SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SIC

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 05-595

54 **TITULO** DERIVADOS DE DIFENILAZETIDINONA PARA TRATAR TRASTORNOS DEL METABOLISMO DE LIPIDOS

51 **CLASIFICACION INTERNACIONAL**

71 **SOLICITANTE** ASTRAZENECA AB

DOMICILIO SODERTALJE, SUECIA

74 **APODERADO** JUAN PABLO CADENA SARMIENTO

22 **SANTAFE DE BOGOTA, D.C.**

(FORMA P 10)

Oficina de Comunicaciones

PETITORIO

AS 95 933

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion 05000595 00000000 Folios 254
Fecha (AMD): 2005-01-05 16:42:47
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad

☐ Capítulo I ☒ Capítulo II

2 SOLICITANTE (71)	Nombre **ASTRAZENECA AB** Dirección. S-151 85 Sodertalje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución Suecia Teléfono: Fax: E-mail	**IDENTIFICACION** C C ☐ NIT ☐ C E. ☐ Otro ☐ Cual_____ Número
3 REPRESENTANTE O APODERADO	Nombre. **JUAN PABLO CADENA SARMIENTO** Dirección Cra. 7 No. 16-56 Piso 9 Teléfono 380-2200 Fax. 380-2700 E-mail	**IDENTIFICACION** C.C ☒ NIT ☐ C E. ☐ Otro ☐ Cual_____ Número 80 410 337 TP 57492
4 INVENTOR (ES) (72)	Nombre: INGEMAR STARKE, MIKAEL ULF JOHAN DAHLSTROM, ANN-MARGRET LINDQVIST, MATS PETER NORDBERG, TORE SKJARET, MALIN ANITA LEMURELL Dirección. AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE, AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE, AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE, AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE, AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE, AstraZeneca R & D Mölndal, S-431 83 Mölndal, Suecia (Respectivam) Nacionalidad o Domicilio: Suecia (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/GB2003/002811 Fecha 01-07-2003
Publicación Internacional No. WO 2004/005247 A1 Fecha 15-01-2004

Título (54): DERIVADOS DE DIFENILAZETIDINONA PARA TRATAR TRASTORNOS DEL METABOLISMO DE LIPIDOS

7 Clasificación Internacional (51) C07D 205/08

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	GB	05-07-2002	0215579 4

9 Comprobante de pago No. 04-93-170-y-05-625 **Fecha** 03-01-2005

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

10 ANEXOS

2

- [x] Comprobante de pago de la tasa de presentación de la solicitud $443.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [x] Otros: Tarjeta de propietarios.

11 FIGURA CARACTERÍSTICA.

12 FIRMA(S) DEL(LOS) SOLICITANTE(S)

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

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

NIT 800.176089-2

SUPERINDUSTRIA Y COMERCIO

Radicacion 05000595 00000000 Folios: 054

Fecha (AMD) 2005-01-05 16 42:47

Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA 04 - 93,170

FECHA DICIEMBRE 1 DE 2004

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
BR.BARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	28028759	01/12/2004	23,220,000 00

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

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL DE PATENTE DE IN	422,000 00
		TOTAL $	422,000 00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT 800.176089-2

CERTIFICACION DE EXCEDENTE 05 - 625
FECHA ENERO 4 DE 2005

SUPERINDUSTRIA Y COMERCIO
Radicacion 05000595 00000000 Folios: 254
Fecha (AMD): 2005-01-05 16:42:47
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	28028773	04/01/2005	1,747,000 00

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

CANT	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	21,000 00
			TOTAL : $	21,000 00

SON VEINTIUNO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO

AS' 95 P33
X
5

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/005247 A1

(51) International Patent Classification[7] C07D 205/08 409/12, A61K 31/397 A61P 3/06, 9/10

(21) International Application Number: PCT/GB2003/002811

(22) International Filing Date: 1 July 2003 (01.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data
0215579.4 5 July 2002 (05.07.2002) GB

(71) Applicant (*for all designated States except MG US*): ASTRAZENECA AB [SE/SE] Sodertalje, S-151 85 (SE).

(71) Applicant (*for MG only*): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): STARKE, Ingemar [SE/SE] AstraZeneca R & D Molndal S-431 83 Molndal (SE). DAHLSTROM, Mikael, Ulf, Johan [FI/SE] AstraZeneca R & D Molndal, S-431 83 Molndal (SE). LINDQVIST, Ann-Margret [SE/SE] AstraZeneca R & D Molndal S-431 83 Molndal (SE). NORDBERG, Mats, Peter [SE/SE] AstraZeneca R & D Molndal S-431 83 Molndal (SE). SKJARET, Tore [NO/SE] AstraZeneca R & D Molndal, S-431 83 Molndal (SE). LEMURELL, Malin, Anita [SE/SE] AstraZeneca R & D Molndal, S-431 83 Molndal (SE)

(74) Agent: ASTRAZENECA Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

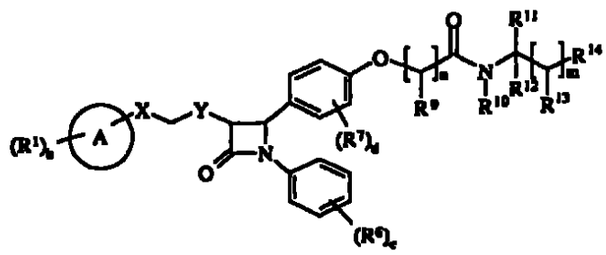
(81) Designated States (*national*): AE, AG, AL, AM, AT AU AZ, BA, BB BG, BR, BY, BZ, CA, CH, CN CO, CR, CU CZ, DE, DK, DM DZ, EC, EE, ES, FI GB GD, GE, GH GM HR, HU ID, IL, IN IS JP KE, KG KP KR, KZ, LC, LK, LR, LS, LT LU LV MA MD MG MK, MN MW MX MZ, NI NO NZ, OM PG PH, PL, PT RO, RU SC SD SE, SG SK,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

(84) Designated States (*regional*): ARIPO patent (GH GM, KE, LS MW MZ, SD, SL, SZ, TZ, UG ZM, ZW), Eurasian patent (AM AZ, BY KG KZ, MD RU TJ TM), European patent (AT BE, BG CH CY CZ, DE, DK, EE, ES FI FR, GB GR, HU IE, IT LU MC, NL, PT RO SE, SI SK, TR), OAPI patent (BF BJ CF CG CI, CM, GA, GN GQ, GW ML, MR, NE, SN TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DIPHENYLAZETIDINONE DERIVATIVES FOR TREATING DISORDERS OF THE LIPID METABOLISM



(I)

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

WO 2004/005247 A1

DIPHENYLAZETIDINONE DERIVATIVES FOR TREATING DISORDERS OF THE LIPID METABOLISM

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

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

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

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

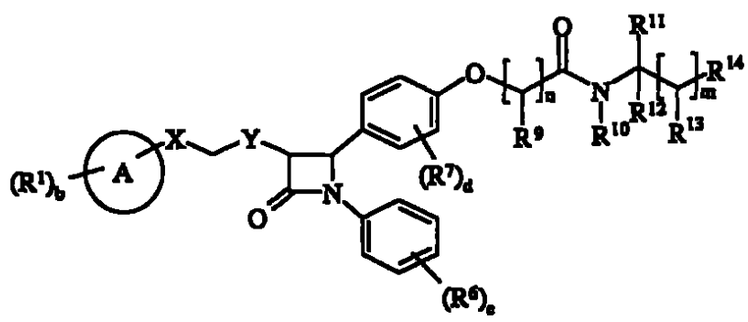
A clear association between reduction of total cholesterol and (LDL) cholesterol and decreased instance of coronary artery disease has been established, and several classes of pharmaceutical agents are used to control serum cholesterol There major options to regulate plasma cholesterol include (i) blocking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

