y luego se agregó un exceso de ácido acético para extinguir la reacción. Se agregaron agua y DCM y la fase acuosa se extrajo tres veces con DCM. Las fases orgánicas combinadas se secaron y concentraron para producir el compuesto del título 40 mg (91%). NMR 0.7-0.85 (m, 6H), 1.0-1.7 (m, 8H), 3.2 (m, 2H), 3.3 (s, 3H), 3.8 (s, 2H), 4.9 (s, 2H), 5.0 (brs, 1H), 7.05-7.15 (m, 3H), 7.3-7.4 (t, 2H), 7.5 (s, 1H), 7.6 (s, 1H).

Método 22 (Preparación 1)

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-bromo-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 14; 500 mg, 0.93 mmol) se disolvió en DMF (10 ml). Se agregó metanotiolato de sodio (200 mg, 2.85 mmol) y la mezcla se agitó durante 2 horas a 50°C. Se agregó ácido acético (0.4 ml) y el solvente se evaporó bajo presión reducida. El residuo se extrajo con EtOAc/agua. La capa EtOAc se separó, se secó y se evaporó bajo presión reducida para producir el compuesto del título 450 mg (96%). NMR (300 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 2H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.8 (s, 2H), 6.6 (s, 1H), 6.9-7.1 (m, 3H), 7.2-7.4 (m, 3H).

Método 22 (Preparación 2)

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4.5-tetrahidro-1,5-benzotiazepina

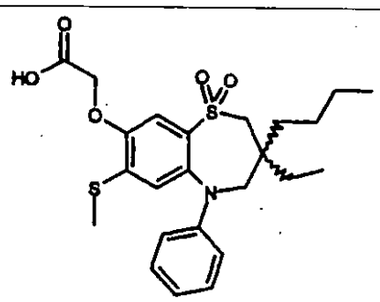
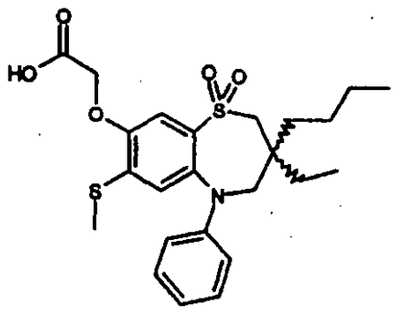
Una solución de NaOH (4.67 g, 116 mmol) en agua (10 ml) se agregó a una solución de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-etoxicarbonil-

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2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 114; 15.45 g, 28.71 mmol) en EtOH (160 ml). La solución se agitó durante 30 minutos a temperatura ambiente. El solvente se retiró bajo presión reducida y el residuo se dividió en porciones entre EtOAc y 1.0 M HCl. La capa acuosa se extrajo dos veces más con EtOAc y los extractos orgánicos combinados se lavaron con salmuera y se concentraron para producir el compuesto del título (14.28 g, 98 %) como un polvo blanco. NMR (500 MHz, DMSO-d_6) 0.65-0.80 (m, 6H), 0.90-1.50 (m, 12H), 2.20 (s, 3H), 3.25 (s, 2H), 3.65 (bs, 2H), 4.80 (s, 2H), 6.70 (s, 1H), 6.80-7.30 (m, 6H), 13.20 (s, 1H).

Método 23-24

Los siguientes compuestos se sintetizaron por el procedimiento de Método 22) (Preparación 1) usando el ácido y la amina apropiados (no se indica la fuente donde se obtiene en el comercio) salvo que las reacciones se llevaron a cabo a temperatura ambiente y en Método 24 para tiempo de reacción extendido.

Mét.	Compuesto	M/z	SM
23	 Enantiómero 1	478	Mét. 18
24	 Enantiómero 2	478	Mét. 19

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Método 25

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

A 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-metoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina (WO9616051; 600 mg, 1.29 mmol) se agregaron DMF (5 ml) y metanotiolato de sodio (450 mg, 6.42 mmol). La reacción se calentó entonces a 60°C durante 1 hora. El baño de aceite se calentó entonces a 120°C durante 4 horas. Para extinguir la reacción, la temperatura se bajó a temperatura ambiente y rápidamente se agregó exceso de ácido acético. La reacción se mantuvo bajo un flujo de nitrógeno a través de hipoclorito de sodio durante 2 horas. Se agregaron agua y EtOAc y la fase acuosa se extrajo tres veces con EtOAc. Las fases orgánicas combinadas se lavaron con agua, se secaron y se concentraron bajo presión reducida. El residuo se purificó entonces mediante cromatografía de destello [DCM: EtOAc, 9:1] para producir el compuesto del título 0.5 g (92%), NMR 0.65-0-8 (m, 6H), 0.95-1.6 (m, 8h), 3.1 (q, 2H), 3.6 (brq, 2H), 6.75 (s, 1H), 6.8 (t, 1H), 6.9 (d, 2H), 7.15 (t, 2H), 7.55 (s, 1H).

Método 26

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-hidroxi-2,3.4,5-tetrahidro-1,5-benzotiazepina

A 1,1-dioxo-3,3-dibutil-5-fenil-7-bromo-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (sintetizada a la manera de WO9616051 para el correspondiente 3-butil-3-etil análogo; 40 mg, 0.08 mmol) se agregó DMF (2 ml), metanotiolato de sodio (60 mg, 0.85 mmol) y borohidruro de sodio (60 mg, 1.6 mmol). La reacción se ejecutó durante la noche a 60°C. Se agregaron más borohidruro de sodio (60 mg, 1.6 mmol) y metanotiolato de sodio (60 mg, 0.85 mmol) y la temperatura se elevó a 120°C. La reacción se calentó a esta temperatura durante 4 horas y luego se enfrió a temperatura ambiente. Luego se agregó ácido acético bajo un flujo de nitrógeno, a través de hipoclorito de sodio durante la noche. Se agregaron

agua y EtOAc y la fase acuosa se extrajo tres veces con EtOAc. Las fases orgánicas combinadas se lavaron con HCl (1M), se secaron y concentraron bajo presión reducida. El residuo se purificó entonces mediante cromatografía de destello [EtOAc: heptano, 1:4] para producir el compuesto del título 0.34 g (93%). NMR 0.7-0.9 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 3H), 3.1 (s, 2H), 3.4 (s, 2H), 3.7 (brs, 2H), 6.7 (s, 1H), 6.85-7.05 (m, 2H), 7.2-7.4 (m, 2H).

Método 27

Sal de amonio de ácido 2-[(2'R)-2'-(*t*-Butoxicarbonilamino)-2'-feniletanoilamino]etanosulfónico

Ácido 2-aminoetanosulfónico (740 mg, 5.91 mmol) y ácido (2R)-2-(*t*-butoxicarbonilamino)-2-fenilacético (1.09 g, 4.34 mmol) se disolvieron en DMF (20 ml). Se agregaron DIPEA (2.8 ml, 16.1 mmol) y TBTU (1.53 g, 4.78 mmol) y la mezcla se agitó durante 2 horas a 60°C. El solvente se evaporó a presión reducida. El residuo se purificó mediante HPLC preparativa usando una gradiente MeCN/tampón de acetato de amonio (5/95 a 100/0) como eluyente para producir el compuesto del título 589 mg (32%). NMR (CD_3OD) 1.43 (s, 9H), 2.85-3.0 (m, 2H), 3.53-3.68 (m, 2H), 5.1 (brs, 1H), 7.25-7.45 (m, 5H).

Método 28

Sal de amonio de ácido 2-((2'R)-2'-amino-2'-feniletanoilamino) etanosulfónico

Sal de amonio de ácido 2-[(2'R)-2'-(*t*-butoxicarbonilamino)-2'-feniletanoilamino]etanosulfónico (Método 27; 589 mg, 1.57 mmol) se disolvió en EtOAc (20 ml) y la mezcla se enfrió en un baño de hielo. Se hizo borbotar gas de cloruro de hidrógeno a través de la reacción, se retiró el baño de hielo y la reacción se dejó reposar durante 30 minutos a temperatura ambiente. El solvente se evaporó a presión reducida. El residuo se volvió a disolver entonces en EtOAc (20 ml) y se enfrió en un baño de hielo. Otra vez se hizo borbotar gas de cloruro de hidrógeno a

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través de la reacción, se retiró el baño de hielo y la reacción se dejó reposar durante 30 minutos a temperatura ambiente. El solvente se evaporó a presión reducida. Se agregó DIPEA en DCM y la mezcla se evaporó a presión reducida. Esto se repitió dos veces. La mezcla se liofilizó para producir el compuesto del título 563 mg (85%) que contenía 1 equivalente de cloruro de di-isopropiletilamonio. NMR (D_2O) 1.35-1.38 (m, 15H), 2.96- 3.12 (m, 2H), 3.21 (q, 2H), 3.50-3.80 (m, 4H), 5.11 (brs, 1H), 7.45-7.55 (m, 5H).

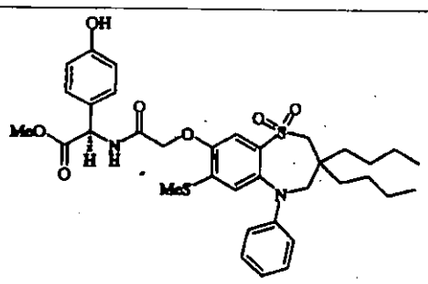
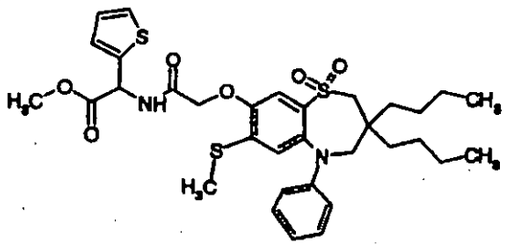
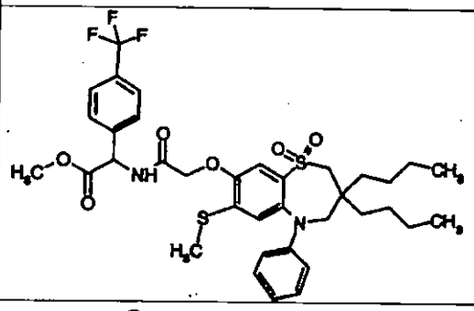
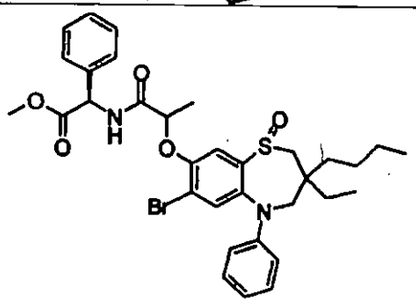
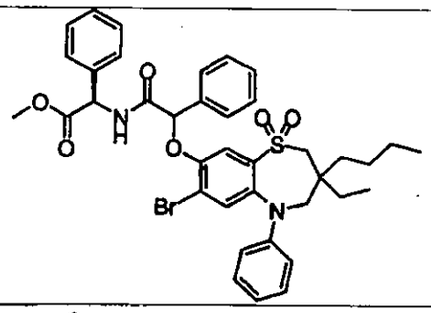
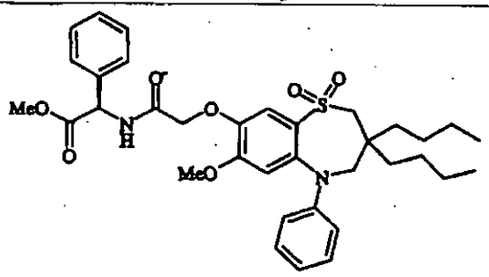
Método 29

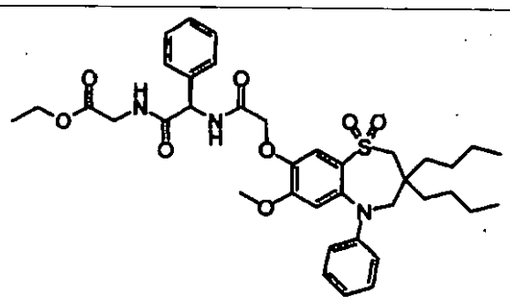
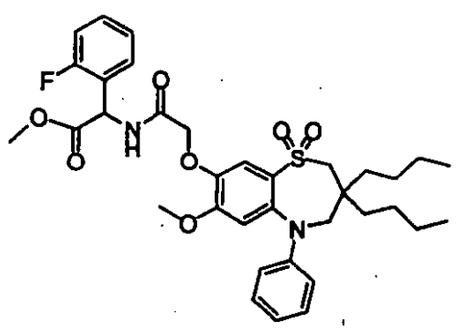
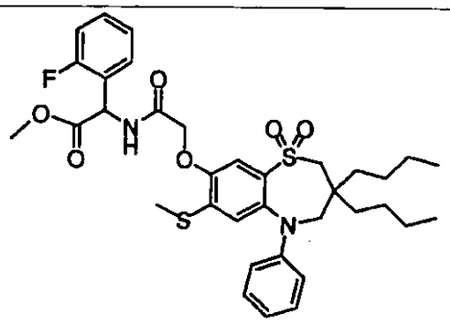
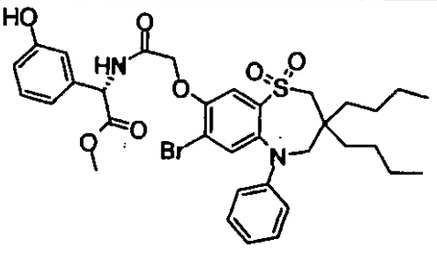
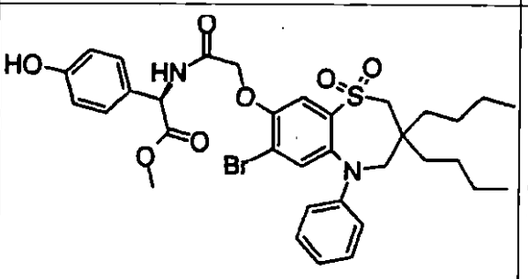
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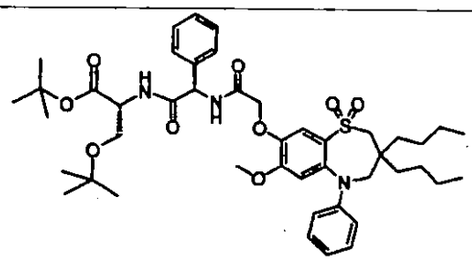
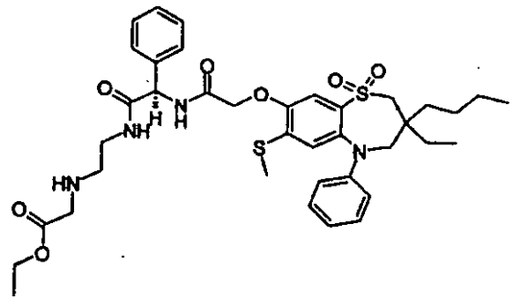
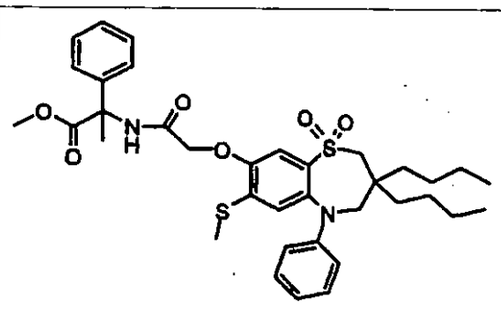
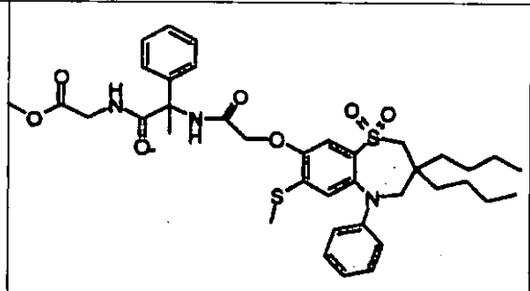
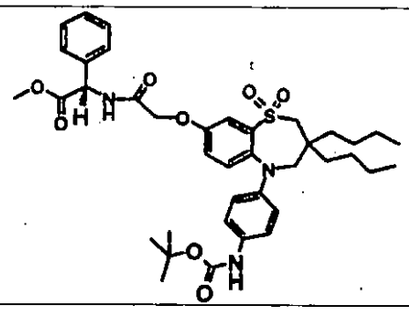
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 22; 250 mg, 0.49 mmol), (R)-2-fenilglicina metil éster clorhidrato (120 mg, 0.60 mmol) y DIPEA (300 mg, 2.3 mmol) se disolvieron en DCM (10 ml) y la mezcla se agitó durante 5 minutos en temperatura ambiente. Se agregó TBTU (210 mg. 0.65 mmol) y la mezcla se agitó durante 30 minutos a temperatura ambiente. El solvente se evaporó bajo presión reducida y el residuo se puso en una columna y el producto se eluyó con DCM/EtOAc (90:10) para producir el compuesto del título 306 mg (95%). NMR (500 MHz) 0.7-0.8(m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 (brs, 2H), 3.6-3.8 (m, 5H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.9 (d, 1H).

