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(54) **BENZOTHIAZEPINE AND BENZOTHIADIAZEPINE DERIVATIVES WITH ILEAL BILE ACID TRANSPORT (IBAT) INHIBITORY ACTIVITY FOR THE TREATMENT HYPERLIPIDAEMIA**

BENZOTHIAZEPIN UND BENZOTHIADIAZEPIN DERIVATIVE MIT HEMMENDER WIRKUNG AUF DEN SÄURETRANSPORT IN DEN GALLENGÄNGEN ZUR BEHANDLUNG VON HYPERLIPIDAEMIA

DERIVES DE BENZOTHIAZEPINE ET DE BENZOTHIADIAZEPINE PRESENTANT UNE ACTIVITE INHIBITRICE DU TRANSPORT DES ACIDES BILIAIRES ILEAUX (IBAT), DESTINES AU TRAITEMENT DE L'HYPERLIPIDEMIE

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(56) References cited:
WO-A-00/47568 WO-A-01/66533
WO-A-02/50051 WO-A-98/38182

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Description

[0001] This invention relates to benzothiazepine and benzothiadiazepine derivatives, or pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof. These benzothiazepines and benzothiadiazepines possess ileal bile acid transport (IBAT) inhibitory activity and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions and they are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said benzothiazepine and benzothiadiazepine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit IBAT in a warm-blooded animal, such as man.

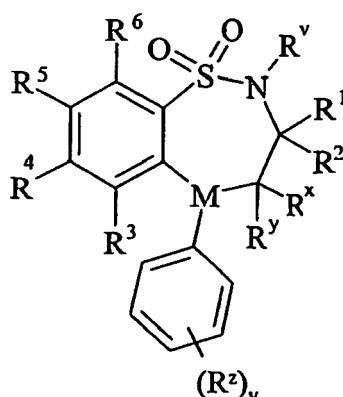
[0002] It is well-known that hyperlipidaemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for cardiovascular atherosclerotic disease (for instance "Coronary Heart Disease: Reducing the Risk; a Worldwide View" Assman 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.

[0003] 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. Substituted compounds possessing such IBAT inhibitory activity have been described, see for instance hypolipidaemic compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/38182, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/4756S, WO 00/61565, 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.

[0004] 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, hypertriglyceridemia, 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, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks.

[0005] The present invention is based on the discovery that certain benzothiazepine and benzothiadiazepine compounds surprisingly inhibit IBAT. Such properties are expected to be of value in the treatment of disease states associated with hyperlipidaemic conditions.

[0006] Accordingly, the present invention provides a compound of formula (I):



(I)

wherein:

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

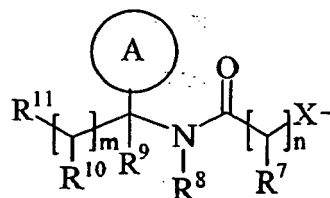
One of R^1 and R^2 are selected from hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl and the other is selected from C_{1-6} alkyl or C_{2-6} alkenyl;

R^x and R^y are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkylS(O) $_3$ wherein a is 0 to 2;

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

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, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl; v is 0-5;

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



(IA)

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, 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} ;

X 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} ;

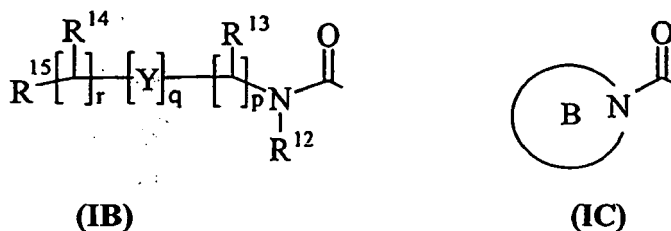
R^8 is hydrogen or C_{1-4} alkyl;

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, -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 C₁₋₆alkyl; or R¹¹ is a group of formula (IB) or (IC):



wherein:

15 **Y** is -N(Rⁿ)-, -N(Rⁿ)C(O)-, -N(Rⁿ)C(O)(CR^sR^t)_vN(Rⁿ)C(O)-, -O-, and -S(O)_a-; wherein a is 0-2, v is 1-2, R^s and R^t are independently selected from hydrogen or C₁₋₄alkyl optionally substituted by R²⁶ and Rⁿ is hydrogen or C₁₋₄alkyl; R¹² is hydrogen or C₁₋₄alkyl;

20 R¹³ and R¹⁴ are independently selected from hydrogen, C₁₋₆alkyl, carbocyclyl or heterocyclyl; and when q is 0, R¹⁴ may additionally be selected from hydroxy; wherein R¹³ and R¹⁴ may be independently optionally substituted by one or more substituents selected from R²⁰;

R¹⁵ is carboxy, 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 C₁₋₆alkyl;

p is 1-3; wherein the values of R¹³ may be the same or different;

q is 0-1;

25 r is 0-3; wherein the values of R¹⁴ may be the same or different;

m is 0-2; wherein the values of R¹⁰ may be the same or different;

n is 1-3; wherein the values of R⁷ may be the same or different;

30 **Ring B** is a nitrogen linked heterocyclyl substituted on carbon by one group selected from R²³, and optionally additionally substituted on carbon by one or more R²⁴; and wherein if said nitrogen linked heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by a group selected from R²⁵;

35 R¹⁶, R¹⁷ and R¹⁸ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, N-(C₁₋₄alkyl) amino, N,N-(C₁₋₄alkyl)₂amino, C₁₋₄alkanoylamino, N-(C₁₋₄alkyl)carbamoyl, N,N-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_a wherein a is 0 to 2, C₁₋₄alkoxycarbonyl, N-(C₁₋₄alkyl)sulphamoyl and N,N-(C₁₋₄alkyl)₂sulphamoyl; wherein R¹⁶, R¹⁷ and R¹⁸ may be independently optionally substituted on carbon by one or more R²¹;

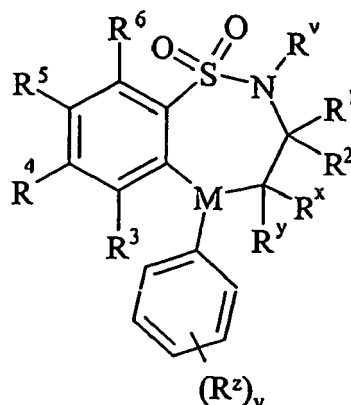
40 R¹⁹, R²⁰, R²⁴ and R²⁶ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, N-(C₁₋₄alkyl)amino, N,N-(C₁₋₄alkyl)₂amino, C₁₋₄alkanoylamino, N-(C₁₋₄alkyl)carbamoyl, N,N-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_a wherein a is 0 to 2, C₁₋₄alkoxycarbonyl, N-(C₁₋₄alkyl)sulphamoyl, N,N-(C₁₋₄alkyl)₂sulphamoyl, carbocyclyl, heterocyclyl, benzyloxycarbonylamino, (C₁₋₄alkyl)₃silyl, sulpho, sulphino, amidino, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^b), wherein R^a and R^b are independently selected from C₁₋₆alkyl; wherein R¹⁹, R²⁰, R²⁴ and R²⁶ may be independently optionally substituted on carbon by one or more R²²;

45 R²¹ and R²² 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, acetoxyl, methylamino, dimethylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, N-methylsulphamoyl and N,N-dimethylsulphamoyl;

50 R²³ is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^g)(OR^h), -P(O)(OH)(OR^g), -P(O)(OH)(R^g) or -P(O)(OR^g)(R^h) wherein R^g and R^h are independently selected from C₁₋₆alkyl;

R²⁵ is selected from C₁₋₆alkyl, C₁₋₆alkanoyl, C₁₋₆alkylsulphonyl, C₁₋₆alkoxycarbonyl, carbamoyl, N-(C₁₋₆alkyl)carbamoyl, N,N-(C₁₋₆alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

55 **[0007]** According to a further aspect of the present invention there is provided a compound of formula (I):



(I)

wherein:

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

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

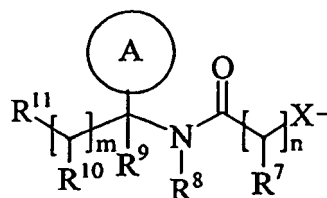
R^x and R^y are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkylS(O)_a wherein a is 0 to 2;

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

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

v is 0-5;

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



(IA)

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

X is -O-, -N(R^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} ;

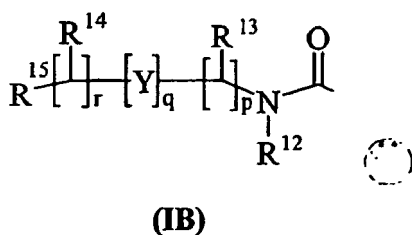
R^8 is hydrogen or C_{1-4} alkyl;

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, -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 C₁₋₆alkyl; or R¹¹ is a group of formula (IB):



wherein:

15 **Y** is N(Rⁿ)-, -N(Rⁿ)C(O)-, -O-, and -S(O)_a-; wherein a is 0-2 and Rⁿ is hydrogen or C₁₋₄alkyl;

R¹² is hydrogen or C₁₋₄alkyl;

R¹³ and **R¹⁴** are independently selected from hydrogen, C₁₋₄alkyl, carbocyclyl or heterocyclyl; wherein R¹³ and R¹⁴ may be independently optionally substituted by one or more substituents selected from R²⁰;

20 **R¹⁵** 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 C₁₋₆alkyl;

p is 1-3; wherein the values of R¹³ may be the same or different;

q is 0-1;

r is 0-3; wherein the values of R¹⁴ may be the same or different;

m is 0-2; wherein the values of R¹⁰ may be the same or different;

25 **n** is 1-3; wherein the values of R⁷ may be the same or different;

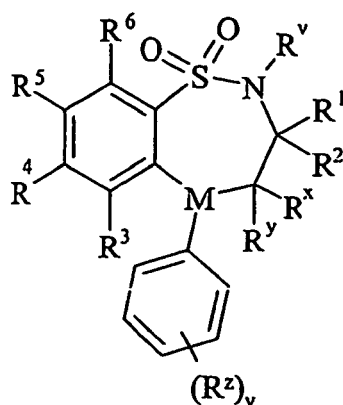
R¹⁶, **R¹⁷** and **R¹⁸** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, N-(C₁₋₄alkyl)amino, N,N-(C₁₋₄alkyl)₂amino, C₁₋₄alkanoylamino, N-(C₁₋₄alkyl)carbamoyl, N,N-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_a wherein a is 0 to 2, C₁₋₄alkoxycarbonyl, N-(C₁₋₄alkyl)sulphamoyl and N,N-(C₁₋₄alkyl)₂sulphamoyl; wherein R¹⁶, R¹⁷ and R¹⁸ may be independently optionally substituted on carbon by one or more R²¹;

30 **R¹⁹** and **R²⁰** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, N-(C₁₋₄alkyl)amino, N,N-(C₁₋₄alkyl)₂amino, C₁₋₄alkanoylamino, N-(C₁₋₄alkyl)carbamoyl, N,N-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_a wherein a is 0 to 2, C₁₋₄alkoxycarbonyl, N-(C₁₋₄alkyl)sulphamoyl, N,N-(C₁₋₄alkyl)₂sulphamoyl, 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 C₁₋₆alkyl; wherein R¹⁹ and R²⁰ may be independently optionally substituted on carbon by one or more R²²;

35 **R²¹** and **R²²** 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;

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

45 **[0008]** According to a further aspect of the present invention there is provided a compound of formula (I):



(I)

wherein:

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

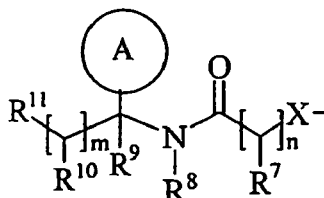
One of R^1 and R^2 are selected from hydrogen or C_{1-6} alkyl and the other is selected from C_{1-6} alkyl;

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

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

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, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl; v is 0-5;

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



(IA)

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, 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} ;

X 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} ;

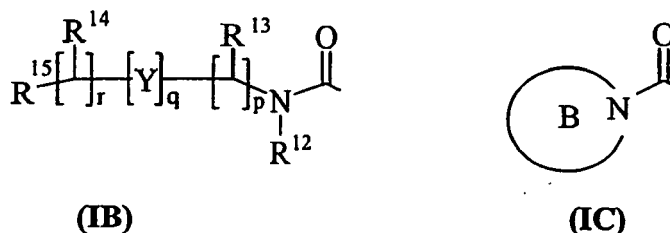
R^7 is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{18} ;

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, -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) or (IC):



wherein:

Y is -N(Rⁿ)-, -N(Rⁿ)C(O)-, -N(Rⁿ)C(O)(CR^sR^t)_vN(Rⁿ)C(O)-, -O-, and -S(O)_a-; wherein a is 0-2, v is 1-2, R^s and R^t are independently selected from hydrogen or C₁₋₄alkyl optionally substituted by R²⁶ and Rⁿ is hydrogen or C₁₋₄alkyl;

R¹² is hydrogen or C₁₋₄alkyl;

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

R¹⁵ is carboxy, 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 C₁₋₆alkyl;

p is 1-3; wherein the values of R¹³ may be the same or different;

q is 0-1;

r is 0-3; wherein the values of R¹⁴ may be the same or different;

m is 0-2; wherein the values of R¹⁰ may be the same or different;

n is 1-3; wherein the values of R⁷ may be the same or different;

Ring B is a nitrogen linked heterocyclyl substituted on carbon by one group selected from R²³, and optionally additionally substituted on carbon by one or more R²⁴; and wherein if said nitrogen linked heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by a group selected from R²⁵;

R¹⁶, **R¹⁷** and **R¹⁸** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, N-(C₁₋₄alkyl)amino, N,N-(C₁₋₄alkyl)₂amino, C₁₋₄alkanoylamino, N-(C₁₋₄alkyl)carbamoyl, N,N-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_a, wherein a is 0 to 2, C₁₋₄alkoxycarbonyl, N-(C₁₋₄alkyl)sulphamoyl and N,N-(C₁₋₄alkyl)₂sulphamoyl; wherein R¹⁶, R¹⁷ and R¹⁸ may be independently optionally substituted on carbon by one or more R²¹;

R¹⁹, **R²⁰**, **R²⁴** and **R²⁶** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, N-(C₁₋₄alkyl)amino, N,N-(C₁₋₄alkyl)₂amino, C₁₋₄alkanoylamino, N-(C₁₋₄alkyl)carbamoyl, N,N-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_a wherein a is 0 to 2, C₁₋₄alkoxycarbonyl, N-(C₁₋₄alkyl)sulphamoyl, N,N-(C₁₋₄alkyl)₂sulphamoyl, carbocyclyl, heterocyclyl, benzyloxycarbonylamino, sulpho, sulphino, amidino, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^b), wherein R^a and R^b are independently selected from C₁₋₆alkyl; wherein R¹⁹, R²⁰, R²⁴ and R²⁶ may be independently optionally substituted on carbon by one or more R²²;

R²¹ and **R²²** 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, acetoxyl, methylamino, dimethylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, N-methylsulphamoyl and N,N-dimethylsulphamoyl;

R²³ is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^g)(OR^h), -P(O)(OH)(OR^g), -P(O)(OH)(R^g) or -P(O)(OR^g)(R^h) wherein R^g and R^h are independently selected from C₁₋₆alkyl;

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

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

[0009] In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C₁₋₆alkyl" includes C₁₋₄alkyl, C₁₋₃alkyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "phenylC₁₋₆alkyl" would include phenylC₁₋₆alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro,

chloro, bromo and iodo.

[0010] 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.

[0011] "Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Preferably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "heteroaryl" are thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranlyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridyl and quinolyl. Preferably the term "heteroaryl" refers to thienyl or indolyl.

[0012] "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.

[0013] 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 -CH₂-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 -CH₂- 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-pyrrolidinyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolyl), 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, tetrahydropyranlyl, piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholino, 1,1-dioxothiomorpholino, tetrahydropyranlyl, 1,3-dioxolanyl, homopiperazinyl, thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, pyranlyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl and 1-isoquinolonyl.

[0014] A "nitrogen linked heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is nitrogen and the heterocyclyl is linked to the carbonyl group of formula (IC) via this nitrogen, which may additionally contain further heteroatoms chosen from nitrogen, sulphur or oxygen, wherein a -CH₂- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form the S-oxides. Preferably a "nitrogen linked heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is nitrogen and the heterocyclyl is linked to the carbonyl group of formula (IC) via this nitrogen, which may additionally contain further heteroatoms chosen from nitrogen, sulphur or oxygen, wherein a -CH₂- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form the S-oxides. Examples and suitable values of the term "nitrogen linked heterocyclyl" are morpholino, pyrrolidin-1-yl, imidazol-1-yl, pyrazolidin-1-yl, piperidin-1-yl and piperazin-1-yl. Particularly a "nitrogen linked heterocyclyl" is pyrrolidin-1-yl.

[0015] A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a -CH₂- 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.

[0016] An example of "C₁₋₆alkanoyloxy" and "C₁₋₄alkanoyloxy" is acetoxyl. Examples of "C₁₋₆alkoxycarbonyl" and "C₁₋₄alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C₁₋₆alkoxy" and "C₁₋₄alkoxy" include methoxy, ethoxy and propoxy. Examples of "C₁₋₆alkanoylamino" and "C₁₋₄alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C₁₋₆alkylS(O)_a" wherein a is 0 to 2" and "C₁₋₄alkylS(O)_a" wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C₁₋₆alkanoyl" and "C₁₋₄alkanoyl" include propionyl and acetyl. Examples of "*N*-(C₁₋₆alkyl)amino" and "*N*-(C₁₋₄alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C₁₋₆alkyl)₂amino" and "*N,N*-(C₁₋₄alkyl)₂amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C₂₋₆alkenyl" and "C₂₋₄alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C₂₋₆alkynyl" and "C₂₋₄alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C₁₋₆alkyl)sulphamoyl" and "*N*-(C₁₋₄alkyl)sulphamoyl" are *N*-(C₁₋₃alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C₁₋₆alkyl)₂sulphamoyl" "*N*-(C₁₋₄alkyl)₂Sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C₁₋₆alkyl)carbamoyl" and "*N*-(C₁₋₄alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C₁₋₆alkyl)₂carbamoyl" and "*N,N*-(C₁₋₄alkyl)₂carbamoyl" are

dimethylaminocarbonyl and methylethylaminocarbonyl. Example of "C₁₋₆alkylsulphonyl" are mesyl and ethylsulphonyl. Examples of "(C₁₋₄alkyl)₃silyl," include trimethylsilyl and methyldiethylsilyl.

[0017] 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, acetic 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.

[0018] 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).

[0019] An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

[0020] 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, alkoxy carbonyl (to give alkyl carbonate esters), dialkylcarbonyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbonyl (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.

[0021] 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*-C₁₋₆alkyl or *N,N*-di-C₁₋₆alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

[0022] 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.

[0023] The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess IBAT inhibitory activity.

[0024] 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.

[0025] Particular values are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

R^v is hydrogen.

R¹ and R² are C₁₋₄alkyl.

R¹ and R² are both butyl.

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

One of R^x and R^y is hydrogen and the other is hydroxy.

R^x and R^y are both hydrogen.

M is -N-.

M is -CH-.

v is 0 or 1.

v is 0.

R^z is C₁₋₄alkyl.

R³ and R⁶ are hydrogen.

R⁴ is methylthio or bromo.

R⁴ is methylthio.

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

R⁴ is bromo, methyl or methylthio.

R⁵ is a group of formula **(IA)** (as depicted above) wherein:

X is -O-;

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

n is 1;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

m is 0;

R¹¹ is a group of formula **(IB)** (as depicted above) wherein:

R¹² is hydrogen;

p is 1 or 2;

R¹³ is hydrogen;

q is 0;

r is 0;

R¹⁵ is carboxy or sulpho; and

R¹⁷ is hydroxy.

R⁵ is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl} carbamoylmethoxy or *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy.

R⁵ is a group of formula **(IA)** (as depicted above) wherein:

X is -O-;

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

n is 1;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

m is 0;

R¹¹ is carboxy, a group of formula **(IB)** (as depicted above) or a group of formula **(IC)** (as depicted above) wherein:

R¹² is hydrogen or C₁₋₄alkyl;

p is 1 or 2;

R¹³ is hydrogen or C₁₋₄alkyl optionally substituted by R²⁰ wherein R²⁰ is hydroxy, carbamoyl, amino, benzyloxycarbonylamino or C₁₋₄alkylS(O)_a wherein a is 0;

R¹⁴ is hydrogen or hydroxy;

q is 0;

r is 0 or 1;

R¹⁵ is carboxy or sulpho;

R¹⁷ is hydroxy; and

Ring B is pyrrolidin-1-yl substituted on carbon by one group selected from R²³; wherein R²³ is carboxy.

R⁵ is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy,

N-{(R)- α -[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl] benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl] benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-carbamoylethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl] benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl] benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3-methylbutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(S)-1-carboxy-2-(S)-2-methylbutyl)carbamoyl]benzyl} carbamoylmethoxy, *N*-{(R)- α -carboxy-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-aminobutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -{(R)-[*N*-(S)-1-carboxy-4-(benzyloxy-carbonylamino)butyl]carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -((S)-2-carboxypyrrolidin-1-ylcarbonyl)benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)-*N*-methylcarbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(R)-2-(R)-1-carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(sulphomethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -carboxybenzyl} carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy or *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy.

R⁵ is a group of formula **(IA)** (as depicted above) wherein:

X is -O-;

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

n is 1;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

m is 0;

R¹¹ is carboxy, a group of formula **(IB)** (as depicted above) or a group of formula **(IC)** (as depicted above) wherein:

R¹² is hydrogen or C₁₋₄alkyl;

p is 1 or 2;

R¹³ is hydrogen or C₁₋₆alkyl optionally substituted by R²⁰ wherein R²⁰ is hydroxy, carbamoyl, amino, benzyloxycarbonylamino, C₁₋₄alkylS(O)_a wherein a is 0 or (C₁₋₄alkyl)₃silyl;

R¹⁴ is hydrogen or hydroxy or C₁₋₆alkyl; wherein R¹⁴ may be optionally substituted by one or more substituents selected from R²⁰;

Y is -N(Rⁿ)C(O)- wherein Rⁿ is hydrogen;

q is 0 or 1;

r is 0 or 1;

R¹⁵ is carboxy or sulpho;

R¹⁷ is hydroxy; and

R²⁰ is selected from hydroxy;

Ring B is pyrrolidin-1-yl or azetidyl substituted on carbon by one group selected from R²³, and optionally additionally substituted on carbon by one or more R²⁴; wherein R²³ is carboxy and R²⁴ is hydroxy.

R⁵ is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-carbamylethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(S)-1-carboxy-2-(S)-2-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-4-hydroxybenzyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-(benzyloxycarbonylamino)butyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-2-carboxypyrrolidin-1-ylcarbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)-*N*-methylcarbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(R)-2-(R)-1-carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(sulphomethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl]carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)-4-(R)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)azetid-1-ylcarbonyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-1-carboxyethyl)carbamoyl]ethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3,3-dimethylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(triethylsilyl)ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy or *N*-{(R)- α -[*N*-((R)-1-carboxy-2-(trimethylsilyl)ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy.

R⁵ is hydrogen.

R⁴ is a group of formula **(IA)**.

R⁵ is a group of formula **(IA)**.

[0026] Therefore in a further aspect of the invention, there is provided a compound of formula **(I)** (as depicted above)

wherein:

R^v is hydrogen;
 R¹ and R² are C₁₋₄alkyl;
 5 R^x and R^y are both hydrogen;
 M is -N-;
 v is 0;
 R³ and R⁶ are hydrogen;
 R⁴ is halo, C₁₋₄alkyl or C₁₋₄alkylS(O)_a wherein a is 0;
 10 R⁵ is a group of formula **(IA)** (as depicted above) wherein:
 X is -O-;
 Ring A is phenyl optionally substituted by one or more substituents selected from R¹⁷;
 n is 1;
 R⁷ is hydrogen;
 15 R⁸ is hydrogen;
 R⁹ is hydrogen;
 m is 0;
 R¹¹ is carboxy, a group of formula **(IB)** (as depicted above) or a group of formula **(IC)** (as depicted above) wherein:
 R¹² is hydrogen or C₁₋₄alkyl;
 20 p is 1 or 2;
 R¹³ is hydrogen or C₁₋₆alkyl optionally substituted by R²⁰ wherein R²⁰ is hydroxy, carbamoyl, amino, benzyloxycarbonylamino, C₁₋₄alkylS(O)_a wherein a is 0 or (C₁₋₄alkyl)₃silyl;
 R¹⁴ is hydrogen or hydroxy or C₁₋₆alkyl; wherein R¹⁴ may be optionally substituted by one or more substituents selected from R²⁰;
 25 Y is -N(Rⁿ)C(O)- wherein Rⁿ is hydrogen;
 q is 0 or 1;
 r is 0 or 1;
 R¹⁵ is carboxy or sulpho;
 R¹⁷ is hydroxy; and
 30 R²⁰ is selected from hydroxy; and
 Ring B is pyrrolidin-1-yl or azetidiny substituted on carbon by one group selected from R²³, and optionally additionally substituted on carbon by one or more R²⁴; wherein R²³ is carboxy and R²⁴ is hydroxy;
 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

35 **[0027]** Therefore in an additional aspect of the invention, there is provided a compound of formula **(I)** (as depicted above) wherein:

R^v is hydrogen;
 R¹ and R² are both butyl;
 40 R^x and R^y are both hydrogen;
 M is -N-;
 v is 0;
 R³ and R⁶ are hydrogen;
 R⁴ is bromo, methyl or methylthio; and
 45 R⁵ is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-carbamoyl-ethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(S)-1-carboxy-2-(S)-2-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)- α -carboxy-4-hydroxybenzyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-(benzyloxy-carbonylamino)butyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -((S)-2-carboxypyrrolidin-1-ylcarbonyl)ben-

zyl]carbamoylemethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)-*N*-methylcarbamoyle]benzyl}carbamoylemethoxy, *N*-{(R)- α -[*N*-(1-(R)-2-(R)-1-carboxy-1-hydroxyprop-2-yl)carbamoyle]benzyl}carbamoylemethoxy, *N*-{(R)- α -[*N*-(sulphomethyl)carbamoyle]benzyl}carbamoylemethoxy, *N*-{(R)- α -carboxybenzyl} carbamoylemethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyle]-4-hydroxybenzyl}carbamoylemethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyle]-4-hydroxybenzyl} carbamoylemethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxybutyl)carbamoyle]-4-hydroxybenzyl} carbamoylemethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyle]-4-hydroxybenzyl} carbamoylemethoxy, *N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyle]propyl}carbamoyle]benzyl} carbamoylemethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)-4-(R)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]benzyl} carbamoylemethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)azetidin-1-ylcarbonyl]benzyl} carbamoylemethoxy, *N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-1-carboxyethyl)carbamoyle]ethyl} carbamoyle]benzyl} carbamoylemethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyle] benzyl}carbamoylemethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3,3-dimethylbutyl)carbamoyle] benzyl}carbamoylemethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyle]-4-hydroxybenzyl} carbamoylemethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(trimethylsilyl)ethyl} carbamoyle]-4-hydroxybenzyl}carbamoylemethoxy or *N*-{(R)- α -[*N*-((R)-1-carboxy-2-(trimethylsilyl)ethyl}carbamoyle]-4-hydroxybenzyl}carbamoylemethoxy;

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

[0028] In another aspect of the invention, preferred compounds of the invention are any one of examples 5, 6, 7, 9, 11, 14, 15, 26, 27, 28, 30 or 33 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