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

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

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

Accordingly there is provided a compound of formula (I)



(I)

wherein

Ring A is selected from phenyl or thienyl,

X is selected from $-CR^2R^3-$, $-O-$, $-NR^z-$ and $-S(O)_a-$, wherein R^z is hydrogen or C_{1-6}alkyl, and a is 0-2,

Y is selected from $-CR^4R^5-$, $-O-$, $-NR^z-$ and $-S(O)_a-$, wherein R^z is hydrogen or C_{1-6}alkyl, and a is 0-2, wherein there is at least one $-CR^2R^3-$ or $-CR^4R^5-$ group,

R^1 is independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy and C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, wherein R^1 is independently optionally substituted on carbon by one or more halo, C_{1-6}alkoxy and hydroxy;

b is 0-3, wherein the values of R^1 may be the same or different,

R^2 and R^3 are independently selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy and C_{1-6}alkanoyloxy; wherein R^2 and R^3 may be independently optionally substituted on carbon by one or more halo or hydroxy; or R^2 and R^3 together form an oxo group,

R^4 and R^5 are independently selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy and C_{1-6}alkanoyloxy; or R^4 and R^5 together form an oxo group,

R^6 is independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, formyl, carbamoyl, carbamoyloxy, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkenyloxy, 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, C_{1-6}alkanoyl-*N*-(C_{1-6}alkyl)amino, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)carbamoyl, *N*,*N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)carbamoyloxy, *N*,*N*-(C_{1-6}alkyl)$_2$carbamoyloxy, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkoxycarbonyl-*N*-(C_{1-6}alkyl)amino, C_{1-6}alkoxycarbonyloxy, C_{1-6}alkoxycarbonylamino, ureido, *N'*-(C_{1-6}alkyl)ureido, *N*-(C_{1-6}alkyl)ureido, *N'*,*N'*-(C_{1-6}alkyl)$_2$ureido, *N'*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkyl)ureido, *N'*,*N'*-(C_{1-6}alkyl)$_2$-*N*-(C_{1-6}alkyl)ureido,

N-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenyl, wherein R^7 is independently optionally substituted on carbon by one or more halo, C_{1-6}alkoxy, hydroxy, amino, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl-*N*-(C_{1-6}alkyl)amino, phenyl, phenoxy, benzoyl, phenylC_{1-6}alkyl and phenylC_{1-6}alkoxy;

c is 0-5, wherein the values of R^6 may be the same or different,

R^7 is 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,

d is 0-4, wherein the values of R^7 may be the same or different,

R^9 is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, wherein R^9 may be optionally substituted on carbon by one or more substituents selected from R^{29}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{24},

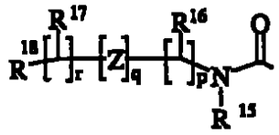
R^{10} is hydrogen or C_{1-4}alkyl,

R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, or R^{11} and R^{12} together form C_{2-6}alkylene, wherein R^{11} and R^{12} or R^{11} and R^{12} together may be independently optionally substituted on carbon by one or more substituents selected from R^{25}, and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{26},

R^{13} is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, wherein R^{13} may be optionally substituted on carbon by one or more substituents selected from R^{27}, and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{28},

R^{14} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1\ 10}$alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkoxycarbonyl, $C_{1\ 10}$alkanoyl, $C_{1\ 10}$alkanoyloxy, *N*-($C_{1\ 10}$alkyl)amino, *N,N*-($C_{1\ 10}$alkyl)$_2$amino, *N,N,N*-(C_{1-10}alkyl)$_3$ammonio, $C_{1\ 10}$alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-($C_{1\ 10}$alkyl)$_2$carbamoyl, $C_{1\ 10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1\ 10}$alkyl)sulphamoyl, *N,N*-($C_{1\ 10}$alkyl)$_2$sulphamoyl, *N*-($C_{1\ 10}$alkyl)sulphamoylamino,

N,N-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{29}-(C_{1-10}alkylene)$_f$-, heterocyclyl-(C_{1-10}alkylene)$_g$-R^{30}-(C_{1-10}alkylene)$_h$-, carboxy, sulpho, sulphino, phosphono, -P(O)(OR^{31})(OR^{32}), -P(O)(OH)(OR^{31}), -P(O)(OH)(R^{31}) or -P(O)(OR^{31})(R^{32}) wherein R^{31} and R^{32} are independently selected from C_{1-6}alkyl, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{34}, or R^{14} is a group of formula (IA)



(IA)

wherein,

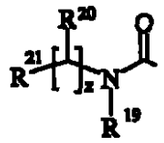
Z is –N(R^{35})-, -N(R^{35})C(O)-, -O-, and -S(O)$_a$-, wherein a is 0-2 and R^{35} is hydrogen or C_{1-4}alkyl,

R^{15} is hydrogen or C_{1-4}alkyl,

R^{16} and R^{17} are independently selected from hydrogen, 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, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, -P(O)(OR^{36})(OR^{37}), -P(O)(OH)(OR^{36}), -P(O)(OH)(R^{36}) or -P(O)(OR^{36})(R^{37}), wherein R^{36} and R^{37} are independently selected from C_{1-6}alkyl, wherein R^{16} and R^{17} may be independently optionally substituted on carbon by one or more substituents selected from R^{38}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{39},

R^{18} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, C_{1-10}alkoxycarbonyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl,

N,N-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{40}-(C_{1-10}alkylene)$_f$- or heterocyclyl-(C_{1-10}alkylene)$_g$-R^{41}-(C_{1-10}alkylene)$_h$-, carboxy, sulpho, sulphino, phosphono, -P(O)(OR^{42})(OR^{43}), -P(O)(OH)(OR^{42}), -P(O)(OH)(R^{42}) or -P(O)(OR^{42})(R^{43}) wherein R^{42} and R^{43} are independently selected from C_{1-6}alkyl, wherein R^{18} may be optionally substituted on carbon by one or more substituents selected from R^{44}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{45}, or R^{18} is a group of formula (IB)



(IB)

wherein

R^{19} is selected from hydrogen or C_{1-6}alkyl,

R^{20} is selected from hydrogen, 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}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, -P(O)(OR^{46})(OR^{47}), -P(O)(OH)(OR^{46}), -P(O)(OH)(R^{46}) or -P(O)(OR^{46})(R^{47}), wherein R^{46} and R^{47} are independently selected from C_{1-6}alkyl, where R^{20} may be independently optionally substituted on carbon by one or more substituents selected from R^{48}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{49},