Métodos 30-45

Los siguientes compuestos se sintetizaron por el procedimiento de Método 29 usando el ácido y la amina apropiados (no se indica la fuente donde se obtiene en el comercio) salvo que el tiempo de reacción se amplió a 2 horas para algunos métodos.

Mét.	Compuesto	NMR o m/z	SM
30		(300 MHz, CD_3OD) 0.8-0.9 (m, 6H),1.1-1.6 (m, 12H), 2.2 (s, 3H), 3.3 (s, 2H), 3.75 (brs, 5H), 4.7-4.8 (m, 2H), 5.45 (s, 1H), 6.7 (s, 1H), 6.8-7.3 (m, 9H), 7.45 (s, 1H)	Mét. 22
31		(300 MHz, CD_3OD) 0.75-0.95 (m, 6H), 1.0-1-6 (m, 12H), 2.1 (s, 3H), 3.2 (s, 2H), 3.7 (s, 5H), 4.65 (s, 2H), 5.85 (s, 1H), 6.7 (s, 1H), 6.9-7.4 (m, 9H)	Mét. 22
32		(300 MHz, CD_3OD) 0.75-0.9 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 3H), 3.2 (s, 2H), 3.75 (s, 5H), 4.7 (brs, 2H), 5.7 (s, 1H), 6.7 (s, 1H), 6.9-7.4 (m, 6H), 7.55-7.8 (m,4H)	Mét. 22 y Mét. 71
33		0.70-0.85 (m, 6H), 0.95-1.75 (m, 8H), 1.55-1.75 (2d, 3H), 3.05-3,30 (m, 2H), 3.55-3.90 (m, 2H), 3.70-3.80 (2s, 3H) 4.75-4.90 (2q, 1H), 5.60 (d, 1H), 7.00-7.55 (m, 12H), 7.80-7.95 (m, 1H)	Mét. 2
34		0.65-0.85 (m, 6H), 0.95-1.65 (m,8H), 3.00-3.15 (m,2H), 3.50-3.80 (m, 2H), 3.70-3.80 (2s, 3H), 5.60 (s, 1H), 5.65 (d, 1H) 7.00-7.60 (m, 17H), 8.05-8.20 (2d, 1H)	Mét. 4
35		(CD_3OD) 0.75-0.85 (m, 6H), 1.00-1.30 (m, 8H), 1.35-1.55 (m, 4H), 3.20 (s,2H), 3.55 (s, 3H), 3.70 (s, 3H), 3.75 (brs, 2H), 4.60 (ABq, 2H), 5.55 (s, 1H), 6.50 (s, 1H), 6.95-	Mét. 4

		7.40 (m, 10H), 7.50 (s, 1H)	
36		707.4	Ej. 12
37		0.75-0.85 (m,6H), 1.00-1.60 (m, 12H), 3.20 (s, 2H), 3.60 (s, 3H), 3.75 (brs, 2H), 3.75 (s, 3H), 4.55 (ABq, 2H), 5.85 (d, 1H), 6.40 (s. 1H), 6.95-7.45 (m, 9H), 7.55 (s. 1H), 8-05 (d, 1H)	Mét. 6
38		0.75-0.85 (m, 6H), 1.00-1.60 (m, 12H), 2.20 (s, 3H), 3.20 (s, 2H), 3.75 (brs, 2H), 3.80 (s, 3H), 4.60 (ABq, 2H), 5.90 (d, 1H), 6.65 (s, 1H), 6.95-7.45 (m, 10H), 7.95 (d, 1H)	Mét. 22
39		(500 MHz) 0.7-0.8 (m, 6H), 1.0-1,5 (m, 12H), 3.2 (m, 2H), 3.7- 3.8 (m, 5H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.8-7.4 (m, 10H), 7.5 (s, 1H)	Mét. 14
40		(300 MHz) 0.7-0.8 (m, 6H), 1.0- 1.6 (m, 12H), 3.2 (brs, 2H), 3.7- 3.8 (m, 5H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.8 (d, 2H), 7.0-7.4 (m, 8H), 7.9 (d, 1H)	Mét. 14

41		766.4 (M-(*t*-butil)+2H)	Ej. 12
42		739.3	Ej. 38
43		667	Mét. 22
44		724	Ej. 18
45		722.5	Mét. 109

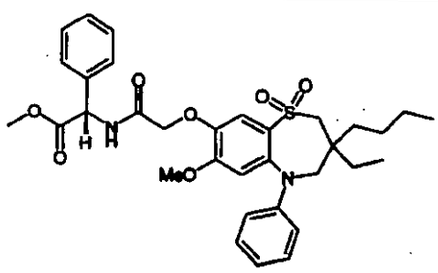
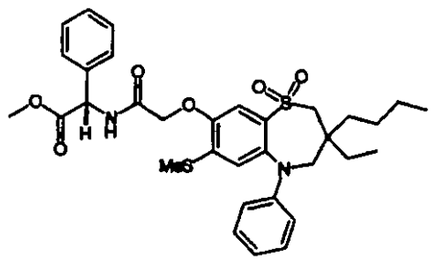
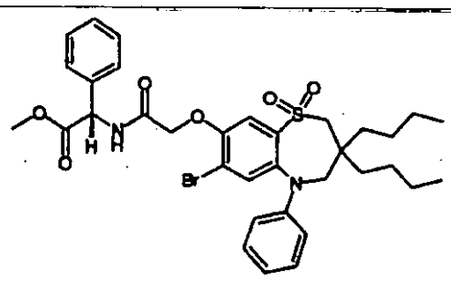
Método 46

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-[*N*-((S)-1'-fenil-1'-metoxicarbonilmetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

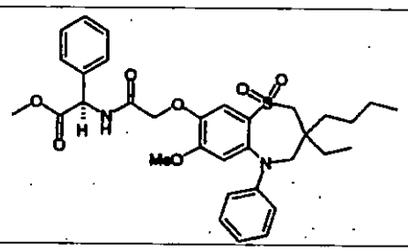
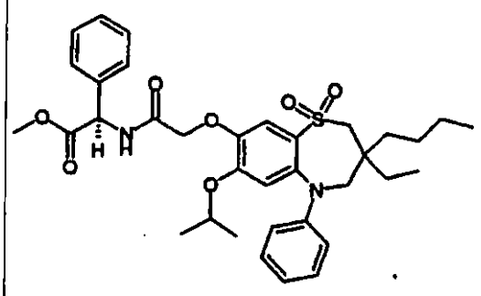
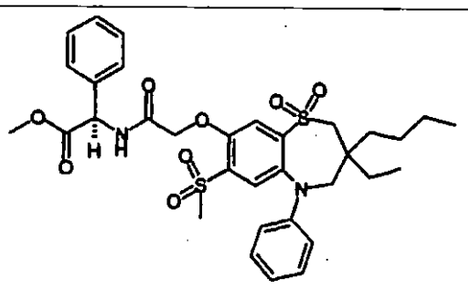
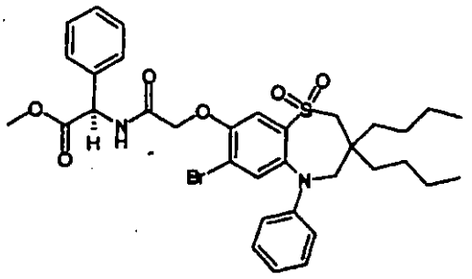
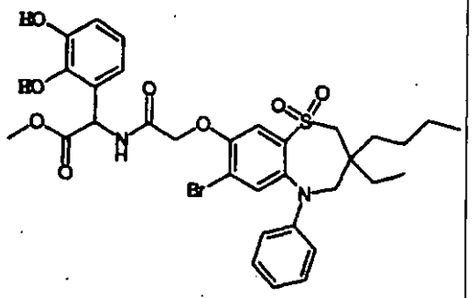
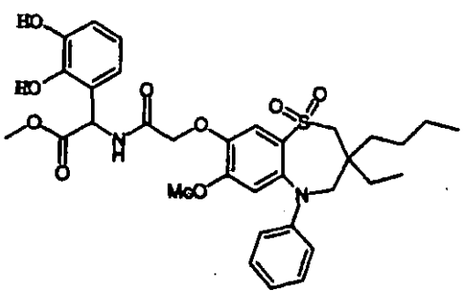
1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-carboximetoxi-2,3,4,5-tetrahidro- 1,5-benzotiazepina (Método 9; 50 mg, 0.098 mmol) se disolvió en DCM (2 ml). Se agregaron metil (2*S*)-amino(fenil)acetato (19 mg, 0.12 mmol) y DIPEA (0.068 ml, 0.39 mmol) y la reacción se agitó durante 2 minutos. Se agregó TBTU (42 mg, 0.13 mmol) y la mezcla se agitó durante 1.5 horas a temperatura ambiente. La mezcla se puso en una columna ISOLUTE pre-empacada y se eluyó con 10 ml DCM/EtOAc 8/2 para producir el compuesto del título 60 mg (93%). M/z 657.5.

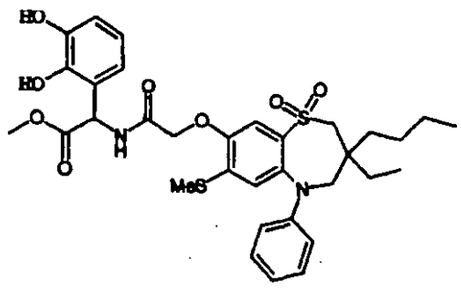
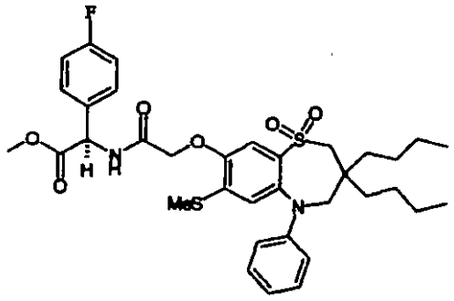
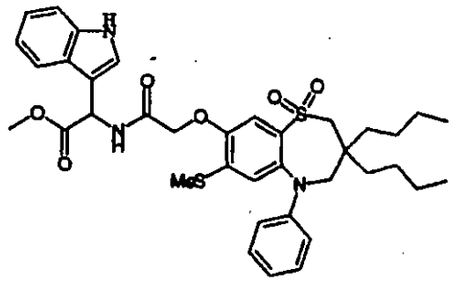
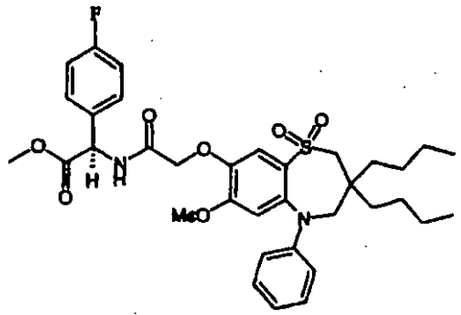
Métodos 47-62

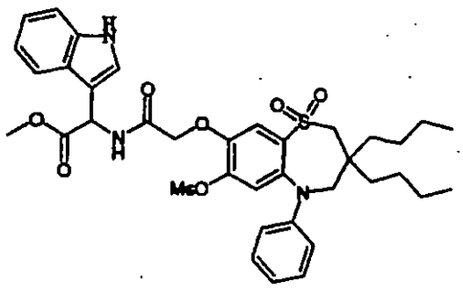
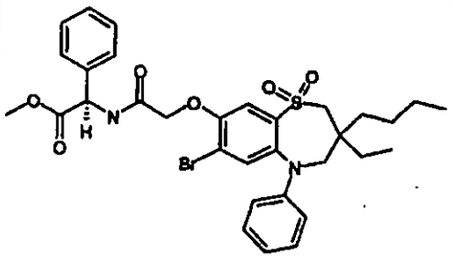
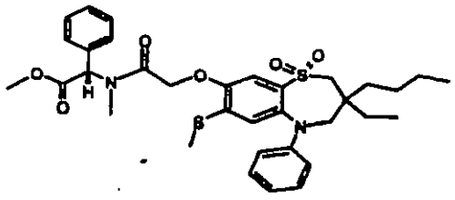
Los siguientes compuestos se sintetizaron por el procedimiento de Método 46 (excepto que los tiempo de reacción fueron durante la noche) usando el ácido y la amina apropiados (no se indica la fuente donde se obtiene en el comercio).

Mét.	Compuesto	NMR o M/z	SM
47		609.4	Mét. 10
48		625.4	Mét. 17
49		685.3	Mét. 14

231

50		609.4	Mét. 10
51		637.4	Mét. 15
52		657.4	Mét. 21
53		685.3	Mét. 14
54		0.73-0.95 (m, 6H), 0.98-1.78 (m, 8H), 3.12-3.28 (m, 2H), 3.6-4.0 (m, 5H), 4.60 (ABq, 2H), 5.79 (d, 1H), 6.0 (brs, 1H), 6.54 (dd, 1H), 6.83 (t, 1H), 6.95 (dd, 1H), 7.0-7.5 (m, 7H), 8.43 (d, NH), 9.32 (brs, 1H)	Mét. 9 y Mét. 74
55		0.75-0.9 (m, 6H), 1.0-1.78 (m, 8H), 3.10-3.26 (m. 2H), 3.63-3.87 (m, 8H), 4.56 (ABq, 2H), 5.76 (d, 1H), 5.99 (brs, 1H), 6.38 (s, 1H), 6.51 (dd, 1H), 6.81 (t, 1H), 6.93 (dd, 1H), 7.0- 7.15	Mét. 10 y Mét. 74

		(m, 3H), 7.23-7.4 (m, 2H), 7.55 (s. 1H), 8.54 (d, NH), 9.45 (brs, 1H)	
56		0.76-0.87 (m, 6H), 1.0-1.8 (m, 8H), 2.23 (s, 3H), 3.1-3.25 (m, 2H), 3.6-3.95 (m, 5H), 4.61 (ABq, 2H), 5.79 (d, 1H), 6.0 (brs, 1H), 6.54 (dd, 1H), 6.65 (s, 1H), 6.83 (t, 1H), 6.92-7.1 (m, 4H), 7.23-7.4 (m, 3H), 8.37 (d, NH), 9.35 (brs, 1H)	Mét. 17 y Mét. 74
57		(CD_3OD) 0.76-0.85 (m, 6H), 1.02- 1.3 (m, 8H), 1.36-1.56 (m, 4H), 2.16 (s, 3H), 3.24 (brs, 2H), 3.66-3.80 (m, 5H), 4.71 (ABq, 2H), 5.57 (s, 1H), 6.71 (s, 1H), 6,98 (t, 1H), 7.06-7.14 (m, 4H), 7.28 (brt, 2H), 7.37-7.45 (m, 3H)	Mét. 22 y Mét. 75
58		(CD_3OD) 0.76-0.85 (m, 6H), 1.02- 1.28 (m, 8H), 1.36-1.56 (m, 4H), 1.96 (s, 3H), 3.24 (brs, 2H), 3.6-3.8 (m, 5H), 4.73 (ABq, 2H), 5.76 (s, 1H), 6.63 (s, 1H), 6.94-7.04 (m, 2H), 7.07-7.15 (m, 3H), 7.27 (t, 2H), 7.31 (s, 1H), 7.37 (d, 1H), 7.42 (s, 1H), 7.56 (d, 1H)	Mét. 22
59		(CD_3OD) 0.80 (brt, 6H), 1.0-1.28 (m, 8H), 1.36-1.54 (m, 4H), 3.22 (brs, 2H), 3.61 (s, 3H), 3.69-3.8 (m, 5H), 4.62 (ABq, 2H), 5.56 (s, 1H), 6.49 (s, 1H), 6.99 (brt, 1H), 7.07-7.16 (m, 4H), 7.29 (brt, 2H), 7.37-7.43 (m, 2H),	Mét. 6 y Mét. 75

		7.52 (s, 1H)	
60		(CD_3OD) 0.75-0.84 (m, 6H), 1.0- 1.29 (m, 8H), 1.35-1.54 (m, 4H), 3.20-3.23 (m, 5H), 3.65-3.8 (m, 5H), 4.64 (ABq, 2H), 5.74 (s, 1H), 6.34 (s, 1H), 6.95-7.04 (m, 2H), 7.09-7.15 (m, 3H), 7.24-7.31 (m, 3H), 7.37 (d, 1H), 7.50-7.54 (m, 2H)	Mét. 6
61[1]		0.74-0.83 (m. 6H), 0.98-1.7 (m, 8H), 3.18 (ABq, 2H), 3.60-3.90 (m, 5H), 4,59 (ABq, 2H), 5.67 (d, 1H), 7.0-7.2 (m, 4H), 7.2-7.55 (m, 8H), 7.91 (d, NH)	Mét. 9
62		639.4	Mét. 17 y Mét. 76

[1] Eluyente era DCM/EtOAc en una gradiente paso a paso de 100/0, 9/1, 8/2.