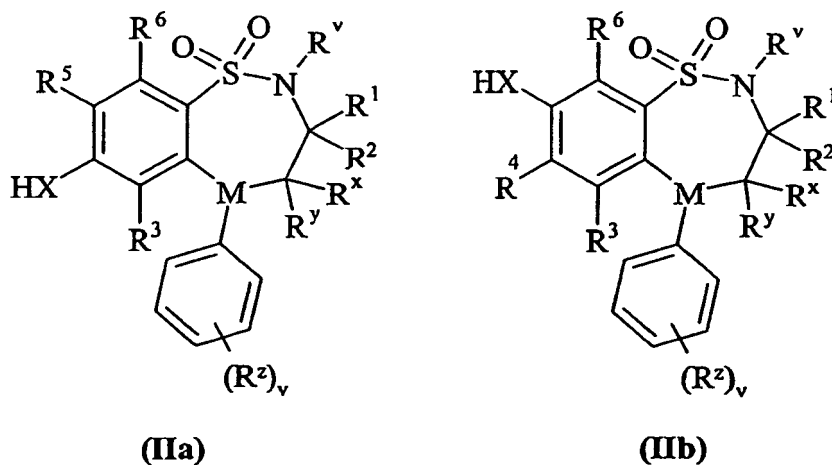
[0029] In another aspect of the invention, preferred compounds of the invention are any one of the examples or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

[0030] Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

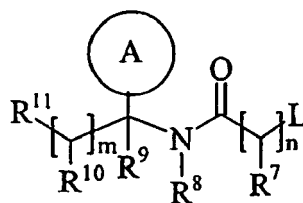
[0031] Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

Process 1): for compounds of formula (I) wherein X is -O-, -NR^a or -S-; reacting a compound of formula (IIa) or (IIb):

[0032]



with a compound of formula (III):

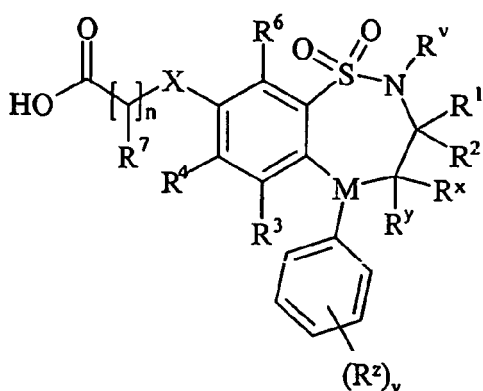


(III)

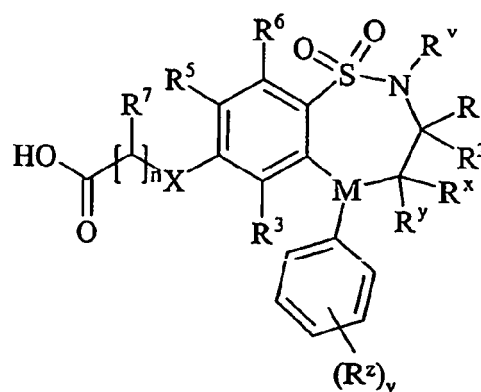
wherein L is a displaceable group;

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

[0033]

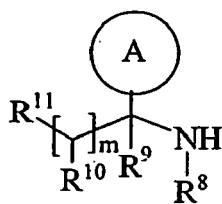


(IVa)



(IVb)

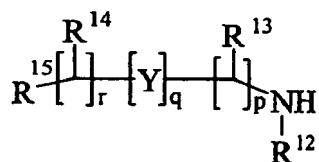
or an activated derivative thereof; with an amine of formula (V):



(V);

Process 3): for compounds of formula (I) wherein R¹¹ is a group of formula (IB); reacting a compound of formula (I) wherein R¹¹ is carboxy with an amine of formula (VI):

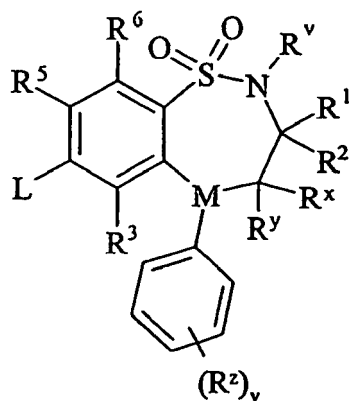
[0034]



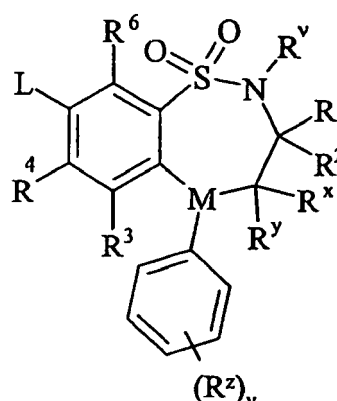
(VI)

Process 4) for compounds of formula (I) wherein one of R⁴ and R⁵ are independently selected from C₁₋₆alkylthio optionally substituted on carbon by one or more R¹⁷; reacting a compound of formula (VIIa) or (VIIb):

[0035]



(VIIa)



(VIIb)

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



wherein R^m is C₁₋₆alkylthio optionally substituted on carbon by one or more R¹⁶;

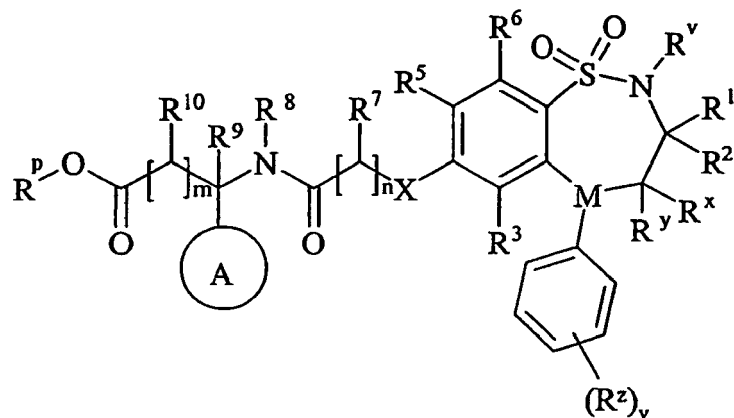
Process 5): for compounds of formula (I) wherein R¹¹ is carboxy; deprotecting a compound of formula (IXa):

[0036]

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(IXa)

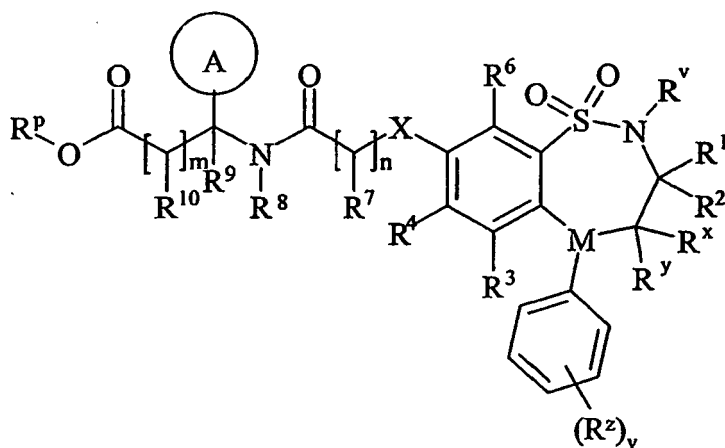
or (IXb):

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(IXb)

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

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

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[0037]

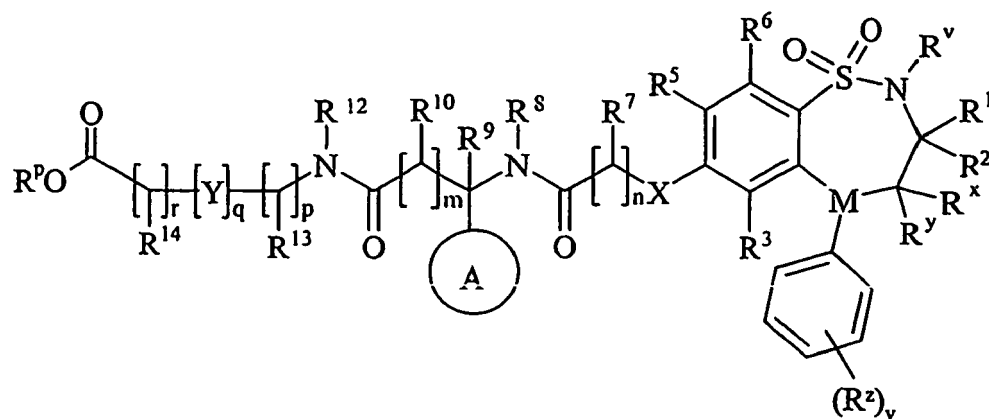
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(Xa)

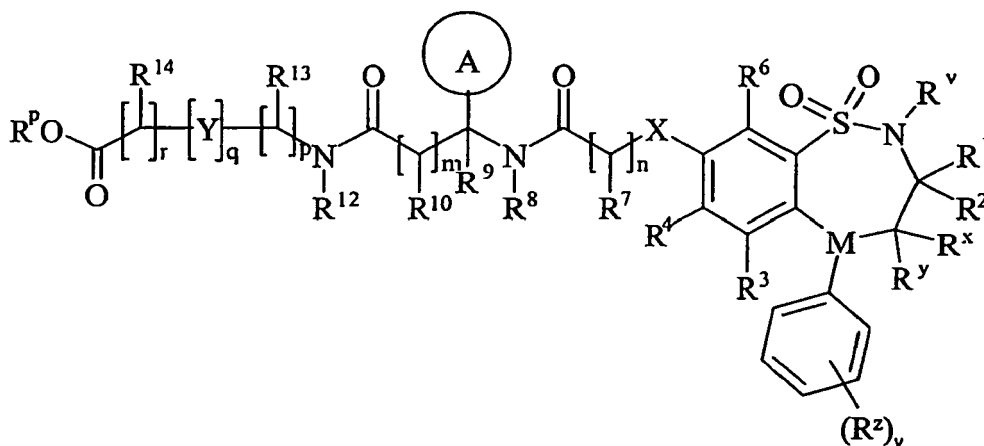
or (Xb):

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(Xb)

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

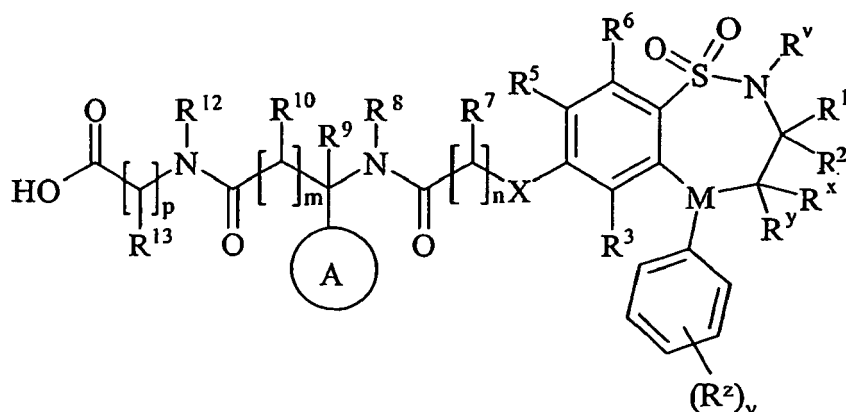
Process 7): for compounds of formula (I) wherein R^{11} is a group of formula (IB) and $N(R^n)C(O)-$; reacting an acid of formula (Xla):

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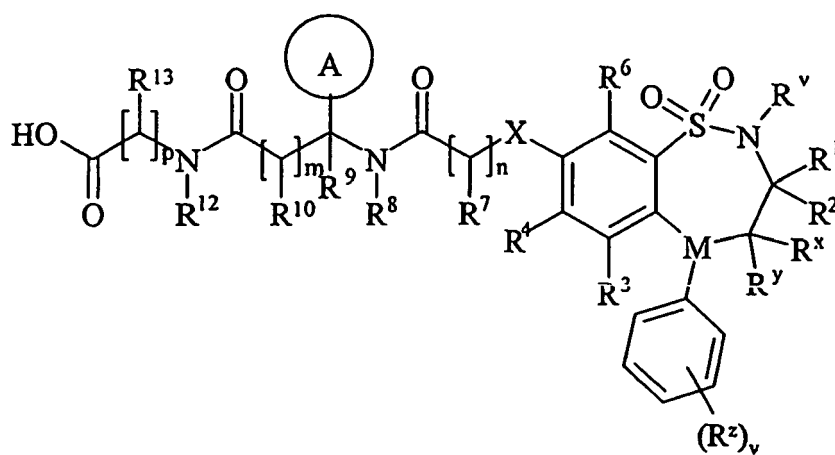
[0038]

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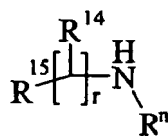
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or (XIb):



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



50 and thereafter if necessary or desirable:

- 55
- 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.

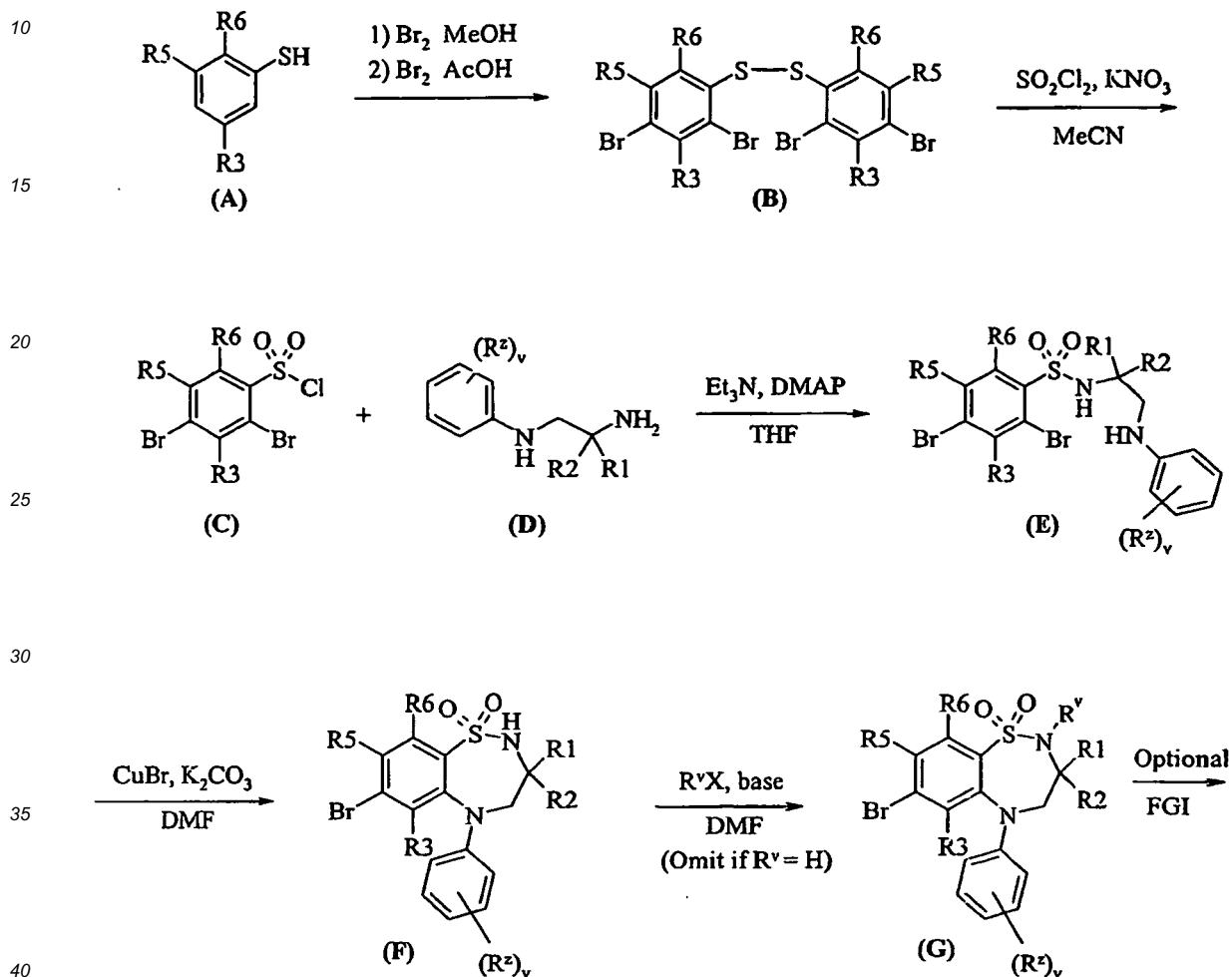
[0039] L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

[0040] R^p together with the -OC(O)- group to which it is attached forms an ester. Preferably R^p is methyl or ethyl. More

preferably R^p is methyl. In another aspect of the invention R^p is C₁₋₆alkyl or phenylC₁₋₆alkyl, preferably C₁₋₄alkyl or benzyl, more preferably *t*-butyl, methyl, ethyl or benzyl.

[0041] Specific reaction conditions for the above reactions are as follows.

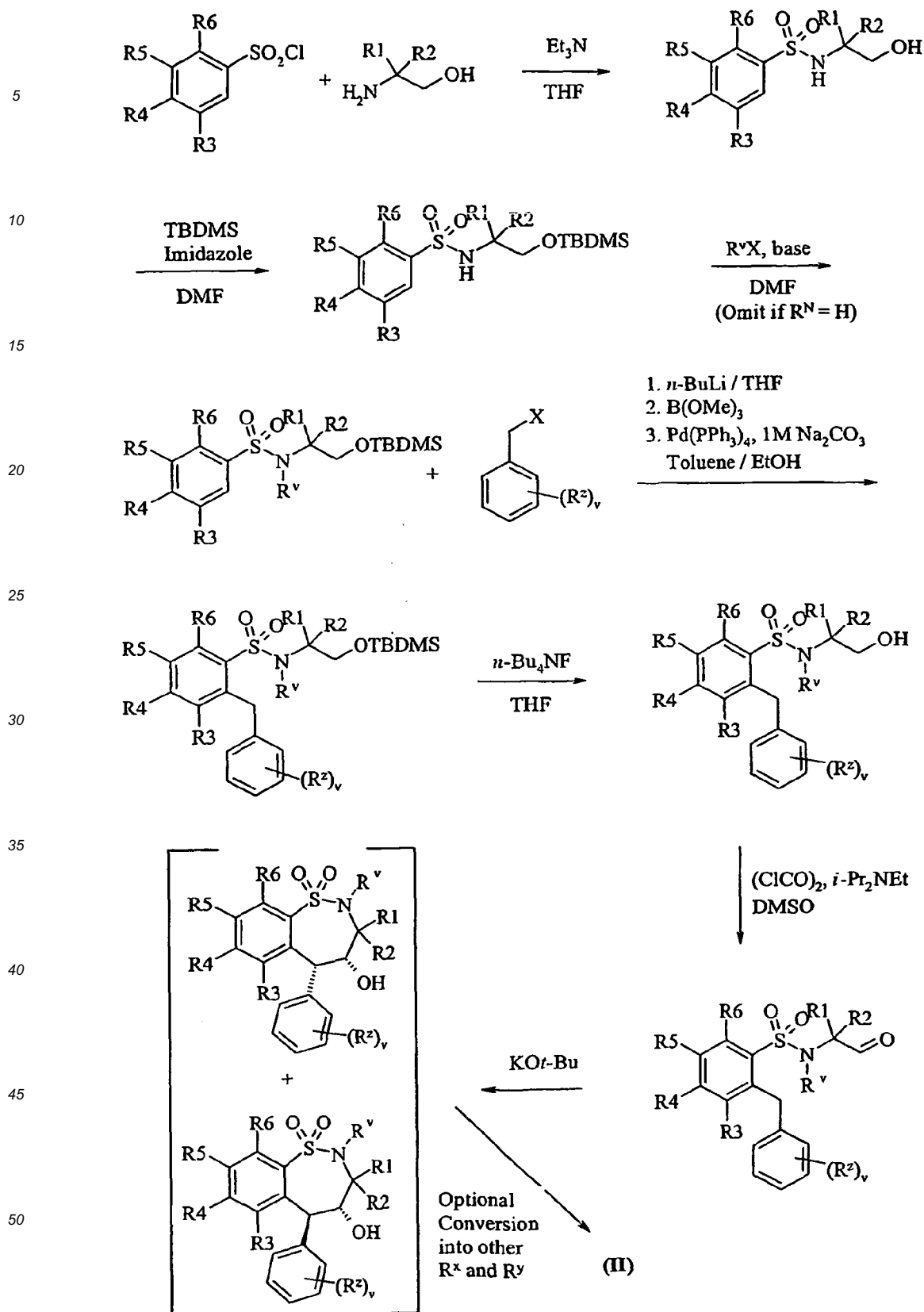
[0042] The bicyclic ring systems of the present invention may be assembled according to Scheme Ia or Scheme Ib. The skilled person will appreciate to make any of the above identified intermediates the value of R⁴ or R⁵ in the following schemes would be replaced with the appropriate group. For example, to synthesize a compound of formula (IIa) R⁴ would be HX in the following scheme.



Scheme Ia

[0043] Wherein FGI is functional interconversion of the Br into other values of R⁴ using procedures known to the skilled person.

[0044] Compounds of formula (A) and (D) are commercially available, or they are known in the literature, or they may be prepared by standard processes known in the art.



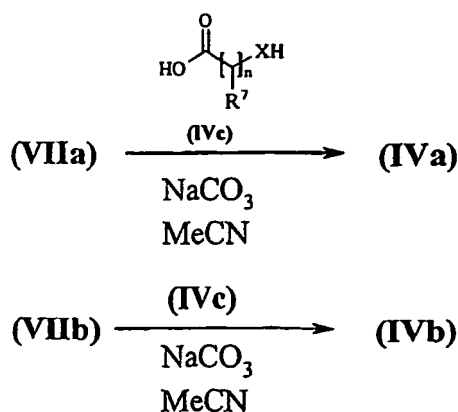
Scheme 1b

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

[0045] Compounds of formula (III) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art. *Process 2*) and *Process 3*) and *Process 7*): Acids and amines may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

[0046] 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.

[0047] Compounds of formula (IVa) or (IVb) wherein X=O-, -NR^a, -S- may be prepared according to Scheme 2:

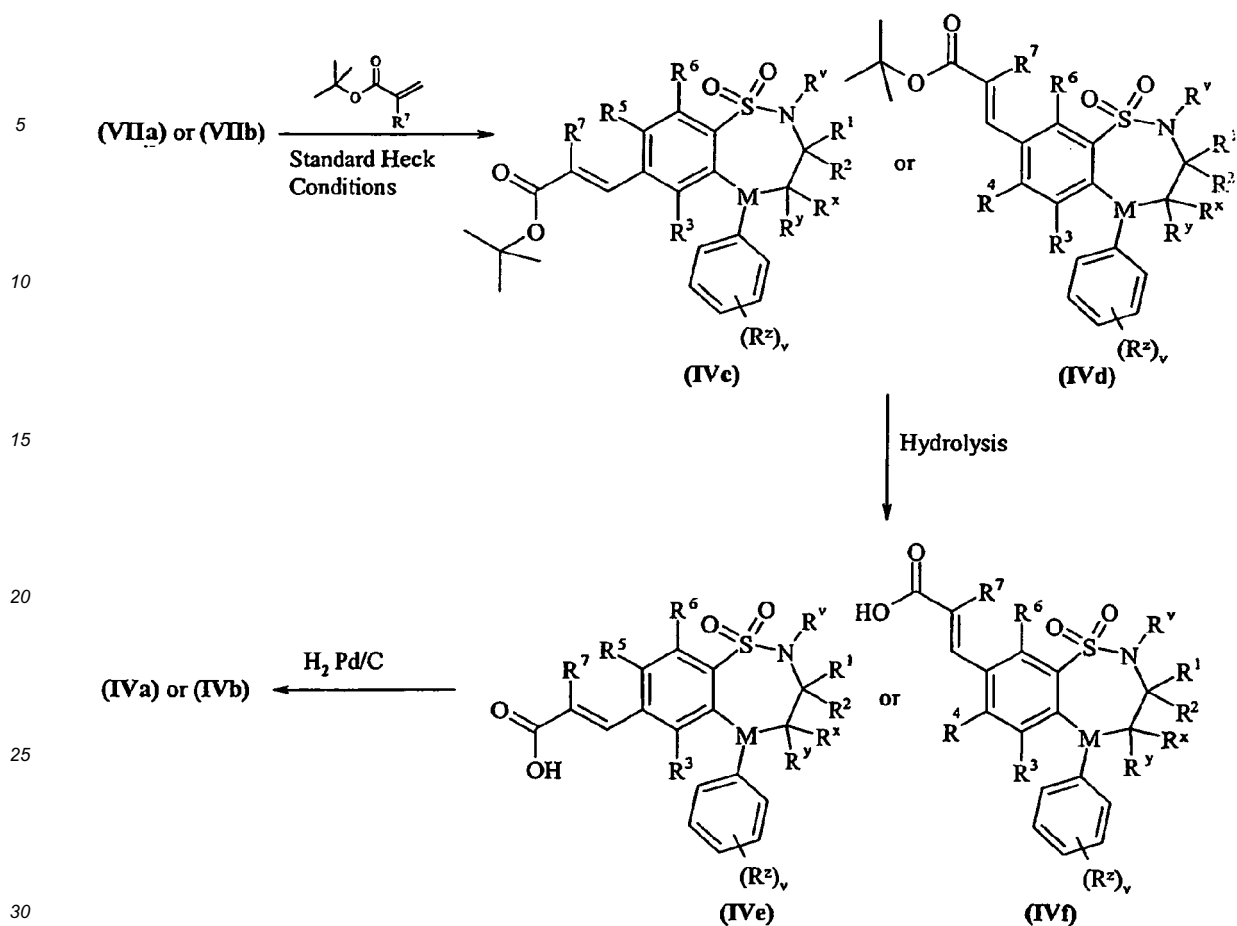


Scheme 2

[0048] Wherein L in (VIIa) and (VIIb) is a displaceable group e.g. bromo, chloro, fluoro, mesyl or tosyl and wherein X is -O-, -S-, NR^a (optionally for -SO- and -SO₂- followed by the oxidation step of Process 1).

[0049] Compounds of formula (IVa) and (IVb) where X is -SO- or -SO₂- may be prepared by oxidising the resulting compounds of formula (IVa) and (IVb) from *Scheme 2* where X is -S-.

[0050] Compounds of formula (Va) or (Vb) wherein X is -CH₂- and n is 1 may be prepared according to *Scheme 3*.



Scheme 3

[0051] The skilled person will appreciate that the above reaction scheme may be manipulated to prepare compounds of formula (Va) or (Vb) where n is 2 or 3.

[0052] Compounds of formula (Xla) and (Xlb) may be prepared by manipulations known to the skilled person of the processes described herein.

[0053] Compounds of formula (IVc), (V), (VI), (XII) and (VII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 4): Compounds of formula (VIIa) and (VIIb) may be reacted with thiols of formula (VIII) in the presence of base, for example an inorganic base such as sodium carbonate or an organic base such as Hunigs base, in the presence of a suitable solvent such as DMF or THF at a temperature in the range of 0°C to reflux.

[0054] Compounds of formula (VIIa) and (VIIb) may be prepared by any of the procedures above for the preparation of compounds of formula (I), but wherein one of R⁴ and R⁵ is L.

[0055] Compounds of formula (VIII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

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

[0056] Esters of formula (IXa), (IXb), (Xa) and (Xb) may be prepared by any of the procedures above for the preparation of compounds of formula (I), but wherein R¹¹ or R¹⁵ is C₁₋₄alkoxycarbonyl.

[0057] 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.

[0058] 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. A particular instance where a protecting group may be used is in protecting the nitrogen in the 2-position of the benzothiadiazepine ring during the synthesis of certain intermediates.

[0059] Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[0060] 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 such 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.

[0061] 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.

[0062] 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.

[0063] The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

[0064] 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).

[0065] 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.

[0066] 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.

[0067] In general the above compositions may be prepared in a conventional manner using conventional excipients.

[0068] 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 0.02-100 mg/kg, preferably 0.02-50 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg, particularly 0.1-10 mg/kg is employed. In another aspect a daily dose in the range 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.

[0069] According to a further aspect of the present invention there is provided a compound of the formula (I), or a

pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

5 [0070] 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.

[0071] 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.

10 [0072] 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.

[0073] 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.

15 [0074] 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, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL) in a warm-blooded animal, such as man.

20 [0075] According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks in a warm-blooded animal, such as man.

25 [0076] 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.

30 [0077] 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.

35 [0078] 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.

40 [0079] 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, hypertriglyceridemia, 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.