R^{21} is selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkoxycarbonyl, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, *N,N N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkyl$S(O)_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl,

carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_s$-R^{50}-(C_{1-10}alkylene)$_r$-, heterocyclyl-(C_{1-10}alkylene)$_s$-R^{51}-(C_{1-10}alkylene)$_r$-, carboxy, sulpho, sulphino, phosphono, -P(O)(OR^{52})(OR^{53}), -P(O)(OH)(OR^{52}), -P(O)(OH)(R^{52}) or -P(O)(OR^{53})(R^{53}) wherein R^{52} and R^{53} are independently selected from C_{1-6}alkyl, wherein R^{21} may be independently optionally substituted on carbon by one or more R^{54}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{55},

p is 1-3, wherein the values of R^{16} may be the same or different;

q is 0-1,

r is 0-3, wherein the values of R^{17} may be the same or different;

m is 0-2, wherein the values of R^{13} may be the same or different,

n is 1-2, wherein the values of R^{9} may be the same or different,

z is 0-3, wherein the values of R^{20} may be the same or different,

R^{23}, R^{25}, R^{27}, R^{33}, R^{38}, R^{44}, R^{48} and R^{54} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, C_{1-10}alkoxycarbonyl, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, *N,N N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_s$-R^{56}-(C_{1-10}alkylene)$_r$-, heterocyclyl-(C_{1-10}alkylene)$_s$-R^{57}-(C_{1-10}alkylene)$_r$-, carboxy, sulpho, sulphino, amidino, phosphono, -P(O)(OR^{58})(OR^{59}), -P(O)(OH)(OR^{58}), -P(O)(OH)(R^{58}) or -P(O)(OR^{59})(R^{59}), wherein R^{58} and R^{59} are independently selected from C_{1-6}alkyl, wherein R^{23}, R^{25}, R^{27}, R^{33}, R^{38}, R^{44}, R^{48} and R^{54} may be independently optionally substituted on carbon by one or more R^{60}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{61},

R^{24}, R^{26}, R^{28}, R^{34}, R^{39}, R^{45}, R^{49}, R^{55} and R^{61} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N N*-(C_{1-6}alkyl)$_2$carbamoyl, benzyl, phenethyl, benzoyl, phenylsulphonyl and phenyl,

R^{29}, R^{30}, R^{40}, R^{41}, R^{50}, R^{51}, R^{56} and R^{57} are independently selected from -O-, -NR^{62}-, -$S(O)_x$-, -$NR^{62}C(O)NR^{63}$-, -$NR^{62}C(S)NR^{63}$-, -OC(O)N=C-, -$NR^{62}C(O)$- or -$C(O)NR^{62}$-, wherein R^{62} and R^{63} are independently selected from hydrogen or C_{1-6}alkyl, and x is 0-2,

R^{60} is 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, and

e, f, g and h are independently selected from 0-2,

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

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only For example, "C_{1-10}alkyl", "C_{1-6}alkyl" and "C_{1-4}alkyl" include propyl, isopropyl and *t*-butyl However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only A similar convention applies to other radicals, for example "phenylC_{1-6}alkyl" would include benzyl, 1-phenylethyl and 2-phenylethyl The term "halo" refers to fluoro, chloro, bromo and iodo

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

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form the S-oxides Particularly a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form S-oxide(s) Examples and suitable values of the term "heterocyclyl" are thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouracilyl,

1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-azabicyclo[2 2 1]heptyl, 4-thiazolidonyl, morpholino, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, 2,3-dihydrobenzofuranyl, benzothienyl, tetrahydropyranyl, piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholino, 1,1-dioxothiomorpholino, tetrahydropyranyl, 1,3-dioxolanyl, homopiperazinyl, thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, pyranyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl and 1-isoquinolonyl

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- Particularly "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 More particularly "carbocyclyl" is cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl or 1-oxoindanyl

An example of "C_{1-10}alkanoyloxy" and "C_{1-6}alkanoyloxy" is acetoxy Examples of "C_{1-10}alkoxycarbonyl" and "C_{1-6}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl Examples of "C_{1-10}alkoxy" and "C_{1-6}alkoxy" include methoxy, ethoxy and propoxy Examples of "C_{1-10}alkanoylamino" and "C_{1-6}alkanoylamino" include formamido, acetamido and propionylamino Examples of "C_{1-6}alkanoyl-*N*-(C_{1-6}alkyl)amino" include acetyl-*N*-methylamino and propionyl-*N*-ethyl-amino Examples of "C_{1-10}alkyl$S(O)_a$ wherein a is 0 to 2" and "C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl Examples of "C_{1-10}alkanoyl" and "C_{1-6}alkanoyl" include C_{1-3}alkanoyl, propionyl and acetyl Examples of "*N*-(C_{1-10}alkyl)amino" and "*N*-(C_{1-6}alkyl)amino" include methylamino and ethylamino Examples of "*N N*-(C_{1-10}alkyl)$_2$amino" and "*N,N*-(C_{1-6}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino Examples of "C_{2-10}alkenyl" and "C_{2-6}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-10}alkynyl" and "C_{2-6}alkynyl" are ethynyl, 1-propynyl and 2-propynyl Examples of "C_{2-6}alkylene" are ethylene, propylene and butylene Examples of "C_{2-6}alkenyloxy" are vinyloxy, allyloxy and 1-propenyloxy Examples of "*N*-(C_{1-10}alkyl)sulphamoyl" and "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(C_{1-3}alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl Examples of "*N*-(C_{1-10}alkyl)$_2$sulphamoyl" and "*N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and

N-(methyl)-*N*-(ethyl)sulphamoyl Examples of "*N*-(C_{1-10}alkyl)carbamoyl" and "*N*-(C_{1-6}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl Examples of "*N,N*-(C_{1-10}alkyl)$_2$carbamoyl" and "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl Examples of "*N*-(C_{1-10}alkyl)carbamoyl" and "*N*-(C_{1-6}alkyl)carbamoyloxy" are methylaminocarbonyloxy and ethylaminocarbonyloxy Examples of "*N,N*-(C_{1-10}alkyl)$_2$carbamoyl" and "*N,N*-(C_{1-6}alkyl)$_2$carbamoyloxy" are dimethylaminocarbonyloxy and methylethylaminocarbonyloxy Examples of "C_{1-6}alkylsulphonyl" are mesyl and ethylsulphonyl Examples of "C_{1-10}alkylsulphonylamino" and "C_{1-6}alkylsulphonylamino" are mesylamino and ethylsulphonylamino Examples of "C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino" are mesyl-*N*-methylamino and ethylsulphonyl-*N*-propylamino Examples of "*N'*-(C_{1-6}alkyl)ureido" are *N'*-methylureido and *N'*-*s*-propylureido Examples of "*N*-(C_{1-6}alkyl)ureido" are *N*-methylureido and *N*-*i*-propylureido Examples of "*N',N'*-(C_{1-6}alkyl)$_2$ureido" are *N',N'*-dimethylureido and *N'*-methyl-*N'*-ethylureido. Examples of "*N'*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkyl)ureido" are *N',N*-dimethylureido and *N'*-methyl-*N*-ethylureido. Examples of "*N',N'*-(C_{1-6}alkyl)$_2$-*N*-(C_{1-6}alkyl)ureido" are *N',N'*-dimethyl-*N*-methylureido and *N'*-methyl-*N'*-ethyl-*N*-*t*-butylureido Examples of "*N,N,N*-(C_{1-10}alkyl)$_3$ammonio" are trimethylamino and methyldiethylamino Examples of "C_{1-10}alkoxycarbonylamino" and "C_{1-6}alkoxycarbonylamino" are methoxycarbonylamino and *t*-butoxycarbonylamino. Examples of "*N*-(C_{1-10}alkyl)sulphamoylamino" are *N*-methylsulphamoylamino and *N*-ethylsulphamoylamino. Examples of "*N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino" are *N,N*-dimethylsulphamoylamino and *N*-methyl-N-ethylsulphamoylamino. Examples of "carbocyclylC_{1-10}alkyl" include benzyl and phenethyl. Examples of "heterocyclylC_{1-10}alkyl" include 2-morpholinopropyl and pyridylmethyl Examples of "phenylC_{1-6}alkoxy" include 2-phenylethoxy and 2-phenylpropoxy

A suitable pharmaceutically acceptable salt of a compound of the invention, or other compounds disclosed herein, is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric, acetate or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a

physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine

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

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

An *in vivo* hydrolysable ester of a compound of the formula (I), or other compounds disclosed herein, containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

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

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

encompasses all such optical, diastereoisomers and geometric isomers that possess cholesterol absorption inhibitory activity

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

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

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

Ring A is selected from thienyl

Ring A is selected from phenyl.