Método 63

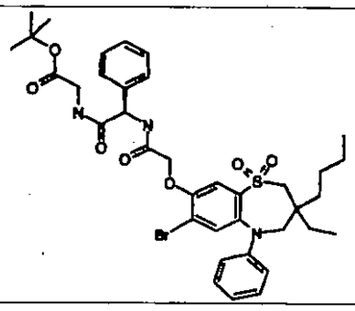
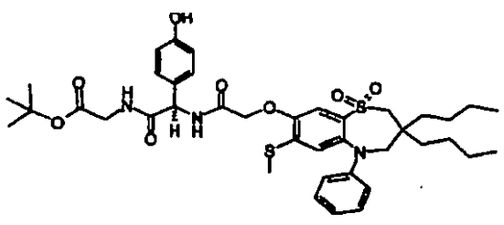
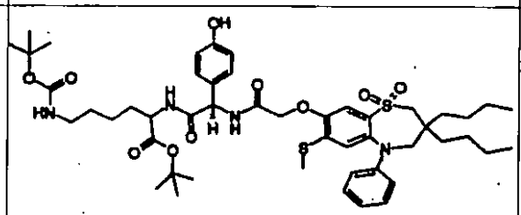
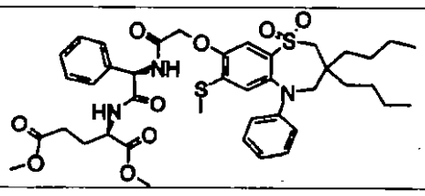
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R')-1'-fenil-1'-[*N*-(*t*-butoxicarbonilmetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

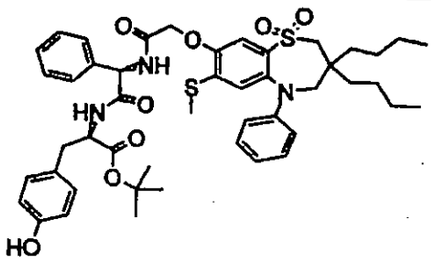
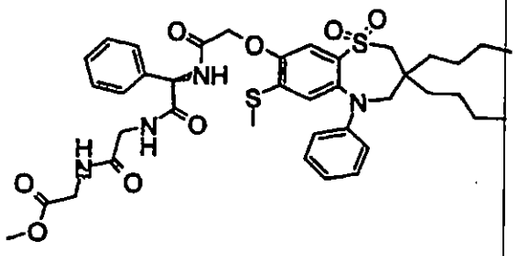
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-(R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 1; 110 mg, 0.17 mmol), éster tert-butilico de glicina (30 mg, 0.23 mmol) y DIPEA (120 mg, 0.93 mmol) se disolvieron en DCM (2 ml). La mezcla se agitó durante 5 minutos a temperatura ambiente. Se agregó TBTU (72 mg, 0,22 mmol) y la mezcla se agitó durante 1 hora a

temperatura ambiente. El solvente se evaporó a presión reducida y el residuo se puso en una columna y el producto se eluyó con DCM/EtOAc (90:10) para producir el compuesto del título 122 mg (94%). NMR (300 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 21H), 2.2 (s, 3H) 3.2 (s, 2H), 3.7-4.0 (m, 4H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.4 (t, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 8.1 (d, 1H).

Métodos 64-69

Los siguientes compuestos se sintetizaron por el procedimiento de Método 63 usando el ácido y la amina apropiados (no se indica la fuente donde se obtiene en el comercio).

Mét.	Compuesto	NMR o M/z	SM
64		756.1	Ej. 22
65		(CD_3OD) 0.75-0.85 (m, 6H), 1.1- 1.3 (m, 8H), 1.4 (s, 9H), 1.45-1.55 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.75 (brs, 1H), 3.85 (s,2H), 4.7 (ABq, 2H), 5.5 (s, 1H), 6.7 (s, 1H), 6.75-7.35 (m, 9H), 7.4 (s, 1H)	Ej. 2
66		937.9 $(M-H)^-$	Ej. 2
67		796.4	Ej.1

68			Ej. 1
69			Ej. 1

Método 70

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-{*N*-((S)-1'-fenil-1'-dietoxifosforil)metil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina

El compuesto del título se sintetizó a partir de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 9) y dietil (*S*)-amino(fenil)metilfosfonato mediante el procedimiento de Ejemplo 33. NMR (600 MHz) 7.77- 7.72 (1H, m), 7.47-7.42 (3H, m), 7.36-7.27 (5H, m), 7-14 (1H, s), 7.10-7.03 (2H, m), 5.55-5.48 (1H, m), 4.63-4.51 (2H, m), 4.14-4.02 (2H, m), 3.99-3.92 (1H, m), 3.81-3.60 (3H, m), 3.22-3.10 (2H, m), 1.65-1.25 (8H, m), 1.19-0.95 (6H, m), 0.78-0.73 (6H, m).

Método 71

4-Trifluorometil-α-metoxicarbonilbencilamina

4-Trifluorometil-α-carboxibencilamina (1.4 g, 1.83 mmol) y cloruro de tienilo se agregaron a metanol (8 ml) y la mezcla se hizo refluir durante 2 horas. El solvente se evaporó bajo presión reducida. El residuo se suspendió en éter dietílico y el producto se extrajo mediante filtración, se lavó con éter y se secó para producir el compuesto del título 0.34 g (69%),

NMR (300 MHz, DMSO-d_6) 3.3 (s, 1H), 5.45 (s, 1H), 7.7-7.9 (m, 4H), 9.25 (brs, 3H).

Método 72

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-(R)-1'-fenil-1'-[*N*-(etoxicarbonilmetil)carbamoil]metil]carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5- benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-((R)-1'-fenil-1'carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 38; 52 mg, 0.082 mmol) clorhidrato éster dietílico de glicina (18 mg, 0.129 mmol) se disolvieron en DCM (2 ml) y se agregó DIPEA (0.70 ml, 0.42 mmol). Después de agitar a temperatura ambiente durante 5 minutos, se agregó TBTU (34 mg, 0.11 mmol) y la mezcla se agitó durante 2 horas. El solvente se evaporó y el residuo se purificó con cromatografía de destello (DCM:EtOAc 10:3) para producir el compuesto del título 50 mg (88%). NMR (500 MHz) 0.86 (m, 6H), 1.10-1.75 (m, 8H), 1,28 (m, 3H), 2.23 (s, 3H), 3.19 (q, 2H), 3,75 (m, 2H), 3.99-4.25 (m, 4H), 4.64 (q, 2H), 5.64 (m, 1H), 6.35 (brs, 1H), 6.69 (s, 1H), 7.03 (t, 1H), 7.09 (d, 1H), 7.29-7.52 (m,7H),8.10(d, 1H).

Método 73

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-1'-fenil-1'-[*N*-1"-metoxicarbonil-1"-fenilmetil)carbamoil]metil} carbamoilmetoxi)-2,3,4,5- tetrahidro-1,5-benzotiazepina

El compuesto del título se sintetizó mediante el procedimiento de Método 72 usando 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-1'-fenil-1'-carboximetil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 38) y clorhidrato de metil (2R)-amino(fenil)acetato.

Método 74

Sal clorhidrato de 1-(1'-metoxicarbonil-1'-aminometil)-2,3-dihidroxifenilo

1-(1'-Carboxi-1'-aminometil)-2,3-dihidroxifenil (40 g, 0.218 mmol) se mezcló con metanol (230 ml). Se hizo borbotar a través gas HCl. La mezcla se hizo refluir durante 2 horas. El solvente se evaporó bajo presión reducida. El producto se cristalizó a partir de metanol/EtOAc/éter dietílico para producir 35.5 g (70 %) del producto del título. NMR (600 MHz, CD_3OD) 3.76 (s, 3H), 5.19 (s, 1H), 6.68-6-75 (m, 2H), 6.85 (dd, 1H).

Método 75

Sal clorhidrato de (R)-1-(1'-metoxicarbonil-1'-aminometil)-4-fluorofenilo

Ácido (2R)-amino(4-fluorofenil)acético (570 mg, 2.77 mmol) se disolvió en metanol (5 ml) y se enfrió en un baño de hielo. Se agregó cloruro de tienilo (2 ml) gota a gota y se dejó que la temperatura alcanzara la temperatura ambiente. Después de 5 horas la mezcla se evaporó bajo presión reducida. El procedimiento se repitió y la reacción se agitó durante la noche. La mezcla se evaporó bajo presión reducida para proporcionar el producto del título en un rendimiento cuantitativo. NMR (500 MHz, CD_3OD) 3.84 (s, 3H), 5.26 (s, 1H), 7.26 (t, 2H), 7.53 (dd, 2H).

Métodos 76-77

Los siguientes compuestos se sintetizaron por el procedimiento de Método 75 usando el ácido y la amina apropiados (no se indica la fuente donde se obtiene en el comercio).

Mét.	Compuesto	NMR	SM
76	(*S*)-α-Metilamino-α-metoxicarbonilbencilo	(CD_3OD) 2.63 (s, 3h), 381 (s, 3H) 5.15 (s, 1H), 7.45-7.55 (m, 5H)	(*S*)-α-Metilamino-α-carboxibencilo
77[1]	α-Metoxicarbonil-*N*-metilbencilamina clorhidrato	(D_2O) 2.65 (s, 3H), 3.81 (s, 3H), 5.15 (s, 1H), 7.45-7.48 (m, 2H), 7.52-7.59 (m, 3H)	(metilamino) (fenil) ácido acético

[1]Total reaction time 5 days

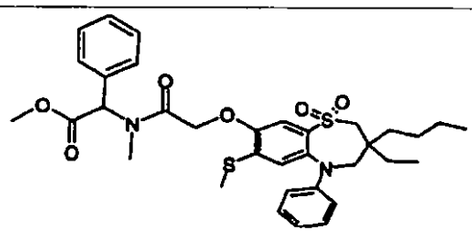
Método 78

1,1-Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-[((R)-α-(*t*-butoxicarbonil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina

tert-Butil (2R)-amino(4-hidroxifenil)acetato (104 mg, 0.47 mmol) y 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 17; 185 mg, 0.39 mmol) se disolvieron en DCM (5 ml) y se agregó lutidina (0.09 ml, 0.77 mmol). Después de agitar a temperatura ambiente durante 5 minutos se agregó o-(7-azabenzomazol-1-il-*N,N,N',N'*-tetrametiluronio hexafluorofosfato (208 mg, 0.55 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Purificación con cromatografía de destello (DCM:EtOAc 10:1→5:1) produjo el compuesto del título (175 mg, 66%). NMR (300 MHz) 0.81 (m,6H), 1.05-1.65 (m, 8H), 1,42 (s, 9H), 2.21 (s, 3H), 3.17 (ABq, 2H), 3.74 (m, 2H), 4.60 (ABq, 2H), 5.22 (brs, 1H), 5,49 (d, 1H), 6.67 (s, 1H), 6.79 (m, 2H), 7.00 (t, 1H), 7.07 (d, 2H), 7.23-7.30 (m, 3H), 7.40 (s, 1H), 7.82 (brd, 1H).

Método 79

Los siguientes compuestos se sintetizaron mediante el procedimiento de Método 78 usando el material base apropiado.

Mét.	Compuesto	M/z	SM
79		639.3	Mét. 17 y Mét. 77

Método 80

Ácido 2-{[(2R)-2-Amino-2-(4-hidroxifenil)etanoil]amino}etanosulfónico

N-Boc-4-hidroxifenilglicina (1.00 g, 3.21 mmol) se disolvió en DMF (5 ml) y se agregó taurina de tetrabutilamonio (2.36 g, 6.42 mmol) junto con 5 ml adicionales de DMF. La suspensión resultante se enfrió en hielo y se agregó TBTU (1.24 g, 3.85 mmol).

El baño de hielo se retiró después de 30 minutos y la mezcla se agitó durante 2 horas antes de filtrarse y concentrarse, se agregó TFA en DCM (20%, 20 ml) y la mezcla de reacción se agitó durante la noche. Se agregó etanol (20 ml) y los solventes se evaporaron. El producto crudo se hizo refluir en etanol (100 ml) durante 1 hora. La filtración proporcionó el compuesto del título puro como un sólido blanco, 626 mg (71%). NMR (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 81

1,1-Dioxo-3-butil-3-etil-5-fenil-7-carboximetiltio-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (113 mg, 0.24 mmol), Cs_2CO_3 (170 mg, 0.52 mmol) y tioglicolato de etilo (0.060 ml, 0.54 mmol) en DMF (4.0 ml) se sometieron a irradiación de microondas en un Sintetizador Smith a 80°C durante 3 minutos y luego a 90°C durante 8 minutos. La mezcla de reacción se diluyó con agua (250 ml) y se extrajo con DCM (5 x 10 ml) y las capas orgánicas recogidas se secaron ($MgSO_4$), se concentraron y se purificaron en una columna corta (éter de petróleo: EtOAc 4:1→ 2:1). El producto resultante se disolvió en THF (2 ml) y agua (2 ml) y se agregó NaOH (aq., 0.5 ml, 1 M) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La reacción se extinguió con HCl (1 M) y la mezcla de reacción se diluyó con agua (10 ml) y se extrajo con DCM (3 x 3 ml). La purificación con HPLC preparativa produjo el compuesto del título (58 mg, 59 %). NMR (300 MHz, CD_3OD) 0.81 (m, 6H), 1.00-1.70 (m, 8H), 3.21 (m, 2H), 3.42 (m, 2H), 3.71 (m, 2H), 3.92 (s, 3H), 6.88 (m, 2H), 7.02 (m, 2H), 7.23 (t, 2H), 7.40 (s, 1H).