45 [0080] 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, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

[0081] 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.

[0082] 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.

[0083] The size of the dose required for the therapeutic or prophylactic treatment will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 0.1-50mg/kg preferably 0.1-10 mg/kg is envisaged.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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.

5 [0092] 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.

10 [0093] 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.

15 [0094] 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.

20 [0095] 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.

25 [0096] 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.

30 [0097] 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.

[0098] 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.

35 [0099] 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.

[0100] 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.

40 [0101] 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.

45 [0102] 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.

50 [0103] 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.

5 **[0104]** 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;
- 10 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.

[0105] According to a further aspect of the present invention there is provided a kit comprising:

- 15 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.

20 **[0106]** 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;
- 25 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.

30 **[0107]** 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.

[0108] 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 wami-blooded animal, such as man.

35 **[0109]** 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.

40 **[0110]** 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.

45 **[0111]** 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.

[0112] 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.

50 **[0113]** 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.

[0114] According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a bile acid binder, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

[0115] 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.

[0116] 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);
- > an antihypertensive compound for example an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic 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.

[0117] 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, benzoilcaptopril, 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.

[0118] Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula (I) include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

[0119] In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to WY-14643, clofibrate, fenofibrate, bezafibrate, GW 9578, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl] propanoic acid and pharmaceutically acceptable salts thereof. Additional suitable PPAR alpha and/or gamma agonists are NN622/Ragaglitazar and BMS 298585.

[0120] 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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.

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] Many of the intermediates described herein are novel and are thus provided as a further feature of the invention. For example compounds of formula **(IXa)**, **(IXb)**, **(Xa)** and **(Xb)** show IBAT inhibitory activity when tested in the above referenced *in vitro* test assay and are thus claimed as a further feature of the invention.

[0131] Thus in a further feature of the invention, there is provided a compound of formula **(IXa)**, **(IXb)**, **(Xa)** or **(Xb)**, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

[0132] Therefore according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(IXa)**, **(IXb)**, **(Xa)** or **(Xb)**, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

[0133] According to an additional aspect of the present invention there is provided a compound of the formula **(IXa)**, **(IXb)**, **(Xa)** or **(Xb)**, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

[0134] Thus according to this aspect of the invention there is provided a compound of the formula **(IXa)**, **(IXb)**, **(Xa)** and **(Xb)**, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use as a medicament.

[0135] According to another feature of the invention there is provided the use of a compound of the formula **(IXa)**, **(IXb)**, **(Xa)** or **(Xb)**, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof as defined hereinbefore in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

[0136] According to another feature of the invention there is provided the use of a compound of the formula **(IXa)**, **(IXb)**, **(Xa)** or **(Xb)**, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof as defined hereinbefore in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

[0137] According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(IXa)**, **(IXb)**, **(Xa)** or **(Xb)**, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

[0138] According to a further feature of this aspect of the invention there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(IXa)**, **(IXb)**, **(Xa)** or **(Xb)**, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

[0139] 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

[0140] 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 CD₃OD (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; LCMS were recorded on

a Waters ZMD, LC column xTerra MS C₈(Waters), detection with a HP 1100 MS-detector diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-detector diode array equipped; unless otherwise stated the mass ion quoted is (MH⁺);

(vi) unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Kromasil C₈, 7 μm, (Akzo Nobel); MeCN and de-ionised water 100 mM ammonium acetate as mobile phases, with suitable composition;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer 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 2g of silica, the silica being contained in a 6ml disposable syringe and supported by a porous disc of 54 Å 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:-

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

Example 1

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

[0141] To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 2; 0.020 g, 3.71*10⁻⁵ mol) in DCM (4 ml) was added (R)-α-[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 5; 0.013 g, 4.82*10⁻⁵ mol) and *N*-methylmorpholine (0.015 ml, 1.48*10⁻⁴ mol). The mixture was stirred for 5 min and then TBTU (0.015 g, 4.82*10⁻⁵ mol) was added. The reaction mixture was stirred overnight and then TFA (1.5 ml) was added. After 1 hour, the solution was diluted with toluene, before the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent. and freeze-dried, to give the title compound in 0.026 g (96 %) as a white solid. NMR (400 MHz, DMSO-d₆) 0.60-0.80 (m, 6H), 0.80-1.60 (m, 12H), 3.30 (dd (AB), 1H), 3.45 (dd (AB), 1H), 3.85 (brs, 2H), 4.70 (d (AB), 1H), 4.75 (d (AB), 1H), 5.60 (d, 1H), 6.90-7.50 (m, 12H), 8.00-8.10 (m, 1H), 8.55 (d, 1H).

Example 2

40 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)-α-[N-(carboxymethyl)carbamoyl] benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

[0142] To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3; 0.016 g, 3.16*10⁻⁵ mol) in DCM (4 ml) was added (R)-α-[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 5; 0.012 g, 4.54*10⁻⁵ mol) and *N*-methylmorpholine (0.015 ml, 1.48*10⁻⁴ mol). The mixture was stirred for 5 min and then TBTU (0.015 g, 4.82*10⁻⁵ mol) was added. The reaction mixture was stirred overnight and then TFA (1.5 ml) was added. After 1 hour, the solution was diluted with toluene, before the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent and freeze-dried, to give the title compound in 0.018 g (82 %) as a white solid. NMR (400 MHz, DMSO-d₆) 0.65-0.80 (m, 6H), 0.85-1.60 (m, 12H), 2.10 (s, 3H), 3.65 (dd (AB), 1H), 3.75 (dd (AB), 1H), 3.85 (brs, 2H), 4.65 (d (AB), 1H), 4.75 (d (AB), 1H), 5.60 (d, 1H), 6.55 (s, 1H), 6.90-7.50 (m, 11H), 8.45 (d, 1H), 8.50-8.60 (m, 1H).

Example 3

55 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-(N-((R)-α-[N-2-sulphoethyl)carbamoyl]-4-hydroxybenzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

[0143] To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothi-

adiazepine (Method 2; 0.050 g, 9.27×10^{-5} mol) in DMF (6 ml) was added 2-[[*(2R)*-2-amino-2-(4-hydroxyphenyl)ethanoyl]amino]ethanesulphonic acid (Method 6; 0.033 g, 1.20×10^{-4} mol) and *N*-methylmorpholine (0.041 ml, 3.72×10^{-4} mol). The mixture was stirred for 10 min and then TBTU (0.039 g, 1.21×10^{-4} mol) was added. The reaction mixture was stirred overnight and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent and freeze-dried, to give the title compound in 0.039 g (53 %) as a white solid. NMR (400 MHz, DMSO- d_6) 0.60-0.80 (m, 6H), 0.80-1.60 (m, 12H), 2.40-2.60 (m, 2H), 3.10-3.50 (m, 2H), 3.85 (brs, 2H), 4.70 (d (AB), 1H), 4.75 (d (AB), 1H), 5.25 (d, 1H), 6.70 (s, 1H), 6.75 (s, 1H), 6.85-7.80 (m, 10H), 8.15-8.25 (m, 1H), 8.45 (d, 1H), 9.40 (brs, 1H).

Example 4

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

[0144] A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3; 0.050 g, 0.099 mmol), *t*-butyl *N*-[[*(2R)*-2-amino-2-phenylethanoyl]-*o*-(*t*-butyl)-*L*-serinate (Method 14; 0.042 g, 0.120 mmol) and *N*-methylmorpholine (0.033 ml, 0.299 mmol) in DCM (4 ml) was stirred at RT for 10 min, after which TBTU (0.041 g, 0.128 mmol) was added. After 8h, the conversion was completed; *m/z*: 839.7. TFA (2 ml) was added and the reaction mixture was stirred for 12 hours. The solution was transferred to a separating funnel and washed twice with water and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.045 g (63 %) as a white solid. NMR (400 MHz, DMSO- d_6): 0.60-0.80 (6H, m), 0.85-1.60 (12H, m), 2.10 (3H, s), 3.40-3.65 (2H, m), 3.85 (2H, brs), 4.10-4.20 (1H, m), 4.70 (1H, d(AB)), 4.75 (1H, d(AB)), 5.70 (1H, d), 6.60 (1H, s), 6.85-7.50 (12H, m), 8.50 (1H, d), 8.60 (1H, d); *in/z*: 839.7.

Example 5

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

[0145] A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((*R*- α -carboxybenzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 0.055 g, 0.086 mmol), *L*-alanine, 1,1-dimethylethyl ester, hydrochloride (0.017 g, 0.098 mmol) and *N*-methylmorpholine (0.028 ml, 0.254 mmol) in DCM (5 ml) was stirred at RT for 10 min, after which TBTU (0.033 g, 0.103 mmol) was added. After 16h the conversion was complete; *m/z*: 767.4. TFA (2.5 ml) was added and the reaction mixture was stirred for 2 hours. The solution was diluted with toluene and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.044 g (72 %) as a white solid. NMR (400 MHz): 0.70-0.85 (6H, m), 0.90-1.70 (12H, m), 1.30 (3H, d), 2.10 (3H, s), 3.95 (2H, brs), 4.25-4.40 (1H, m), 4.60 (1H, d(AB)), 4.65 (1H, d(AB)), 5.60 (1H, s), 6.60 (1H, s), 6.95-7.50 (11H, m); *m/z*: 767.4.

Example 6

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

[0146] A solution of 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((*R*- α -carboxybenzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 0.055 g, 0.086 mmol), butanoic acid, 2-amino-, 1,1-dimethylethyl ester, hydrochloride, (2*S*)-(0.020 g, 0.102 mmol) and *N*-methylmorpholine (0.035 ml, 0.316 mmol) in DCM (5 ml) was stirred at RT for 10 min, after which TBTU (0.036 g, 0.112 mmol) was added. After 19h additional butanoic acid, 2-amino-, 1,1-dimethylethyl ester, hydrochloride, (2*S*)-(0.020 g, 0.102 mmol), *N*-methylmorpholine (0.035 ml, 0.316 mmol) and TBTU (0.036 g, 0.112 mmol) were added. After 68h, the conversion was completed; *m/z*: 781.5. TFA (2 ml) was added and the reaction mixture was stirred for 7h and then additional TFA (2 ml) was added. After 18h the reaction was completed. The solution was transferred to a separating funnel and washed twice with water and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1 M ammonium acetate buffer as eluent. The title compound was obtained in 0.026 g (41 %) as a white solid. NMR (400 MHz, DMSO- d_6): 0.65 (3H, t), 0.65-0.80 (6H, m), 0.85-1.75 (14H, m), 2.10 (3H, s), 3.80 (2H, brs), 3.95-4.10 (1H, m), 4.65 (1H, d(AB)), 4.75 (1H, d(AB)), 5.65 (1H, d), 6.55 (1H, s), 6.85-7.50 (12H, m), 8.50 (1H, d), 8.60 (1H, d); *m/z* 781.5.

Example 7

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

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[0147] A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 0.055 g, 0.086 mmol), S-methyl-L-cysteine tert-butyl ester (Pestic. Sci.; EN; 45; 4; 1995; 357-362; 0.020 g, 0.105 mmol) and N-methylmorpholine (0.035 ml, 0.317 mmol) in DCM (5 ml) was stirred at RT for 10 min, after which TBTU (0.036 g, 0.112 mmol) was added. After 19h additional S-methyl-L-cysteine tert-butyl ester (0.020 g, 0.105 mmol), N-methylmorpholine (0.035 ml, 0.317 mmol) and TBTU (0.036 g, 0.112 mmol) were added. After 68 h the conversion was complete; m/z: 811.6 (M-1)⁻. TFA (1.5 ml) was added and the reaction mixture was stirred for 7h and additional TFA (1.5 ml) was added. After 18 h the reaction was complete. The solution was transferred to a separating funnel and washed twice with water and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.042 g (65 %) as a white solid. NMR (400 MHz, DMSO-d₆): 0.65-0.80 (6H, m), 0.85-1.60 (12H, m), 1.85 (3H, s), 2.10 (3H, s), 2.60-2.80 (2H, m), 3.80 (2H, brs), 4.20-4.35 (1H, m), 4.65 (1H, d(AB)), 4.75 (1H, d(AB)), 5.65 (1H, d), 6.55 (1H, s), 6.85-7.50 (12H, m), 8.45 (1H, d), 8.65 (1H, d).

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Example 8

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

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[0148] N-Methylmorpholine (0.034 ml, 0.314 mmol), TBTU (0.033 g, 0.103 mmol) and L-asparagine, 1,1-dimethylethyl ester, monohydrochloride (0.021 g, 0.093 mmol) was successively added to a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 0.050 g, 0.078 mmol) in DCM (5 ml). After 2h there were still starting material left and additional N-methylmorpholine (0.035 ml, 0.314 mmol) and TBTU (0.033 g, 0.103 mmol) were added. After 12h the conversion was complete; m/z: 810.5. The solution was diluted with water (~5 ml) and then extracted three times with ether. The combined organic phases was dried over magnesium sulphate and concentrated. The residue was dissolved in a mixture of DCM (5 ml) and TFA (2.5 ml) and the solution was stirred for 21 hours. The solution was transferred to a separating funnel and washed with water and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.022 g (37 %) as a white solid. NMR (400 MHz, DMSO-d₆): 0.60-0.80 (6H, m), 0.80-1.60 (12H, m), 2.10 (3H, s), 2.25-2.70 (2H, m), 3.80 (2H, brs), 4.35-4.45 (1H, m), 4.65 (1H, d(AB)), 4.75 (1H, d(AB)), 5.60 (1H, d), 6.55 (1H, s), 6.70-7.60 (14H, m), 8.45 (1H, d), 8.55-8.70 (1H, m); m/z 810.5.

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Example 9

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

[0149] The title compound was synthesized using the procedure of Example 3 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3; 43mg, 0.085mmol). The solvent was evaporated after 3 hours and the crude product was purified by preparative HPLC (C8 column, 50x250mm) using a gradient (40/60 to 60/40) of MeCN/0.1M ammonium acetate buffer as eluent. Lyophilization yielded 38mg (57% yield) of the title compound. NMR (400MHz): 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 2.8-3.0 (m, 2H), 3.55-3.7 (m, 2H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.35 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H) 7.15-7.4 (m, 7H), 8.15 (t, 1H); m/z: 763.

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Example 10

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

[0150] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18; 50mg, 0.076mmol) was dissolved in DCM (4ml). Glycine tert-butyl ester (12mg, 0.091mmol), 2,6-lutidine (20 μ l, 0.15mmol) and TBTU (30mg, 0.091mmol) were added successively.

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After 3h DMF (2ml) was added and a clear solution was obtained. Glycine *tert*-butyl ester (0.04mmol), 2,6-lutidine (0.15mmol) and TBTU (2x0.03mmol) were added and the mixture was stirred for an additional 3h. The reaction mixture was concentrated and then extracted between aqueous KHSO₄ (0.05M, pH=1) and EtOAc (2x20ml). The organic phase was washed with brine, dried and concentrated to yield an oil containing the *tert*-butyl ester of the title compound. M/z: 769 and 786 (M+18 (NH₄⁺)). DCM (4ml) and TFA (1.5ml) were added. The mixture was stirred for 2 hours and was then concentrated and purified by preparative HPLC on a C8 column (50x250mm) using a gradient (20/80 to 50/50) of MeCN/0.1M ammonium acetate buffer as eluent. Lyophilization yielded the title compound in 52% (28mg). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.9 (ABq, 2H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.45 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H) 7.15-7.4 (m, 7H); m/z: 730 (M+18 (NH₄⁺)).

Example 11

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

[0151] The title compound was synthesized by the procedure described in Example 10 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18; 50mg, 0.076mmol) and *tert*-butyl L-alaninate hydrochloride. The intermediate *tert*-butyl ester of the title compound was confirmed. M/z: 783 and 800 (M+18 (NH₄⁺)). Hydrolysis and purification by preparative HPLC yielded the title compound in 20 mg (37% yield). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.3 (d, 3H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.35 (q, 1H), 4.6 (ABq, 2H), 5.45 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H) 7.15-7.4 (m, 7H); m/z: 744.

Example 12

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

[0152] The title compound was synthesized by the procedure described in Example 10 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18; 50mg, 0.076mmol) and *tert*-butyl *o*-(*tert*-butyl)-L-serinate hydrochloride. The intermediate ester was confirmed; m/z: 755. Hydrolysis and purification by preparative HPLC yielded the title compound in 19 mg (33% yield). M/z: 743 (M+1). NMR (400MHz): 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.65-3.8 (m, 2H), 3.95 (brs, 2H), 4.33 (t, 1H), 4.6 (ABq, 2H), 5.5 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H) 7.15-7.4 (m, 7H).

Example 13

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

[0153] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 50mg, 0.078mmol) was dissolved in 3ml DCM. Tetrabutylammonium taurine (88mg, 0.236mmol) was added and the mixture was stirred for 30 min. TBTU (30mg, 0.093mmol) was added and the mixture was stirred overnight. The solution was concentrated and purified by preparative HPLC using a C8 column (50x250mm). A gradient (20/80 to 60/40) of MeCN/0.1M ammonium acetate buffer was used as eluent. Lyophilization yielded 43mg of a product mixture, which was further purified by flash chromatography (5g) using a gradient of 3-20% MeOH in DCM as eluent. The fractions containing the title compound were collected and concentrated. MeOH and water were added and lyophilization yielded 17mg (29% yield). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 2.85-3.0 (m, 2H), 3.5-3.7 (m, 2H), 3:95 (brs, 2H), 4.6 (ABq, 2H), 5.45 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H) 7.15-7.45 (m, 10H); m/z: 747.

Example 14

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

[0154] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahy-

dro-1,2,5-benzothiadiazepine (Example 25; 50mg, 0.078mmol) was dissolved in 1ml DMF and 1ml DCM. *o*-*tert*-Butyl-(L)-threonine *tert*-butyl ester (22mg, 0.095mmol) and *N*-methylmorpholine (17 μ l, 0.154mmol) were added and the mixture was stirred for 20min. TBTU (30mg, 0.093mmol) was added and the solution was stirred for 2 hours and concentrated. DCM (20ml) was added and the solution was washed with 10ml brine, dried and concentrated to 3ml. The intermediate ester was confirmed; m/z: 853. TFA (0.5ml) was added and the solution was stirred overnight. Additionally 0.5ml TFA was added and after 3h the mixture was concentrated and purified by preparative HPLC on a C8 column (50x250mm). A gradient (20/80 to 60/40) of MeCN/0.1M ammonium acetate buffer was used as eluent. Lyophilization gave the title compound in 61 % yield (36mg). NMR (400MHz) 0.8 (t, 6H), 0.9 (d, 3H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.15-4.25 (m, 1H), 4.35 (d, 1H), 4.6 (ABq, 2H), 5.65 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), 7.1 (d, 2H), 7.15-7.4 (m, 6H), 7.5 (d, 2H); m/z: 741.

Example 15

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

[0155] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((*R*)- α -carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 50mg, 0.078mmol) was dissolved in 2ml DMF. *tert*-Butyl (L)-valinate (20mg, 0.095mmol) and *N*-methylmorpholine (17 μ l, 0.154mmol) were added and the mixture was stirred for 20min. TBTU (30mg, 0.093mmol) was added and the solution was stirred overnight. Additional *N*-methylmorpholine (8 μ l, 0.078mmol) and TBTU (3x5mg, 0.047mmol) were added and the mixture was stirred overnight and concentrated. The residue was purified by flash chromatography (2g) using EtOAc:hexane (3:7) as eluent. The collected fraction was washed with 5% NaHCO₃ (10ml), 0.1M KHSO₄ (15ml) and brine before it was dried and concentrated. The intermediate *tert*-butyl ester of the title compound was confirmed; m/z: 812 (M+18 (NH₄⁺)). DCM (4ml) and TFA (1.5ml) were added and the mixture was stirred overnight, concentrated and purified by preparative HPLC on a C8 column (50x250mm). A gradient (20/80 to 60/40) of MeCN/0.1M ammonium acetate buffer was used as eluent. Lyophilization gave the title compound in 31% yield (18mg). NMR (400MHz) 0.65-0.85 (m, 12H), 0.95-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.0-2.2 (m, 1H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.3 (d, 1H); 4.6 (ABq, 2H), 5.65 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), 7.2 (d, 2H), 7.25-7.4 (m, 6H), 7.5 (d, 2H); m/z: 739.

Example 16

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

[0156] The title compound was synthesized by the procedure given in Example 15 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((*R*)- α -carboxybenzyl) carbamoylmethoxy]-3,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 50mg, 0.078mmol) and *tert*-butyl (L)-leucinate (21mg, 0.095mmol). The DMF was removed and 20ml EtOAc was added and washed with NaHCO₃ (5%, 10ml), 0.1M KHSO₄ (15ml) and brine before it was dried and concentrated. The resulting residue was purified by flash chromatography as described. The intermediate *tert*-butyl ester of the title compound was confirmed; m/z: 826 (M+18 (NH₄⁺)). Hydrolysis and purification by preparative HPLC gave the title compound in 21 % yield (12mg). NMR (400MHz) 0.7 (dd, 6H), 0.75-0.85 (m, 6H), 0.95-1.2 (m, 6H), 1.25-1.7 (m, 9H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.3-4.4 (m, 1H), 4.6 (ABq, 2H), 5.55 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), 7.2 (d, 2H), 7.25-7.4 (m, 6H), 7.5 (d, 2H); m/z: 753.

Example 17

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

[0157] The title compound was synthesized by the procedure given in Example 15 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((*R*)- α -carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 50mg, 0.078mmol) and *tert*-butyl (L)-iso-leucinate (21mg, 0.095mmol). The DMF was removed and 20ml EtOAc was added and washed with NaHCO₃ (5%, 10ml), 0.1M KHSO₄ (15ml) and brine before it was dried and evaporated. No purification by flash chromatography was performed. The intermediate *tert*-butyl ester of the title compound was confirmed; m/z: 809. Hydrolysis and purification by preparative HPLC gave the title compound in 37% yield (22mg). NMR (400MHz) 0.65-1.4 (m, 22H), 1.4-1.5 (m, 2H), 1.5-1.7 (m, 2H), 1.75-1.85 (m, 1H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.25 (d, 1H), 4.6 (ABq, 2H), 5.6 (s, 1H), 6.6 (s, 1H), 7.05 (t, 1H), 7.2 (d, 2H), 7.25-7.4 (m, 6H), 7.45 (d, 2H); m/z: 753.

Example 18

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

[0158] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3; 295mg, 0.58mmol) was dissolved in 10 ml DCM. 4-(1-(R)-*t*-Butoxycarbonyl-1-aminomethyl)phenol (Method 7; 160mg, 0.72mmol), 2,6-lutidine (140 μ l, 1.20mmol) and TBTU (230mg, 0.72mmol) were added successively. The mixture was stirred for 3h. Additionally 4-(1-(R)-*t*-butoxycarbonyl-1-aminomethyl)phenol (10mg, 0.04mmol) was added and stirring was continued for 2h. DCM (20ml) was added and the solution was washed with NaHCO₃ (5%, 20ml), KHSO₄ (0.3M; 20ml), brine (20ml) before it was dried and concentrated to a volume of 10 ml. The *tert*-butyl ester of the title compound was confirmed; m/z: 729 (M+18 (NH₄⁺)). TFA (1.3ml) was added and the mixture was stirred for 4.5h and concentrated. The crude product was purified by preparative HPLC using a C8 column (50x500mm) and a gradient (40/60 to 70/30 over 40 min) of MeCN/0.1M ammonium acetate buffer as eluent. Lyophilization yielded the title compound in 77.5% (302mg). NMR (400MHz) 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.3 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H) 7.15-7.4 (m, 7H); m/z: 673 (M+18 (NH₄⁺)).

Example 19

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

[0159] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -{N-[(S)-1-(*t*-butoxycarbonyl)-4-(benzyloxycarbonylamino)butyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 8; 0.006 mg) was dissolved in DCM (0.2 ml), TFA (1 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. DCM and TFA were removed at reduced pressure and the residue was purified by preparative HPLC using MeCN/NH₄⁺ buffer 50/50 as eluent. The acetonitrile was evaporated and lyophilisation gave the title compound in 37% yield (21.9 mg). M/z: 754.4 and 752.4 (M-H)⁻.

Example 20

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

[0160] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -{N-[(S)-1-(*t*-butoxycarbonyl)-4-(benzyloxycarbonylamino)butyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 8; 0.006 mg) was dissolved in DCM (0.1ml), TFA (0.15 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. DCM and TFA were removed at reduced pressure and the residue was purified by preparative HPLC using MeCN/NH₄⁺ buffer 55/45 as eluent. The acetonitrile was evaporated and lyophilisation gave the title compound in 35% yield (2 mg). M/z: 888.7 and 886.7 (M-H)⁻.

Example 21

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

[0161] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[(S)-2-(*t*-butoxycarbonyl) pyrrolidin-1-ylcarbonyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 10; 41 mg, 0.052 mmol) was dissolved in DCM : TFA 4:1 (3 ml) and stirred for 3 hours. The reaction mixture was evaporated under reduced pressure. The residue was purified by preparative HPLC using an acetonitrile/ammonium acetate buffer gradient (5/95 to 100/0) as eluent. 26.5 mg (70%) of the title compound was obtained after lyophilisation. M/z 737.3034.

Example 22

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

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[0162] The title compound was synthesized from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-(*t*-butoxycarbonylmethyl)-*N*-methylcarbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 11) by the method of Example 21. NMR (500MHz, 2 rotamers 3:1 mixture):Major rotamer: 0.8 (brt, 6H), 1.0-1.24 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.51 (m, 2H), 1.56-1.68 (m, 2H), 2.09 (s, 3H), 3.0 (s, 3H) 3.75-4.21 (m, 4H), 4.60 (ABq, 2H), 6.01 (s, 1H), 6.58 (s,1H), 7.05 (t, 1H), 7.16-7.28 (m, 3H), 7.3-7.45 (m, 5H), 7.48 (brd, 2H) additional peaks from the minor rotamer at 2.14 (s), 3.0 (s), 4.56 (Abq), 5.81 (s), 6.61 (brs); m/z 711.4.

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Example 23

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

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[0163] The title compound was synthesized from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(R)- α -{*N*-[1-(R)-2-(R)-1-(*t*-butoxycarbonyl)-1-hydroxy-prop-2-yl]carbamoyl} benzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 12) by the method of Example 21. M/z 741.3.

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Example 24

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

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[0164] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(R)- α -carboxybenzyl} carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 50 mg, 0.078 mmol), aminomethanesulfonic acid (15 mg, 0.088 mmol) and *N*-methylmorpholine (17.2 μ l, 0.156 mmol) were dissolved in DMF (2ml). Tetrabutylammoniumhydrogensulfate (35 mg,0.103 mmol) was added and the mixture was heated for 15 minutes at 60°C. After removing heating TBTU (45 mg, 0.14 mmol) was added. The reaction mixture was stirred in room temperature 40 minutes then 60°C for one hour. After being stirred overnight 35 mg TBTU was added. After 6 hours 29 mg TBTU in small portions was added and the reaction mixture was stirred overnight. The mixture was evaporated under reduced pressure. The product was purified using preparative HPLC using an acetonitrile/ammonium acetate buffer gradient (5/95 to 100/0) as eluent. To give 10 mg (17%) of the title compound as a ammonium salt. NMR (600MHz) 0.77 (brt, 6H), 0.97-1.22 (m, 6H), 1.24-1.48 (m, 4H), 1.51-1.68 (m, 2H), 2.08 (s, 3H), 3.7-4.18 (m, 2H), 4.24 (d, 1H), 4.39 (d, 1H), 4.62 (ABq, 2H), 5.62 (s, 1H), 6.58 (brs, 1H), 7.02 (brt, 1H), 7.14-7.23 (m, 2H), 7.24-7.36 (m, 6H), 7.45 (d, 2H); m/z 732.9.