X is $-CR^2R^3-$

X is -O-

X is $-NR^z-$, wherein R^z is hydrogen or C_{1-6}alkyl

X is $-S(O)_a-$, wherein a is 0-2

X is $-CR^2R^3-$ wherein one of R^2 and R^3 is hydrogen and the other is hydroxy

X is $-CH_2-$

X is -CH(OH)-

X is -C(O)-

X is -S-

X is -S(O)-

X is $-S(O)_2-$

X is selected from $-CR^2R^3-$, -O- and $-S(O)_a-$, wherein a is 0-2.

X is selected from $-CR^2R^3-$, -O- and $-S(O)_a-$, wherein a is 0-2, and R^2 and R^3 are independently selected from hydrogen and hydroxy; or R^2 and R^3 together form an oxo group

X is selected from $-CH_2-$, -CH(OH)-, -C(O)-, -O- -S-, -S(O)-and $-S(O)_2-$

Y is $-CR^4R^5-$

Y is -O-

Y is $-NR^z-$, wherein R^z is hydrogen or C_{1-6}alkyl

Y is $-S(O)_a-$, wherein a is 0-2.

Y is $-CR^4R^5-$ wherein R^4 and R^5 are both hydrogen.

Y is $-CH_2-$

Y is -S-

Y is -S(O)-

Y is selected from $-CR^4R^5-$ and $-S(O)_a-$, a is 0 or 1

Y is selected from $-CR^4R^5-$ and $-S(O)_a-$, a is 0 or 1, wherein R^4 and R^5 are both hydrogen.

Y is $-CH_2-$, -S- or -S(O)-

X is $-CR^2R^3-$ and Y is $-CR^4R^5-$ wherein one of R^2 and R^3 is hydrogen and the other is hydroxy, and wherein R^4 and R^5 are both hydrogen.

X is $-CH_2-$ and Y is -S-

X is -C(O)- and Y is -S-

X is $-CH_2-$ and Y is -S(O)-.

X is -C(O)- and Y is -S(O)-

X is $-CH_2-$ and Y is $-S(O)_2-$

X is -C(O)- and Y is $-S(O)_2-$

X is -O- and Y is $-CH_2-$

X is -CHOH- and Y is $-S(O)_a-$, wherein a is 0-2.

X is -CHOH- and Y is -S-

X is - CHOH- and Y is -S(O)-

X is - CHOH- and Y is $-S(O)_2-$

R^1 is halo

R^1 is fluoro

R^1 is 4-fluoro if Ring A is phenyl

b is 0-2, wherein the values of R^1 may be the same or different.

b is 0-1

b is 1

b is 0

b is 1, wherein the substituent is para to the X group if Ring A is phenyl

R^2 and R^3 are independently selected from hydrogen and hydroxy, or R^2 and R^3 together form an oxo group

R^2 and R^3 are independently selected from hydrogen and hydroxy

One of R^2 and R^3 is hydrogen and the other is hydroxy

R^4 and R^5 are both hydrogen.

R^6 is halo or C_{1-6}alkoxy

R^6 is halo.

R^6 is fluoro or methoxy

R^6 is fluoro

R^6 is 4-fluoro or 4-methoxy

R^6 is 4-fluoro

c is 0-2, wherein the values of R^6 may be the same or different.

c is 0-1

c is 1

c is 0

c is 1, wherein the substituent is para to the nitrogen of the azetidin-2-one ring.

R^7 is halo, methoxy or ethoxy

R^7 is fluoro or methoxy

d is 0-2, wherein the values of R^7 may be the same or different.

d is 0-1

d is 0

R^9 is hydrogen

R^{10} is hydrogen.

R^{11} and R^{12} are independently selected from hydrogen or carbocyclyl

R^{11} and R^{12} are independently selected from hydrogen or phenyl

One of R^{11} and R^{12} is hydrogen and the other is phenyl or both R^{11} and R^{12} are hydrogen.

R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl or carbocyclyl, wherein R^{11} and R^{12} may be independently optionally substituted on carbon by one or more substituents selected from R^{25}

R^{11} and R^{12} are independently selected from hydrogen, methyl, ethyl, butyl, isobutyl or phenyl, wherein R^{11} and R^{12} may be independently optionally substituted on carbon by one or more substituents selected from R^{25}

R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl or carbocyclyl, wherein R^{11} and R^{12} may be independently optionally substituted on carbon by one or more substituents selected from R^{25}, wherein R^{25} is selected from hydroxy, amino, carbamoyl, C_{1-10}alkoxycarbonyl, C_{1-10}alkoxycarbonylamino, carbocyclyl or carboxy; wherein R^{25} may be optionally substituted on carbon by one or more R^{60}, wherein R^{60} is hydroxy

R^{11} and R^{12} are independently selected from hydrogen, methyl, ethyl, butyl, isobutyl or phenyl, wherein R^{11} and R^{12} may be independently optionally substituted on carbon by one or more substituents selected from R^{25}, wherein R^{25} is selected from hydroxy, amino, carbamoyl, ethoxycarbonyl, *t*-butoxycarbonylamino, phenyl or carboxy; wherein R^{25} may be optionally substituted on carbon by one or more R^{60}, wherein R^{60} is hydroxy

R^{11} and R^{12} are independently selected from hydrogen, methyl, hydroxymethyl, 2-carbamoylethyl, 2-(ethoxycarbonyl)ethyl, 2-carboxyethyl, 4-(*t*-butoxycarbonylamino)butyl, 4-aminobutyl, isobutyl, phenyl, 4-hydroxyphenyl and 4-hydroxybenzyl.

One of R^{11} and R^{12} is hydrogen and the other is selected from hydrogen, methyl, hydroxymethyl, 2-carbamoylethyl, 2-(ethoxycarbonyl)ethyl, 2-carboxyethyl, 4-(*t*-butoxycarbonylamino)butyl, 4-aminobutyl, isobutyl, phenyl, 4-hydroxyphenyl and 4-hydroxybenzyl

R^{13} is hydrogen

R^{14} is $C_{1\ 10}$alkyl, $C_{1\ 10}$alkoxycarbonyl or carboxy, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{35}, or R^{14} is a group of formula (IA) as depicted above

R^{14} is C_{1-6}alkyl, C_{1-6}alkoxycarbonyl or carboxy; wherein R^{14} may be optionally substituted on carbon by one or more hydroxy; or R^{14} is a group of formula (IA) as depicted above.