Método 82

1,1-Dioxo-3-butil-3-etil-5-fenil-7-etoxicarbonilmetiltio-8-carboximetoxi-2,3,4,5- tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 9; 50 mg, 0.098 mmol) y Cs_2CO_3 (51 mg, 0.15 mmol) se agregaron a DMF (2.0 ml) y se agregó tioglicolato de etilo (0.02 ml, 0.15 mmol). La mezcla de reacción se sometió a irradiación de microondas en un Sintetizador Smith a 150°C durante 5 minutos.

La mezcla de reacción se diluyó con agua (100 ml), se acidificó con HCl (1 M), se extrajo con DCM (3 x 10 ml) y las capas orgánicas recogidas se secaron ($MgSO_4$) para proporcionar (el compuesto del título crudo (54 mg). M/z 550.2.

Método 83 y Método 84

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Enantiómero 1): y 1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-hidroxi-2,3,4,5-tetrahidro-1,5- benzotiazepina (Enantiómero 2)

Los dos enantiómeros de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (WO 96/16051) se obtuvieron mediante separación de la mezcla racémica correspondiente usando HPLC preparativa. La columna utilizada fue una Chiralpak AD (20 x 250 mm i.d., 10 mm) y la fase móvil fue una mezcla heptano / IPA en proporción 90/10. El racemato inyectado (17-3 mg in IPA (1 ml)) se eluyó con un flujo de 10 ml/min y el cromatograma fue seguido por detección UV a 285nm. En total se separaron 260 mg de racemato que produjeron 121 mg del primer enantiómero eluyente (Enantiómero 1) y 115 mg del segundo enantiómero eluyente (Enantiómero 2). Rendimiento total 91%. Cada uno de los dos enantiómeros se obtuvo en 99.4% e.e.

Método 85

(R)-*N*-Benciloxicarbonil-α-[*N'*-(*t*-butoxicarbonilmetil)carbamoil] bencilamina.

(R)-*N'*-Benciloxicarbonil-α-carboxibencilamina (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). Después de agitar 5 minutos a 0°C se agregó TBTU (12.4 g, 38.6 mmol) y la agitación se continuó 1 hora 30 minutos a 0°C y 3 horas 45 minutos a temperatura ambiente. La mezcla de reacción se lavó con agua (2 x 100 ml), se secó ($MgSO_4$) y purificó con cromatografía de destello (DCM:EtOAc 7:1 → 5:1) para producir el compuesto del título (13 g, 94 %). NMR (500 MHz) 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 86

(R)-α-[*N*-(*t*-Butoxicarbonilmetil)carbamoilbencilamina

(R)-*N*-Benciloxicarbonil-α-[*N'*-(*t*-butoxicarbonilmetil)carbamoil] bencilamina (Método 85; 12.8 g, 32.2 mmol) se disolvió en EtOH (99%, 200 ml) y tolueno (50 ml). Se agregó Pd/C (10%, 0.65 g) y la hidrogenación se llevó a cabo a presión atmosférica durante 5 horas 30 minutos a temperatura ambiente. La mezcla de reacción se filtró a través de tierra de diatomeas y los solventes se evaporaron para producir el compuesto del título (8.4 g, 99 %). NMR (600 MHz) 1.45 (s, 9H), 3.93 (m, 2H), 4.54 (s, 1H), 7.31-7.42 (m, 5H), 7.51 (brs, 1H).

Método 87

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-(S)-(α-metoxicarbonilbencil) carbamoilmetoxi]2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro- 1,5-benzotiazepina (Método 22; 50 mg, 0.099 mmol) se disolvió en DCM (2 ml). Se agregó clorhidrato de metil éster de (S)-fenilglicina (24.8 mg, 0.123 mmol) y diisopropil etil amina (70 □l, 0.401 mmol). La

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mezcla se agitó durante 15 minutos y luego se agregó TBTU (38 mg, 0.118 mmol). La reacción se concluyó después de 1.5 horas (LC/MS). El producto crudo se purificó mediante cromatografía de destello usando cloroformo/EtOAc (8/2) como el eluyente (88.6%; 55.2 mg, 0.064 mmol). M/z 653.

Método 88

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-((S)-α-[*N'*-(metoxicarbonilmetil)carbamoil]bencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-(S)-(α-carboxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Ejemplo 88; 25 mg, 0.039 mmol) y glicina metil éster (7.5 mg, 0.059 mmol) se disolvieron en DCM (2 ml). Se agregaron sucesivamente diisopropil etil amina (27 ml, 0.158 mmol) y TBTU (15 mg, 0.047 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente. El producto crudo se purificó mediante cromatografía de destello usando DCM/EtOAc (8/2) como eluyente, rendimiento del 79% (22 mg). M/z 710.

Método 89

1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-(2-carboxietoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

Hidróxido de sodio (38 mg, 0.95 mmol) se disolvió en etanol (2.5 ml) y luego se agregó 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (WO 96/16051; 200 mg, 0.443 mmol). Después de agitar a temperatura ambiente durante 5 minutos, se agregó ácido 3-bromopropiónico (68 mg, 0.443 mmol) y la mezcla de reacción se hizo refluir durante 20 horas. Se agregó ácido acético. El solvente se evaporó bajo presión reducida y el residuo se extrajo con EtOAc/agua. La capa orgánica se separó, se lavó con agua, se secó y se evaporó bajo presión reducida. El producto crudo se purificó mediante cromatografía de columna usando DCM/MeOH (100:5) como eluyente para

producir el compuesto del título 89 mg (38%). NMR (CD_3OD) 0.75-0.83 (m, 6H), 1.0-1.25 (m, 4H), 1.38-1.65 (m, 4H), 2.82 (m, 2H), 3.26 (s, 2H), 3.50-3.90 (m, 2H), 4.33 (t, 2H), 6.99 (t, 1H), 7.07-7.13 (m, 3H), 7.28 (t,2H), 7.53 (s, 1H).

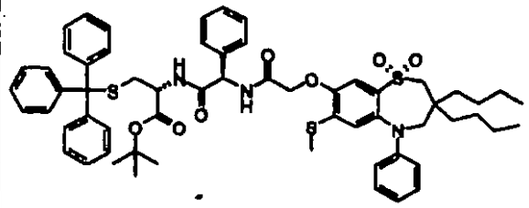
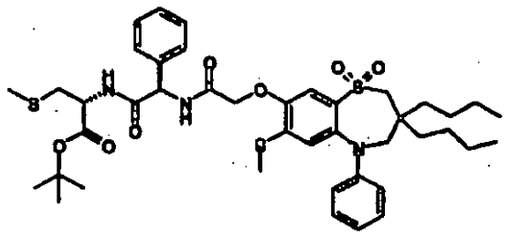
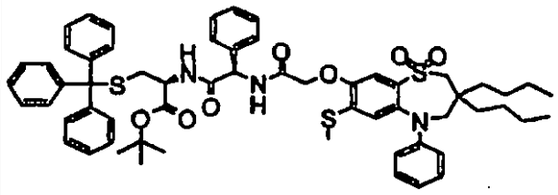
Método 90

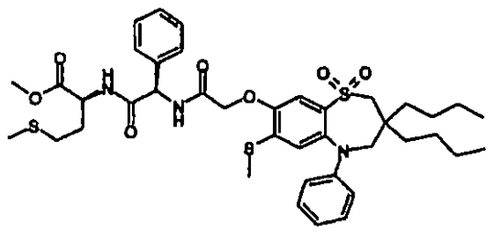
1,1-Dioxo-3-butil-3-etil-5-fenil-7-bromo-8-(2-{*N*-(R)-α-(*t*-butoxi carbonil)bencil]carbamoil}etoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3-butil-3-etil-5-fenil-7-bromo-8-(2-carboxietoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 89; 70 mg, 0.134 mmol) **y** (R)-α-(*t*-butoxicarbonil)bencilamina (J. Amer. Chem. Soc.; EN; 117; 44; 1995; 10879-10888; 35 mg, 0.169 mmol) en DCM (2.5 ml) se agregó 2,6-lutidina (29 mg, 0.268 mmol) y TBTU (56 mg, 0.174 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2.5 horas, luego se diluyó con DCM. La solución se lavó con $NaHCO_3$ (aq, sat), agua, se secó y el solvente se evaporó bajo presión reducida. El residuo se suspendió en éter/éter de petróleo y los cristales se filtraron para producir el compuesto del título 85 mg (89%). NMR (500 MHz) 0.79-0.86 (m, 6H), 1.04-1.28 (m, 4H), 1.35-1.56 (m, 11H), 1.60-1.77 (m, 2H), 2.82 (t, 2H), 3.13-3.25 (m, 2H), 3.72 (brs, 2H), 4.35-4.44 (m, 2H), 5.54 (d, 1H), 6.95 (d, 1H), 7.04 (t, 1H), 7.08 (d, 2H), 7.15 (s, 1H), 7.29-7.43 (m, 6H), 7.52 (s, 1H).

Métodos 91-94

Los siguientes compuestos se sintetizaron por el procedimiento de Ejemplo 104 usando el material base apropiado (se indica la fuente de amina donde no se obtiene en el comercio).

Mét.	Compuesto	NMR (500 MHz) y m/z	SM
91		0.77-0.86 (m, 6H), 1.03-1.62 (m, 21H), 2.21 (s, 3H), 2.32 (dd, 1H), 2.54 (dd, 1H), 3.14 (s, 2H), 3.74 (brs, 2H), 4.48-4.53 (m, 1H), 4.60 (dd, 2H), 5.57 (d, 1H), 6.33 (d, 1H), 6.67 (s, 1H), 7.01 (t, 1H), 7.09 (d, 2 H), 7.17-7.40 (m, 21H), 7.50 (d, 2H), 8.10 (d, 1H); m/z 1040.83	Ej. 1; 1
92		0.78-0.86 (m, 6H), 1.05-1.27 (m, 8H), 1.36-1.58 (m, 13H), 1.78 (s, 3H), 2.23 (s, 3H), 2.77-2.92 (m, 2H), 3.19 (s, 2H), 7.75 (brs, 2H), 4.64 (dd, 2H), 4.72-4.77 (m, 1H), 6.68 (s, 1H), 6.81 (d, 1H), 7.01 (t, 1H), 7.09 (d, 2H), 7.27-7.42 (m, 6H), 7.50 (d, 2H), 8.16 (d, 1H); m/z 812.23	Ej. 1; 2
93		0.74-0.81 (m, 6H), 1.0-1.22 (m, 8H), 1.29-1.62 (m, 13H), 2.13 (s, 3H), 2.50-2.64 (m, 2H), 3.14 (s, 2H), 3.69 (brs, 2H), 4.42-4.48 (m, 1H), 4.58 (dd. 2H), 5.45 (d, 1H), 6.13 (d, 1H), 6.62 (s, 1H), 6.96 (t, 1H), 7.04 (d, 2H), 7.17-7.21 (m, 3H), 7.23-7.37 (m, 18H), 7.41 (d,2H), 8.0 (d, 1H)	Ej. 1; Mét. 113

94		0.81-0.87 (m, 6H), 1.06-1.29 (m, 8H), 1.39-1.61 (m, 4H), 1.78 (brs, 2H), 1.94 (s, 3H), 2.07-2.17 (m, 1H), 2.20- 2.27 (m, 4H), 3.31 (s, 2H), 3.77 (brs, 2H), 3.80 (s, 3H), 4.65 (dd, 2H), 4.76- 4.82 (m, 1H), 5.65-5.70 (m, 1H), 6.69(s, 1H),7.04 (t, 1H), 7.12(d,2H), 7.29-7.44 (m, 7H), 7.52 (d, 2H), 8.16 (d, 1H)	Ej. [1]

[1] *t*-butil L-(S-tritil)cisteinato clorhidrato: Org- Pre. Proced. Int.; 1999, 31:571-572

[2] S-metil-L-cisteína tert-butil éster: Pestic. Sci.; EN; 45; 4; 1995; 357-362

Método 95

3,3-Dibutil-4-oxo-5-(4-clorofenil)-7-bromo-8-metoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina

Una mezcla de 3,3-dibutil-4-oxo-7-bromo-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (WO 95/04534; 1.0 g, 2.5 mmol), 4-bromoclorobenceno (4.78 g, 24.98 mmol), bromuro de cobre (36 mg, 0.25 mmol) y carbonato de potasio (0.35 g, 2.5 mmol) se hizo refluir durante 20 horas. La mezcla de reacción se cargó en una columna y el producto se eluyó con 5% EtOAc/éter de petróleo (0.8 g, rendimiento 63%). NMR (500 MHz) 0.86-0.92 (m, 6H), 1.16-1.35 (m, 8H), 1.45-1.65 (m, 4H), 3.16 (s, 2H), 3.96 (s, 3H), 7.06-7.10 (m, 2H), 7.19 (s, 1H), 7.29 (s, 1H), 7.33-7.38 (m, 2H). M/z 511.

Método 96

1,1-Dioxo-3,3-dibutil-4-oxo-5-(4-clorofenil)-7-bromo-8-metoxi-2,3,4.5-tetrahidro-1,5- benzotiazepina

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A una mezcla de 3,3-dibutil-4-oxo-5-(4-clorofenil)-7-bromo-8-metoxi-2,3,4,5- tetrahidro-1,5-benzotiazepina (Método 95; 0.67 g, 1.304 mmol), DCM (34 ml), agua (34 ml) y carbonato de potasio (0.554 g, 4.0 mmol) se agregó a 0°C ácido m-cloroperoxibenzoico (0.78 g, 3.2 mmol) en una porción. La mezcla de reacción se agitó a 0 °C durante 10 horas y luego a temperatura ambiente durante 14 horas. Se agregaron DCM (100 ml) y $NaHCO_3$ (aq, sat; 150 ml). La capa orgánica se separó, se lavó con salmuera, se secó y se evaporó bajo presión reducida para producir el compuesto del título 0.68 g (96%). NMR (600 MHz) 0.7-0.92 (m, 6H), 1.0-1.60 (m, 10H), 1.70-1.92 (m, 2H), 2.30-3.7 (m, 2H), 3.99 (s, 3H), 7.16-7.20 (m, 2H), 7.24 (s, 1H), 7.34-7.37 (m, 2H), 7.44 (s, 1H); m/z 543.

Método 97

1,1-Dioxo-3,3-dibutil-4-oxo-5-(4-clorofenil)-7-metiltio-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

Metanotiolato de sodio (0.43 g, 6-08 mmol) se agregó a una solución de 1,1-dioxo-3,3-dibutil-4-oxo-5-(4-clorofenil)-7-bromo-8-metoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina (Método 96; 0.66 g, 1.22 mmol) en DMF anhidro (11 ml) bajo nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 72 horas. El solvente se evaporó bajo presión reducida y el residuo se extrajo con triclorometanoe/agua.

La capa orgánica se separó, se lavó con salmuera, se secó y se evaporó bajo presión reducida. El producto crudo se purificó mediante cromatografía de columna usando DCM como eluyente para producir el compuesto del título 0.6 g (96%). NMR (500 MHz) 0.80-1.0 (m, 6H), 1.10-1.6 (m, 10H), 1.70-2.0 (m, 2H), 2.28 (s, 3H), 3.37-3.70 (m, 2H), 4.04 (s, 3H), 6.65 (s, 1H), 7.25-7.30 (m, 2H), 7.35-7.42 (m, 3H); m/z 510.4.