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Example 25

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

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[0165] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(R)- α -(*t*-butoxycarbonyl)benzyl] carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 9; 762 mg, 1.09 mmol) was dissolved in a mixture of TFA (6.65 ml) and triethylsilane (0.350 ml). The reaction mixture was stirred for one hour and then evaporated under reduced pressure to give the title compound in a quantitative yield (714 mg). NMR (500MHz): 0.8 (brt, 6H), 0.96-1.25 (m, 6H), 1.25-1.4 (m, 2H),1.42-1.51 (m, 2H), 1.57-1.69 (m, 2H), 2.11 (s, 3H), 3.8-4.15 (m, 2H), 4.66 (ABq, 2H), 5.49-5.53 (m, 1H), 6.61 (s, 1H), 7.06 (t, 1H), 7.18-7.26 (m, 2H), 7.28-7.45 (m, 8H), 8.35 (d, NH); m/z 640.2.

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Example 26

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

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[0166] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(R)- α -carboxy-4-hydroxybenzyl} carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18; 100mg, 0.152mmol) was dissolved in 3ml DMF. *o*-*tert*-Butyl-(L)-threonine *tert*-butyl ester (50mg, 0.216mmol) and *N*-methylmorpholine (34 μ l, 0.309mmol) were added and

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

Example 27

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

[0167] The title compound was synthesized by the procedure described in Example 26 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18; 70mg, 0.108mmol) and tert-butyl (L)-valinate (31mg, 0.148mmol). The intermediate *tert*-butyl ester of the title compound was confirmed. M/z: 811. Hydrolysis and purification by preparative HPLC yielded the title compound in 56 mg (69% yield). NMR (400MHz) 0.7-0.75 (m, 16H), 0.79 (t, 6H), 0.96-1.24 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.54-1.7 (m, 2H), 2.0-2.2 (m, 1H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.22 (d, 1H), 4.6 (ABq, 2H), 5.54 (s, 1H), 6.58 (s, 1H), 6.75 (d, 2H), 7.03 (t, 1H), 7.2 (d, 2H), 7.23-7.37 (m, 5H); m/z: 755.

Example 28

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

[0168] The title compound was synthesized by the procedure described in Example 26 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18; 36mg, 0.054mmol) and tert-butyl (L)-norvalinate hydrochloride (16mg, 0.076mmol). The intermediate *tert*-butyl ester of the title compound was confirmed. M/z: 811. Hydrolysis and purification by preparative HPLC yielded the title compound in 23 mg (56% yield). NMR (400MHz) 0.7-0.85 (m, 9H), 0.97-1.22 (m, 8H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.5-1.8 (m, 4H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.27 (dd, 1H), 4.6 (ABq, 2H), 5.45 (s, 1H), 6.58 (s, 1H), 6.75 (d, 2H), 7.03 (t, 1H), 7.19 (d, 2H), 7.23-7.37 (m, 5H); m/z: 755.

Example 29

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

[0169] A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18; 0.075 g, 0.114 mmol), butanoic acid, 2-amino-, 1,1-dimethylethyl ester, hydrochloride, (2S)-(0.031 g, 0.160 mmol) and N-methylmorpholine (0.050 ml, 0.457 mmol) in DMF (4 ml) was stirred at RT for 10 min, after which TBTU (0.048 g, 0.149 mmol) was added. After 1h, the conversion to the ester was complete. M/z: 797.4. The solution was diluted with toluene and then concentrated. The residue was dissolved in a mixture of DCM (5 ml) and TFA (2 ml) and the mixture was stirred for 7h. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a gradient of 20-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.056 g (66 %) as a white solid. NMR (400 MHz, DMSO-d₆): 0.70 (3H, t), 0.70-0.80 (6H, m), 0.85-1.75 (14H, m), 2.10 (3H, s), 3.80 (2H, brs), 4.00-4.15 (1H, m), 4.65 (1H, d(AB)), 4.70 (1H, d(AB)), 5.50 (1H, d), 6.60 (1H, s), 6.65-7.40 (11H, m), 8.35 (1H, d), 8.50 (1H, d) 9.40 (1H, brs).

Example 30

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

[0170] A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl) carbamoyl-

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methoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18, 0.075 g, 0.114 mmol), S-methyl-L-cysteine tert-butyl ester (Pestic. Sci.; EN; 45; 4; 1995; 357-362; 0.031 g, 0.160 mmol) and N-methylmorpholine (0.050 ml, 0.457 mmol) in DMF (4 ml) was stirred at RT for 10 min, after which TBTU (0.048 g, 0.149 mmol) was added. After 1h, the conversion to the ester was complete. M/z: 829.5. The reaction mixture was diluted with formic acid (15 ml) and stirred at 50 °C for 17h. The solution was diluted with toluene and then concentrated. The residue was purified by preparative HPLC using a gradient of 20-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.070 g (79 %) as a white solid. NMR (400 MHz, DMSO-d₆): 0.605-0.80 (6H, m), 0.80-1.60 (12H, m), 1.85 (3H, s), 2.10 (3H, s), 2.60-2.80 (2H, m), 3.85 (2H, brs), 4.15-4.30 (1H, m), 4.65 (1H, d(AB)), 4.70 (1H, d(AB)), 5.50 (1H, d), 6.60 (1H, s), 6.60-7.35 (11H, m), 8.30 (1H, d), 8.40 (1H, d), 9.40 (1H, brs).

Example 31

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

[0171] A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methyl-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 5; 0.050 g, 0.105 mmol), (R)-α-[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 86 of WO 02/50051; 0.039 g, 0.148 mol) and N-methylmorpholine (0.046 ml, 0.417 mmol) in DCM (4 ml) was stirred at RT for 20 min, after which TBTU (0.044 g, 0.137 mmol) was added. After 1h, the conversion to the ester (m/z: 721.2 (M+1)⁺) was completed. The solvent was removed under reduced pressure and the residue was dissolved in formic acid (5 ml). The solution was stirred for 17 hours and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.044 g (63 %) as a white solid. NMR (400 MHz, DMSO-d₆): 0.65-0.80 (6H, m), 0.85-1.60 (12H, m), 2.10 (3H, s), 3.40-3.65 (2H, m), 3.70 (2H, bs), 4.60 (1H, d(AB)), 4.70 (1H, d(AB)), 5.55 (1H, d), 6.70 (1H, s), 6.80-7.50 (12H, m), 8.20-8.30 (1H, m), 8.55 (1H, d).

Example 32

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

[0172] A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methyl-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 16; 0.050 g, 0.105 mmol), (R)-α-[N-[(S)-1-(*t*-butoxycarbonyl)propyl]carbamoyl]-4-hydroxybenzylamine (Method 19; 0.045 g, 0.146 mmol) and N-methylmorpholine (0.047 ml, 0.427 mmol) in DCM (4 ml) was stirred at RT for 15 min, after which TBTU (0.044 g, 0.137 mmol) was added. After 17 h, the conversion to the ester (m/z: 765.7 (M+1)⁺) was completed. The solvent was removed under reduced pressure and the residue was dissolved in formic acid (5 ml). The solution was stirred for 3 days and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.017 g (23 %) as a white solid. NMR (400 MHz, DMSO) 0.60 (3H, t), 0.65-0.80 (6H, m), 0.85-1.75 (14H, m), 2.10 (3H, s), 3.75 (2H, bs), 3.90-4.05 (1H, m), 4.60 (1H, d(AB)), 4.65 (1H, d(AB)), 5.50 (1H, d), 6.65-7.30 (11H, m), 8.15 (1H, d), 8.40 (1H, d).

Example 33

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

[0173] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)-α-[N-((S)-1-[N-((S)-2-(*t*-butoxy)-1-(*t*-butoxycarbonyl)ethyl]carbamoyl)propyl)carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 20; 14 mg, 0.015 mmol) was dissolved in a mixture of DCM:TFA (3:1, 4 ml). The reaction mixture was stirred for 3.5 hours. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC using a MeCN/0.1 M ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound, 8 mg (65%). NMR (400 MHz): 0.7-0.83 (m, 9H), 0.9-1.40 (m, 8H), 1.40-1.52 (m, 2H), 1.52-1.70 (m, 3H), 1.77-1.88 (m, 1H), 2.11 (s, 3H), 3.8-4.1 (m, 4H), 4.29 (dd, 1H), 4.37 (t, 1H), 4.63 (ABq, 2H), 5.57 (s, 1H), 6.60 (s, 1H), 7.04 (brt, 1H), 7.20 (brd, 2H), 7.25-7.40 (m, 6H), 7.47 (d, 2H); m/z 812.3.

Example 34

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

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[0174] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[2-(*S*)-2-(methoxycarbonyl)-4-(*R*)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 21; 23 mg, 0.030 mmol) was dissolved in THF:H₂O (1:1, 1ml). Lithium hydroxide (monohydrate, 2 mg, 0.048 mmol) was added and the mixture was stirred for 2 hours. 50% Starting material remained so additional lithium hydroxide (3 mg) was added and left for an hour. The reaction was still not complete so further lithium hydroxide (2 mg) was added and the reaction was stirred overnight. The product was purified by preparative HPLC using a MeCN/0.1 M ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound, 12 mg (53%). M/z 753.04.

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Example 35

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

[0175] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[2-(*S*)-2-(*t*-butoxycarbonyl)azetidin-1-ylcarbonyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 22; 27.5 mg, 0.035 mmol) was dissolved in DCM (3 ml) and TFA (1ml) was added. The reaction was stirred for 1.5 hours. The solvent was evaporated under reduced pressure. The product was lyophilised to give 25 mg of the title compound. M/z 722.92.

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Example 36

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

[0176] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-{(S)-1-[*N*-{(S)-1-(*t*-butoxycarbonyl)ethyl]carbamoyl]ethyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 26; 34 mg, 0.041 mmol) was dissolved in a mixture of DCM:TFA (3:1,4 ml). The reaction mixture was stirred for 2 hours. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC using a MeCN/0.1 M ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound, 23 mg (72%). NMR (500 MHz, CD₃OD) 0.81 (bt, 6H), 0.88-1.54 (m, 16H), 1.56-1.71 (m, 2H), 2.11 (s, 3H), 3.8-4.2 (m, 2H), 4.33-4.42 (m, 2H), 4.66 (ABq, 2H), 5.55 (s, 1H), 6.61 (s, 1H), 7.07 (t, 1H), 7.22 (brd, 2H), 7.28-7.43 (m, 6H), 7.48 (d, 2H); m/z 782.1.

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Example 37

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

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

[0177] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(R)- α -carboxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 51mg, 0.080mmol) was dissolved in 2ml DMF. *t*-Butyl 4-methyl D,L-leucinate (Method 27; 23mg, 0.114mmol), *N*-methylmorpholine (18 μ l, 0.163 mmol) and TBTU (31mg, 0.097mmol) were added successively and the mixture was stirred for 2 hours. One drop of formic acid was added and the mixture was extracted between EtOAc and water. The aqueous phase (pH=3) was washed with EtOAc. The combined organic layers were washed with 5%NaHCO₃ and brine and was then dried with Na₂SO₄ and evaporated to dryness. The intermediate *t*-butyl ester of the title compound was confirmed. M/z: 823. DCM (2ml) and TFA (0.5ml) were added and the solution was stirred overnight. The mixture was concentrated and purified using preparative HPLC on a C8 column (50x250mm). A step gradient of MeCN (20-50%) in 0.1M ammonium acetate buffer was used as eluent. The two diastereomers separated under these conditions and they were collected and lyophilized separately. The first eluting diastereomer was obtained in 5mg (16%yield) and the second eluting diastereomer was obtained in 3mg (10% yield). The absolute configuration was assigned by comparison of NMR-spectra with related compounds and the first eluting diastereomer was found to be the (R,R)-diastereomer and the second eluting diastereomer was the (R,S)-diastereomer. M/z: 767. NMR of the (R,R)-diastereomer (440MHz): 0.79 (t, 6H), 0.95 (s, 9H), 0.99-1.22 (m, 6H), 1.25-1.39 (m, 2H), 1.40-1.51 (m, 2H),

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1.57-1.68 (m, 3H), 1.80 (dd, 1H), 2.08 (s, 3H), 3.95 (brs, 2H), 4.47 (dd, 1H), 4.63 (Abq, 2H), 5.61 (s, 1H), 6.58 (s, 1H), 7.04 (t, 1H), 7.20 (d, 2H), 7.25-7.35 (m, 6H), 7.43-7.47 (m, 2H). And NMR of the (R,S)-diastereomer (400MHz): 0.7 (s, 9H), 0.79 (t, 6H), 0.99-1.22 (m, 6H), 1.25-1.39 (m, 2H), 1.40-1.51 (m, 3H), 1.55-1.70 (m, 2H), 1.76 (dd, 1H), 2.12 (s, 3H), 3.95 (brs, 2H), 4.35 (dd, 1H), 4.60 (Abq, 2H), 5.54 (s, 1H), 6.60 (s, 1H), 7.04 (t, 1H), 7.20 (d, 2H), 7.24-7.37 (m, 6H), 7.39-7.46 (m, 2H).

Example 38

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

[0178] The title compound was prepared by the procedure of Example 37 starting from 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18; 53mg, 0.081mmol). The intermediate t-butyl ester was confirmed. M/z: 839. Only one of the diastereomers were collected from the preparative HPLC purification of the racemic title compound. It was obtained in 4mg (12%) and was assigned to be the (R,R)-diastereomer from comparison of NMR-data of related compounds. M/z: 783. NMR (400MHz): 0.79 (t, 6H), 0.95 (s, 9H), 0.99-1.22 (m, 6H), 1.25-1.39 (m, 2H), 1.40-1.51 (m, 2H), 1.56-1.68 (m, 3H), 1.79 (dd, 1H), 2.08 (s, 3H), 3.96 (brs, 2H), 4.47 (dd, 1H), 4.62 (Abq, 2H), 5.47 (s, 1H), 6.58 (s, 1H), 6.73 (d, 2H), 7.04 (t, 1H), 7.19 (d, 2H), 7.24-7.35 (m, 5H).

Example 39

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

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

[0179] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 18; 55mg, 0.084mmol) and methyl 3-(trimethylsilyl)alaninate (Method 28; 19mg, 0.108mmol) were dissolved in 3.5ml DMF. N-Methyl morpholine (18 μ l, 0.163mmol) and TBTU (32mg, 0.101mmol) were added successively and the mixture was stirred for 2 hours. One drop of formic acid was added and the mixture was then extracted between EtOAc and water. The aqueous phase (pH=3) was washed with EtOAc. The combined organic phases were washed with 1% NaHCO₃, brine and was then dried with Na₂SO₄ and concentrated. The intermediate methyl ester was confirmed. M/z: 813. THF (2ml), water (2ml) and LiOH (10mg, 0.418mmol) were added and the mixture was stirred over night. The mixture was purified using preparative HPLC on a C8 column (50x100mm). A gradient from 20 to 50% MeCN in 0.1M ammonium acetate buffer was used as eluent. The two diastereomers were separated under these conditions and were collected separately. Lyophilisation yielded 8mg (24% yield) of the first eluting diastereomer and 8.4mg (25% yield) of the second. The absolute configurations were assigned from comparison with NMR-data of related compounds and the first eluting diastereomer was found to be the (R,R)-diastereomer and the second eluting diastereomer was the (R,S)-diastereomer. M/z: 799. NMR of the (R,R)-diastereomer (400MHz): -0.16 (s, 9H), 0.79 (t, 6H), 0.9-1.22 (m, 8H), 1.25-1.40 (m, 2H), 1.40-1.52 (m, 2H), 1.55-1.68 (m, 2H), 2.11 (s, 3H), 3.95 (brs, 2H), 4.29-4.35 (m, 1H), 4.58 (Abq, 2H), 5.45 (s, 1H), 6.59 (s, 1H), 6.73 (d, 2H), 7.04 (t, 1H), 7.17-7.27 (m, 5H), 7.32 (t, 2H); and of the (R,S)-diastereomer (400MHz): 0.04 (s, 9H), 0.79 (t, 6H), 1.00-1.22 (m, 8H), 1.25-1.40 (m, 2H), 1.40-1.52 (m, 2H), 1.55-1.68 (m, 2H), 2.08 (s, 3H), 3.95 (brs, 2H), 4.40-4.46 (m, 1H), 4.62 (Abq, 2H), 5.49 (s, 1H), 6.58 (s, 1H), 6.73 (d, 2H), 7.04 (t, 1H), 7.14-7.36 (m, 7H).

Preparation of Starting Materials

[0180] The starting materials for the Examples above are either commercially available or are readily prepared by standard Methods from known materials. For Example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Method 1

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

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

[0181] To a suspension of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (prepared according to WO 98/38182; 0.218 g, 5.65×10^{-4} mol) in DMF (5 ml) was added NaSMe (0.210 g, 2.83 mmol, 95 %), and the mixture was stirred for 5 hours at 120°C. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.5 M HCl. The aqueous layer was extracted twice more with EtOAc and the combined organic extracts were dried (MgSO_4) and concentrated. The residue was dissolved in MeCN (7 ml) and ethyl bromoacetate (0.063 ml, 5.65×10^{-4} mol), tetrabutylammonium bromide (0.018 g, 5.65×10^{-5} mol) and sodium carbonate (0.250 g, 2.36 mmol) were added. The mixture was stirred over night at 80°C. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.5 M HCl. The organic layer was washed with brine, dried (MgSO_4) and concentrated. Flash chromatography on silica gel (Hex:EtOAc-6:1) gave the title compounds as colourless oils: 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, 0.187 g (58 %). NMR (400 MHz, CDCl_3) 0.70-0.80 (m, 6H), 0.90-1.70 (m, 15H), 3.90 (brs, 2H), 4.25 (q, 2H), 4.35 (brs, 1H), 4.65 (s, 2H), 6.95-7.40 (m, 7H); and 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, 0.024 g (8 %). NMR (400 MHz, CDCl_3) 0.70-0.85 (m, 6H), 0.90-1.70 (m, 15H), 2.10 (s, 3H), 3.90 (brs, 2H), 4.20 (brs, 1H), 4.25 (q, 2H), 4.65 (s, 2H), 6.55 (s, 1H), 6.95-7.35 (m, 6H).

Method 2

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

[0182] To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 1; 0.184 g, 3.24×10^{-4} mol) in EtOH (7 ml) was added NaOH (0.052 g, 1.30 mmol) and the mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.5 M HCl. The aqueous layer was extracted twice more with EtOAc and the combined organic extracts were washed with brine and concentrated. The crude product was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent and freeze-dried to give the title compound in 0.173 g (99 %) as a white solid. NMR (400 MHz, CD_3OD) 0.70-0.85 (m, 6H), 0.95-1.70 (m, 12H), 3.90 (brs, 2H), 4.50 (s, 2H), 6.90-7.40 (m, 7H).

Method 3

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

[0183] To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 1; 0.024 g, 4.49×10^{-5} mol) in EtOH (3 ml) was added NaOH (0.007 g, 1.80×10^{-4} mol) and the mixture was stirred over night. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent and freeze-dried. The title compound was obtained in 0.021 g (92 %) as a white solid. NMR (400 MHz, CD_3OD) 0.70-0.85 (m, 6H), 1.00-1.70 (m, 12H), 2.10 (s, 3H), 3.90 (brs, 2H), 4.55 (s, 2H), 6.60 (s, 1H), 6.90-7.35 (m, 6H).

Method 3

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

[0184] 1,1-Dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-methylthio-8-(*t*-butoxycarbonylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 25; 6.902 g, 10.11 mmol) was dissolved in a mixture of TFA (50 ml) and Et_3Si (8 ml) and the solution was stirred for 90 min at RT. The solvent was removed under reduced pressure and the residue was dissolved in *t*-BuOMe (100 ml). The organic phase was washed with water (20 ml) and then extracted three times with diluted NaOH (2x50 ml 0.5M). The combined aqueous extracts were acidified with diluted HCl (70 ml, 1M) (pH 1-2) and were then extracted twice with *t*-BuOMe (2x50 ml). The ether layer was washed with brine, dried over MgSO_4 and concentrated. 4.694 g (92 %) of the desire product as brown oil were obtained. NMR (400 MHz, CD_3OD): 0.70-0.85 (m, 6H), 1.00-1.25 (m, 6H), 1.25-1.50 (m, 4H), 1.55-1.70 (m, 2H), 2.10 (s, 3H), 3.90 (brs, 2H), 4.55 (s, 2H), 6.60 (s, 1H), 6.95-7.35 (m, 6H).

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

5 **[0185]** (2*R*)-{[(Benzyloxy)carbonyl]amino}(phenyl)acetic acid (10 g, 35.0 mmol) and *t*-butylglycine hydrochloride (6.3 g, 37.4 mmol) was dissolved in DCM (200 ml) with 2,6-lutidine (8.2 ml, 70.4 mmol). After stirring 5 min at 0°C TBTU (12.4 g, 38.6 mmol) was added and stirring was continued for 1.5 hours at 0°C and 3.75 hours at room temperature. The reaction mixture was washed with water (2 x 100 ml), dried (MgSO₄) and purified with flash chromatography (DCM:EtOAc 7:1→5:1) to give the title compound (13 g, 94 %). NMR (500 MHz, CDCl₃): 1.45 (s, 9H), 3.84 (d, 1H), 4.00 (dd, 1H), 5.10 (m, 2H), 5.28 (brs, 1H), 6.13 (brs, 1H), 6.23 (brs, 1H), 7.30-7.44 (m, 10H).

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

15 **[0186]** (R)-N-Benzyloxycarbonyl- α -[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 4; 12.8 g, 32.2 mmol) was dissolved in EtOH (99%, 200 ml) and toluene (50 ml). Pd/C (10%, 0.65 g) was added and hydrogenation was performed at atmospheric pressure for 5.5 hours at room temperature. The reaction mixture was filtered through diatomaceous earth and the solvents were evaporated to give the title compound (8.4 g, 99 %). NMR (600 MHz, CDCl₃): 1.45 (s, 9H), 3.93 (m, 2H), 4.54 (s, 1H), 7.31-7.42 (m, 5H), 7.51 (brs, 1H).

Method 62-[[2*R*]-2-Amino-2-(4-hydroxyphenyl)ethanol]amino]ethanesulphonic acid

25 **[0187]** *N*-Boc-(D)-4-hydroxyphenylglycine (1.00 g, 3.21 mmol) was dissolved in DMF (5 ml) and tetrabutylammonium taurine (2.36 g, 6.42 mmol) was added together with additionally 5 ml DMF. The resulting suspension was cooled on ice and TBTU (1.24 g, 3.85 mmol) was added. The ice bath was removed after 30 min and the mixture was stirred for 2 hours before it was filtered and concentrated. TFA in DCM (20%, 20ml) was added and the reaction mixture was stirred over night. Ethanol (20 ml) was added and the solvents evaporated. The crude product was refluxed in ethanol (100 ml) for 1 hour. Filtration yielded the pure title compound as a white solid, 626mg (71%). NMR (DMSO-d₆): 2.4-2.6 (m, 2H), 3.2-3.4 (m, 2H), 4.79 (s, 1H), 6.78 (d, 2H), 7.23 (d, 2H), 8.22 (t, 1H), 8.4 (brs, 3H), 9.7 (s, 1H).

Method 74-(1-(R)-*t*-Butoxycarbonyl-1-aminomethyl)phenol

35 **[0188]** Sulfuric acid (conc, 1ml) was added to a solution of D-(R)-4-hydroxyphenylglycine (1.0g, 6.0mmol) in 1,4-dioxane (8ml) placed in a Teflon[®] flask. The flask was cooled to -78°C and isobutylene (8g, 142.6mmol, condensed at -78°C) was added. The flask was placed in an autoclave at room temperature and stirred for 15h. The autoclave was cooled on ice before opened. The excess isobutylene was allowed to evaporate and the remaining solution was poured into aqueous NaOH (2M, 20ml) and was extracted with diethyl ether to remove formed by-product. The aqueous phase was slightly acidified to attain pH=10 using 2M HCl and was extracted with diethyl ether (3x75ml). The organic phase was washed with brine, dried and concentrated. The obtained product was recrystallized in diethyl ether/hexane. Mass: 0.55g (41%). NMR (600MHz, CDCl₃) 1.45 (s, 9H), 4.45 (s, 1H), 6.8 (d, 2H), 7.25 (d, 2H); m/z: 224.

Method 81,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -{N-[(S)-1-(*t*-butoxycarbonyl)-4-(benzyloxycarbonylamino)butyl]carbamoyl]benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

50 **[0189]** 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 53 mg, 0.083 mmol), *tert*-butyl N⁵-[(benzyloxy)carbonyl]-L-ornithinate (35 mg, 0.098 mmol), N-methyl morpholine (0.027 m) were dissolved in DCM (5 ml). The mixture was stirred at room temperature for 10 min, where after TBTU (32 mg, 0,10 mmol) was added and the reaction mixture was stirred for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by chromatography using DCM:EtOAc, 5:1 as eluent to give the title compound 57 mg (72%). M/z= 944.7 and 942.7 (M-H)⁻.

Method 9

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

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[0190] 1,1-Dioxo-3,3-dibutyl-*S*-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3; 627 mg, 1.24 mmol) was dissolved in DCM (25 ml), *tert*-butyl (2*R*)-amino(phenyl)acetate (308 mg, 1.48 mmol), 2,6-dimethylpyridine (288 μ l, 2.47 mmol) and TBTU (477 mg, 1.48 mmol) were added. The mixture was stirred for 3.5 hours. The reaction mixture was evaporated under reduced pressure. The product was purified using an Isolute column (10g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0 then 95:5. Approximately 694mg pure compound was collected. Another fraction was purified a second time using an Isolute column (10g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0,95:5 then 90:10. The pure fraction was added to the first fraction yielding 787 mg (91%) of the title compound. NMR (400MHz, CDCl₃) 0.78 (t, 6H), 0.92-1.12 (m, 4H), 1.12-1.46 (m, 6H), 1.54 (s, 9H), 1.58-1.72 (m, 2H), 2.14 (s, 3H), 3.8-4.05 (m, 2H), 4.32 (brs, NH), 4.56 (ABq, 2H), 5.56 (d, 1H), 6.56 (s, 1H), 7.04 (t, 1H), 7.10 (brd, 2H) 7.24-7.42 (m, 8H), 7.84 (d, NH); m/z 694.7 (M-H)⁺.

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Method 10

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

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[0191] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-*N*-[(*R*)- α -carboxybenzyl] carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 50 mg, 0.078 mmol) and *tert*-butyl L-prolinate (15 mg, 0.088 mmol) were dissolved in DCM (2ml) and *N*-methylmorpholine (17.2 μ l, 0.156 mmol) and TBTU (45 mg, 0.14 mmol) were added. The reaction mixture was stirred for 3 hours then additional *tert*-butyl L-prolinate (15 mg, 0.088 mmol) was added. The reaction mixture was stirred over night. The reaction mixture was put directly on an Isolute column (2g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0,95:5,90:10 then 80:20 to give the title compound (41 mg, 66%). M/z 793.2.

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Method 11

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

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[0192] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-*N*-[(*R*)- α -carboxybenzyl] carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 50 mg, 0.078 mmol) and *tert*-butyl *N*-methylglycinate (15 mg, 0.10 mmol) were dissolved in DCM (2ml) and *N*-methylmorpholine (17.2 μ l, 0.156 mmol) and TBTU (45 mg, 0.14 mmol) were added. The reaction mixture was stirred for 4 hours. The reaction mixture was put directly on an Isolute column (2g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0,95:5,90:10 then 80:20 to give the title compound (30 mg, 50%). M/z 767.4.

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Method 12

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

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[0193] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-*N*-[(*R*)- α -carboxybenzyl] carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 50 mg, 0.078 mmol) and *tert*-butyl (2*R*,3*R*)-3-amino-2-hydroxybutanoate (15 mg, 0.086 mmol) were dissolved in DCM (2ml) and DMF (1ml) and *N*-methylmorpholine (17.2 μ l, 0.156 mmol) and TBTU (45 mg, 0.14 mmol) were added. The reaction mixture was stirred for 4 hours. The reaction mixture was put directly on an Isolute column (2g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5, 90:10 then 80:20 to give the title compound (33 mg, 53%). M/z 797.3.