R^{14} is 1,2,3,4,5-pentahydroxypentyl, *t*-butoxycarbonyl or carboxy, or R^{14} is a group of formula (IA) as depicted above

R^{14} is hydroxy, $C_{1\ 10}$alkyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkoxycarbonyl, carboxy or sulpho, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, or R^{14} is a group of formula (IA) (as depicted above)

R^{14} is hydroxy, pentyl, methoxy, ethoxycarbonyl, *t*-butoxycarbonyl, carboxy or sulpho, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, or R^{14} is a group of formula (IA) (as depicted above)

R^{15} is hydrogen.

R^{16} and R^{17} are independently selected from hydrogen, carboxy or C_{1-6}alkoxycarbonyl

R^{16} and R^{17} are independently selected from hydrogen, carboxy or *t*-butoxycarbonyl

One of R^{16} and R^{17} is hydrogen, and the other is hydrogen, carboxy or *t*-butoxycarbonyl

R^{16} and R^{17} are independently selected from hydrogen, carboxy, C_{1-6}alkyl and C_{1-6}alkoxycarbonyl

R^{16} and R^{17} are independently selected from hydrogen, carboxy, C_{1-6}alkyl and *t*-butoxycarbonyl.

R^{18} is selected from hydroxy, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkoxycarbonyl or carboxy

R^{18} is selected from hydroxy, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl or carboxy

R^{18} is selected from hydroxy, *t*-butoxy, *t*-butoxycarbonyl or carboxy

R^{18} is selected from hydroxy, $C_{1\ 10}$alkyl, $C_{1\ 10}$alkoxy, C_{1-10}alkoxycarbonyl, carboxy and sulpho

R^{18} is selected from hydroxy, methyl, *t*-butoxy, ethoxycarbonyl, *t*-butoxycarbonyl, carboxy and sulpho

p is 1

q is 0

r is 0 or 1

m is 0.

m is 1

m is 0 or 1

n is 1

R^{14} is hydroxy, $C_{1\ 10}$alkyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkoxycarbonyl, carboxy or sulpho, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, or R^{14} is a group of formula (IA) (as depicted above) wherein

R^{15} is hydrogen,

R^{16} and R^{17} are independently selected from hydrogen, carboxy, C_{1-6}alkyl and C_{1-6}alkoxycarbonyl,

R^{18} is selected from hydroxy, $C_{1\ 10}$alkyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkoxycarbonyl, carboxy and sulpho,

p is 1,

q is 0,

r is 0 or 1,

m is 0 or 1,

n is 1, and

R^{33} is hydroxy

R^{14} is hydroxy, pentyl, methoxy, ethoxycarbonyl, *t*-butoxycarbonyl, carboxy or sulpho, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, or R^{14} is a group of formula (IA) (as depicted above) wherein

R^{15} is hydrogen,

R^{16} and R^{17} are independently selected from hydrogen, carboxy, C_{1-6}alkyl and *t*-butoxycarbonyl,

R^{18} is selected from hydroxy, methyl, *t*-butoxy, ethoxycarbonyl, *t*-butoxycarbonyl, carboxy and sulpho,

p is 1,

q is 0;

r is 0 or 1,

m is 0 or 1,

n is 1, and

R^{33} is hydroxy

R^{25} is selected from hydroxy, amino, carbamoyl, $C_{1\ 10}$alkoxycarbonyl, $C_{1\ 10}$alkoxycarbonylamino, carbocyclyl or carboxy, wherein R^{25} may be optionally substituted on carbon by one or more R^{60}

R^{25} is selected from hydroxy, amino, carbamoyl, ethoxycarbonyl, *t*-butoxycarbonylamino, phenyl or carboxy; wherein R^{25} may be optionally substituted on carbon by one or more R^{60}

R^{25} is selected from hydroxy, amino, carbamoyl, $C_{1\ 10}$alkoxycarbonyl, $C_{1\ 10}$alkoxycarbonylamino, carbocyclyl or carboxy, wherein R^{25} may be optionally substituted on carbon by one or more R^{60}, wherein R^{60} is hydroxy

R^{25} is selected from hydroxy, amino, carbamoyl, ethoxycarbonyl, *t*-butoxycarbonylamino, phenyl or carboxy, wherein R^{25} may be optionally substituted on carbon by one or more R^{60}, wherein R^{60} is hydroxy

R^{33} is hydroxy

R^{60} is hydroxy

The side chain R^{14}-[$C(R^{13})_m$-$C(R^{11})(R^{12})$-$N(R^{10})$-C(O)-$[C(R^5)]_n$-O- is *N*-(2-sulphoethyl)carbamoylmethoxy; *N*-(carboxymethyl)carbamoylmethoxy; *N*-(2-hydroxyethyl)carbamoylmethoxy; *N*-(2-methoxyethyl)carbamoylmethoxy; *N*-[2-(carboxy)ethyl]carbamoylmethoxy, *N*-[(S)-1-(carboxy)ethyl]carbamoylmethoxy; *N*-[(R)-1-(carboxy)ethyl]carbamoylmethoxy, *N*-[(S)-α-(carboxy)benzyl]carbamoylmethoxy,

N-[(R)-α-(carboxy)benzyl]carbamoylmethoxy;

N-(*t*-butoxycarbonylmethyl)carbamoylmethoxy;

N-[2-(*t*-butoxycarbonyl)ethyl]carbamoylmethoxy,

N-[(S)-1,3-bis-(carboxy)propyl]carbamoylmethoxy,

N-((R)-1-carboxy-3-methylbutyl)carbamoylmethoxy;

N-[(S)-1-(*t*-butoxycarbonyl)ethyl]carbamoylmethoxy;

N-[(R)-1-(*t*-butoxycarbonyl)ethyl]carbamoylmethoxy;

N-[(R)-α-(*t*-butoxycarbonyl)benzyl]carbamoylmethoxy;

N-[(S)-1-(carboxy)-5-(amino)pentyl]carbamoylmethoxy;

N-[(R)-1-(carboxy)-2-(hydroxy)ethyl]carbamoylmethoxy;

N-[(S)-1,3-bis-(ethoxycarbonyl)propyl]carbamoylmethoxy;

N-[(R)-α-(carboxy)-4-(hydroxy)benzyl]carbamoylmethoxy;

N-[*N*-(carboxymethyl)carbamoylmethyl]carbamoylmethoxy;

N-[(S)-1-(carboxy)-3-(carbamoyl)propyl]carbamoylmethoxy,

N-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-[*N*-(methoxycarbonylmethyl)carbamoylmethyl]carbamoylmethoxy;

N-((S)-1-{*N*-[(S)-1-(carboxy)ethyl]carbamoyl}ethyl)carbamoylmethoxy,

N-((2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoylmethoxy;

N-{(R)-α-[*N*-(*t*-butoxycarbonylmethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy;

N-{*N*-[(R)-1-(carboxy)-2-(hydroxy)ethyl]carbamoylmethyl}carbamoylmethoxy;

N-[(S)-1-(*t*-butoxycarbonyl)-5-(*t*-butoxycarbonylamino)pentyl]carbamoylmethoxy;

N-((S)-1-{*N*-[(S)-1-(*t*-butoxycarbonyl)ethyl]carbamoyl}ethyl)carbamoylmethoxy;