Método 98

1,1-Dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-4-oxo-5-(4-clorofenil)-7-metiltio-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 97; 0.41 g, 0.79 mmol) en éter anhidro (15 ml) se agregó $LiAlH_4$ (0.15 g, 3.97 mmol) bajo nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 2.5 horas. El matraz de reacción se enfrió a 0°C; y el exceso de $LiAlH_4$ se extinguió agregando agua (0.3 ml) y 2 M NaOH acuoso (0.3 ml). La mezcla se filtró y el filtrado se secó y se evaporó bajo presión reducida. El producto crudo se purificó mediante cromatografía de columna usando DCM como eluyente para producir el compuesto del título 0.265 g (68%). NMR (300 MHz) 0.8-0.90 (m, 6H), 1.0-1.47 (m, 12H), 2.33 (s, 3H), 3.17 (s, 2H), 3.70 (s, 2H), 3-93 (s, 3H), 7.03-7.08 (m, 3H), 7.23-7.32 (m, 3H); m/z 496.

Método 99

1,1-Dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 98; 0.26 g 0.52 mmol) en DCM anhidro (10 ml) se agregó tribromuro de bromo (2.63 g, 10,48 mmol) bajo nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 2.5 horas. El matraz de reacción se enfrió a 0°C, agua (20 ml) y se agregó monohidrato de hidrazina (0.5 ml). La capa orgánica se separó, se secó y se evaporó bajo presión reducida. El producto crudo se purificó mediante cromatografía de columna usando DCM/EtOAc (100:5 y 100:10) como eluyente para proporcionar el compuesto del título 0.20 g (80%). NMR (500 MHz) 0.85 (t, 6H), 1.03-1.28 (m, 8H), 1.35-1.46 (m, 4H), 2.39 (s,3H), 3.21 (s, 2H), 3.73 (s, 2H), 7.04 (d, 2H), 7.29-7.34 (m, 3H), 7.44 (s, 1H); m/z 482.

Método 100

1,1-Dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-etoxicarbonilmetoxi-2,3,4,5- tetrahidro-1,5-benzotiazepina

Bromoacetato de etilo (0.101 g, 0.604 mmol) se agregó a una mezcla de 1,1-dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina(Método 99; 0.194 g, 0.402 mmol), Na_2CO_3 anhidro (0.192 g, 1.81 mmol) y bromuro de tetrabutil amonio en MeCN (5 ml). La mezcla de reacción se hizo refluir durante 3.5 horas. El solvente se evaporó bajo presión reducida y el residuo se extrajo con DCM/agua. La capa orgánica se separó, se secó y se evaporó bajo presión reducida. El producto crudo se purificó mediante cromatografía de columna usando DCM/EtOAc (100:5 y 100:10) como eluyente para producir el compuesto del título 0.197 g (86%). NMR (300 MHz) 0.80-0.89 (m, 6H), 1.0-1.45 (m, 15H), 2.34 (s, 3H), 3.16 (s, 2H), 3.68 (s, 2H), 4.30 (q, 2H), 4.71 (s, 2H), 7.05-7.11 (m, 3H), 7.19 (s, 1H), 7.29-7.35 (m, 2H). .

Método 101

1,1-Dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 100; 0.195 g, 0.343 mmol) en etanol (8 ml) se agregó NaOH (1.03 mmol in 0.5 ml agua). La mezcla de reacción se agitó a temperatura ambiente durante 70 minutos y luego se extinguió agregando ácido acético (0.3 ml). El solvente se evaporó bajo presión reducida y el residuo se extrajo con DCM/agua. La capa orgánica se separó, se lavó con salmuera, se secó y se evaporó bajo presión reducida para producir el compuesto del título 0.169 g (91%). NMR (500 MHz, CD_3OD) 0.86 (t, 6H), 1.11-1.28 (m, 8H), 1.37-1.44 (m, 4H), 2.33 (s, 3H), 3.25 (s, 2H), 3.55 (s, 2H), 4.73 (s, 2H), 7.10-7.15 (m, 3H), 7.26 (s, 1H); 7.28-7.32 (m, 2H).

Método 102

1,1-Dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-[*N*-{(R)-α-[*N'*-(*t*-butoxicarbonilmetil)carbamoil]bencil]carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5- benzotiazepina

A una solución de 1,1-dioxo-3,3-dibutil-5-(4-clorofenil)-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 101; 100 mg, 0.185 mmol) y (R)-α-[*N*-(*t*-butoxicarbonilmetil)carbamoil]bencilamina (Método 86; 56 mg, 0.213 mmol) en DCM (4 ml) se agregó 2,6-lutidina (40 mg, 0.37 mmol) y TBTU (89 mg, 0.28 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas y luego se agregó EtOAc y la solución se lavó con agua. La capa orgánica se separó, se secó y se evaporó bajo presión reducida. El producto crudo se purificó mediante cromatografía de columna usando DCM/MeOH (100:3) como eluyente para producir el compuesto del título 0.129 g (89%). NMR (600 MHz) 0.78-82 (m, 6H), 1.01-1.23 (m, 8H), 1.30-1.42 (m, 13H), 2.32 (s, 3H), 3.10-3.16 (m, 2H), 3.62-3.68 (m, 2H), 3.81-3.87 (m, 1H), 3.95-4.03 (m, 1H), 4.52 (dd, 2H), 5.57 (d, 1H), 6.27 (t. 1H), 7.01-7.07 (m, 3H), 7.20-7.43 (m, 8H), 8.02 (d, 1H).

Método 103

3,3-Dibutil-4-oxo-5-(4-nitrofenil)-8-metoxi-2.3,4.5-tetrahidro-1,5-benzotiazepina

A 3,3-dibutil-4-oxo-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (sintetizada mediante el procedimiento de WO9616051 para el correspondiente 3-butil-3-etil análogo; 2.9 g, 9.0 mmol) se agregó p-nitrofenilbromuro (24 g, 119 mmol), K_2CO_3 (1.6 g, 12 mmol) y CuI (180 mg, 0.95 mmol). La mezcla de reacción se calentó a 200°C durante la noche. Luego se dejó enfriar a temperatura ambiente y el sólido resultante se purificó mediante cromatografía usando DCM como eluyente. Las fracciones que contenían el producto se concentraron bajo presión reducida y se agregó EtOH (95%) y el p-nitrofenilbromuro insoluble se extrajo entonces por filtración. El residuo se purificó nuevamente mediante cromatografía de destello usando DCM como eluyente. El producto no era todavía puro, de modo que el residuo se purificó entonces mediante cromatografía de destello usando EtOAc : heptano, 1:9 como eluyente para producir el compuesto del título 2.57 g (64%). NMR (600 MHz) 0.77-0.87

(m, 6H), 1.12-1.31 (m, 8H), 1.4-1.6 (m, 4H), 3.09 (brs, 2H), 3.79 (s, 3H), 6.72-6.83 (m, 2H), 7.18-7.27 (m, 3H), 8.3 (d, 2H).

Método 104

1,1-Dioxo-3,3-dibutil-4-oxo-5-(4-nitrofenil)-8-metoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina

A 3,3-dibutil-4-oxo-5-(4-nitrofenil)-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 103; 2.57 g, 5.8 mmol) se agregó DCM (130 ml), agua (130 ml) y K_2CO_3 (2.44 g, 17.6 mmol). La mezcla de reacción se enfrió a 0°C y se agregó ácido m-cloroperoxibenzoico (3.42 g, 13.9 mmol) en una porción. Se dejó concluir la reacción durante la noche con la temperatura subiendo lentamente a temperatura ambiente. Entonces se agregó $NaHCO_3$ acuoso (sat) se agregó y se separaron las dos capas. Luego se extrajo la capa de agua tres veces con DCM. Las capas orgánicas combinadas se secaron, se filtraron y se evaporaron bajo presión reducida. El producto se purificó mediante cromatografía de destello usando DCM como eluyente para producir el compuesto del título 2.4 g (87%). M/z 475.4.

Método 105

1,1-Dioxo-3,3-dibutil-5-(4-aminofenil)-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

A $LiAlH_4$ (5.76 g, 151 mmol) se agregó THF (200 ml). La mezcla de reacción se enfrió a 0 °C, y se agregó H_2SO_4 (4.06 ml, 76 mmol) lentamente con una jeringa. Una vez concluida la adición, la reacción se agitó durante 10 minutos. Entonces se agregó a 0°C 1,1-dioxo-3,3-dibutil-4-oxo-5-(4-nitrofenil)-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 104; 2.57 g, 5.06 mmol) disuelto en THF (50 ml). Después de agitar vigorosamente durante se retiró el baño de enfriamiento y la reacción se calentó a 40°C durante la noche. Entonces se agregaron $Na_2SO_4.10H_2O$ (3-4 cucharaditas de té), agua (8 ml), NaOH (15%, aq) (8 ml), agua (25 ml) y MeOH (30 ml) en ese orden. El precipitado se retiró mediante filtración y

se enjuagó con DCM/MeOH. El solvente se secó, se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía de destello usando DCM : EtOAc, 9:1 luego 3:1 como eluyente para producir el compuesto del título 0.6 g (27%). M/z 431.3.

Método 106

1,1-Dioxo-3,3-dibutil-5-(4-aminofenil)-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-(4-aminofenil)-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 105; 918 mg, 2.13 mmol) se disolvió en DMF (seco, 20 ml). Se agregó tiometóxido de sodio (810 mg, 11.6 mmol). La mezcla de reacción se trató a 100-120°C durante cuatro horas, luego a temperatura ambiente durante la noche. Se agregó ácido acético (3 ml) y la mezcla se lavó con nitrógeno (g) y el gas de condujo a través de un matraz que contenía hipoclorito de sodio con el fin de destruir el metil mercaptano formado. Se agregó agua y la capa de se extrajo dos veces con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó, se filtró y se evaporó bajo presión reducida. La mezcla contenía DMF, de manera que se agregó tolueno y salmuera (todo no se disolvió). La capa de agua se extrajo dos veces con tolueno. Las capas orgánicas combinadas se lavaron una vez con salmuera. El embudo de separación se lavó con EtOAc con el fin de disolver todo. Se combinaron las soluciones de tolueno y EtOAc, se secaron, se filtraron y se evaporaron bajo presión reducida. El residuo se purificó mediante cromatografía de destello usando DCM:EtOAc, 7:3 como eluyente para producir el compuesto del título 0.6 g (27%). M/z 417.4.

Método 107

1,1-Dioxo-3,3-dibutil-5-(4-*t*-butoxicarbonilaminofenil)-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-(4-aminofenil)-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 106; 600 mg, 1.44 mmol se disolvió en THF (10 ml). Se agregó Di-*t*-butildicarbonato (314 mg, 1.44 mmol) y la mezcla

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se agitó a 60°C durante dos horas y temperatura ambiente durante 3 días. El solvente se evaporó bajo presión reducida. Se agregó EtOAc y la capa orgánica se lavó una vez con solución de $KHSO_4$ (0.3M, aq) y una vez con salmuera, se secó, se filtró y se evaporó bajo presión reducida. El residuo se purificó mediante cromatografía de destello usando DCM:EtOAc, 9:1 como eluyente para producir el compuesto del título 0.597 g (80%). M/z 517.3.

Método 108

1,1-Dioxo-3,3-dibutil-5-(4-*t*-butoxicarbonilaminofenil)-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-(4-*t*-butoxicarbonilaminofenil)-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 107; 597 mg, 1.16mmol) se disolvió en MeCN (20 ml), K_2CO_3 (480 mg, 3.5 mmol), bromuro de tetrabutilamonio (54 mg, 0.17 mmol) y se agregó bromoacetato de etilo (167µl, 1.5 mmol). La mezcla se calentó a 60°C durante la noche.

El solvente se evaporó bajo presión reducida. Se agregó EtOAc y agua y la capa de agua se extrajo dos veces con EtOAc. La capa orgánica combinada se lavó una vez con salmuera, se secó, se filtró y se evaporó bajo presión reducida para proporcionar el compuesto del título 0.617 g (89%). M/z 603.3.

Método 109

1,1-Dioxo-3,3-dibutil-5-(4-*t*-butoxicarbonilaminofenil)-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-(4-*t*-butoxicarbonilaminofenil)-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 108; 607 mg, 1.0 mmol) se disolvió en THF (6 ml), H_2O (6 ml) y se agregó LiOH (127 mg, 3.02 mmol, monohidrato). La mezcla se agitó durante 1 hora. La mezcla se vertió enagua y la solución se acidificó usando solución de HCl (aq, 1M). La capa de agua se extrajo dos veces con EtOAc. La capa orgánica combinadase lavó una vez con salmuera, se secó, se filtró y

se evaporó bajo presión reducida para producir el compuesto del título 0.571 g (99%). M/z 575.4.)

Método 110

1,1-Dioxo-3,3-dibutil-5-(4-aminofenil)-8-[*N*-(α-(R)-metoxicarbonilbencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-(4-*t*-butoxicarbonilaminofenil)-8-[*N*-(α-(R)-metoxicarbonilbencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 45; 562 mg, 0.78 mmol) se disolvió en DCM (18 ml). Se agregó TFA (4 ml) y la mezcla de reacción se agitó durante 3 horas. El solvente se evaporó bajo presión reducida. El residuo se dividió en porciones entre EtOAc y solución de NaOH (1M, aq). La fase acuosa se extrajo una vez más con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó, se filtró y se evaporó bajo presión reducida para producir el compuesto del título 440 mg (91%). M/z 622.5.

Método 111

1,1-Dioxo-3,3-dibutil-5-[4-(*N'*-*t*-butilureido)fenil]-8-[*N*-(α-(R)-metoxicarbonilbencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3,3-dibutil-5-(4-aminofenil)-8-[*N*-(α-(R)-metoxicarbonilbencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 110; 40 mg, 0.064 mmol) se disolvió en DMF (1 ml). Se agregó *t*-butil isocianato (8.3µl, 0.071 mmol). La mezcla de reacción se agitó a 60-80°C durante la noche. Se agregó tert-butil isocianato (20µl, 0.171 mmol). La mezcla de reacción se agitó a 60-80°C durante 2 días y luego a temperatura ambiente durante pocos días. El solvente se evaporó bajo presión reducida. El producto se purificó mediante HPLC preparativa usando una gradiente MeCN/tampón de acetato de amonio (5/95 a 100/0) como eluyente para proporcionar el producto del título, 30 mg (65%). M/z 721.6.

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Método 112

1,1 -Dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-(α-metoxicarbonilmetil-bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

El compuesto del título se sintetizó a partir de 1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 17) y metil 3-amino-3-fenilpropanoato (Helv. Chim. Acta; EN; 83; 6; 2000; 1256 - 1267) mediante el procedimiento de Ejemplo 56. M/z 639.4.

Método 113

t-Butil D-(S-tritil)cisteinato clorhidrato

A una suspensión vigorosamente agitada de S-tritil-D-cisteína (2.0 g, 5.5 mmol) en *t*-butil acetato (35 ml), se agregó gota a gota 70% $HClO_4$ (1.6 ml). La mezcla de reacción se agitó a temperatura ambiente durante 70 minutos y se agregaron EtOAc (50 ml) $NaHCO_3$ (aq, sat) a pH 8.0. Se extrajo por filtración el precipitado S-tritil-D-cisteína sin reaccionar. La capa orgánica se separó, se lavó con 0.5 M HCl (2 x 75 ml) y salmuera, se secó y se evaporó para producir el compuesto del título 2.02 g (81%). NMR (500 MHz): 1.43 (s, 9H), 2.83-2.95 (m, 2H), 3.41-3.48 (m, 1H), 7.21-7.37 (m, 9H), 7.46 (d, 6H).

Método 114

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-etoxicarbonil,2,3,4,5-tetrahidro-1,5- benzotiazepina

A una suspensión de 1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 26; 12.85 g, 28.71 mmol) en MeCN (150 ml) se agregó bromoacetato de etilo (3.85 ml, 34.6 mmol), bromuro de tetrabutil amonio (0.925 g, 2.869 mmol) y carbonato de sodio (12.85 g, 121.2 mmol). La mezcla se calentó bajo reflujo durante 5 horas. El solvente se retiró bajo presión reducida y el residuo se dividió en porciones entre DCM y 0.5 M HCl. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró. Cromatografía usando DCM/EtOAc (9:1)

como eluyente produjo el producto deseado (15.45 g) como un aceite marrón. NMR 0.70-0.85 (m, 6H), 1.00-1.55 (m, 15H), 2.15 (s, 3H), 3.10 (s, 2H), 3.70 (bs, 2H), 4.25 (q, 2H), 4.70 (s, 2H), 6.65 (s, 1H), 6.90-7.30 (m, 6H).