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Method 13

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

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[0194] (2*R*)-[(Benzyloxy)carbonyl]amino}(phenyl)acetic acid (2.0 g, 7.0 mmol) and *t*-butyl *O*-(*t*-butyl)-L-serinate (2.0

g, 7.9 mmol) and 2.6-lutidine were dissolved in DCM (30 ml). After stirring 5 min at 0°C TBTU (2.5 g, 7.8 mmol) was added and stirring was continued 30 min at 0°C and 4 h. at room temperature. The reaction mixture was washed with water (2 x 100 ml), dried and purified with flash chromatography (DCM) to give the title compound (3.3g, 97 %). NMR (300 MHz): 1.05 (s, 9H), 1.45 (s, 9H), 3.4-3.8 (m, 2H), 4.5 (brs, 1H), 4.85(s, 2H), 5.1 (s, 2H), 5.4 (s, 1H), 7.25-7.5 (m, 10 H).

Method 14

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

[0195] *t*-Butyl *N*-((2*R*)-2-[(benzyloxy)carbonyl]amino)-2-phenylethanoyl)-*o*-(*t*-butyl)-*L*-serinate (Method 13; 3.3 g, 6.8 mmol) was dissolved in EtOH (95%, 30 ml) and a catalytic amount of Pd/C (5%)(50% in water) was added and hydrogenation was performed at atmospheric pressure for 3 h. at room temperature. The reaction mixture was filtered through diatomaceous earth and the solvent was evaporated to give the title compound (2.35 g, 98 %). NMR (500 MHz): 1.1 (s, 9H), 1.45 (s, 9H), 3.45-3.8 (m, 2H), 4.5 (t, 1H), 4.55 (s, 1H), 4.85 (s, 2H), 7.3-7.5 (m, 5H).

Method 15

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

[0196] To a cooled solution (-78 °C) of 1,1-dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 23; 2.10 g, 3.41 mmol) in THF (50 ml) was added dropwise a solution of *n*-BuLi (2.35 ml, 3.75 mmol, 1.6 M in hexane). After stirring at -78 °C for 20 minutes, MeI (2.42 g, 17.1 mmol) was added. The mixture was stirred at -78 °C for 10 minutes and at room temperature for 18 hours. Diethyl ether (50 ml) was added and the organic phase was washed with 10 % NH₄Cl (aq, 50 ml) and brine (50 ml). After drying, filtration and concentration the crude product was subjected to flash chromatography (Hexane: EtOAc -95:5) to give 0.4 gram (21 %) of the title product as colourless oil. NMR (300 MHz, CDCl₃): 0.60-0.70 (m, 6H), 0.70-0.90 (m, 4H), 0.90-1.35 (m, 8H), 2.00 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.00-4.20 (m, 2H), 4.35-4.60 (m, 2H), 6.65-6.85 (m, 3H), 6.90-7.10 (m, 3H), 7.15-7.30 (m, 5H).

Method 16

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

[0197] To a solution (0 °C) of trifluoroacetic acid (30 ml) and triethylsilane (1.03 g, 8.85 mmol) was added a solution of 1,1-dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-methyl-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 15; 0.92 g, 1.77 mmol) in DCM (2 ml). The reaction mixture was stirred at room temperature for 30 minutes. After concentration of the reaction mixture, the residue was dissolved in diethyl ether (50 ml) and washed with water (25 ml) and sodium bicarbonate (10 %, 25 ml). After drying, filtration and concentration the crude product was subjected to flash chromatography on silica gel (Hexane: EtOAc -90:10) to give 0.58 g of a grey solid. To a solution (0°C) of this solid in dichloromethane (30 ml) was added dropwise BBr₃ in DCM (1M in DCM, 10.2 ml, 10.2 mmol). The reaction mixture was stirred at room temperature for 45 minutes and then it was washed with sodium bicarbonate (10 %, 25 ml) and water (25 ml). After drying, filtration and concentration the crude product (0.55g, grey solid) was dissolved in MeCN (30 ml). The solution was added K₂CO₃ (0.22g, 1.58 mmol) and tetra-*n*-butyl ammonium bromide (10 mg) followed by ethyl bromoacetate (0.25 g, 1.51 mmol). The reaction mixture was stirred at 80 °C for 1.5 h and then evaporated under reduced pressure. The residue was dissolved in EtOAc (50 ml) and washed with NH₄Cl (aq, 10 %) and brine. After drying, filtration and concentration the crude product was subjected to flash chromatography (Hex: EtOAc 9:1-8:2) to afford 0.58 g of an off-white solid. The solid was dissolved in THF: H₂O (4:1, 25ml) and LiOH (0.097 g, 2.31 mmol) was added. The reaction mixture was stirred at room temperature for 40 min. The mixture was evaporated under reduced pressure, dissolved in water (50 ml) and acidified with 1M HCl. The aqueous layer was extracted 2x with diethyl ether.

Evaporation of the solvent under reduced pressure gave 0.46 g (55%) of the title compound. NMR (300 MHz, acetone-*d*₆): 0.70-0.90 (m, 6H), 0.95-1.80 (m, 12H), 2.15 (s, 3H), 3.85-4.15 (m, 2H), 4.85 (s, 2H), 6.00 (s, 1H), 6.80 (s, 1H), 6.90-7.05 (m, 1H), 7.10-7.45 (m, 5H).

Method 17(R)-N-Benzyloxycarbonyl- α -carboxy-4-hydroxybenzylamine

5 **[0198]** (R)-*p*-Hydroxyphenylglycine (5.00 g, 29.9 mmol) was mixed with water (50 ml). Sodium bicarbonate (6.3g, 75.0 mmol) was added to the slurry and a white suspension was the result after 10 min stirring. Benzyl chloroformate (5.1 ml, 33.9 mmol) was added from a dropping funnel over 20 min and the mixture was stirred vigorously. After 2h, water (300ml) was added and the suspension was extracted with ether (200ml). The white solid did not dissolve and more water and ether were added. LC/MS indicated that the solid was product. The clear part of the aqueous phase was collected and acidified upon a white precipitate was formed. This was left over the weekend and was then filtered off. The remaining aqueous phase containing undissolved material was acidified as well and was extracted with EtOAc (3x). Also here a precipitate remained between the phases. This was collected with the organic layer. The EtOAc phase was evaporated. Toluene was added 2x to remove water. The two fractions of white solid were added together and recrystallized in DCM (200ml). The cooled mixture was filtered and 4.77g (53 %) of white solid were obtained. NMR (400 MHz, DMSO- d_6): 5.00 (1H, d), 5.00 (2H, s), 6.70 (2H, d), 7.05-7.50 (7H, m), 7.90 (1H, d).

Method 18(R)-N-Benzyloxycarbonyl- α -{N-[(S)-1-(*t*-butoxycarbonyl)propyl]carbamoyl}-4-hydroxybenzylamine

20 **[0199]** A solution of (R)-N-benzyloxycarbonyl- α -carboxy-4-hydroxybenzylamine (Method 17; 2.00 g, 6.64 mmol), (2S)-2-amino butanoic acid *t*-butyl ester (1.30 g, 6.64 mmol) and N-methylmorpholine (2.0 g, 19.8 mmol) in DCM (30 ml) was stirred at RT for 5 min, after which TBTU (2.60 g, 8.10 mmol) was added. The reaction mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (DCM: Acetone - 60:40). The product was crystallized from toluene (20 ml) giving 1.85 g of the desired product as a white solid. NMR (400 MHz): 0.80 (3H, t), 1.45 (9H, s), 1.50-1.80 (2H, m), 4.10-4.20 (1H, m), 5.05 (1H, d(AB)), 5.15 (1H, d(AB)), 6.75 (2H, d), 7.20-7.40 (7H, m).

Method 19(R)- α -{N-[(S)-1-(*t*-Butoxycarbonyl)propyl]carbamoyl}-4-hydroxybenzylamine

30 **[0200]** A mixture of (R)-N-Benzyloxycarbonyl- α -{N-[(S)-1-(*t*-butoxycarbonyl)propyl] carbamoyl}-4-hydroxybenzylamine (Method 18; 1.80 g, 4.07 mmol) and Pd/C (0.2 g, 5 %) in ethanol (30 ml, 95 %) was stirred under hydrogen gas at room temperature for 2 hours. The reaction mixture was filtered through silica gel (2g) and concentrated. The residue was dissolved in acetone (20 ml) and methanesulphonic acid (0.40 g, 4.16 mmol) was added. No crystallization was obtained and the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC using a gradient of 20-50% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.350 g (28 %) as a white solid. NMR (400 MHz, DMSO- d_6): 0.75 (3H, t), 1.40 (9H, s), 1.50-1.75 (2H, m), 2.70 (1H, s), 4.00-4.10 (1H, m), 4.30 (1H, s), 6.65 (2H, d), 7.15 (2H, d), 8.15 (1H, d).

Method 201,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[N-((S)-1-{N-[(S)-2-(*t*-butoxy)-1-(*t*-butoxycarbonyl)ethyl]carbamoyl]propyl)carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

45 **[0201]** 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[N-((S)-1-carboxypropyl) carbamoyl]benzyl)carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 6, 15 mg, 0.021 mmol), *tert*-butyl *O*-(*tert*-butyl)-L-serinate hydrochloride (5.4 mg, 0.021 mmol) and N-methylmorpholine (4.6 μ l, 0.042 mmol) was dissolved in DMF (1 ml). TBTU (12.5 mg, 0.039 mmol) was added and the mixture was stirred for one hour. *tert*-butyl *O*-(*tert*-butyl)-L-serinate hydrochloride (0.8 mg, 0.0031 mmol) was added and the mixture was stirred for a couple of minutes. The solvent was evaporated under reduced pressure and co-evaporated a few times with toluene. The product was purified using a pre-packed ISOLUTE column (Silica, 2g) and eluted with a stepwise gradient using DCM:EtOAc 100:0 (10 ml) 95:5 (10 ml) 90:10 (10 ml) 80:20 (10 ml), to give 14 mg of the title compound. M/z 924.7.

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Method 21

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

[0202] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 54 mg, 0.084 mmol), methyl (4R)-4-hydroxy-L-prolinate hydrochloride (18.4 mg, 0.10 mmol) and N-methylmorpholine (13.9 μ l, 0.13 mmol) was dissolved in DMF (2 ml). TBTU (32.5 mg, 0.101 mmol) was added and the mixture was stirred for three hours. The solvent was evaporated under reduced pressure. The product was purified two times using a pre-packed ISOLUTE column (Silica, 2g) and eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5, 90:10, 80:20 and 60:40, to give 23 mg of the title compound. M/z 767.0.

Method 22

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

[0203] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 50 mg, 0.078 mmol), *tert*-butyl (2S)-azetidine-2-carboxylate (17.4 mg, 0.111 mmol) and N-methylmorpholine (10.3 μ l, 0.094 mmol) was dissolved in DMF (2 ml). TBTU (30 mg, 0.094 mmol) was added and the mixture was stirred for four hours. The solvent was evaporated under reduced pressure. The product was purified using a pre-packed ISOLUTE column (Silica, 2g) and eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5, 90:10, 80:20, to give 27.5 mg of the title compound. M/z 777.6 (M-H).

Method 23

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

[0204] To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (prepared according to WO 98/38182; 0.200 g, 0.404 mmol) in MeCN (5 ml) where added *p*-methoxybenzyl chloride (0.066 ml, 0.486 mmol), CsI (0.010 g, 0.038 mmol) and Cs₂CO₃ (0.263 g, 0.807 mmol) and the mixture was stirred at 60 °C for 4h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.5M HCl (aq). The organic layer was washed with brine, dried over MgSO₄ and concentrated. The residue was filtered through silica gel (DCM: EtOAc -9:1) to give the title compound in 0.257 g (~quant) as an off-white solid. NMR (400 MHz, CDCl₃): 0.60-0.75 (m, 6H), 0.75-1.20 (m, 8H), 1.25-1.45 (m, 2H), 1.80-2.00 (m, 2H), 3.80 (s, 3H), 3.90 (s, 3H), 4.05-4.30 (m, 2H), 4.45-4.65 (m, 2H), 6.70-7.45 (m, 11H).

Method 24

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

[0205] NaSMe (0.150 g, 2.03 mmol, 95 %) was added to a solution of 1,1-dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 23; 0.249 g, 0.404 mmol) in DMF (5 ml). The mixture was stirred at RT for 2h, after which the temperature was raised to 80 °C and more NaSMe (0.090 g, 1.22 mmol) was added. After 20h at 80 °C the mixture was added water (5 ml) and 1M HCl (aq) (pH~4). The solution was extracted three times with Et₂O and the combined organic layers was washed with brine, dried over MgSO₄ and concentrated. The crude product was purified by flash chromatography on silica gel (Hex: EtOAc-4:1), which gave the title compound in 0.188 g (82%) as tan solid. NMR (500 MHz, CDCl₃): 0.60-0.75 (m, 6H), 0.75-1.20 (m, 8H), 1.25-1.40 (m, 2H), 1.80-2.00 (m, 2H), 2.20 (s, 3H), 3.80 (s, 3H), 4.20 (brs, 2H), 4.50 (brs, 2H), 6.05 (brs, 1H), 6.75-6.85 (m, 3H), 7.00-7.10 (m, 3H), 7.20-7.35 (m, 4H), 7.50 (s, 1H).

Method 25

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

[0206] A solution of 1,1-dioxo-2-(4-methoxybenzyl)-3,3-dibutyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-

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1,2,5-benzothiadiazepine (Method 24; 4.487 g, 7.889 mmol) in MeCN (100ml) was added t-butyl bromide (0.262g, 0.813 mmol), t-butyl bromoacetate (1.46ml, 9.880 mmol) and potassium carbonate (anhydrous, 3.28g, 23.7 mmol) in this order. The mixture was heated to 55°C for 2.5h, after which it was cooled to RT and left stirring over night. The solvent was evaporated until a yellowish slurry remained, which was extracted between diethyl ether (150ml) and water (100ml). The aqueous phase was washed with ether (100ml) and the combined ether layers were washed with 0.1M KHSO₄ (aq, 100ml), brine (100ml) and were dried. The ether was removed under reduced pressure and the beige solid obtained was dried under reduced pressure for 4h (5.355 g, 99 %). NMR (400 MHz, CDCl₃): 0.60-1.25 (m, 14H), 1.25-1.40 (m, 2H), 1.50 (s, 9H), 1.75-2.00 (m, 2H), 2.10 (s, 3H), 3.80 (s, 3H), 4.20 (brs, 2H), 4.50 (brs, 2H), 4.60 (s, 2H), 6.45 (s, 1H), 6.75-6.85 (m, 2H), 7.00-7.15 (m, 3H), 7-20-7.40 (m, 5H).

Method 26

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

[0207] 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)-α-carboxybenzyl] carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Example 25; 58 mg, 0.091 mmol), *tert*-butyl L-alanyl-L-alaninate hydrochloride (27.5 mg, 0.11 mmol) and N-methylmorpholine (20 μl, 0.18 mmol) was dissolved in DMF (2 ml). TBTU (35 mg, 0.18 mmol) was added and the mixture was stirred for 2-3 hours. The solvent was evaporated under reduced pressure. The product was purified using a pre-packed ISOLUTE column (Silica, 2g) and eluted with a stepwise gradient using DCM:EtOAc 100:0, 95:5,90:10 and 80:20 to give 34 mg (45%) of the title compound. M/z 838.5.

Method 27

tert-Butyl 4-methylleucinate

[0208] 4-Methylleucine (500mg, 3.44mmol) was suspended in 10 ml *t*-butyl acetate. Perchloric acid (0.2ml, 3.49mmol) was added and the flask was stopped with a septum and stirred over night. Analysis was performed using TLC (DCM:MeOH, 9:1; staining with a ninhydrine/EtOH solution). The solution was poured into a flask containing 30ml EtOAc and 30 ml 5% Na₂CO₃. The aq-layer turned acidic and 2M NaOH was added until pH was approximately 7. The phases were separated and the aq-phase was washed with 2x30ml EtOAc. The combined organic phases were washed with brine, dried with Na₂SO₄ and evaporated. A oil was obtained which was co-evaporated with toluene and then with diethyl ether before being placed under vacuum for two days. Mass 665 mg (96% yield). NMR (CDCl₃): 1.0 (s, 9H), 1.5 (s, 9H), 1.65-1.95 (m, 2H), 3.82 (t, 1H).

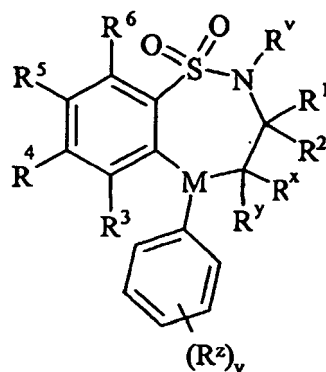
Method 28

Methyl 3-(trimethylsilyl)alaninate

[0209] 3-Trimethylsilyl alanine (J. Organomet. Chem., 628, (2001), 183-194; 19mg, 0.118mmol) was mixed with 3ml BF₃-MeOH (14%, 3.7mmol) in a sealed tube and heated to 70°C. Analysis was performed using TLC (MeOH:DCM 1:9, stained w. ninhydrine in ethanol). The mixture was heated for 3h and was then cooled to ambient temperature. The mixture was poured into a mixture of 3ml EtOAc and 2ml water containing Na₂CO₃. More Na₂CO₃ (5%-aq) was added until pH ca 7. The aqueous phase was washed with EtOAc (2x3ml). The combined organic layers were washed with brine (1ml), dried with Na₂SO₄ and evaporated. The product was obtained as a white film. Mass: 19mg (92% yield). NMR (CDCl₃): 0.1 (s, 9H), 1.2-1.4 (m, 2H), 3.8 (s, 3H), 4.2 (brs, 1H).

Claims

1. A compound of formula (I):



(I)

wherein:

R^v is selected from hydrogen or C₁₋₆alkyl;

One of **R¹** and **R²** are selected from hydrogen, C₁₋₆alkyl or C₂₋₆alkenyl and the other is selected from C₁₋₆alkyl or C₂₋₆alkenyl;

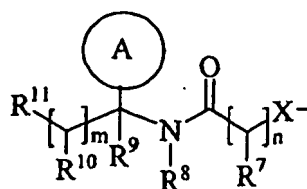
R^x and **R^y** are independently selected from hydrogen, hydroxy, amino, mercapto, C₁₋₆alkyl, C₁₋₆alkoxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkylS(O)_a wherein a is 0 to 2;

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

R^z is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0 to 2, C₁₋₆alkoxycarbonyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl;

v is 0-5;

one of **R⁴** and **R⁵** is a group of formula (IA):



(IA)

R³ and **R⁶** and the other of **R⁴** and **R⁵** are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, *N*-(C₁₋₄alkyl)amino, *N,N*-(C₁₋₄alkyl)₂amino, C₁₋₄alkanoylamino, *N*-(C₁₋₄alkyl)carbamoyl, *N,N*-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_n wherein a is 0 to 2, C₁₋₄alkoxycarbonyl, *N*-(C₁₋₄alkyl)sulphamoyl and *N,N*-(C₁₋₄alkyl)₂sulphamoyl; wherein R³ and R⁶ and the other of R⁴ and R⁵ may be optionally substituted on carbon by one or more R¹⁶;

X is -O-, -N(R^a)-, -S(O)_b- or -CH(R⁸)-; wherein R^a is hydrogen or C₁₋₆alkyl and b is 0-2;

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

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

R⁸ is hydrogen or C₁₋₄alkyl;

R⁹ is hydrogen or C₁₋₄alkyl;

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

R¹¹ is carboxy, sulfo, sulphino, phosphono, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) or

2. A compound of formula (I) as claimed in claim 1 wherein R^v is hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.
- 5 3. A compound of formula (I) as claimed in either of claims 1 or 2 wherein R¹ and R² are both butyl or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.
- 10 4. A compound of formula (I) as claimed in any one of claims 1-3 wherein R^x and R^y are both hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.
- 15 5. A compound of formula (I) as claimed in any one of claims 1-4 wherein M is -N- or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.
- 20 6. A compound of formula (I) as claimed in any one of claims 1-5 wherein v is 0 or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.
- 25 7. A compound of formula (I) as claimed in any one of claims 1-6 wherein R³ and R⁶ are hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.
- 30 8. A compound of formula (I) as claimed in any one of claims 1-7 wherein R⁴ is bromo, methyl or methylthio or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.
- 35 9. A compound of formula (I) as claimed in any one of claims 1-8 wherein R⁵ is a group of formula (IA) (as depicted in claim 1) wherein:

X is -O-;

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

n is 1;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

m is 0;

R¹¹ is carboxy, a group of formula (IB) (as depicted above) or a group of formula (IC) (as depicted above) wherein:

R¹² is hydrogen or C₁₋₄alkyl;

p is 1 or 2;

R¹³ is hydrogen or C₁₋₆alkyl optionally substituted by R²⁰ wherein R²⁰ is hydroxy, carbamoyl, amino, benzylloxycarbonylamino, C₁₋₄alkylS(O)_a wherein a is 0 or (C₁₋₄alkyl)₃silyl;

R¹⁴ is hydrogen or hydroxy or C₁₋₆alkyl; wherein R¹⁴ may be optionally substituted by one or more substituents selected from R²⁰;

Y is -N(Rⁿ)C(O)- wherein Rⁿ is hydrogen;

q is 0 or 1;

r is 0 or 1;

R¹⁵ is carboxy or sulpho;

R¹⁷ is hydroxy; and

R²⁰ is selected from hydroxy;

Ring B is pyrrolidin-1-yl or azetidiny substituted on carbon by one group selected from R²³, and optionally additionally substituted on carbon by one or more R²⁴; wherein R²³ is carboxy and R²⁴ is hydroxy;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.

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

R^v is hydrogen;

R¹ and R² are both butyl;

R^x and R^y are both hydrogen;

M is -N-;

v is 0;

R³ and R⁶ are hydrogen;

R⁴ is bromo, methyl or methylthio; and

R⁵ is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-carbamylethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-hydroxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(S)-1-carboxy-2-(S)-2-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -carboxy-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-aminobutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-4-(benzyloxycarbonylamino)butyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -((S)-2-carboxypyrrolidin-1-ylcarbonyl)benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(carboxymethyl)-*N*-methylcarbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(1-(R)-2-(R)-1-carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-(sulphomethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -carboxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl]carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)-4-(R)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[2-(S)-2-(carboxy)azetid-1-ylcarbonyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-1-carboxyethyl)carbamoyl]ethyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-3,3-dimethylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-carboxy-3,3-dimethylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-carboxy-2-(trimethylsilyl)ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy or *N*-{(R)- α -[*N*-((R)-1-carboxy-2-(trimethylsilyl)ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.

11. A compound of formula (I) selected from:

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

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

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

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

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

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

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

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

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

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

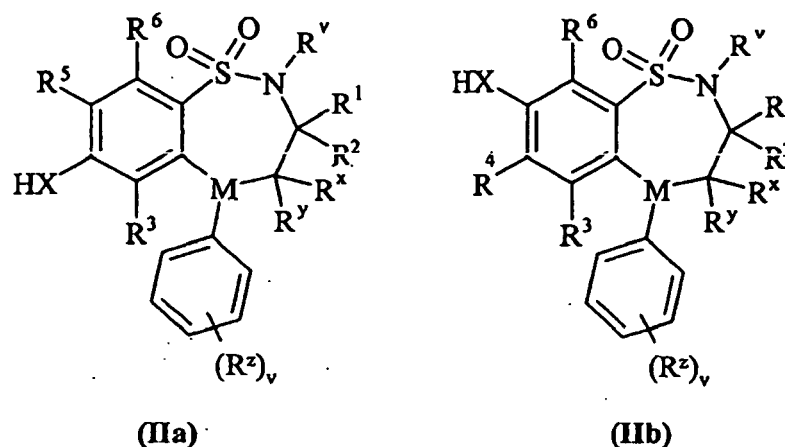
or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.

12. A compound of formula (I) selected from:

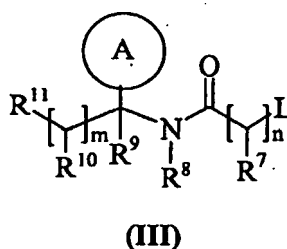
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-{(S)-1-carboxypropyl} carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and
 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-{(R)- α -carboxy-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.