N-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]4-hydroxybenzyl}carbamoylmethoxy,

N-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy,

N-{*N*-[(R)-1-(*t*-butoxycarbonyl)-2-(*t*-butoxy)ethyl]carbamoylmethyl}carbamoylmethoxy; or

N-((R)-α-{*N*-(S)-[1-(*t*-butoxycarbonyl)-2-(*t*-butoxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy

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

Ring A is phenyl,

X is $-CR^2R^3-$,

Y is $-CR^4R^5-$,

R^1 is halo,

b is 1,

One of R^2 and R^3 is hydrogen and the other is hydroxy;

R^4 and R^5 are both hydrogen,

R^6 is halo,

c is 1,

d is 0,

R^9 is hydrogen,

R^{10} is hydrogen,

R^{11} and R^{12} are independently selected from hydrogen or carbocyclyl,

R^{14} is $C_{1\ 10}$alkyl, $C_{1\ 10}$alkoxycarbonyl or carboxy; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, or R^{14} is a group of formula (IA) as depicted above,

R^{15} is hydrogen,

R^{16} and R^{17} are independently selected from hydrogen, carboxy or C_{1-6}alkoxycarbonyl,

R^{18} is selected from hydroxy, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkoxycarbonyl or carboxy,

p is 1,

q is 0,

r is 0 or 1,

m is 0,

n is 1,

R^{33} is hydroxy;

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

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

Ring A is selected from phenyl,

X is $-CR^2R^3-$ and Y is $-CR^4R^5-$ wherein one of R^2 and R^3 is hydrogen and the other is hydroxy; and wherein R^4 and R^5 are both hydrogen,

R^1 is 4-fluoro,

b is 1,

R^6 is 4-fluoro;

c is 1,

d is 0,

R^9 is hydrogen,

R^{10} is hydrogen,

One of R^{11} and R^{12} is hydrogen and the other is phenyl or both R^{11} and R^{12} are hydrogen,

R^{14} is 1,2,3,4,5-pentahydroxypentyl, *t*-butoxycarbonyl or carboxy; or R^{14} is a group of formula (IA) as depicted above,

R^{15} is hydrogen,

One of R^{16} and R^{17} is hydrogen, and the other is hydrogen, carboxy or *t*-butoxycarbonyl,

R^{18} is selected from hydroxy, *t*-butoxy, *t*-butoxycarbonyl or carboxy,

p is 1,

q is 0,

r is 0 or 1,

m is 0,

n is 1,

R^{33} is hydroxy;

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

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

Ring A is selected from phenyl or thienyl,

X is selected from $-CR^2R^3-$, -O- and $-S(O)_a-$, wherein a is 0-2, and R^2 and R^3 are independently selected from hydrogen and hydroxy, or R^2 and R^3 together form an oxo group,

Y is selected from $-CR^4R^5-$ and $-S(O)_a-$, a is 0 or 1, wherein R^4 and R^5 are both hydrogen,

R^1 is halo,

b is 0-1,

R^6 is halo,

c is 0-1,

d is 0,

R^9 is hydrogen,

R^{10} is hydrogen,

R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl or carbocyclyl, wherein R^{11} and R^{12} may be independently optionally substituted on carbon by one or more

substituents selected from R^{25}, wherein R^{25} is selected from hydroxy, amino, carbamoyl, C_{1-10}alkoxycarbonyl, C_{1-10}alkoxycarbonylamino, carbocyclyl or carboxy, wherein R^{25} may be optionally substituted on carbon by one or more R^{60}, wherein R^{60} is hydroxy;

R^{13} is hydrogen,

R^{14} is hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, C_{1-10}alkoxycarbonyl, carboxy or sulpho, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, or R^{14} is a group of formula (IA) (as depicted above) wherein

R^{15} is hydrogen,

R^{16} and R^{17} are independently selected from hydrogen, carboxy, C_{1-6}alkyl and C_{1-6}alkoxycarbonyl,

R^{18} is selected from hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, C_{1-10}alkoxycarbonyl, carboxy and sulpho,

p is 1,

q is 0,

r is 0 or 1,

m is 0 or 1,

n is 1, and

R^{33} is hydroxy;

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

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

Ring A is selected from phenyl or thienyl,

X is selected from $-CH_2-$, -CH(OH)-, -C(O)-, -O- -S-, -S(O)-and $-S(O)_2-$,

Y is $-CH_2-$, -S- or -S(O)-,

R^1 is fluoro,

b is 0-1,

R^6 is fluoro,

c is 0-1,

d is 0,

R^9 is hydrogen,

R^{10} is hydrogen,

One of R^{11} and R^{12} is hydrogen and the other is selected from hydrogen, methyl, hydroxymethyl, 2-carbamoylethyl, 2-(ethoxycarbonyl)ethyl, 2-carboxyethyl,

4-(*t*-butoxycarbonylamino)butyl, 4-aminobutyl, isobutyl, phenyl, 4-hydroxyphenyl and 4-hydroxybenzyl,

R^{13} is hydrogen,

R^{14} is hydroxy, pentyl, methoxy, ethoxycarbonyl, *t*-butoxycarbonyl, carboxy or sulpho, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{35}, or R^{14} is a group of formula (IA) (as depicted above) wherein,

R^{15} is hydrogen,

R^{16} and R^{17} are independently selected from hydrogen, carboxy, C_{1-6}alkyl and *t*-butoxycarbonyl,

R^{18} is selected from hydroxy, methyl, *t*-butoxy, ethoxycarbonyl, *t*-butoxycarbonyl, carboxy and sulpho,

p is 1,

q is 0,

r is 0 or 1,

m is 0 or 1,

n is 1, and

R^{35} is hydroxy;

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

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

In another aspect of the invention, preferred compounds of the invention are:

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

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(R)-α-(carboxy)benzyl]carbamoylmethoxy}phenyl)azetidin-2-one,

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one,

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[*N*-(carboxymethyl)carbamoylmethyl]carbamoylmethoxy}phenyl)azetidin-2-one,

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(2-hydroxyethyl)carbamoylmethoxy]phenyl}azetidin-2-one,

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(2-methoxyethyl) carbamoylmethoxy]phenyl}azetidin-2-one,

3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one,

3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one,

3-(R)-4-(R)-1-(phenyl)-3-[2-(thien-3-yl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one,

3-(R)-4-(R)-1-(phenyl)-3-[2-(thien-3-yl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one,

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

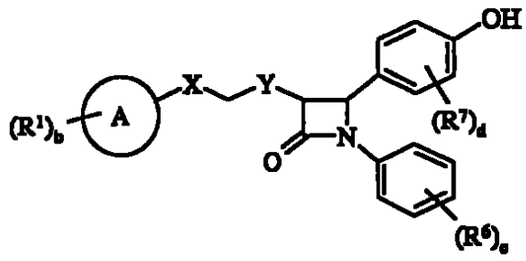
3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one,

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

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

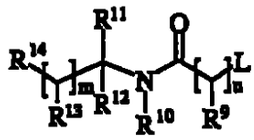
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of

Process 1) reacting a compound of formula (II)



(II)