Método 115

1,1-Dioxo-3-butil-3-etil-5-fenil-8-carboximetoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina (Método 116; 0.48 g, 1.04 mmol) se disolvió en etanol (10 ml). Se agregó NaOH (0.30 g, 7.5 mmol) y la mezcla se hizo refluir durante 30 minutos. Se agregó ácido acético (1 ml). El solvente se evaporó bajo presión reducida y el residuo se extrajo con DCM/agua. La capa DCM se separó, se secó y se evaporó. Se obtuvo 0.44 g (97%) del compuesto del título. NMR (300 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 8H), 3.1-3.3 (m, 2H), 3.5-3.8 (m, 2H), 4.6 (s, 3H), 6.8-7.3 (m, 7H), 7.5 (s, 1H).

Método 116

1,1-Dioxo-3-butil-3-etil-5-fenil-8-etoxicarbonilmetoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina

1,1-Dioxo-3-butil-3-etil-5-fenil-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (WO9616051; 0.40 g, 1.07 mmol), bromoacetato de etilo (0.23 g, 1.38 mmol), carbonato de sodio (0.50 g, 4.7 mmol) y bromuro de tetrabutil amonio (30 mg, 0.093 mmol) se agregaron a MeCN (10 ml). La mezcla se hizo refluir durante 18 horas y luego se evaporó bajo presión reducida. El residuo se extrajo con DCM/agua. La capa DCM se separó y se evaporó bajo presión reducida. El residuo se purificó mediante cromatografía de columna. El producto se eluyó con DCM/EtOAc (90:10). Se obtuvo 0.480 g (97%) del compuesto del título. NMR (300 MHz) 0.7-0.85 (m, 6H), 1.0-1.7 (m, 11H), 3.1-3.3 (m, 2H), 3.6-3.8 (m, 2H), 4.3 (q, 2H), 4.6 (s, 2H), 6.9-7.3 (m, 7H), 7.5 (d, 1H).

Método 117

1,1-Dioxo-3,3-dipropil-5-fenil-7-metiltio-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina

A una suspensión de 1,1-dioxo-3,3-dipropil-5-fenil-7-bromo-8-metoxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (preparada de acuerdo con WO 96/16051 usando pasos sintéticos idénticos salvo que el material base se escogió para proporcionar el compuesto dipropilo en vez del compuesto butilo/etilo; 0.756 g, 1.62 mmol) en DMF (40 ml) se agregó NaSMe (0.605 g, 8,20 mmol, 95 %), y la mezcla se agitó durante la noche a 120°C. El solvente se retiró bajo presión reducida y el residuo se dividió 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 compuesto del título se obtuvo en 0.665 g (98 %). NMR (500 MHz, DMSO-d_6) 0.60-0.80 (m, 6H), 1.05-1.50 (m, 8H), 2.15 (s, 3H), 3.20 (s, 2H), 3.65 (brs, 2H), 6.65 (s, 1H), 6.75-6.95 (m, 3H), 7.10-7.25 (m, 2H), 7.30 (s, 1H), 10.5 (s, 1H).

Método 118

1,1-Dioxo-3,3-dipropil-5-fenil-7-metiltio-8-carboximetoxi-2,3,4,5-tetrahidro-1,5- benzotiazepina

A una suspensión de 1,1-dioxo-3,3-dipropil-5-fenil-7-metiltio-8-hidroxi-2,3,4,5-tetrahidro-1,5-benzotiazepina (Método 117; 0.665 g, 1.58 mmol) en MeCN (10 ml) se agregó bromoacetato de etilo (0.262 ml, 2.35 mmol), bromuro de tetrabutil amonio (0.051 g, 0.158 mmol) y carbonato de sodio (0.870 g, 8.21 mmol). La mezcla se agitó durante la noche a 80°C. El solvente se retiró bajo presión reducida y el residuo se dividió en pociones entre EtOAc y 0.5 M HCl. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El residuo se filtró a través de una columna corta de sílice (DCM:EtOAc-9:1), se concentró y se disolvió en EtOH (10 ml). Se agregó una solución de NaOH (0.25 g, 6.25 mmol) en agua (1 ml) y la solución se agitó durante la noche a temperatura ambiente. El solvente se retiró bajo presión reducida y el residuo se dividió en

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porciones entre EtOAc y 0.5 M HCl. La capa acuosa se extrajo dos veces más con EtOAc y los extractos orgánicos combinados se lavaron con salmuera y se concentraron. El producto crudo se purificó mediante HPLC preparativa usando un tampón MeCN/acetato de amonio para producir el compuesto del título en 0.441 g (58 %) como un sólido blanco. NMR (DMSO-d_6) 0.55-0.75 (m, 6H), 1.05-1.50 (m, 8H), 2.15 (s, 3H), 3.20 (s, 2H), 3,65 (brs, 2H), 4.50 (s, 2H), 6.65 (s, 1H), 6.80-7.00 (m, 3H), 7.15 (s, 1H), 7.15-7.25 (m, 2H).

Ejemplo 121

Las siguientes ilustran formas representativas de dosificación farmacéutica que contienen el compuesto de fórmula (**I**), o su sal, solvato, solvato de dicha sal o profármaco de aceptación farmacéutica (en lo sucesivo compuesto X), para uso terapéutico o profiláctico en humanos:-

(a): Tableta I	**mg/tableta**
Compuesto X	100
Lactosa Ph.Eur	182.75
Croscarmelosa sódica	12.0
Pasta de almidón de maíz (5% p/v pasta)	2.25
Estearato de magnesio	3.0

(b): Tableta II	**mg/tableta**
Compuesto X	50
Lactosa Ph.Eur	223.75
Croscarmelosa sódica	6.0
Almidón de maíz	15.0
Polivinilpirrolidona (5% p/v pasta)	2.25
Estearato de magnesio	3.0

(c): Tableta III	**mg/tableta**
Compuesto X	1.0

Lactosa Ph.Eur	93.25
Croscarmelosa sódica	4.0
Pasta de almidón de maíz (5% p/v pasta)	0.75
Estearato de magnesio	1.0

(d): Cápsula	**mg/cápsula**
Compuesto X	10
Lactosa Ph.Eur	488.5
Estearato de magnesio	1.5

(e): Inyección I	**(50 mg/ml)**
Compuesto X	5.0% p/v
1M Solución de hidróxido de sodio	15.0% v/v
0.1M Ácido clorhídrico	(para ajustar pH a 7.6)
Polietilen glicol 400	4.5% p/v
Agua para inyección	a 100%

(f): Inyección II	**10 mg/ml**
Compuesto X	1.0% p/v
Fosfato de sodio BP	3.6% p/v
0.1M Solución de hidróxido de sodio	15.0% v/v
Agua para inyección	a 100%

(g): Inyección III	**(1 mg/ml, tamponada a pH 6)**
Compuesto X	0.1% p/v
Fosfato de sodio BP	2.26% p/v
Ácido cítrico	0.38% p/v
Polietilen glicol 400	3.5% p/v
Agua para inyección	a 100%

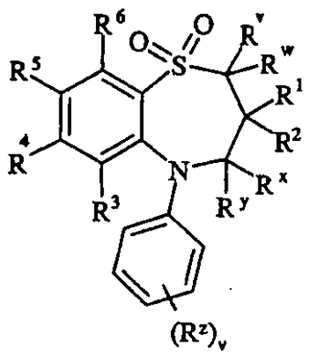
Nota

Las formulaciones anteriores pueden obtenerse mediante procedimientos convencionales bien conocidos en el arte farmacéutico. Las tabletas (a)-(c) pueden recubrirse entéricamente por medios convencionales, por ejemplo, para proporcionar un recubrimiento de ftalato acetato de celulosa.

Reivindicaciones

Lo que se reivindica es:

1. Un compuesto de la formula (**I**)



(I)

en donde:

$\mathbf{R^v}$ y $\mathbf{R^w}$ se seleccionan independientemente de hidrógeno o C_{1-6}alquilo;

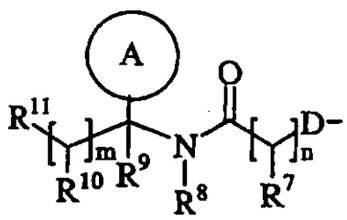
$\mathbf{R^1}$ y $\mathbf{R^2}$ se seleccionan independientemente de hidrógeno o C_{1-6}alquilo;

$\mathbf{R^x}$ y $\mathbf{R^y}$ se seleccionan independientemente de hidrógeno o C_{1-6}alquilo, o uno de R^x y R^y es hidrógeno o C_{1-6}alquilo y el otro es hidroxi o C_{1-8}alcoxi;

$\mathbf{R^z}$ se selecciona de halo, nitro, ciano, hidroxi, amino, carboxi, 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}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, ureido, *N'*-(C_{1-6}alquil)ureido, *N*-(C_{1-6}alquil)ureido, *N',N'*-(C_{1-6}alquil)$_2$ureido, *N'*-(C_{1-6}alquil)-*N*-(C_{1-6}alquil)ureido, *N',N'*-(C_{1-6}alquil)$_2$-*N*-(C_{1-6}alquil)ureido, *N'*-(C_{1-6}alquil)sulfamoilo y *N,N*-(C_{1-6}alquil)$_2$sulfamoilo;

v es 0-5;

uno de $\mathbf{R^4}$ y $\mathbf{R^5}$ es un grupo de fórmula **(IA)**:



(IA)

$\mathbf{R^3}$ y $\mathbf{R^6}$ y los demás de $\mathbf{R^4}$ y $\mathbf{R^5}$ se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, 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}alquil$S(O)_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N,N*-(C_{1-4}alquil)$_2$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 más R^{16};

D es -O-, -N(R^a)-, -$S(O)_b$- o -CH(R^3)-; 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};

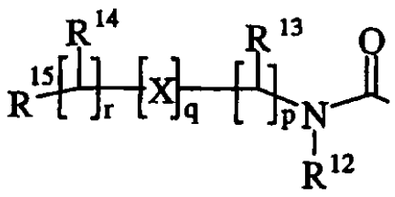
$\mathbf{R^7}$ es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo; en donde R^7 se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{18};

$\mathbf{R^8}$ es hidrógeno o C_{1-4}alquilo;

$\mathbf{R^9}$ es hidrógeno o C_{1-4}alquilo;

$\mathbf{R^{10}}$ 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};

$\mathbf{R^{11}}$ es carboxi, sulfo, sulfino, fosfono, tetrazolilo, -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 fórmula **(IB):**



(IB)

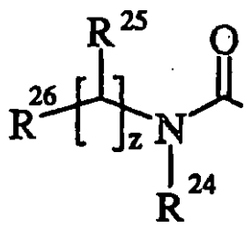
en donde:

X es -N(R^q)-, -N(R^q)C(O)-, -O-, y -S(O)$_a$-; en donde a es 0-2 y $\mathbf{R^q}$ es hidrógeno o C_{1-4}alquilo;

$\mathbf{R^{12}}$ es hidrógeno o C_{1-4}alquilo;

$\mathbf{R^{13}}$ y $\mathbf{R^{14}}$ se seleccionan independientemente de hidrógeno, C_{1-4}alquilo, carbociclilo, heterociclilo o R^{23}; en donde dicho C_{1-4}alquilo, carbociclilo o heterociclilo puede sustituirse opcionalmente en forma independiente por uno o más sustituyentes seleccionados de R^{20};

$\mathbf{R^{15}}$ es carboxi, sulfo, sulfino, fosfono, tetrazolilo, -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; o R^{15} es un grupo de fórmula **(IC):**



(IC)

en donde:

$\mathbf{R^{24}}$ se selecciona de hidrógeno o C_{1-4}alquilo;

$\mathbf{R^{25}}$ se selecciona de hidrógeno, C_{1-4}alquilo, carbociclilo, heterociclilo o R^{27}; en donde dicho C_{1-4}alquilo, carbociclilo o heterociclilo puede sustituirse opcionalmente en forma independiente por uno o más sustituyentes seleccionados de R^{28};

$\mathbf{R^{26}}$ se selecciona de carboxi, sulfo, sulfino, fosfono, tetrazolilo, -P(O)(OR^g) (OR^h), -P(O)(OH)(OR^g), -P(O)(OH)(R^g) o –P(O)(OR^g)(R^h) en donde R^g y R^h 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;

z es 0-3; en donde los valores de R^{25} pueden ser los mismos o diferentes;

R^{16}, **R^{17}** y **R^{18}** se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, 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}alcoxicarbonilo, *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 opcionalmente en forma independiente en carbono por uno o más R^{21};

R^{19}, **R^{20}**, **R^{23}**, **R^{27}** y **R^{28}** se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, 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}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo, *N,N*-(C_{1-4}alquil)$_2$sulfamoilo, carbociclilo, heterociclilo, sulfo, sulfino, amidino, fosfono, -P(O)(OR^a)(OR^b),-P(O)(OH)(OR^a),-P(O)(OH)(OR^a) 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}, R^{20}, R^{23}, R^{27} y R^{28} pueden sustituirse opcionalmente en forma independiente en carbono por uno o más R^{22};

$\mathbf{R^{21}}$ y $\mathbf{R^{22}}$ se seleccionan independientemente de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carboxi, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxicarbonilo, 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 profármaco.