13. A process for preparing a compound of formula (I) as claimed in claims 1-11 or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof which process comprises of:

Process 1): for compounds of formula (I) wherein X is -O-, -NR^a or -S-; reacting a compound of formula (IIa) or (IIb):

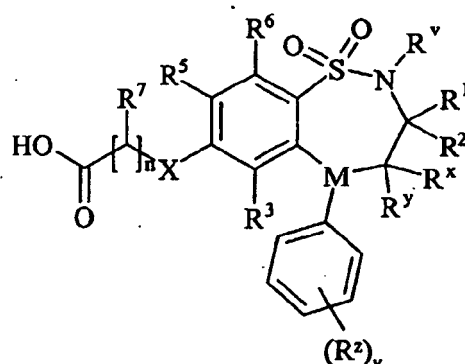
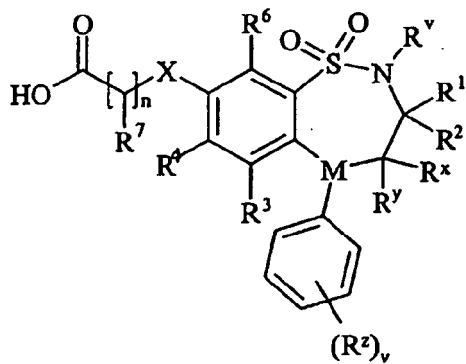


with a compound of formula (III):

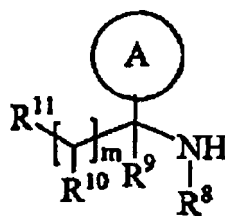


wherein L is a displaceable group;

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

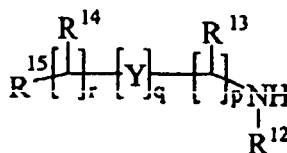


or an activated derivative thereof; with an amine of formula (V):



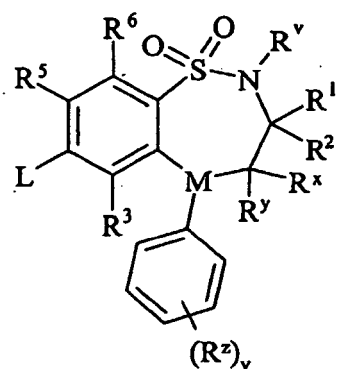
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Process 3): for compounds of formula (I) wherein R¹¹ is a group of formula (IB); reacting a compound of formula (I) wherein R¹¹ is carboxy with an amine of formula (VI):

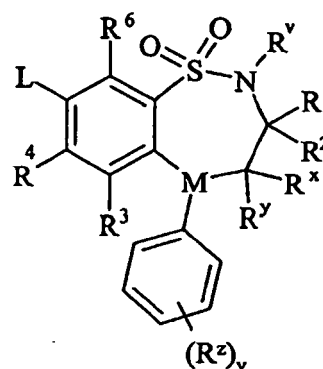


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Process 4) for compounds of formula (I) wherein one of R⁴ and R⁵ are independently selected from C₁₋₆alkylthio optionally substituted on carbon by one or more R¹⁷; reacting a compound of formula (VIIa) or (VIIb):



(VIIa)



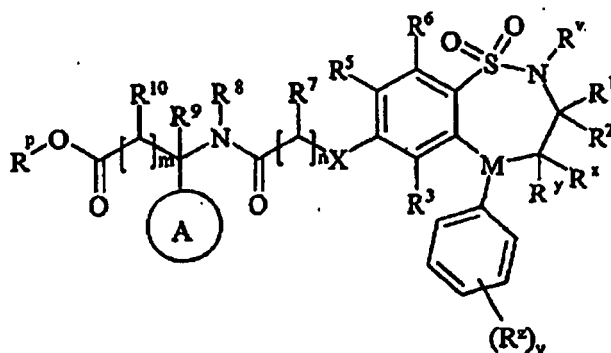
(VIIb)

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



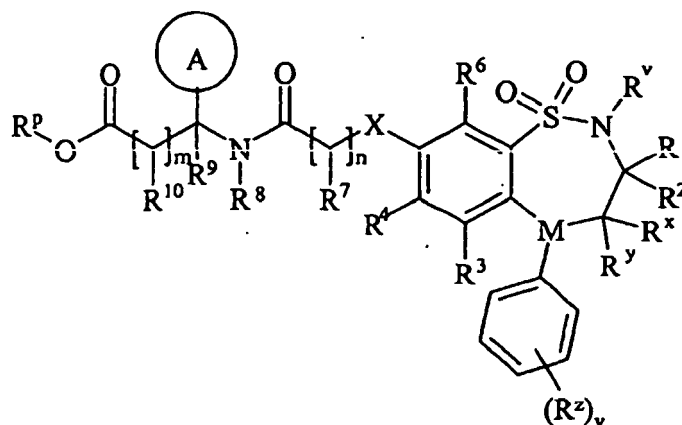
wherein R^m is C_{1-6} alkylthio optionally substituted on carbon by one or more R^{16} ;

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



(IXa)

or (IXb):



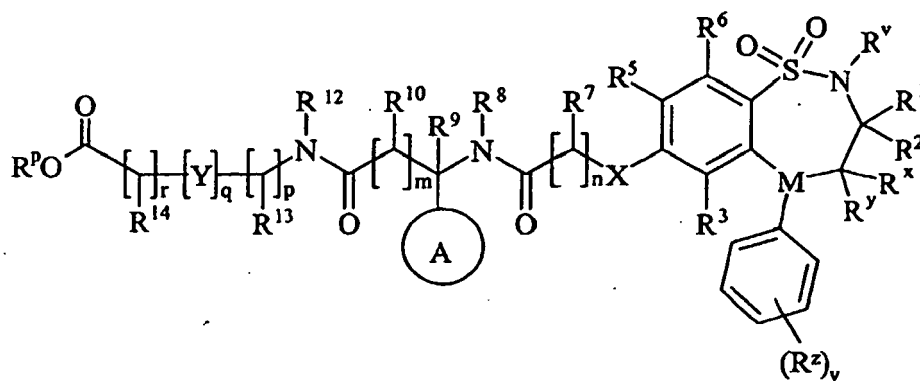
(IXb)

wherein R^p together with the $-OC(O)-$ group to which it is attached forms an ester;
Process 6): for compounds of formula (I) wherein R^{11} is a group of formula (IB) and R^{15} is carboxy; deprotecting
 a compound of formula (Xa):

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(Xa)

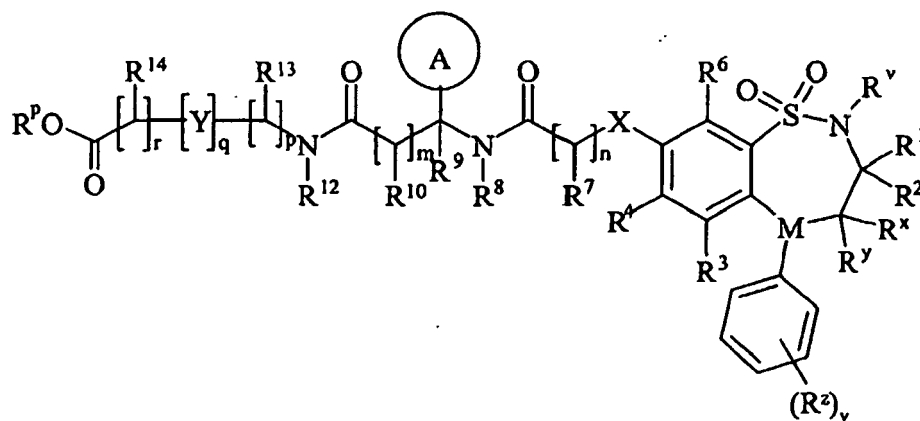
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or (Xb):

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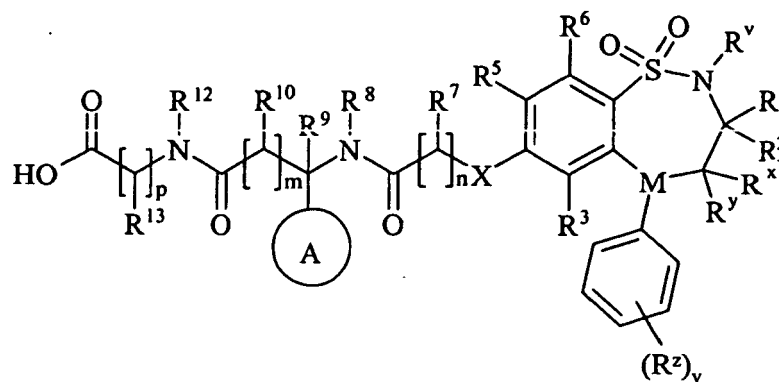
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wherein R^p together with the $-OC(O)-$ group to which it is attached forms an ester;
 or *Process 7*): for compounds of formula (I) wherein R^{11} is a group of formula (IB) and Y is $N(R^n)C(O)-$; reacting
 an acid of formula (XIa):

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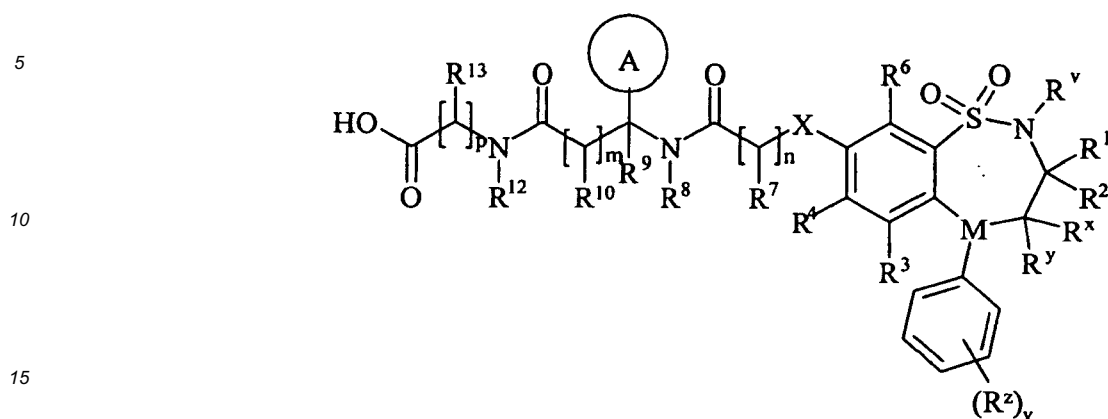
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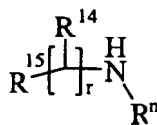
(XIa)

or (XIb):



(XIb)

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



(XII)

and thereafter if necessary or desirable:

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- 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, an in vivo hydrolysable ester or an in vivo hydrolysable amide.

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14. A compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12 for use as a medicament.

15. A compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12 for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

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16. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

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17. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

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18. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, in association with a pharmaceutically-acceptable diluent or carrier.

19. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt,

solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, in association with a pharmaceutically acceptable diluent or carrier.

- 5 **20.** A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.
- 10 **21.** A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, 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.
- 15 **22.** A composition combination or use according to claims 19, 21, 30, 32, 33 or 35 wherein the HMG Co-A reductase inhibitor is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.
- 20 **23.** A composition, combination or use according to claims 19, 21, 30, 32, 33 or 35 wherein the HMG Co-A reductase inhibitor is rosuvastatin, or a pharmaceutically acceptable salt thereof.
- 25 **24.** A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12 and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.
- 30 **25.** A composition according to any one of claims 24, 42 or 43 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.
- 35 **26.** The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof as claimed in any one of claims 1 to 12, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.
- 40 **27.** The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, in the manufacture of a medicament for use in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL) in a warm-blooded animal, such as man.
- 45 **28.** The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, in the manufacture of a medicament for use in the treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks in a wann-blooded animal, such as man.
- 50 **29.** The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, 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.
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30. A combination, comprising, 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 12, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.
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31. A combination comprising a compound of the formula (I), or a pharmaceutically acceptable salt, solvate solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, and a bile acid binder.
- 15
32. A combination, comprising 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 12, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, and a bile acid binder.
- 20
33. 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 12, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.
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34. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, 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.
- 30
35. 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 12, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide 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.
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36. The composition, combination or use according to any one of claims 20, 21, 31, 32, 34 and 35 wherein the bile acid binder is a resin.
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37. The composition, combination or use according to any one of claims 20, 21, 31, 32, 34 and 35 wherein the bile acid binder is cholestyramine or cholestipol.
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38. 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, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of a cholesterol absorption antagonist.
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39. A combination treatment according to claim 38 wherein the cholesterol absorption antagonist is an azetidinone.
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40. A combination treatment according to claim 38 or claim 39 wherein the cholesterol absorption antagonist is SCH 58235.
41. A composition, combination or use according to claims 19, 21, 30, 32, 33 or 35 wherein the HMG Co-A reductase inhibitor is fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin or rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, or a pharmaceutically acceptable salt thereof.
42. A combination comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, as claimed in any one of claims 1 to 12 and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt thereof.
43. 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 12 and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

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44. A compound of formula (IXa), (IXb), (Xa) or (Xb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt, an in vivo hydrolysable ester or an in vivo hydrolysable amide thereof.

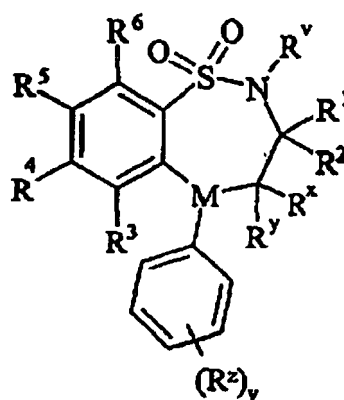
10 Patentansprüche

1. Verbindung der Formel (I):

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(I)

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worin:

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R^v unter Wasserstoff oder C_{1-6} -Alkyl ausgewählt ist; einer der Reste R^1 und R^2 unter Wasserstoff, C_{1-6} -Alkyl oder C_{2-6} -Alkenyl ausgewählt ist und der andere unter C_{1-6} -Alkyl oder C_{2-6} -Alkenyl ausgewählt ist; R^x und R^y unabhängig voneinander unter Wasserstoff, Hydroxy, Amino, Mercapto, C_{1-6} -Alkyl, C_{1-6} -Alkoxy, N -(C_{1-6} -Alkyl) amino, N,N -(C_{1-6} -Alkyl) $_2$ amino, C_{1-6} -Alkyl-S(O) $_a$, worin a für 0 bis 2 steht, ausgewählt sind; M unter -N- oder -CH- ausgewählt ist;

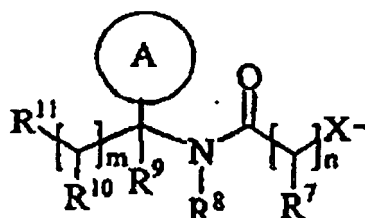
40

R^z unter Halogen, Nitro, Cyano, Hydroxy, Amino, Carboxy, Carbamoyl, Mercapto, Sulfamoyl, C_{1-6} -Alkyl, C_{2-6} -Alkenyl, C_{2-6} -Alkinyl, 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} -Alkyl-S(O) $_a$, worin a für 0 bis 2 steht, C_{1-6} -Alkoxy-carbonyl, N -(C_{1-6} -Alkyl)sulfamoyl und N,N -(C_{1-6} -Alkyl) $_2$ sulfamoyl ausgewählt ist; v für 0-5 steht;

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einer der Reste R^4 und R^5 für eine Gruppe der Formel (IA) steht:

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(IA)

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R³ und R⁶ und der andere der Reste R⁴ und R⁵ unabhängig voneinander unter Wasserstoff, Halogen, Nitro, Cyano, Hydroxy, Amino, Carboxy, Carbamoyl, Mercapto, Sulfamoyl, C₁₋₄-Alkyl, C₂₋₄-Alkenyl, C₂₋₄-Alkynyl, C₁₋₄-Alkoxy, C₁₋₄-Alkanoyl, C₁₋₄-Alkanoyloxy, N-(C₁₋₄-Alkyl) amino, N,N-(C₁₋₄-Alkyl)₂amino, C₁₋₄-Alkanoylamino, N-(C₁₋₄-Alkyl)carbamoyl, N,N-(C₁₋₄-Alkyl)₂carbamoyl, C₁₋₄-Alkyl-S(O)_a, worin a für 0 bis 2 steht, C₁₋₄-Alkoxy-carbonyl, N-(C₁₋₄-Alkyl)-sulfamoyl und N,N-(C₁₋₄-Alkyl)₂sulfamoyl ausgewählt sind; wobei R³ und R⁶ und der andere der Reste R⁴ und R⁵ gegebenenfalls an Kohlenstoff durch einen oder mehrere Reste R¹⁶ substituiert sein können;

X für -O-, -N(R^a)-, -S(O)_b- oder -CH(R^a)- steht, wobei R^a für Wasserstoff oder C₁₋₆-Alkyl steht und b für 0-2 steht; der Ring A für Aryl oder Heteroaryl steht, wobei der Ring A gegebenenfalls durch einen oder mehrere unter R¹⁷ ausgewählte Substituenten substituiert ist;

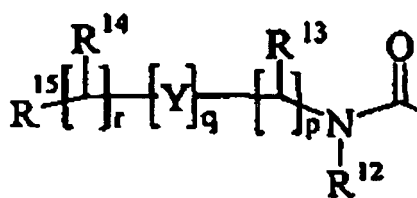
R⁷ für Wasserstoff, C₁₋₄-Alkyl, Carbocyclyl oder Heterocyclyl steht; wobei R⁷ gegebenenfalls durch einen oder mehrere unter R¹⁸ ausgewählte Substituenten substituiert ist;

R⁸ für Wasserstoff oder C₁₋₄-Alkyl steht;

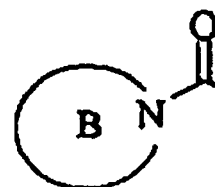
R⁹ für Wasserstoff oder C₁₋₄-Alkyl steht;

R¹⁰ für Wasserstoff, C₁₋₄-Alkyl, Carbocyclyl oder Heterocyclyl steht; wobei R¹⁰ gegebenenfalls durch einen oder mehrere unter R¹⁹ ausgewählte Substituenten substituiert ist;

R¹¹ für Carboxy, Sulfo, Sulfino, Phosphono, -P(O) (OR^c) (OR^d), -P(O) (OH)(OR^c), -P(O) (OH)(R^d) oder -P(O) (OR^c) (R^d) steht, wobei R^c und R^d unabhängig unter C₁₋₆-Alkyl ausgewählt sind; oder R¹¹ für eine Gruppe der Formel (IB) oder (IC) steht:



(IB)



(IC)

worin:

Y für -N(Rⁿ)-, -N(Rⁿ)C(O)-, -N(Rⁿ)C(O)(CR^sR^t), N(Rⁿ)C(O)-, -O- und -S(O)_a- steht, wobei a für 0-2 steht, v für 1-2 steht, R^s und R^t unabhängig voneinander unter Wasserstoff oder gegebenenfalls durch R²⁶ substituiertem C₁₋₄-Alkyl ausgewählt sind und Rⁿ für Wasserstoff oder C₁₋₄-Alkyl steht;

R¹² für Wasserstoff oder C₁₋₄-Alkyl steht;

R¹³ und R¹⁴ unabhängig voneinander unter Wasserstoff, C₁₋₆-Alkyl, Carbocyclyl oder Heterocyclyl ausgewählt sind; und wenn q für 0 steht, R¹⁴ zusätzlich unter Hydroxy ausgewählt sein kann; wobei R¹³ und R¹⁴ unabhängig voneinander gegebenenfalls durch einen oder mehrere unter R²⁰ ausgewählte Substituenten substituiert sein können;

R¹⁵ für Carboxy, Sulfo, Sulfino, Phosphono, -P(O)(OR^e) (OR^f), -P(O) (OH) (OR^e), -P(O)(OH)(R^e) oder -P(O)(OR^e)(R^f) steht, wobei R^e und R^f unabhängig unter C₁₋₆-Alkyl ausgewählt sind;

p für 1-3 steht; wobei die Werte von R¹³ gleich oder verschieden sein können;

q für 0-1 steht;

r für 0-3 steht; wobei die Werte von R¹⁴ gleich oder verschieden sein können;

m für 0-2 steht; wobei die Werte von R¹⁰ gleich oder verschieden sein können;

n für 1-3 steht; wobei die Werte von R⁷ gleich oder verschieden sein können;

der Ring B für über Stickstoff gebundenes Heterocyclyl, das an Kohlenstoff durch eine unter R²³ ausgewählte Gruppe substituiert ist und gegebenenfalls zusätzlich an Kohlenstoff durch einen oder mehrere Reste R²⁴ substituiert ist, steht; wobei dann, wenn das über Stickstoff gebundene Heterocyclyl eine -NH-Gruppierung enthält, dieser Stickstoff gegebenenfalls durch eine unter R²⁵ ausgewählte Gruppe substituiert sein kann;

R¹⁶, R¹⁷ und R¹⁸ unabhängig voneinander unter Halogen, Nitro, Cyano, Hydroxy, Amino, Carboxy, Carbamoyl, Mercapto, Sulfamoyl, C₁₋₄-Alkyl, C₂₋₆-Alkenyl, C₂₋₄-Alkynyl, C₁₋₄-Alkoxy, C₁₋₄-Alkanoyl, C₁₋₄-Alkanoyloxy, N-(C₁₋₄-Alkyl)amino, N,N-(C₁₋₄-Alkyl)₂amino, C₁₋₄-Alkanoylamino, N-(C₁₋₄-Alkyl)-carbamoyl, N,N-(C₁₋₄-Alkyl)₂carbamoyl, C₁₋₄-AlkylS(O)_a, worin a für 0 bis 2 steht, C₁₋₄-Alkoxy-carbonyl, N-(C₁₋₄-Alkyl) sulfamoyl und N,N-(C₁₋₄-Alkyl)₂sulfamoyl ausgewählt sind; wobei R¹⁶, R¹⁷ und

R¹⁸ unabhängig voneinander gegebenenfalls an Kohlenstoff durch einen oder mehrere Reste R²¹ substituiert

sein können;

R¹⁹, R²⁰, R²⁴ und R²⁶ unabhängig voneinander unter Halogen, Nitro, Cyano, Hydroxy, Amino, Carboxy, Carbamoyl, Mercapto, Sulfamoyl, C₁₋₄-Alkyl, C₂₋₄-Alkenyl, C₂₋₄-Alkyl, C₁₋₄-Alkoxy, C₁₋₄-Alkanoyl, C₁₋₄-Alkanoyloxy, N-(C₁₋₄-Alkyl) amino, N,N-(C₁₋₄-Alkyl)₂amino, C₁₋₄-Alkanoylamino, N-(C₁₋₄-Alkyl)-carbamoyl, N,N-(C₁₋₄-Alkyl)₂carbamoyl, C₁₋₄-AlkylS(O)_a, worin a für 0 bis 2 steht, C₁₋₄-Alkoxy-carbonyl, N-(C₁₋₄-Alkyl) sulfamoyl, N,N-(C₁₋₄-Alkyl)₂sulfamoyl, Carbocyclyl, Heterocyclyl, Benzyloxycarbonylamino, (C₁₋₄-Alkyl)₃silyl, Sulfo, Sulfino, Amidino, Phosphono, -P(O) (OR^a) (OR^b), -P(O) (OH) (OR^a), -P(O) (OH) (R^a) oder -P(O) (OR^a) (R^b) ausgewählt sind, wobei R^a und R^b unabhängig voneinander unter C₁₋₆-Alkyl ausgewählt sind; wobei R¹⁹, R²⁰, R²⁴ und R²⁶ unabhängig voneinander gegebenenfalls an Kohlenstoff durch einen oder mehrere Reste R²² substituiert sein können;

R²¹ und R²² unabhängig voneinander unter Halogen, Hydroxy, Cyano, Carbamoyl, Ureido, Amino, Nitro, Carboxy, Carbamoyl, Mercapto, Sulfamoyl, Trifluormethyl, Trifluormethoxy, Methyl, Ethyl, Methoxy, Ethoxy, Vinyl, Allyl, Ethinyl, Methoxycarbonyl, Formyl, Acetyl, Formamido, Acetylamino, Acetoxy, Methylamino, Dimethylamino, N-Methylcarbamoyl, N,N-Dimethylcarbamoyl, Methylthio, Methylsulfinyl, Mesyl, N-Methylsulfamoyl und N,N-Dimethylsulfamoyl ausgewählt sind;

R²³ für Carboxy, Sulfo, Sulfino, Phosphono, -P(O) (OR^g) (OR^h), -P(O) (OH)(OR^g), -P(O) (OH)(R^g) oder -P(O)(OR^g)(R^h) steht, wobei R^g und R^h unabhängig voneinander unter C₁₋₆-Alkyl ausgewählt sind;

R²⁵ unter C₁₋₆-Alkyl, C₁₋₆-Alkanoyl, C₁₋₆-Alkylsulfonyl, C₁₋₆-Alkoxy-carbonyl, Carbamoyl, N-(C₁₋₆-Alkyl) carbamoyl, N,N-(C₁₋₆-Alkyl)₂carbamoyl, Benzyl, Benzyloxycarbonyl, Benzoyl und Phenylsulfonyl ausgewählt ist; oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.

2. Verbindung der Formel (I) nach Anspruch 1, worin R^v für Wasserstoff steht, oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.
3. Verbindung der Formel (I) nach Anspruch 1 oder 2, worin die Reste R¹ und R² beide für Butyl stehen, oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.
4. Verbindung der Formel (I) nach einem der Ansprüche 1-3, worin R^x und R^y beide für Wasserstoff stehen, oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.
5. Verbindung der Formel (I) nach einem der Ansprüche 1-4, worin M für -N- steht, oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.
6. Verbindung der Formel (I) nach einem der Ansprüche 1-5, worin v für 0 steht, oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.
7. Verbindung der Formel (I) nach einem der Ansprüche 1-6, worin R³ und R⁶ für Wasserstoff stehen, oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.
8. Verbindung der Formel (I) nach einem der Ansprüche 1-7, worin R⁴ für Brom, Methyl oder Methylthio steht, oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.
9. Verbindung der Formel (I) nach einem der Ansprüche 1-8, worin R⁵ für eine Gruppe der Formel (IA) (wie in Anspruch 1 dargestellt) steht, worin:

X für -O- steht;

der Ring A für gegebenenfalls durch einen oder mehrere unter R¹⁷ ausgewählte Substituenten substituiertes Phenyl steht;

n für 1 steht;

R⁷ für Wasserstoff steht;

R⁸ für Wasserstoff steht;
 R⁹ für Wasserstoff steht;
 m für 0 steht;
 R¹¹ für Carboxy, eine Gruppe der Formel (IB) (wie oben dargestellt) oder eine Gruppe der Formel (IC) (wie
 oben dargestellt) steht, worin:
 R¹² für Wasserstoff oder C₁₋₄-Alkyl steht;
 p für 1 oder 2 steht;
 R¹³ für Wasserstoff oder gegebenenfalls durch R²⁰ substituiertes C₁₋₆-Alkyl steht, wobei R²⁰ Hydroxy, Carba-
 moyl, Amino, Benzyloxycarbonylamino, C₁₋₄-Alkyl-S(O)_a, worin a für 0 steht, oder (C₁₋₄-Alkyl)₃ silyl bedeutet;
 R¹⁴ für Wasserstoff oder Hydroxy oder C₁₋₆-Alkyl steht; wobei R¹⁴ gegebenenfalls durch einen oder mehrere
 unter R²⁰ ausgewählte Substituenten substituiert sein kann;
 Y für -N(Rⁿ)C(O)- steht, worin Rⁿ Wasserstoff bedeutet;
 q für 0 oder 1 steht;
 r für 0 oder 1 steht;
 R¹⁵ für Carboxy oder Sulfo steht;
 R¹⁷ für Hydroxy steht und
 R²⁰ unter Hydroxy ausgewählt ist;
 der Ring B für Pyrrolidin-1-yl oder Azetidiny, das gegebenenfalls an Kohlenstoff durch eine unter R²³ ausge-
 wählte Gruppe substituiert ist und gegebenenfalls zusätzlich an Kohlenstoff durch einen oder mehrere Reste
 R²⁴ substituiert ist; wobei R²³ für Carboxy steht und R²⁴ für Hydroxy steht;
 oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer
 Ester oder ein in vivo hydrolysierbares Amid davon.

10. Verbindung der Formel (I) (wie in Anspruch 1 dargestellt), worin:

R^v für Wasserstoff steht;
 R¹ und R² beide für Butyl stehen;
 R^x und R^y beide für Wasserstoff stehen;
 M für -N- steht;
 v für 0 steht;
 R³ und R⁶ für Wasserstoff stehen;
 R⁴ für Brom, Methyl oder Methylthio steht und
 R⁵ für N-{(R)-α-[N-(Carboxymethyl)carbamoyl]-benzyl}carbamoylmethoxy, N-{(R)-α-[N-(2-Sulfoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-2-hydroxyethyl)-carbamoyl]benzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxypropyl)-carbamoyl]benzyl}carbamoylmethoxy, N-{(R)-α-[N-((R)-1-Carboxy-2-methylthioethyl)carbamoyl]-benzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-2-carbamylethyl)carbamoyl]benzyl}-carbamoylmethoxy, N-{(R)-α-[N-(2-Sulfoethyl)-carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, N-{(R)-α-[N-(Carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-2-hydroxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-2-hydroxyethyl)carbamoyl]benzyl}-carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-3-methylbutyl)carbamoyl]-benzyl}carbamoylmethoxy, N-{(R)-α-[N-(1-(S)-1-Carboxy-2-(S)-methylbutyl)carbamoyl]benzyl}-carbamoylmethoxy, N-((R)-α-Carboxy-4-hydroxybenzyl)carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-4-aminobutyl)carbamoyl]benzyl}carbamoylmethoxy, N-((R)-α-[N-((S)-1-Carboxy-4-(benzyloxycarbonylamino)butyl)carbamoyl]benzyl}carbamoylmethoxy, N-[(R)-α-((S)-2-Carboxypyrrolidin-1-yl-carbonyl)benzyl]carbamoylmethoxy, N-{(R)-α-[N-(Carboxymethyl)-N-methylcarbamoyl]benzyl}carbamoylmethoxy, N-{(R)-α-[N-(1-(R)-2-(R)-1-Carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl}carbamoylmethoxy, N-{(R)-α-[N-(Sulfomethyl)carbamoyl]-benzyl}carbamoylmethoxy, N-((R)-α-Carboxybenzyl)-carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}-carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxybutyl)-carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, N-{(R)-α-[N-((R)-1-Carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-Carboxypropyl)carbamoyl]-4-hydroxybenzyl}-carbamoylmethoxy, N-{(R)-α-[N-((S)-1-[N-((S)-2-Hydroxy-1-carboxyethyl)carbamoyl]propyl)-carbamoyl]benzyl}carbamoylmethoxy, N-{(R)-α-[2-(S)-2-(Carboxy)-4-(R)-(hydroxy)pyrrolidin-1-yl-carbonyl]benzyl}carbamoylmethoxy, N-{(R)-α-[2-(S)-2-(Carboxy)azetidyn-1-yl-carbonyl]benzyl}carbamoylmethoxy, N-{(R)-α-[N-((S)-1-[N-((S)-1-Carboxyethyl)carbamoyl]ethyl)carbamoyl]benzyl}carbamoylmethoxy,

yl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-Carboxy-3,3-dimethylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-Carboxy-3,3-dimethylbutyl)carbamoyl]benzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((R)-1-Carboxy-3,3-dimethylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy, *N*-{(R)- α -[*N*-((S)-1-Carboxy-2-(trimethylsilyl)ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy oder *N*-{(R)- α -[*N*-((R)-1-Carboxy-2-(trimethylsilyl)ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy steht;

oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.

11. Verbindung der Formel (I), ausgewählt unter:

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((R)-1-Carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-Carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-Carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-Carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-Carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-Carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-Carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-Carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-Carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((R)-1-Carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin und
 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-((S)-1-Carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin;

oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.