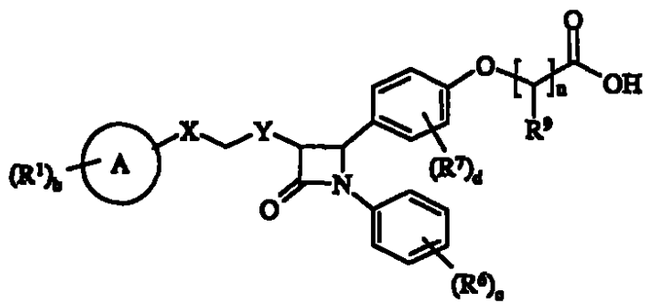
with a compound of formula (III)



(III)

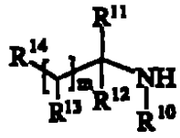
wherein L is a displaceable group,

Process 2) reacting an acid of formula (IV)



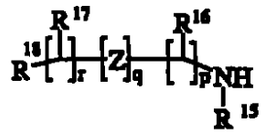
(IV)

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



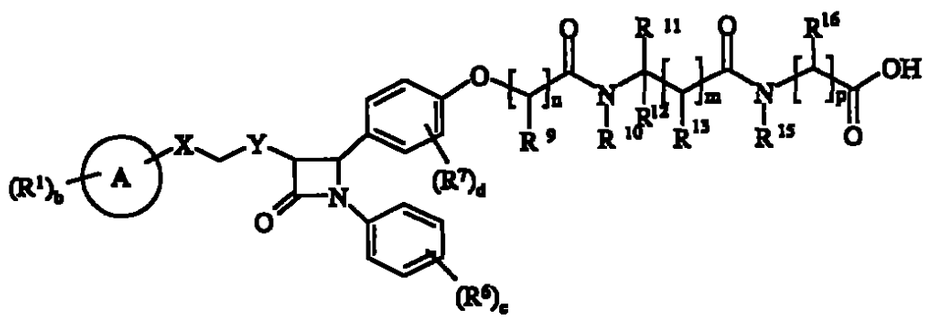
(V)

Process 3). for compounds of formula (I) wherein R^{14} is a group of formula (IA), reacting a compound of formula (VI) wherein R^{14} is carboxy, or an activated derivative thereof, with an amine of formula (VI)·



(VI)

Process 4). for compounds of formula (I) wherein R^{14} is a group of formula (IA), Z is $-N(R^{35})C(O)-$ and q is 1, reacting an acid of formula (VII)



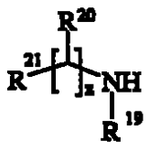
(VII)

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



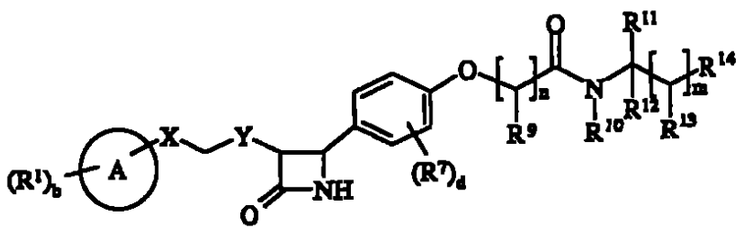
(VIII)

Process 5). for compounds of formula (I) wherein R^{14} is a group of formula (IA) and R^{18} is a group of formula (IB), reacting an acid of formula (I) wherein R^{14} is a group of formula (IA) and R^{18} is carboxy, or an activated derivative thereof, with an amine of formula (IX)



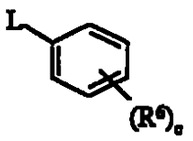
(IX)

Process 6). reacting a compound of formula (X)



(X)

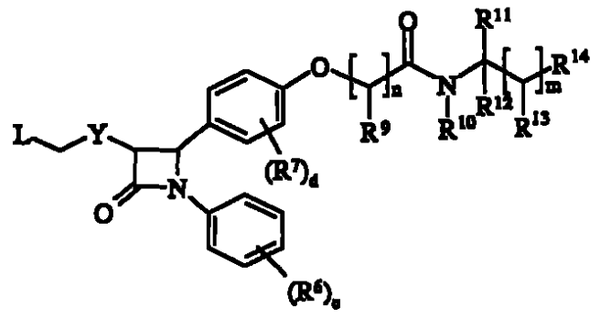
with a compound of formula (XI)



(XI)

wherein L is a displaceable group,

Process 7) for compounds of formula (I) wherein X is selected from -O-, -NR^z- and -$S(O)_a$- wherein a is 0, reacting a compound of formula (XII)



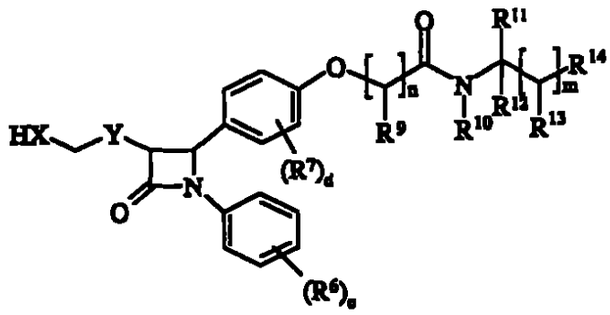
(XII)

wherein L is a displaceable group, with a compound of formula (XIII)



(XIII)

Process 8). for compounds of formula (I) wherein X is selected from -O-, -NR^z- and -$S(O)_a$- wherein a is 0, reacting a compound of formula (XIV)



(XIV)

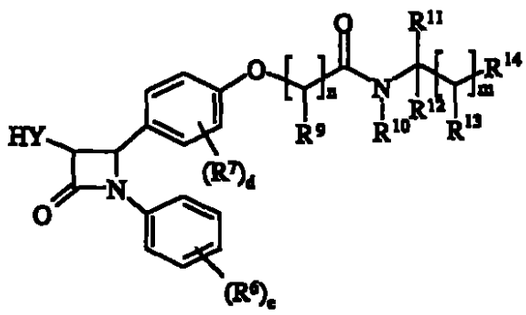
with a compound of formula (XV)



(XV)

wherein L is a displaceable group,

Process 9). for compounds of formula (I) wherein Y is selected from -O-, -NR^z- and -$S(O)_a$- wherein a is 0; reacting a compound of formula (XVI)



(XVI)

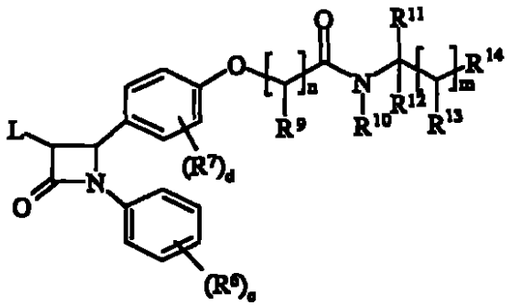
with a compound of formula (XVII):



(XVII)

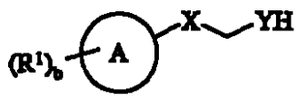
wherein L is a displaceable group,

Process 10). for compounds of formula (I) wherein Y is selected from -O-, -NR^2- and -$S(O)_a$- wherein a is 0, reacting a compound of formula (XVIII)



(XVIII)

wherein L is a displaceable group, with a compound of formula (XIX)



(XIX)

Process 11) for compounds of formula (I) wherein X or Y is -$S(O)_a$- and a is 1 or 2,

oxidizing a compound of formula (I) wherein X or Y is -$S(O)_a$- and a is 0 (for compounds of formula (I) wherein and a is 1 or 2) or a is 1 (for compounds of formula (I) wherein and a is 2),

and thereafter if necessary or desirable.