2. Un compuesto de la fórmula (**I**) de acuerdo con reivindicación 1 en donde R^v y R^w son ambos hidrógeno o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

3. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 ó 2 en donde R^1 y R^2 se seleccionan independientemente de etilo, propilo o butilo o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

4. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 3 en donde R^x y R^y son ambos hidrógeno o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

5. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 4 en donde R^z se selecciona de halo, amino, C_{1-6}alquilo, C_{1-6}alcoxicarbonilamino o *N'*-(C_{1-6}alquil)ureido o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

6. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 5 en donde v es 0 ó 1 o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

7. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 6 en donde R^3 es hidrógeno o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

8. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 7 en donde el R^4 o R^5 que no es el grupo de fórmula **(IA)** se selecciona de hidrógeno, halo, C_{1-4}alcoxi o C_{1-4}alquil$S(O)_a$ en donde a es 0 a 2; en donde ese R^4 o R^5 puede sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{16} se selecciona independientemente de hidroxi, carboxi, y *N*,*N*-(C_{1-4}alquil)$_2$amino o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

9. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 8 en donde R^5 es un grupo de fórmula (**IA**) (como se describe en reivindicación 1) y R^4 es metiltio o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

10. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 9 en donde R^6 es hidrógeno o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

11. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 10 en donde en el grupo de fórmula (**IA**):

D es -O- o -S-;

Anillo A es fenilo, tienilo o indolilo; en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, hidroxi, metoxi o trifluorometil;

R^7 es hidrógeno, metilo o fenilo;

R^8 es hidrógeno o metilo;

R^9 es hidrógeno o metilo;

R^{10} es hidrógeno;

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

R^{11} es carboxi, -P(O)(OH)(OEt) o un grupo de fórmula **(IB)** (como se describe en reivindicación 1); o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

12. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 11 en donde en el grupo de fórmula (**IB**):

R^{12} es hidrógeno o metilo;

R^{13} es hidrógeno, metilo, etilo, butilo o fenilo o R^{23}; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; R^{20} es hidroxi, metiltio, metoxi, amino, imidazolilo o mercapto; en donde R^{20} puede sustituirse opcionalmente en forma independiente en carbono por uno o más hidroxi; R^{23} es carboxi;

X es-NH- o -NHC(O)-;

R^{14} se selecciona de hidrógeno, metilo o fenilo; en donde dicho metilo o fenilo puede sustituirse opcionalmente por uno o más sustituyentes seleccionados de hidroxi;

R^{15} es carboxi, sulfo, 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 metilo o etilo o R^{15} es un grupo de fórmula **(IC)** (como se describe en Reivindicación 1);

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

q es 0-1; y

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

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

13. Un compuesto de la fórmula (**I**) de acuerdo con una cualquiera de las reivindicaciones 1 a 12 en donde en el grupo de fórmula (**IC**):

$\mathbf{R^{24}}$ es hidrógeno;

$\mathbf{R^{25}}$ es hidrógeno;

$\mathbf{R^{26}}$ es carboxi; y

z es 1;

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

14. Un compuesto de la fórmula (**I**) (como se describe en reivindicación 1) en donde:

$\mathbf{R^v}$ y $\mathbf{R^w}$ son ambos hidrógeno;

$\mathbf{R^1}$ y $\mathbf{R^2}$ se seleccionan independientemente de C_{1-4}alquilo;

$\mathbf{R^x}$ y $\mathbf{R^y}$ son ambos hidrógeno;

$\mathbf{R^z}$ se selecciona de halo, amino, C_{1-6}alquilo, C_{1-6}alcoxicarbonilamino o

N'-(C_{1-6}alquil)ureido;

v es 0 ó 1;

$\mathbf{R^3}$ y $\mathbf{R^6}$ son hidrógeno;

uno de $\mathbf{R^4}$ y $\mathbf{R^5}$ es un grupo de fórmula **(IA)** (como se describe más arriba) y el otro se selecciona de hidrógeno, halo, C_{1-4}alcoxi o C_{1-4}alquil$S(O)_a$ en donde a es 0 a 2; en donde ese R^4 o R^5 puede sustituirse opcionalmente en carbono por uno o más R^{16}; en donde R^{16} se selecciona independientemente de hidroxi, carboxi y *N*,*N*-(C_{1-4}alquil)$_2$amino;

D es -O- o -S-;

$\mathbf{R^7}$ es hidrógeno, metilo o fenilo;

$\mathbf{R^8}$ es hidrógeno o metilo;

Anillo A es arilo o heteroarilo; en donde Anillo A se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{17}; en donde R^{17} se selecciona de halo, hidroxi, C_{1-4}alquilo o C_{1-4}alcoxi; en donde R^{17} puede sustituirse opcionalmente en carbono por uno o más R^{21}; en donde R^{21} se selecciona de halo;

$\mathbf{R^9}$ es hidrógeno o metilo;

$\mathbf{R^{10}}$ es hidrógeno;

R^{11} es carboxi, -P(O)(OH)(OR^c) en donde R^c se selecciona de C_{1-4}alquil o un grupo de fórmula **(IB)** (como se describe más arriba);

R^{12} es hidrógeno o metilo;

X es -NH- o -NHC(O)-;

R^{13} es hidrógeno, C_{1-4}alquilo, carbociclilo o R^{23}; en donde R^{13} se sustituye opcionalmente por uno o más sustituyentes seleccionados de R^{20}; en donde R^{20} es hidroxi, C_{1-4}alquil$S(O)_a$ en donde a es 0, C_{1-4}alcoxi, amino, carbociclilo, heterociclilo o mercapto; en donde R^{20} pueden sustituirse opcionalmente en forma independiente en carbono por uno o más R^{22}; R^{22} se selecciona de hidroxi; y R^{23} es carboxi;

R^{14} se selecciona de hidrógeno, C_{1-4}alquilo o carbociclilo; en donde dicho C_{1-4}alquilo o carbociclilo puede sustituirse opcionalmente por uno o más sustituyentes seleccionados de R^{20}; y R^{20} es hidroxi;

R^{15} es carboxi, sulfo, 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_{1-4}alquilo o R^{15} es un grupo de fórmula **(IC)** (como se describe más arriba);

R^{24} es hidrógeno;

R^{25} es hidrógeno;

R^{26} es carboxi;

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 1-2; en donde los valores de R^7 pueden ser los mismos o diferentes;

z es 0-1; en donde los valores de R^{25} pueden ser los mismos o diferentes;

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

15. Un compuesto de la fórmula (**I**) (como se describe en reivindicación 1) seleccionado de:

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*'-(carboximetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*'-(carboximetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*'-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*'-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*'-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*'-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*'-(2-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*'-(2-carboxietil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*'-(5-carboxipentil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

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1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-(2-sulfoetil) carbamoil]-2-fluorobencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hidroxi-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hidroxi-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hidroxi-1-carboxietil)carbamoil]-2-hidroxietil}carbamoil)bencil] carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-((etoxi) (metil)fosforil-metil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{2-[(hidroxi)(metil)fosforil]etil}carbamoil)bencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-metiltio-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{2-[(metil) (etil)fosforil]etil}carbamoil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N*'-{2-[(metil)(hidroxi)fosforil]etil}carbamoil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

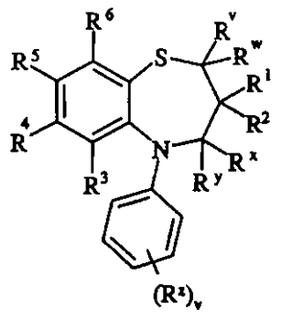
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[(R)-*N*'-(2-metilsulfinil-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina; y

1,1-dioxo-3,3-dibutil-5-fenil-7-metoxi-8-[*N*-{(R)-α-[*N*'-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina;

o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

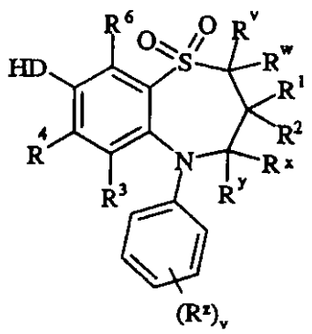
16. Un proceso para preparar un compuesto de la fórmula **(I)** como se reivindica en una cualquiera de las reivindicaciones 1 a 15 que consta de:-

Proceso 1): oxidar una benzotiazepina de fórmula **(II):**

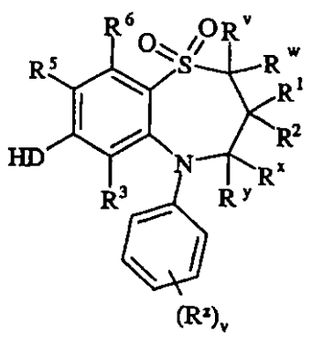


(II)

Proceso 2): para compuestos de fórmula **(I)** en donde D es -O-, -NR^a o -S-; hacer reaccionar un compuesto de fórmula **(IIIa)** o **(IIIb):**

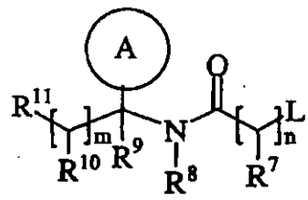


(IIIa)



(IIIb)

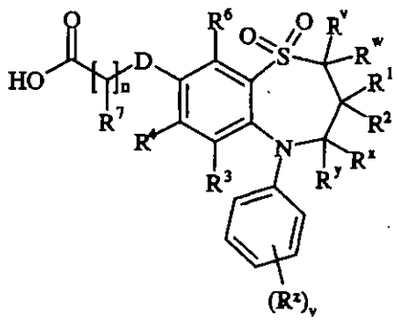
con un compuesto de fórmula (IV):



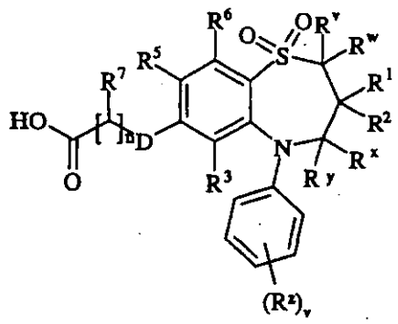
(IV)

en donde L es un grupo desplazable;

Proceso 3): hacer reaccionar un ácido de **(Va)** o **(Vb):**

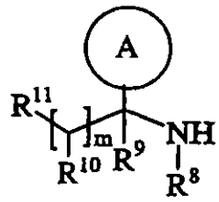


(Va)



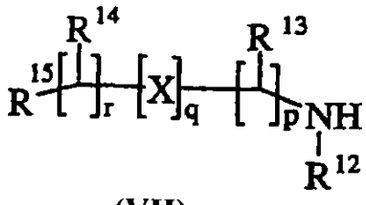
(Vb)

o su derivado activado; con una amina de fórmula **(VI)**:



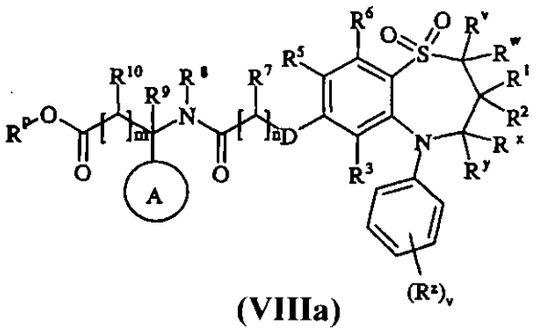
(VI)

Proceso 4): 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 fórmula **(VII)**;



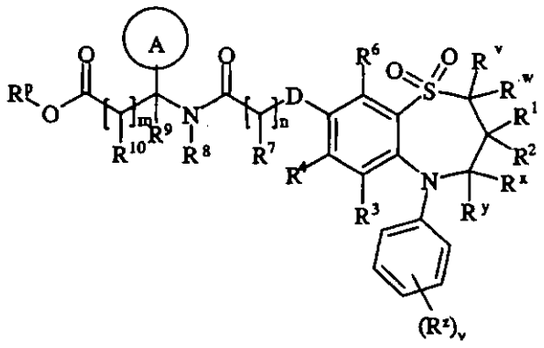
(VII)

Proceso 5): para compuestos de fórmula **(I)** en donde R^{11} es carboxi; desproteger un compuesto de fórmula (**VIIIa**):



(VIIIa)

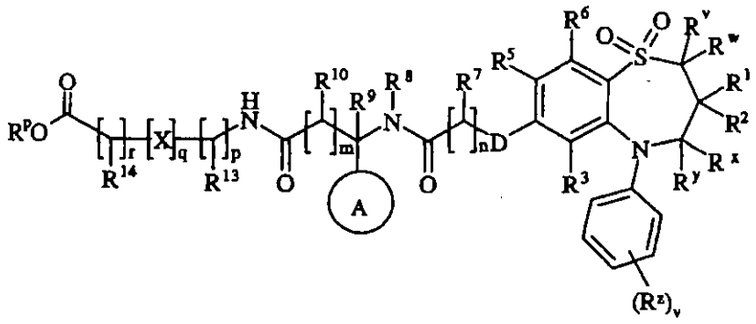
o **(VIIIb)**



(VIIIb)

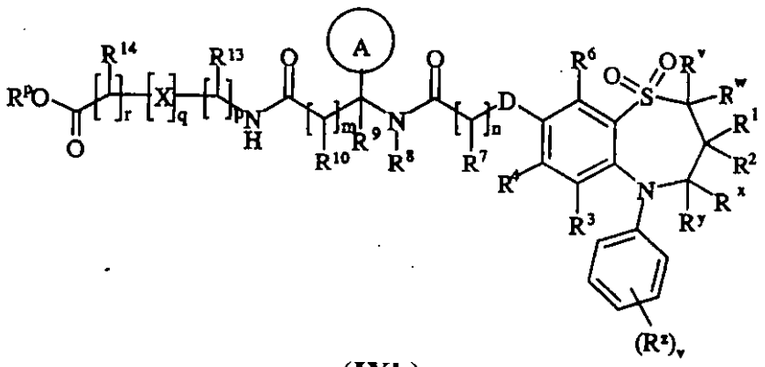
en donde R^p es C_{1-4}alquilo;

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 (**IXa**):



(IXa)

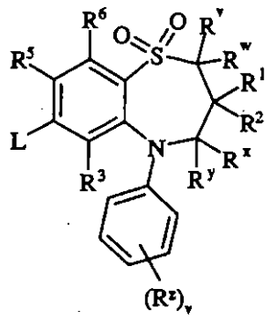
o **(IXb)**



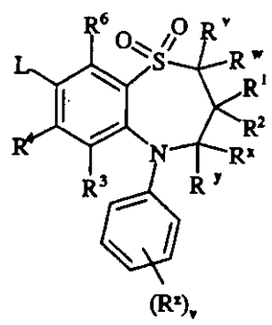
(IXb)

en donde R^p es C_{1-4}alquilo;

Proceso 7) para compuestos de fórmula **(I)** en donde uno de R^4 y R^5 se seleccionan independientemente de C_{1-4}alquiltio sustituido opcionalmente en carbono por uno o más R^{16}; hacer reaccionar un compuesto de fórmula **(Xa)** o **(Xb)**:



(Xa)



(Xb)

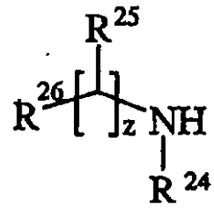
en donde L es un grupo desplazable; con un tiol de fórmula **(XI)**:

R^y-H

(XI)

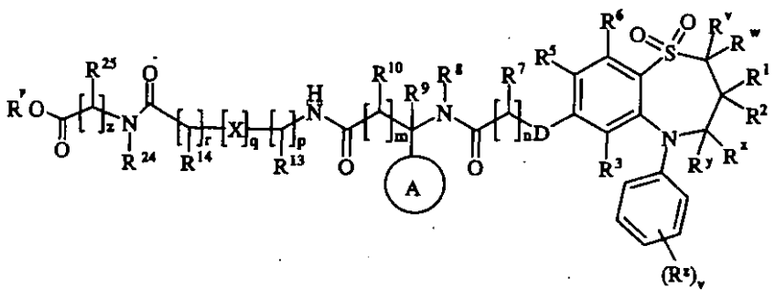
en donde R^y es C_{1-4}alquiltio sustituido opcionalmente en carbono por uno o más R^{16};

Proceso 8) para compuestos de fórmula **(I)** en donde R^{15} es un grupo de fórmula **(IC)** hacer reaccionar un compuesto de fórmula **(IXa)** o **(IXb)** en donde R^p es hidrógeno con un compuesto de fórmula **(XII)**:



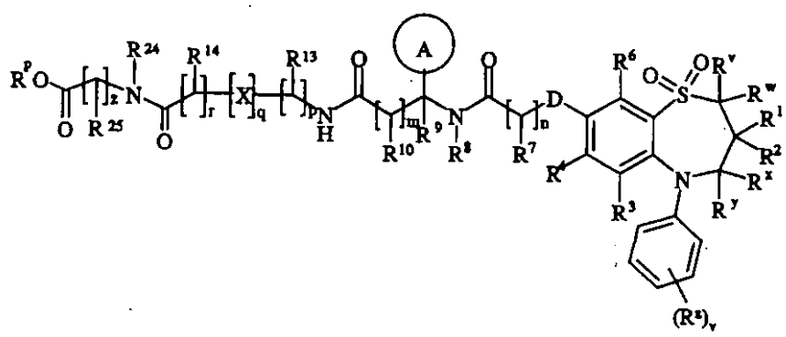
(XII)

Proceso 9): para compuestos de fórmula **(I)** en donde R^{11} es un grupo de fórmula **(IB)** y R^{15} es un grupo de fórmula **(IC)** y R^{26} es carboxi; desproteger un compuesto de fórmula **(XIIIa):**



(XIIIa)

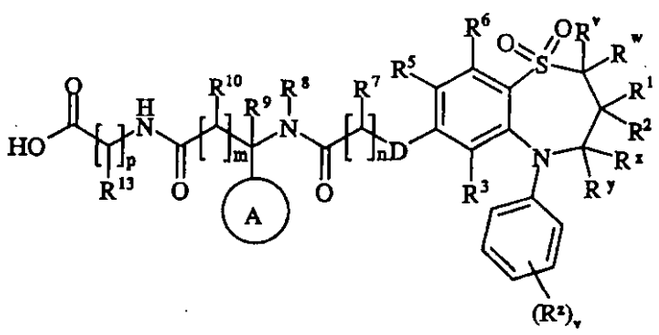
o **(XIIIb):**



(XIIIb)

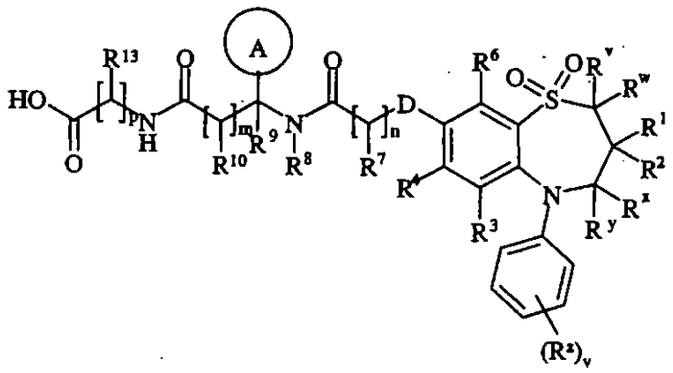
y R^p es C_{1-4}alquilo;

Proceso 10): para compuestos de fórmula **(I)** en donde X es $-N(R^q)C(O)-$; hacer reaccionar un compuesto de fórmula **(XIVa)**:



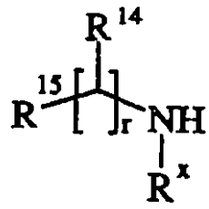
(XIVa)

o **(XIVb)**



(XIVb)

con un compuesto de fórmula (**XV**):



(XV)

y, posteriormente, si es necesario o deseable:

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

ii) retirar cualesquiera grupos protectores;

iii) formar una sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

17. Un compuesto de la fórmula **(I),** o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1 a 15 para uso como un medicamento.