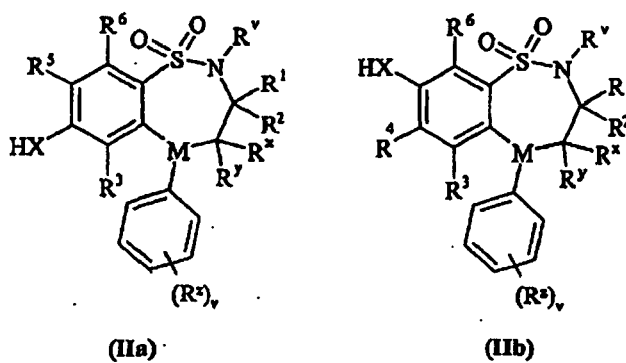
12. Verbindung der Formel (I), ausgewählt unter:

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

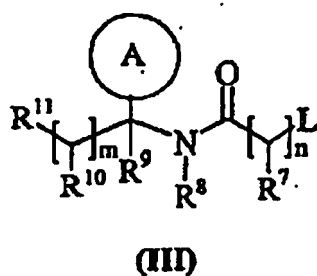
oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.

13. Verfahren zur Herstellung einer Verbindung der Formel (I) nach einem der Ansprüche 1-11 oder eines pharmazeutisch annehmbaren Salzes, Solvats, Solvats eines derartigen Salzes oder eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon, bei dem man:

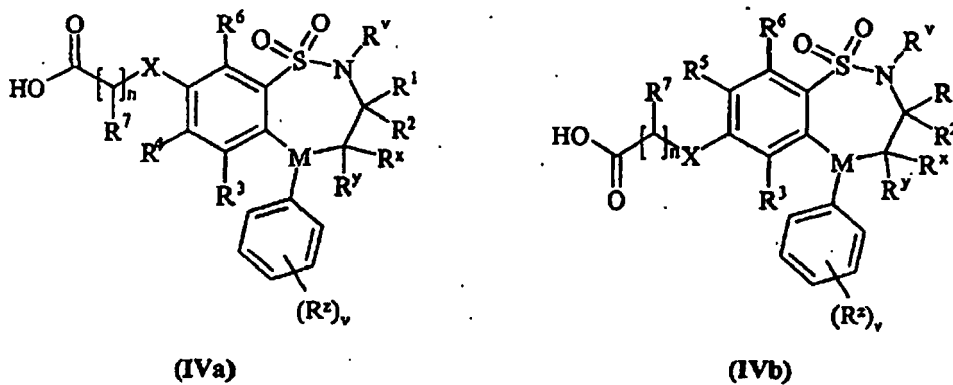
Verfahren 1): für Verbindungen der Formel (I), worin X für -O-, -NR^a oder -S- steht, eine Verbindung der Formel (IIa) oder (IIb):



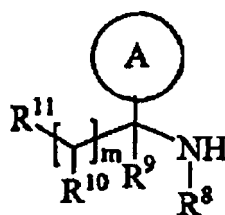
mit einer Verbindung der Formel (III):



worin L für eine Abgangsgruppe steht, umgesetzt;
Verfahren 2): eine Säure der Formel (IVa) oder (IVb):



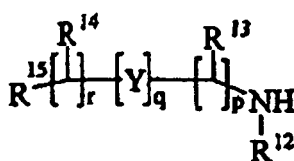
oder ein aktiviertes Derivat davon mit einem Amin der Formel (V):



(V)

umsetzt;

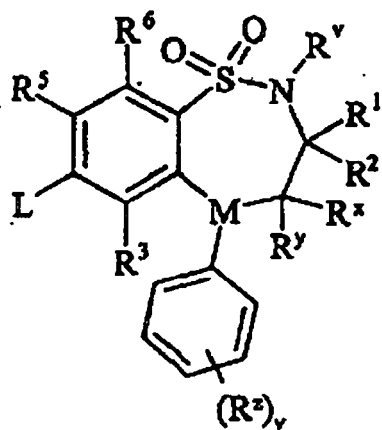
Verfahren 3): für Verbindungen der Formel (I), worin R¹¹ für eine Gruppe der Formel (IB) steht, eine Verbindung der Formel (I), worin R¹¹ für Carboxy steht, mit einem Amin der Formel (VI):



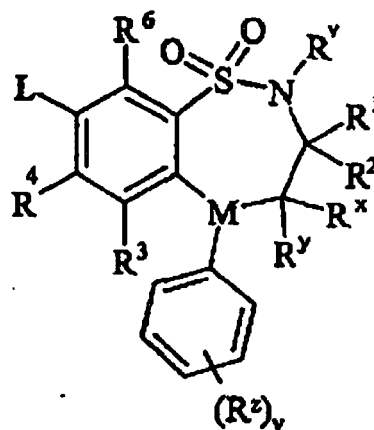
(VI)

umsetzt;

Verfahren 4): für Verbindungen der Formel (I), worin einer der Reste R⁴ und R⁵ unabhängig voneinander unter C₁₋₆-Alkylthio, das gegebenenfalls an Kohlenstoff durch einen oder mehrere Reste R¹⁷ substituiert ist, ausgewählt ist, eine Verbindung der Formel (VIIa) oder (VIIb):



(VIIa)



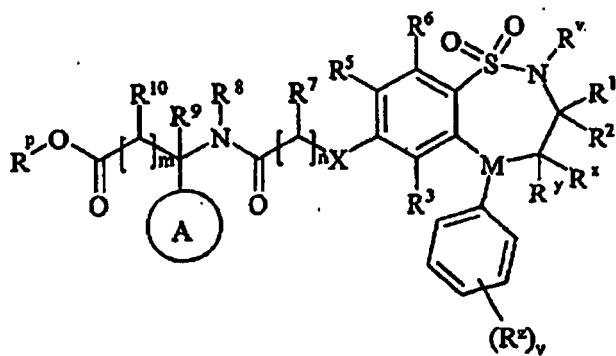
(VIIb)

worin L für eine Abgangsgruppe steht, mit einem Thiol der Formel (VIII):

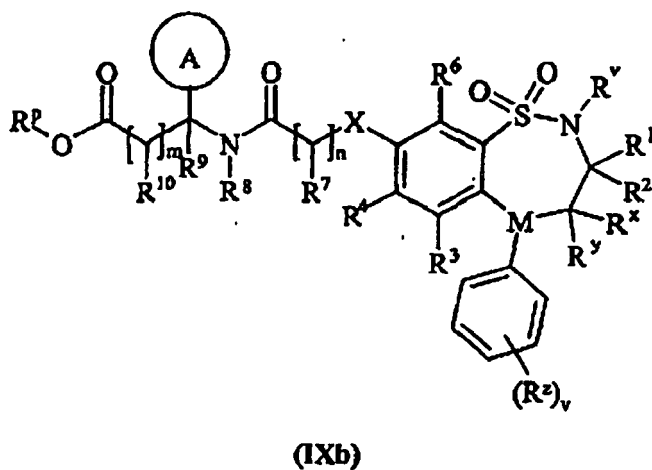


worin R^m für C₁₋₄-Alkylthio, das gegebenenfalls an Kohlenstoff durch einen oder mehrere Reste R¹⁶ substituiert ist, steht, umsetzt;

Verfahren 5): für Verbindungen der Formel (I), worin R¹¹ für Carboxy steht, eine Verbindung der Formel (IXa):



oder (IXb):



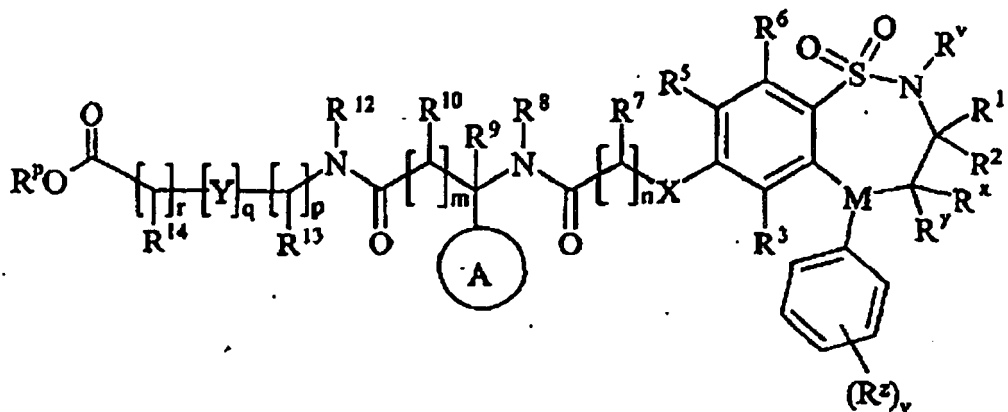
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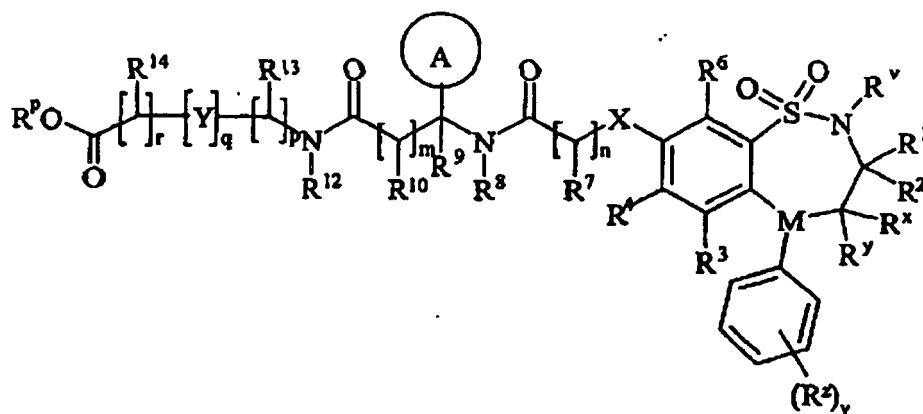
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worin der Rest R^p gemeinsam mit der $-OC(O)$ -Gruppe, an den er gebunden ist, einen Ester bildet, entschützt;
Verfahren 6): für Verbindungen der Formel (I), worin R^{11} für eine Gruppe der Formel (IB) steht und R^{15} für
 Carboxy steht, eine Verbindung der Formel (Xa) :



(Xa)

oder (Xb) :

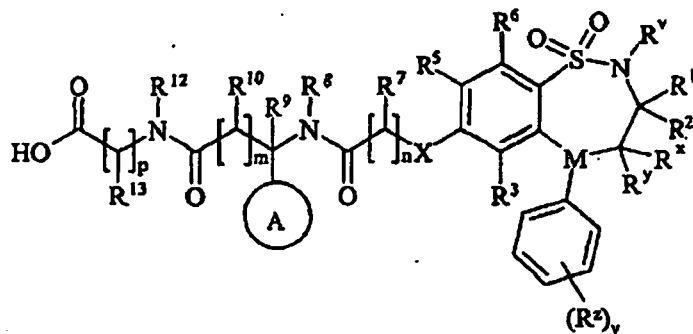


(Xb)

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worin der Rest R^p gemeinsam mit der $-OC(O)-$ Gruppe, an den er gebunden ist, einen Ester bildet, entschützt; oder Verfahren 7) : für Verbindungen der Formel (I), worin R^{11} für eine Gruppe der Formel (IB) steht und Y für $-N(R^n)C(O)-$ steht, eine Säure der Formel (XIa):



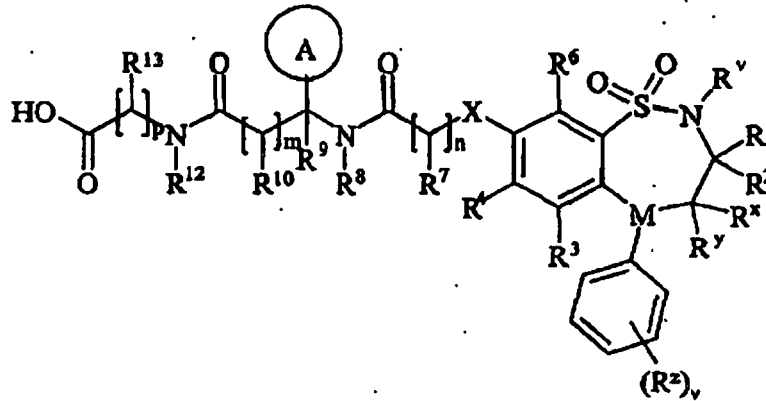
(XIa)

oder (XIb):

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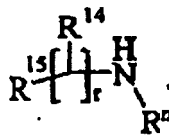


(XIb)

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oder ein aktiviertes Derivat davon mit einem Amin der Formel (XII):

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(XII)

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umsetzt;
und danach, falls erforderlich oder erwünscht:

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- i) eine Verbindung der Formel (I) in eine andere Verbindung der Formel (I) umwandelt;
- ii) gegebenenfalls vorhandene Schutzgruppen abspaltet;
- iii) ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon bildet.

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14. Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon nach einem der Ansprüche 1 bis 12 zur Verwendung als Medikament.

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15. Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon nach einem der Ansprüche 1 bis 12 zur Verwendung bei einem Verfahren zur prophylaktischen oder therapeutischen Behandlung eines Warmblüters wie des Menschen.

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16. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon nach einem der Ansprüche 1 bis 12 bei der Herstellung eines Medikaments zur Verwendung bei der Erzielung einer IBAT-hemmenden Wirkung bei einem Warmblüter wie dem Menschen.

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17. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon nach einem der Ansprüche 1 bis 12 bei der Erzielung einer IBAT-hemmenden Wirkung bei einem Warmblüter wie dem Menschen.

- 5
18. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon nach einem der Ansprüche 1 bis 12 zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.
- 10
19. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes oder ein Prodrug davon nach einem der Ansprüche 1 bis 12 und einen HMG-Co-A-Reduktaseinhibitor oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.
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20. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon nach einem der Ansprüche 1 bis 12 und einen Gallensäurebinder zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.
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21. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon nach einem der Ansprüche 1 bis 12 und einen HMG-Co-A-Reduktaseinhibitor oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes oder ein Prodrug davon und einen Gallensäurebinder zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.
- 25
22. Zusammensetzung, Kombination oder Verwendung nach einem der Ansprüche 19, 21, 30, 32, 33 oder 35, bei der es sich bei dem HMG-Co-A-Reduktaseinhibitor um Atorvastatin oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon handelt.
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23. Zusammensetzung, Kombination oder Verwendung nach einem der Ansprüche 19, 21, 30, 32, 33 oder 35, bei der es sich bei dem HMG-Co-A-Reduktaseinhibitor um Rosuvastatin oder ein pharmazeutisch annehmbares Salz davon handelt.
- 35
24. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon nach einem der Ansprüche 1 bis 12 und einen PPAR-alpha- und/oder PPAR-gamma-Agonisten oder ein pharmazeutisch annehmbares Salz davon zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.
- 40
25. Zusammensetzung, Kombination oder Verwendung nach einem der Ansprüche 24, 42 oder 43, bei der es sich bei dem PPAR-alpha- und/oder PPAR-gamma-Agonisten um (S)-2-Ethoxy-3-[4-(2-(4-methansulfonyloxyphenyl)ethoxy)phenyl]propansäure oder ein pharmazeutisch annehmbares Salz davon handelt.
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26. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon nach einem der Ansprüche 1 bis 12 bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung von hyperlipidämischen Zuständen bei einem Warmblüter wie dem Menschen.
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27. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon nach einem der Ansprüche 1 bis 12 bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung von dyslipidämischen Zuständen und Störungen wie Hyperlipidämie, Hypertriglyceridämie, Hyperbetalipoproteinämie (hohem LDL), Hyperpräbetalipoproteinämie (hohem VLDL), Hyperchylomikronämie, Hypolipoproteinämie, Hypercholesterinämie, Hyperlipoproteinämie und Hypoalphalipoproteinämie (niedrigem HDL) bei einem Warmblüter wie dem Menschen.
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28. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon nach einem der Ansprüche 1 bis 12 bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung von verschiedenen klinischen Zuständen wie Atherosklerose, Arteriosklerose, Arrhythmie, hyperthrombotischen

Zuständen, vaskulärer Dysfunktion, endothelialer Dysfunktion, Herzversagen, koronaren Herzerkrankungen, Herz-Kreislauf-Erkrankungen, Myokardinfarkt, Angina pectoris, peripheren Gefäßerkrankungen, Entzündungen von kardiovaskulären Geweben wie Herz, Klappen, Gefäßsystem, Arterien und Venen, Aneurysmen, Stenose, Restenose, vaskulären Plaques, vaskulären Fettstreifen, Leukozyten-, Monozyten- und/oder Makrophageninfiltrat, Intimaverdickung, Mediaverdünnung, infektiösem und chirurgischem Trauma und Gefäßthrombose, Schlaganfall und transitorischen ischämischen Attacken bei einem Warmblüter wie dem Menschen.

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29. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon nach einem der Ansprüche 1 bis 12 bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung von Atherosklerose, koronaren Herzerkrankungen, Myokardinfarkt, Angina pectoris, peripheren Gefäßerkrankungen, Schlaganfall und transitorischen ischämischen Attacken bei einem Warmblüter wie dem Menschen.

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30. Kombination, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solut oder Solut eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon nach einem der Ansprüche 1 bis 12 und einen HMG-Co-A-Reduktaseinhibitor oder ein pharmazeutisch annehmbares Salz, Solut oder Solut eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon.

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31. Kombination, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solut oder Solut eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon nach einem der Ansprüche 1 bis 12 und einen Gallensäurebinder.

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32. Kombination, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solut oder Solut eines derartigen Salzes oder ein Prodrug davon nach einem der Ansprüche 1 bis 12 und einen HMG-Co-A-Reduktaseinhibitor oder ein pharmazeutisch annehmbares Salz, Solut oder Solut eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon und einen Gallensäurebinder.

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33. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes oder eines Prodrug davon nach einem der Ansprüche 1 bis 12 und eines HMG-Co-A-Reduktaseinhibitors oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes oder eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung von hyperlipidämischen Zuständen bei einem Warmblüter wie dem Menschen.

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34. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon nach einem der Ansprüche 1 bis 12 und eines Gallensäurebinders bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung von hyperlipidämischen Zuständen bei einem Warmblüter wie dem Menschen.

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35. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes oder eines Prodrug davon nach einem der Ansprüche 1 bis 12, eines HMG-Co-A-Reduktaseinhibitors oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon und eines Gallensäurebinders bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung von hyperlipidämischen Zuständen bei einem Warmblüter wie dem Menschen.

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36. Zusammensetzung, Kombination oder Verwendung nach einem der Ansprüche 20, 21, 31, 32, 34 und 35, bei der es sich bei dem Gallensäurebinder um ein Harz handelt.

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37. Zusammensetzung, Kombination oder Verwendung nach einem der Ansprüche 20, 21, 31, 32, 34 und 35, bei der es sich bei dem Gallensäurebinder um Cholestyramin oder Cholestipol handelt.

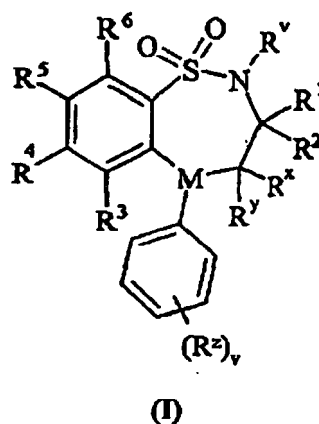
38. Kombinationsbehandlung, bei der man eine wirksame Menge einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon nach einem der Ansprüche 1 bis 12, gegebenenfalls zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger, bei gleichzeitiger, aufeinanderfolgender oder separater Verabreichung eines Cholesterinresorptionsantagonisten verabreicht.

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39. Kombinationsbehandlung nach Anspruch 38, bei der es sich bei dem Cholesterinresorptionsantagonisten um ein Azetidinon handelt.
40. Kombinationsbehandlung nach Anspruch 38 oder 39, bei der es sich bei dem Cholesterinresorptionsantagonisten um SCH 58235 handelt.
41. Zusammensetzung, Kombination oder Verwendung nach einem der Ansprüche 19, 21, 30, 32, 33 oder 35, bei der es sich bei dem HMG-Co-A-Reduktaseinhibitor um Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Atorvastatin, Cerivastatin, Bervastatin, Dalvastatin, Mevastatin und Rosuvastatin oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon oder ein pharmazeutisch annehmbares Salz davon handelt.
42. Kombination, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz, Solvat oder Solvat eines derartigen Salzes, einen in vivo hydrolysierbaren Ester oder ein in vivo hydrolysierbares Amid davon nach einem der Ansprüche 1 bis 12 und einen PPAR-alpha- und/oder PPAR-gamma-Agonisten oder ein pharmazeutisch annehmbares Salz davon.
43. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes oder eines Prodrug davon nach einem der Ansprüche 1 bis 12 und eines PPAR-alpha- und/oder PPAR-gamma-Agonisten oder eines pharmazeutisch annehmbaren Salzes, Solvats oder Solvats eines derartigen Salzes, eines in vivo hydrolysierbaren Esters oder eines in vivo hydrolysierbaren Amids davon bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung von hyperlipidämischen Zuständen bei einem Warmblüter wie dem Menschen.
44. Verbindung der Formel (IXa), (IXb), (Xa) oder (Xb) oder ein pharmazeutisch annehmbares Salz, Solvat, Solvat eines derartigen Salzes, ein in vivo hydrolysierbarer Ester oder ein in vivo hydrolysierbares Amid davon.

Revendications

1. Composé de formule (I) :



dans laquelle :

R^v est sélectionné parmi hydrogène ou alkyle en C_{1-6} ;

l'un parmi R^1 et R^2 est sélectionné parmi hydrogène, alkyle en C_{1-6} ou alcényle en C_{2-6} et

l'autre est sélectionné parmi alkyle en C_{1-6} ou alcényle en C_{2-6} ;

R^x et R^y sont sélectionnés indépendamment parmi hydrogène, hydroxy, amino, mercapto, alkyle en C_{1-6} , alcoxy en C_{1-6} , N-(alkyl(C_{1-6}))amino, N,N-(alkyl(C_{1-6}))₂amino, alkyl(C_{1-6})S(O)_a dans lequel a vaut 0 à 2 ;

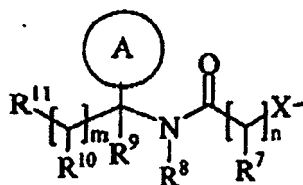
M est sélectionné parmi -N- ou -CH-;

R^z est choisi parmi halogéno, nitro, cyano, hydroxy, amino, carboxy, carbamoyle, mercapto, sulfamoyle, alkyle

en C₁₋₆, alcényle en C₂₋₆, alcynyle en C₂₋₆, alcoxy en C₁₋₆, alcanoyle en C₁₋₆, alcanoyl (C₁₋₆) oxy, N-(alkyl(C₁₋₆))amino, N,N-(alkyl(C₁₋₆))₂amino, alcanoyl (C₁₋₆) amino, N-(alkyl(C₁₋₆)) carbamoyle, N,N-(alkyl(C₁₋₆))₂carbamoyle, alkyl (C₁₋₆) S (O)_a dans lequel a vaut 0 à 2, alcoxy (C₁₋₆) carbonyle, N-(alkyl(C₁₋₆)) sulfamoyle et N,N-(alkyl(C₁₋₆))₂sulfamoyle ;

v vaut 0-5 ;

l'un parmi R⁴ et R⁵ est un groupement de formule (IA) :



(IA)

R³ et R⁶ et l'autre parmi R⁴ et R⁵ sont sélectionnés indépendamment parmi hydrogène, halogéno, nitro, cyano, hydroxy, amino, carboxy, carbamoyle, mercapto, sulfamoyle, alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, alcoxy en C₁₋₄, alcanoyle en C₁₋₄, alcanoyl (C₁₋₄) oxy, N-(alkyl(C₁₋₄))amino, N,N-(alkyl(C₁₋₄))₂amino, alcanoyl(C₁₋₄)amino, N-(alkyl(C₁₋₄))carbamoyle, N,N-(alkyl(C₁₋₄))₂carbamoyle, alkyl(C₁₋₄)S(O)_a dans lequel a vaut 0 à 2, alcoxy(C₁₋₄)carbonyle, N-(alkyl(C₁₋₄))sulfamoyle et N,N-(alkyl(C₁₋₄))₂sulfamoyle ; dans laquelle R³ et R⁶ et l'autre parmi R⁴ et R⁵ peuvent être éventuellement substitués sur carbone par un ou plusieurs R¹⁶ ;

X est -O-, -N(R^a)-, -S(O)_b- ou -CH(R^a)- ; où R^a est hydrogène ou alkyle en C₁₋₆ et b vaut 0-2 ; le Cycle A est aryle ou hétéroaryle ; où le Cycle A est éventuellement substitué par un ou plusieurs substituants sélectionnés parmi R¹⁷ ;

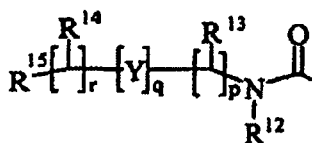
R⁷ est hydrogène, alkyle en C₁₋₄, carbocyclyle ou hétérocyclyle ; où R⁷ est éventuellement substitué par un ou plusieurs substituants sélectionnés parmi R¹⁸ ;

R⁸ est hydrogène ou alkyle en C₁₋₄ ;

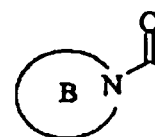
R⁹ est hydrogène ou alkyle en C₁₋₄ ;

R¹⁰ est hydrogène, alkyle en C₁₋₄, carbocyclyle ou hétérocyclyle ; où R¹⁰ est éventuellement substitué par un ou plusieurs substituants sélectionnés parmi R¹⁹ ;

R¹¹ est carboxy, sulfo, sulfino, phosphono, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) ou -P(O)(OR^c)(R^d) où R^c et R^d sont sélectionnés indépendamment parmi alkyle en C₁₋₆ ; où R¹¹ est un groupement de formule (IB) ou (IC) :



(IB)



(IC)

dans laquelle :

Y est -N(Rⁿ)-, -N(Rⁿ)C(O)-, -N(Rⁿ)C(O)(CR^sR^t)_vN(Rⁿ)C(O)-, -O-, et -S(O)_a- ; dans lequel a est 0-2, v est 1-2, R^s et R^t sont sélectionnés indépendamment parmi hydrogène ou alkyle en C₁₋₄ éventuellement substitué par R²⁶ et

Rⁿ est hydrogène ou alkyle en C₁₋₄ ;

R¹² est hydrogène ou alkyle en C₁₋₄ ;

R¹³ et R¹⁴ sont sélectionnés indépendamment parmi hydrogène, alkyle en C₁₋₆, carbocyclyle ou hétérocyclyle ; et lorsque q est 0, R¹⁴ peut en outre être sélectionné parmi hydroxy ; où R¹³ et R¹⁴ peuvent être éventuellement

substitués indépendamment par un ou plusieurs substituants sélectionnés parmi R²⁰;

R¹⁵ est carboxy, sulfo, sulfino, phosphono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) ou -P(O)(OR^e)(R^f) où R^e et R^f sont sélectionnés indépendamment parmi alkyle en C₁₋₆;

p vaut 1-3 ; où les valeurs de R¹³ peuvent être identiques ou différentes ;

q vaut 0-1 ;

r vaut 0-3 ; où les valeurs de R¹⁴ peuvent être identiques ou différentes ;

m vaut 0-2 ; où les valeurs de R¹⁰ peuvent être identiques ou différentes ;

n vaut 1-3 ; où les valeurs de R⁷ peuvent être identiques ou différentes ;

le Cycle B est un hétérocyclyle lié par azote substitué sur carbone par un groupement sélectionné parmi R²³, et éventuellement substitué en outre sur carbone par un ou plusieurs R²⁴; et

où si ledit hétérocyclyle lié par azote contient un motif -NH-, cet azote peut être éventuellement substitué par un groupement sélectionné parmi R²⁵ ;

R¹⁶, R¹⁷ et R¹⁸ sont sélectionnés indépendamment parmi halogéno, nitro, cyano, hydroxy, amino, carboxy, carbamoyle, mercapto, sulfamoyle, alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, alcoxy en C₁₋₄, alcanoyloxy en C₁₋₄, alcanoyl(C₁₋₄)oxy, N-(alkyl(C₁₋₄))amino, N,N-(alkyl(C₁₋₄))₂-amino, alcanoyl(C₁₋₄)amino, N-(alkyl(C₁₋₄))carbamoyle, N,N-(alkyl(C₁₋₄))₂carbamoyle, alkyl(C₁₋₄)S(O)_a dans lequel a vaut 0 à 2, alcoxy(C₁₋₄)carbonyloxy, N-(alkyl(C₁₋₄))sulfamoyle et N,N-(alkyl(C₁₋₄))₂sulfamoyle ; où R¹⁶, R¹⁷ et R¹⁸ peuvent être éventuellement substitués indépendamment sur carbone par un ou plusieurs R²¹;

R¹⁹, R²⁰, R²⁴ et R²⁶ sont sélectionnés indépendamment parmi halogéno, nitro, cyano, hydroxy, amino, carboxy, carbamoyle, mercapto, sulfamoyle, alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, alcoxy en C₁₋₄, alcanoyloxy en C₁₋₄, alcanoyl(C₁₋₄)oxy, N-(alkyl(C₁₋₄))amino, N,N-(alkyl(C₁₋₄))₂amino, alcanoyl(C₁₋₄)amino, N-(alkyl(C₁₋₄))carbamoyle, N,N-(alkyl(C₁₋₄))₂carbamoyle, alkyl(C₁₋₄)S(O)_a dans lequel a vaut 0 à 2, alcoxy(C₁₋₄)carbonyloxy, N-(alkyl(C₁₋₄)) sulfamoyle, N,N-(alkyl(C₁₋₄))₂sulfamoyle, carbocyclyle, hétérocyclyle, benzyloxy-carbonylamino, (alkyl(C₁₋₄))₃silyloxy, sulfo, sulfino, amidino, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) ou -P(O)(OR^a)(R^b), où R^a et R^b sont sélectionnés indépendamment parmi alkyle en C₁₋₆ ;

où R¹⁹, R²⁰, R²⁴ et R²⁶ peuvent être éventuellement substitués indépendamment sur carbone par un ou plusieurs R²²

R²¹ et R²² sont sélectionnés indépendamment parmi halogéno, hydroxy, cyano, carbamoyle, uréido, amino, nitro, carboxy, carbamoyle, mercapto, sulfamoyle, trifluorométhyle, trifluorométhoxy, méthyle, éthyle, méthoxy, éthoxy, vinyle, allyle, éthynyle, méthoxycarbonyloxy, formyle, acétyle, formamido, acétylamino, acétoxy, méthylamino, diméthylamino, N-méthylcarbamoyle, N,N-diméthylcarbamoyle, méthylthio, méthylsulfinyloxy, mésyle, N-méthylsulfamoyle et N,N-diméthylsulfamoyle ;

R²³ est carboxy, sulfo, sulfino, phosphono, -P(O)(OR^g)(OR^h), -P(O)(OH)(OR^g), -P(O)(OH)(R^g) ou -P(O)(OR^g)(R^h) où R^g et R^h sont sélectionnés indépendamment parmi alkyle en C₁₋₆ ;

R²⁵ est sélectionné parmi alkyle en C₁₋₆, alcanoyloxy en C₁₋₆, alkyl(C₁₋₆)sulfonyloxy, alcoxy(C₁₋₆)carbonyloxy, carbamoyle, N-(alkyl(C₁₋₆))carbamoyle, N,N-(alkyl(C₁₋₆))₂carbamoyle, benzyle, benzyloxy-carbonyloxy, benzoyloxy et phénylsulfonyloxy ; ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.

2. Composé de formule (I) selon la revendication 1, dans laquelle R^v est hydrogène ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.
3. Composé de formule (I) selon l'une quelconque des revendications 1 ou 2, dans laquelle R¹ et R² sont tous deux butyle, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.
4. Composé de formule (I) selon l'une quelconque des revendications 1-3, dans laquelle R^x et R^y sont tous deux hydrogène, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.
5. Composé de formule (I) selon l'une quelconque des revendications 1-4, dans laquelle M est -N- ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.
6. Composé de formule (I) selon l'une quelconque des revendications 1-5, dans lequel v vaut 0, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.

7. Composé de formule (I) selon l'une quelconque des revendications 1-6, dans laquelle R³ et R⁶ sont hydrogène, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.

5 8. Composé de formule (I) selon l'une quelconque des revendications 1-7, dans laquelle R⁴ est bromo, méthyle ou méthylthio ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.

10 9. Composé de formule (I) selon l'une quelconque des revendications 1-8, dans laquelle R⁵ est un groupement de formule (IA) (telle qu'illustrée selon la revendication 1) dans laquelle :

X est -O- ;

le Cycle A est phényle éventuellement substitué par un ou plusieurs substituants sélectionnés parmi R¹⁷ ;

n vaut 1 ;

15 R⁷ est hydrogène ;

R⁸ est hydrogène ;

R⁹ est hydrogène ;

m vaut 0 ;

20 R¹¹ est carboxy, un groupement de formule (IB) (telle qu'illustrée ci-dessus) ou un groupement de formule (IC) (telle qu'illustrée ci-dessus) dans lesquelles :

R¹² est hydrogène ou alkyle en C₁₋₄ ;

p vaut 1 ou 2 ;

25 R¹³ est hydrogène ou alkyle en C₁₋₆ éventuellement substitué par R²⁰ où R²⁰ est hydroxy, carbamoyl, amino, benzyloxycarbonylamino, alkyl(C₁₋₄)S(O)_a dans lequel a vaut 0 ou (alkyl(C₁₋₄))₃silyle ;

R¹⁴ est hydrogène ou hydroxy ou alkyle en C₁₋₆; dans lequel R¹⁴ peut éventuellement être substitué par un ou plusieurs substituants sélectionnés parmi R²⁰ ;

Y est -N(Rⁿ)C(O)- dans lequel Rⁿ est hydrogène ;

q vaut 0 ou 1 ;

r vaut 0 ou 1 ;

30 R¹⁵ est carboxy ou sulfo ;

R¹⁷ est hydroxy ; et

R²⁰ est sélectionné parmi hydroxy ;

le Cycle B est pyrrolidin-1-yle ou azétidinyle substitué sur carbone par un groupement sélectionné parmi R²³, et éventuellement substitué en outre sur carbone par un ou plusieurs R²⁴ ; où R²³ est carboxy et R²⁴ est hydroxy ;

35 ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.

40 10. Composé de formule (I) (telle qu'illustrée selon la revendication 1) dans laquelle :

R^v est hydrogène ;

R¹ et R² sont tous deux butyle ;

R^x et R^y sont tous deux hydrogène ;

M est -N- ;

45 v vaut 0 ;

R³ et R⁶ sont hydrogène ;

R⁴ est bromo, méthyle ou méthylthio ; et

50 R⁵ est N-((R)-α-[N-(carboxyméthyl)carbamoyl]-benzyl)carbamoylméthoxy, N-((R)-α-[N-(2-sulfoéthyl)carbamoyl]-4-hydroxybenzyl)carbamoylméthoxy, N-((R)-α-[N-((S)-1-carboxy-2-hydroxyéthyl)carbamoyl]benzyl)-carbamoylméthoxy, N-((R)-α-[N-((S)-1-carboxy-éthyl)carbamoyl]benzyl)carbamoylméthoxy, N-((R)-α-[N-((S)-1-carboxypropyl)carbamoyl]benzyl)carbamoylméthoxy, N-((R)-α-[N-((R)-1-carboxy-2-méthylthioéthyl)-carbamoyl]benzyl)carbamoylméthoxy, N-((R)-α-[N-((S)-1-carboxy-2-carbamoyléthyl)carbamoyl]benzyl)-carbamoylméthoxy, N-((R)-α-[N-(2-sulfoéthyl)carbamoyl]-4-hydroxybenzyl)-carbamoylméthoxy, N-((R)-α-[N-(carboxyméthyl)-carbamoyl]-4-hydroxybenzyl)carbamoylméthoxy, N-((R)-α-[N-((S)-1-carboxyéthyl)carbamoyl]-4-hydroxybenzyl)carbamoylméthoxy, N-((R)-α-[N-((S)-1-carboxy-2-hydroxyéthyl)carbamoyl]-4-hydroxybenzyl)carbamoylméthoxy, N-((R)-α-[N-(2-sulfoéthyl)carbamoyl]benzyl)carbamoylméthoxy, N-((R)-α-[N-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl)carbamoylméthoxy, N-((R)-α-[N-((S)-1-carboxy-2-méthylpropyl)carbamoyl]benzyl)carbamoylméthoxy, N-((R)-α-[N-((S)-1-carboxy-3-méthylbutyl)carbamoyl]ben-

zyl}carbamoylméthoxy, N-((R)- α -[N-(1-(S)-1-carboxy-2-(S)-2-méthylbutyl)carbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -carboxy-4-hydroxybenzyl)carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxy-4-aminobutyl)carbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxy-4-(benzyloxy-carbonylamino)butyl)carbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-2-carboxypyrrolidin-1-ylcarbonyl)benzyl}carbamoylméthoxy, N-((R)- α -[N-(carboxyméthyl)-N-méthylcarbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -[N-(1-(R)-2-(R)-1-carboxy-1-hydroxyprop-2-yl)carbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -[N-(sulfométhyl)carbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -carboxybenzyl)carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxy-2-méthylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy, N-((R)- α -[N-((R)-1-carboxy-2-méthylthioéthyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-[N-((S)-2-hydroxy-1-carboxyéthyl)carbamoyl]-propyl}carbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -[2-(S)-2-(carboxy)-4(R)-4-(hydroxy)pyrrolidin-1-ylcarbonyl]benzyl}carbamoylméthoxy, N-((R)- α -[2-(S)-2-(carboxy)azétidin-1-ylcarbonyl]benzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-[N-((S)-1-carboxyéthyl)carbamoyl]éthyl}carbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -[N-((R)-1-carboxy-3,3-diméthylbutyl)carbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxy-3,3-diméthylbutyl)carbamoyl]benzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxy-3,3-diméthylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy, N-((R)- α -[N-((S)-1-carboxy-2-(triméthylsilyl)éthyl]carbâmoyl]-4-hydroxybenzyl}carbamoylméthoxy ou N-((R)- α -[N-((R)-1-carboxy-2-(triméthylsilyl)éthyl]carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy,

ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.

11. Composé de formule (I) choisi parmi :

- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((R)-1-carboxy-2-méthylthio-éthyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxy-2-méthylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxypropyl)carbamoyl]benzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxyéthyl)carbamoyl]benzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxyéthyl)carbamoyl]-4-hydroxybenzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxy-2-méthylthioéthyl)carbamoyl]-benzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-[N-((S)-2-hydroxy-1-carboxyéthyl)-carbamoyl]propyl}carbamoyl]benzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ; et
- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxy-2-méthylpropyl)carbamoyl]benzyl}carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;

ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.

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12. Composé de formule (I) choisi parmi :

- la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-(N-((R)- α -[N-((S)-1-carboxypropyl)carbamoyl]-4-hydroxyben-

zyl}, carbamoylméthoxy)-2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ; et
 la 1,1-dioxo-3,3-dibutyl-5-phényl-7-méthylthio-8-[N-((R)- α -carboxy-4-hydroxybenzyl)carbamoylméthoxy]-
 2,3,4,5-tétrahydro-1,2,5-benzothiadiazépine ;

5 ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un
 amide hydrolysable *in vivo* de celui-ci.

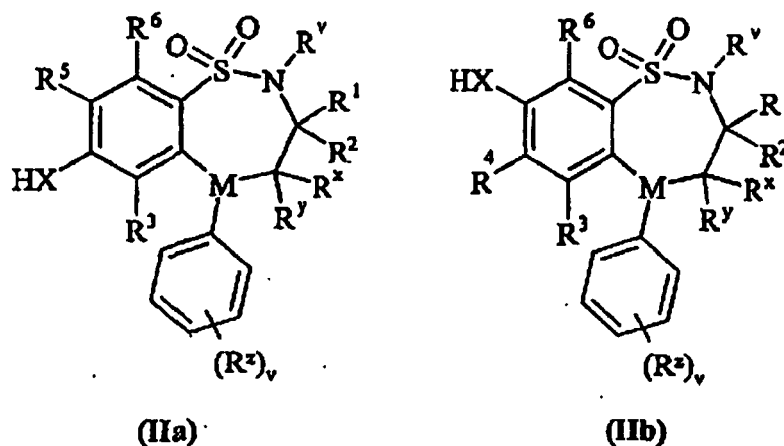
13. Procédé de préparation d'un composé de formule (I) selon les revendications 1-11 ou d'un sel ou solvat pharma-
 ceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo*
 10 de celui-ci lequel procédé comprend :

Procédé 1) : pour les composés de formule (I) dans laquelle X est -O-, -NR^a ou -S- ; la réaction d'un composé
 de formule (IIa) ou (IIb) :

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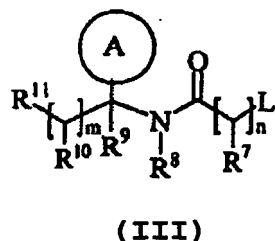


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avec un composé de formule (III) :

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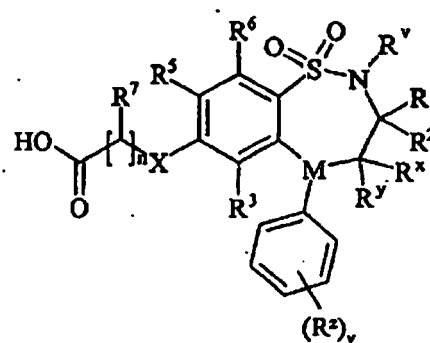
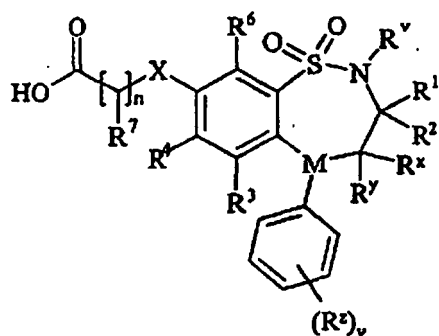


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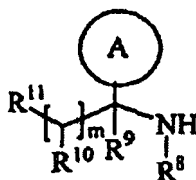
dans laquelle L est un groupement mobile ;
Procédé 2) : la réaction d'un acide de formule (IVa) ou (IVb) :

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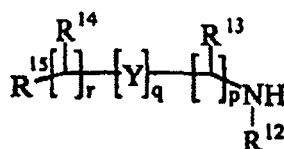
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ou d'un dérivé activé de celui-ci ; avec une amine de formule (V) :



30 Procédé 3) : pour les composés de formule (I) dans laquelle R¹¹ est un groupement de formule (IB) ; la réaction d'un composé de formule (I) dans laquelle R¹¹ est carboxy avec une amine de formule (VI) :

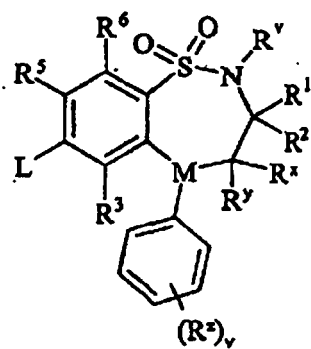


40 Procédé 4) : pour les composés de formule (I) dans laquelle l'un parmi R⁴ et R⁵ est sélectionné indépendamment parmi alkyl(C₁₋₆)thio éventuellement substitué sur carbone par un ou plusieurs R¹⁷ ; la réaction d'un composé de formule (VIIa) ou (VIIb) :

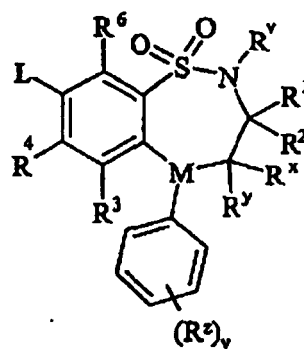
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(VIIa)

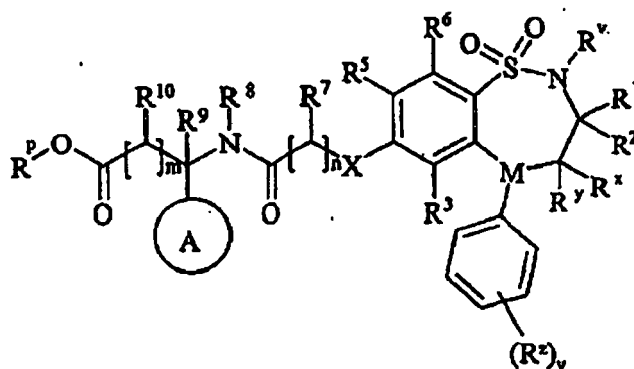


(VIIb)

dans laquelle L est un groupement mobile ; avec un thiol de formule (VIII) :



dans laquelle R^m est alkyl (C_{1-6}) thio éventuellement substitué sur carbone par un ou plusieurs R^{16} ;
Procédé 5) : pour les composés de formule (I) dans lequel R^{11} est carboxy ; la déprotection d'un composé de
 formule (IXa) :



(IXa)

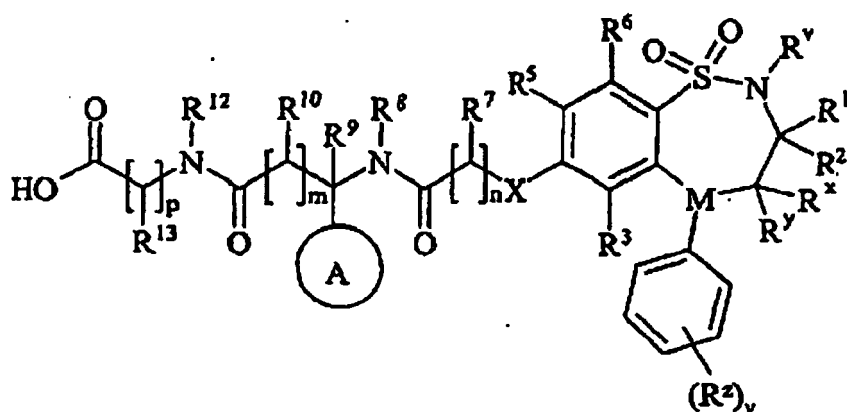
ou (IXb) :

dans laquelle R^p, conjointement avec le groupement -OC(O)- auquel il est lié, forme un ester ;
 Ou Procédé 7) : pour les composés de formule (I) dans laquelle R¹¹ est un groupement de formule (IB) et est
 -N(Rⁿ)C(O)- ; la réaction d'un acide de formule (XIa) :

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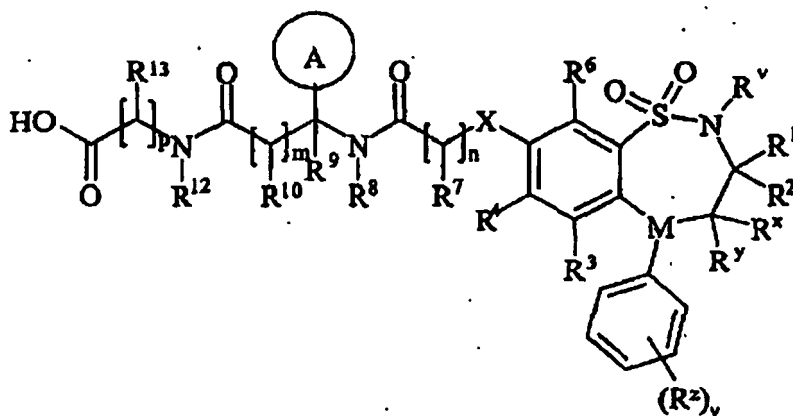
(XIa)

ou (XIb) :

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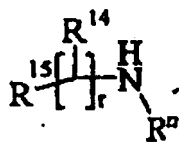
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(XIb)

ou d'un dérivé activé de celui-ci ; avec une amine de formule (XII) :

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(XII)

et ensuite, si nécessaire ou désirable :

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- i) la conversion d'un composé de formule (I) en un autre composé de formule (I) ;
- ii) l'élimination des éventuels groupements protecteurs ;
- iii) la formation d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydroly-

sable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci.

- 5 14. Composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, pour une utilisation comme médicament.
- 10 15. Composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, pour une utilisation dans une méthode de traitement prophylactique ou thérapeutique d'un animal à sang chaud, tel que l'homme.
- 15 16. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, dans la fabrication d'un médicament pour une utilisation dans la production d'un effet d'inhibition d'IBAT chez un animal à sang chaud, tel que l'homme.
- 20 17. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, dans la production d'un effet d'inhibition d'IBAT chez un animal à sang chaud, tel que l'homme.
- 25 18. Composition pharmaceutique comprenant un composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, en association avec un diluant ou véhicule pharmaceutiquement acceptable.
- 30 19. Composition pharmaceutique comprenant un composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel ou une pro-drogue de celui-ci, selon l'une quelconque des revendications 1 à 12, et un inhibiteur de la HMG Co-A réductase, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, en association avec un diluant ou véhicule pharmaceutiquement acceptable.
- 35 20. Composition pharmaceutique comprenant un composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, et un chélateur des acides biliaires, en association avec un diluant ou véhicule pharmaceutiquement acceptable.
- 40 21. Composition pharmaceutique comprenant un composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, et un inhibiteur de la HMG Co-A réductase, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel ou une pro-drogue de celui-ci, et un chélateur des acides biliaires, en association avec un diluant ou véhicule pharmaceutiquement acceptable.
- 45 22. Composition, association ou utilisation selon les revendications 19, 21, 30, 32, 33 ou 35, dans laquelle l'inhibiteur de la HMG Co-A réductase est l'atorvastatine, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celle-ci.
- 50 23. Composition, association ou utilisation selon les revendications 19, 21, 30, 32, 33 ou 35, dans laquelle l'inhibiteur de la HMG Co-A réductase est la rosuvastatine, ou un sel pharmaceutiquement acceptable de celle-ci.
- 55 24. Composition pharmaceutique comprenant un composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, et un agoniste de PPAR alpha et/ou gamma, ou un sel pharmaceutiquement acceptable de celui-ci, en association avec un diluant ou véhicule pharmaceutiquement acceptable.
25. Composition selon l'une quelconque des revendications 24, 42 ou 43, dans laquelle l'agoniste de PPAR alpha et/ou gamma est l'acide (S)-2-éthoxy-3-[4-(2-{4-méthanesulfonyloxyphényl}éthoxy)phényl]propanoïque ou un sel pharmaceutiquement acceptable de celui-ci.

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26. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, dans la fabrication d'un médicament pour une utilisation dans le traitement de conditions d'hyperlipidémie chez un animal à sang chaud, tel que l'homme.
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27. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, dans la fabrication d'un médicament pour une utilisation dans le traitement de conditions de dyslipidémie et de troubles tels que l'hyperlipidémie, l'hypertriglycéridémie, l'hyperbêtalipoprotéïnémie (LDL élevées), l'hyperprébetalipoprotéïnémie (VLDL élevées), l'hyperchylomicronémie, l'hypolipoprotéïnémie, l'hypercholestérolémie, l'hyperlipoprotéïnémie et l'hypoalphalipoprotéïnémie (HDL faibles) chez un animal à sang chaud, tel que l'homme.
- 15
28. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, dans la fabrication d'un médicament pour une utilisation dans le traitement de différentes conditions cliniques telles que l'athérosclérose, l'artériosclérose, l'arythmie, les conditions hyperthrombotiques, le dysfonctionnement vasculaire, le dysfonctionnement endothélial, l'insuffisance cardiaque, les maladies coronariennes, les maladies cardiovasculaires, l'infarctus du myocarde, l'angine de poitrine, les maladies vasculaires périphériques, les inflammations des tissus cardiovasculaires tels que le cœur, les valvules, la vascularisation, les artères et veines, les anévrismes, la sténose, la resténose, les plaques vasculaires, les stries lipidiques vasculaires, les infiltrations de leucocytes, monocytes et/ou macrophages, l'épaississement de l'intima, le désépaississement de la media, les traumatismes infectieux et chirurgicaux et la thrombose vasculaire, les accidents vasculaires cérébraux et les attaques ischémiques transitoires chez un animal à sang chaud, tel que l'homme.
- 20
29. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, dans la fabrication d'un médicament pour une utilisation dans le traitement de l'athérosclérose, des maladies coronariennes, de l'infarctus du myocarde, de l'angine de poitrine, des maladies vasculaires périphériques, des accidents vasculaires cérébraux et des attaques ischémiques transitoires chez un animal à sang chaud, tel que l'homme.
- 25
30. Association comprenant un composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel ou une pro-drogue de celui-ci, selon l'une quelconque des revendications 1 à 12, et un inhibiteur de HMG Co-A réductase, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.
- 30
31. Association comprenant un composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, et un liant d'acides biliaires.
- 35
32. Association comprenant un composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel ou une pro-drogue de celui-ci, selon l'une quelconque des revendications 1 à 12, et un inhibiteur de HMG Co-A réductase, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, et un liant d'acides biliaires.
- 40
33. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel ou d'une pro-drogue de celui-ci, selon l'une quelconque des revendications 1 à 12, d'un inhibiteur de HMG Co-A réductase, ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, dans la fabrication d'un médicament pour une utilisation dans le traitement de conditions d'hyperlipidémie chez un animal à sang chaud, tel que l'homme.
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34. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, d'un liant d'acides biliaires, dans la fabrication d'un médicament pour une utilisation dans le traitement de conditions d'hyperlipidémie chez un animal à sang chaud, tel que l'homme.
- 50
35. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, d'un liant d'acides biliaires, dans la fabrication d'un médicament pour une utilisation dans le traitement de conditions d'hyperlipidémie chez un animal à sang chaud, tel que l'homme.
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sel ou d'une pro-drogue de celui-ci, selon l'une quelconque des revendications 1 à 12, d'un inhibiteur de HMG Co-A réductase, ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, et d'un liant d'acides biliaires, dans la fabrication d'un médicament pour une utilisation dans le traitement de conditions d'hyperlipidémie chez un animal à sang chaud, tel que l'homme.

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36. Composition, association ou utilisation selon l'une quelconque des revendications 20, 21, 31, 32, 34 et 35, dans laquelle le liant d'acides biliaires est une résine.

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37. Composition, association ou utilisation selon l'une quelconque des revendications 20, 21, 31, 32, 34 et 35, dans laquelle le liant d'acides biliaires est la cholestyramine ou le cholestipol.

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38. Traitement associatif comprenant l'administration d'une quantité efficace d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, éventuellement conjointement avec un diluant ou véhicule pharmaceutiquement acceptable, avec l'administration simultanée, séquentielle ou séparée d'un antagoniste de l'absorption du cholestérol.

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39. Traitement associatif selon la revendication 38, dans lequel l'antagoniste de l'absorption du cholestérol est une azétidinone.

40. Traitement associatif selon la revendication 38 ou la revendication 39, dans lequel l'antagoniste de l'absorption du cholestérol est le SCH 58235.

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41. Composition, association ou utilisation selon les revendications 19, 21, 30, 32, 33 ou 35, dans laquelle l'inhibiteur de HMG Co-A réductase est la fluvastatine, la lovastatine, la pravastatine, la simvastatine, l'atorvastatine, la céri-vastatine, la bervastatine, la dalvastatine, la mévastatine ou la rosuvastatine, ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci.

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42. Association comprenant un composé de formule (I), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci, selon l'une quelconque des revendications 1 à 12, et un agoniste de PPAR alpha et/ou gamma, ou un sel pharmaceutiquement acceptable de celui-ci.

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43. Utilisation d'un composé de formule (I), ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel ou d'une pro-drogue de celui-ci, selon l'une quelconque des revendications 1 à 12, et d'un agoniste de PPAR alpha et/ou gamma, ou d'un sel ou solvat pharmaceutiquement acceptable, d'un solvat d'un tel sel, d'un ester hydrolysable *in vivo* ou d'un amide hydrolysable *in vivo* de celui-ci, dans la fabrication d'un médicament pour une utilisation dans le traitement de conditions d'hyperlipidémie chez un animal à sang chaud, tel que l'homme.

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44. Composé de formule (IXa), (IXb), (Xa) ou (Xb), ou un sel ou solvat pharmaceutiquement acceptable, un solvat d'un tel sel, un ester hydrolysable *in vivo* ou un amide hydrolysable *in vivo* de celui-ci.

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