18. Un compuesto de la fórmula **(I),** o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1 a 15 para uso en un método de tratamiento terapéutico o profiláctico de un animal de sangre caliente, como el hombre.

19. **El** uso de un compuesto de la fórmula **(I),** o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1 a 15 en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre.

20. Un método para producir un efecto inhibidor de IBAT en un animal de sangre caliente, como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula **(I),** o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1 a 15.

21. Una composición farmacéutica que comprende un compuesto de la fórmula **(I),** o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1 a 15, en asociación con un transportador o diluyente de aceptación farmacéutica.

22. Una composición farmacéutica que comprende un compuesto de la fórmula **(I),** o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1 a 15, y un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, en asociación con un transportador o diluyente de aceptación farmacéutica.

23. Una composición farmacéutica que comprende un compuesto de la fórmula **(I),** o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1 a 15, y un ligador de ácido biliar, en asociación con un transportador o diluyente de aceptación farmacéutica.

24. Una composición farmacéutica que comprende un compuesto de la fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1 a 15, y un inhibidor de HMG Co-A reductasa, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, y un ligador de ácido biliar en asociación con un transportador o diluyente de aceptación farmacéutica.

25. Una composición de acuerdo con reivindicación 22 o reivindicación 24 en donde el inhibidor de HMG Co-A reductasa es atorvastatina, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

26. Una composición de acuerdo con reivindicación 22 o reivindicación 24 en donde el inhibidor de HMG Co-A reductasa es rosuvastatina, o su sal de aceptación farmacéutica.

27. Una composición farmacéutica que comprende un compuesto de la fórmula **(I)**, o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1 a 15 y un agonista PPAR gamma y/o alfa, o su sal de aceptación farmacéutica, en asociación con un transportador o diluyente de aceptación farmacéutica.

28. Una composición de acuerdo con reivindicación 27 en donde el agonista PPAR gamma y/o alfa es ácido (S)-2-etoxi-3-[4-(2-{4-metanosulfoniloxifenil} etoxi)fenil]propanoico o su sal de aceptación farmacéutica.

29. Un compuesto de fórmula **(VIIIa)**, **(VIIIb)**, **(IXa)**, **(IXb)**, **(XIIIa)** o **(XIIIb)** (como se describe en reivindicación 16) o su sal de aceptación farmacéutica, solvato, solvato de dicha sal o profármaco.

TRATADO SOBRE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

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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/)* 05/07/2002
No. de Expediente del Solicitante o Apoderado 100248	**COMUNICACIÓN IMPORTANTE**

No. de Solicitud Internacional	Fecha Internacional de Presentación *(día/mes/año)*	Fecha de Prioridad *(día/mes/año)*
PCT / GB 01/ 05554	17/12/2001	21/12/2000

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.

Para efectos de decidir si la invención reivindicada es patentable o no, las Oficinas seleccionadas pueden aplicar criterios adicionales a, o diferentes de, los criterios en los cuales se basa el informe de examen preliminar internacional (véase Artículos 27 (5), 33 (5)). Los criterios adicionales pueden incluir, por ejemplo, exención de patentabilidad y los requerimientos si se permite la divulgación y de claridad y soporte de las reivindicaciones.

Nombre y dirección postal de la oficina encargada del examen internacional	Empleado Autorizado
Oficina Europea de Patentes, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+ 31-70) 340-2040 Fax: (+ 31-70) 340-3016	**SMITH K M** Tel.: (+49-89) 2399 2828

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TRATADO SOBRE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 PCT)

No. de Expediente del Solicitante o Apoderado	**PROCEDIMIENTO POSTERIOR**	véase comunicación sobre el envío del informe de examen preliminar internacional (Formulario PCT/IPEA/416)
100248		
No. Solicitud Internacional	Fecha Internacional de Presentación *(día/mes/año)*	Fecha de Prioridad *(día/mes/año)*
PCT / GB 01/ 05554	17/12/2001	21/12/2000
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC		
C07D281/10		
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 36.

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 70.16 y Sección 607 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 ☒ Comprobación justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones en apoyo de esta comprobación
- VI ☐ Ciertos documentos enumerados
- VII ☐ Ciertas deficiencias del registro internacional
- VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición	Fecha de la conclusión de este informe
11/06/2002	02/07/2002
Nombre y dirección postal de la oficina encargada del examen internacional	Empleado Autorizado
Oficina Europea de Patentes, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+ 31-70) 340-2040 Fax: (+ 31-70) 340-3016	**VERHULST W** Tel.: (+49-89) 2399 2828

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

No. de Solicitud Internacional PCT / GB 01/ 05554

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.

CONSULADO GENERAL DE COLOMBIA
3RD FLOOR, 15-19 GREAT TITCHFIELD STREET, LONDON W1P 7FB
TELEPHONE 020-7637 9893 • TELEFAX 020-7637 5604
E-MAIL consulco@consulco.demon.co.uk

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El suscrito Cónsul General de Colombia en Londres, vistos los documentos presentados ante este Despacho,

CERTIFICA

Que, **J.B. HODGSON,** Notario Público de Macclesfield, Cheshire, Inglaterra, legalizó la firma del documento precedente y su firma se encuentra certificada por **J. GARBRAH,** Oficial de del Ministerio de Relacione Exteriores Británico, firma que se encuentra registrada en este Consulado General.

Que, **AstraZeneca AB,** es una Sociedad constituída, organizada y existente en Sodertalje, Suecia, y que cumple con su objeto social de acuerdo con las leyes de ese país.

Que, **DAVID ERIC GILES,** en su calidad de Representante Legal de la mencionada Sociedad, debidamente autorizado otorga el documento precedente y su firma se encuentra legalizada por **J.B. HODGSON,** Notario Público de Macclesfield, Cheshire, Inglaterra, Gran Bretaña.

El Cónsul General no asume responsabilidad por el contenido del mencionado documento.

Dado en Londres, Inglaterra, Gran Bretaña, a los quince (15) días del mes de Noviembre de dos mil (2000).

Certificación No.11 /1722
Derechos: U$ 106,00 CANCELADOS

JAIRO H. BERRIO VILLARREAL
Cónsul General

HUGO NAVARRO ALVAREZ
TRADUCTOR E. INTERPRETE OFICIAL
Res. 1876 Ministerio 1993

CONSULADO GENERAL DE COLOMBIA

En la Notaría Ciento Cincuenta se coteja la presente fotocopia con la fotocopia auténtica que se ha tenido a la vista
Fecha: DIC. 2 2000
NOTARIO CIENTO CINCUENTA
Agustín Castillo Zárate
Santafé de Bogotá D.C. Colombia

COMO NOTARIO CIENTO CINCUENTA Y SEIS DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA CONCUERDA CON ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. 15 DIC 2000
NOTARIA CIENTO CINCUENTA Y SEIS

REPUBLICA DE COLOMBIA
Rosa Falla Laiseca
Notaria
Ciento Cincuenta y Seis
(E)

BRIGARD & CASTRO

SANTAFE DE BOGOTA - COLOMBIA

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PODER

Yo (nosotros) ASTRAZENECA AB

Domiciliado(s) en: S-151 85, Sodertalje, SUECIA

Nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones relvindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, 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

Firma

Nombre
Cargo

NOTARIA Cuarenta de este círculo se coteió la presente fotocopia que coincide con la tomada del original que se ha tenido a la vista. Fecha DIC. 20 2002 NOTARIO CUARENTA Agustín Castillo Zárate Santafé de Bogotá D.C., Colombia

POWER OF ATTORNEY

I (We ASTRAZENECA AB

Domiciled in: S-151 85, Sodertalje SWEDEN

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, of Santafé de 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 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 kinds 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. As the aforementioned (we) hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in

This 10 NOV 2000 day

Signature

Name DAVID ERIC GILES
Title DIRECTOR IP SERVICES

5 DIC 2000 MAGGLES CASTRO DE PARDO NOTARIA 40 BOGOTA D.C. COLOMBIA Rosa Falla Lee Notaria Carrera 8 No. 16-56 Piso 9 Cel. 2824 y 2825

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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 ASTRAZENECA AB

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 10 day of November of 2000
Personally appeared before me
DAVID ERIC GILES
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

DIRECTOR IP SERVICES

of ASTRAZENECA AB

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that 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 3RD JANUARY 2000

and that he (she) who grants the present power of attorney is its Representative.

Notary Public (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de
compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que antecede, quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Notary Public (Seal)

LEGALIZACION ANTE CONSUL COLOMBIANO ES REQUERIDA

LEGALIZATION BEFORE COLOMBIAN CONSUL IS REQUIRED

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UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

No. **D644894**

Date **14 November, 2000**

This document bears
the signature / seal of **J B Hodgson**

HUGO [illegible]O ALVAREZ
TRADUCTOR INTERPRETE OFICIAL
Res. 2078 Minjusticia 1993

Acting in the capacity of **Notary Public**

Signed by: **J. Garbrah**

FOREIGN AND COMMONWEALTH OFFICE LONDON

For Her Majesty's Principal Secretary of State
For Foreign and Commonwealth Affairs

Notaría Cuarenta de este círculo se cotejó la presente fotocopia que coincide con la fotocopia autenticada que se ha tenido a la vista
Fecha DIC. 2002
NOTARIO CUARENTA
Justin Castillo Zárate
Santafé de Bogotá D.C., Colombia

COMO NOTARIO CUARENTA Y SEIS DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
BOGOTA D.C. REPUBLICA DE COLOMBIA
15 DIC 2000
NOTARIO CUARENTA Y SEIS

REPUBLICA DE COLOMBIA
Rosa Falla Laiseca
Notaria
Cuarenta y Seis (E)
Notaría Cuarenta y Seis del Círculo

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TRADUCCION OFICIAL No. 432/2000 de las legalizaciones que se encuentran a continuación de un Poder otorgado ASTRAZENECA AB, una compañía domiciliada en S-151 85. Sodertalje, SUECIA al doctor **RAMIRO CASTRO y HECTOR GOMEZ**, Santafé de Bogotá, D.C., Colombia, del inglés al español, las cuales para su identificación se sella con el Sello del Traductor al mismo tiempo que la presente.-

++

ANEXOS: El Poder arriba mencionado, Certificación Notarial, Certificación por el Secretario de Estado Principal de Su Majestad Para los Asuntos de la Comunidad y el Extranjero en Londres, Inglaterra, Certificación del Consulado General de Colombia en Londres, Inglaterra, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

++

Firma Ilegible (Firmado)
Notario Público
SELLO NOTARIAL EN RELIEVE.

++

REINO UNIDO DE LA GRAN BRETAÑA E IRLANDA DEL NORTE

No. D644894
Fecha...14 de Noviembre del año 2000.....
Este documento porta
la firma/sello de D. B. Hodgson
.....
actuando en la capacidad de
Notario Público
.....
Firmado por: J. Garbrah

Firma Ilegible (firmado)

COMO NOTARIO CUARENTA Y SEIS DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA COINCIDE CON ORIGINAL QUE HE TENIDO A LA VISTA.
BOGOTA D.C. REPUBLICA DE COLOMBIA
15 DIC 2000
NOTARIO CUARENTA Y SEIS DEL CIRCULO
Rosa Falla Laiseca
Notaria
Cuarenta y seis
(E)

En la Notaría Cuarenta de este círculo se copió la presente fotocopia que coincide con la fotocopia autenticada que se ha tenido a la vista
Fecha DIC. 2002
NOTARIO CUARENTA
Agustín Castillo Zárate
Santafé de Bogotá D.C. Colombia

HUGO NAVARRO ALVAREZ
TRADUCTOR E INTERPRETE OFICIAL
Res. 1676 Minjusticia 1993

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Por el Secretario de Estado Principal de Su Majestad para los Asuntos de la Comunidad y el Extranjero.

SELLO EN RELIEVE.

HAY SELLO DE LA COMUNIDAD
Y EL EXTRANJERO EN LONDRES,
INGLATERRA.

++

EN ESPAÑOL: La Certificación del Consulado General de Colombia en Londres, Inglaterra bajo el Número de Certificación 11/1722 de fecha 15 de Noviembre del año 2000; Autenticación Hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el Número 481834 de fecha 29 de Noviembre del año 2000.

(Pagados Derechos por valor de $106.00 Dólares)

++

ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS ADJUNTOS.

HUGO NAVARRO ALVAREZ
TRADUCTOR E. INTERPRETE OFICIAL
Res. 1876 Minjusticia 1993

Resolución Número 1876 del Ministerio de Justicia
Fecha: 4 de Diciembre del año 2000.



Por el Secretario de Estado Principal de
Su Majestad para los Asuntos de la
Comunidad y el Extranjero

SELLO EN RELIEVE

HAY SELLO DE LA COMUNIDAD
Y EL EXTRANJERO EN LONDRES,
INGLATERRA.

++

EN ESPAÑOL: La Certificacion del Consulado General de Colombia en Londres, Inglaterra bajo el Numero de Certificacion 111723 de fecha 15 de Noviembre del año 2000; Autenticacion Hecha por el Ministerio de Relaciones Exteriores de Colombia bajo el Numero 49/02A de fecha 20 de Noviembre del año 2000.

(Pagados Derechos por valor de $106.00 Dolares)

++

ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS ADJUNTOS

Resolución Número 1078 del [illegible]
Fecha 4 de Dicie[illegible] del año [illegible]

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

SUPERINDUSTRIA Y COMERCIO

Fecha: Radicacion : 03054743 00000000 Folios: 289
Fecha (AMD): 2003-06-27 16:37:01
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

294 290

2020
Bogotá, D.C.,

Doctor:
Ramiro Castro Duque
Apoderado
Astrazeneca AB

Oficio N° 01295

ASUNTO:

Radicación N°	03 054743
Solicitud internacional	PCTGB01/05554
Fecha inicio fase nacional	21/07/2003
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 06 FEB. 2004.

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