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

ii) removing any protecting groups,

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

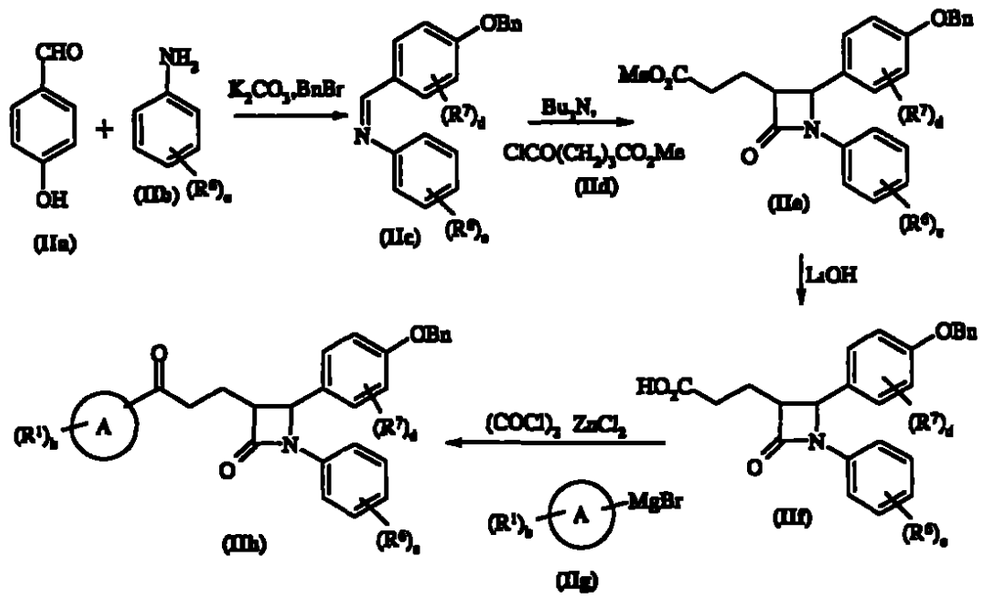
iv) separating two or more enantiomers

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

Specific reaction conditions for the above reactions are as follows

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

Compounds of formula (II) wherein X is $-CR^2R^3-$, Y is selected from $-CR^4R^5-$, R^2 and R^3 together form an oxo group and R^4 and R^5 are both hydrogen, may be prepared according to the following scheme:



Scheme 1

Followed by removal of the benzyl protecting group.

Compounds of formula (II) with different values of X and Y may be prepared by the above scheme, but with modifications that would be known to the skilled man. For example

compound (IIh) could be modified to give other values of R^2 and R^3 or compound (IId) could be substituted for an alternative compound that had the desired functionality, this compound could potentially include Ring A

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)*, *Process 3)*, *Process 4)* and *Process 5)*. Acids and amines may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C

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

Acids of formula (IV) and (VII) may be prepared from compounds of formula (II) by reacting them with the appropriate, optionally protected, side chain using the conditions of *Process 1)*

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

Process 6) Compounds of formula (X) may be reacted with compounds of formula (XI) 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, DMF or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux Alternatively this reaction may be performed using transition metal chemistry known to the skilled person, for example copper or palladium chemistry

Compounds of formula (X) may be prepared according to Scheme 1 with a suitable replacement for compound (IIb), for example benzylamine, followed by debenzylation at an appropriate point in the synthetic scheme.

Compounds of formula (XI) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art. *Process 7), Process 8), Process 9)* and *Process 10)* these compounds may be reacted together in the presence of a base for example an inorganic base such as sodium carbonate, or an organic base such as Hunigs base, in the presence of a suitable solvent such as acetonitrile, dichloromethane or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux

Compounds of formula (XII), (XIV), (XVI) and (XVIII) may be prepared according to Scheme 1 with a suitable replacement for compound (IId)

Compounds of formula (XIII), (XV), (XVII) and (XIX) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 11). These compounds may be oxidised under standard sulphur oxidation conditions, for example using hydrogen peroxide and trifluoroacetic acid at a temperature in the range of 0°C to reflux, preferably at or near room temperature.

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

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

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T W Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999) Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

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

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

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

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

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

In vivo testing of cholesterol absorption inhibitors

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

References

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

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

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

Absorption

The absorption of the compounds of formula (I) was tested in a Caco-2 cells model (Gastroenterology 1989, 96, 736)

The data below shoes that Example 24 shows much lower absorption compared with ezetimibe (US RE37721)

Compound	Example 24	Ezetimibe
Apparent partition coefficient, P_{app} [cm/s]	0.24×10^{-06}	21×10^{-06}

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

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

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

The compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range of approximately 0 02-100 mg/kg, preferably 0 02 –50 mg/kg, and this normally provides a therapeutically-effective dose A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg, particularly 0 1-10 mg/kg is employed. In another aspect a daily dose in the rage of 0 01-20 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

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

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

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

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

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

Herein, where the production of a cholesterol absorption inhibitory effect or a cholesterol lowering effect is stated, suitably this relates to the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man Additionally is relates to the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL) in a warm-blooded animal, such as man Furthermore it relates to the treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks in a warm-blooded animal, such as man It also relates to the treatment of atherosclerosis, coronary heart diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks in a warm-blooded animal, such as man.

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

lesions, a method of inhibiting the destabilization of atherosclerotic lesions, a method for preventing atherosclerotic plaque rupture and a method of treating unstable angina.

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

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

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

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

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

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with cholesterol biosynthesis inhibitors, or pharmaceutically acceptable salts,

solvates, solvates of such salts or prodrugs thereof Suitable cholesterol biosynthesis inhibitors include HMG Co-A reductase inhibitors, squalene synthesis inhibitors and squalene epoxidase inhibitors. A suitable squalene synthesis inhibitor is squalestatin 1 and a suitable squalene epoxidase inhibitor is NB-598

In this aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with an HMG Co-A reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof Suitable HMG Co-A reductase inhibitors, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are statins well known in the art. Particular statins are fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin and rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof A further particular statin is pitvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof A more particular statin is atorvastatin calcium salt. A further particular statin is rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof A preferable particular statin is rosuvastatin calcium salt.

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

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

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

inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier

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

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

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

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

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

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

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

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

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

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

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

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

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

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with an ileal bile acid (IBAT) inhibitor or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof Suitable compounds possessing 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 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/66533, WO 02/50051 and EP 0 864 582 and the compound described in these patent applications, particularly claim 1, are incorporated herein by reference

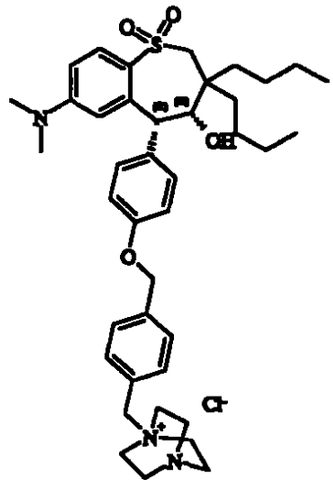
Further suitable compounds possessing IBAT inhibitory activity have been described in WO 94/24087, WO98/07749, WO 98/56757, WO 99/32478, WO 99/35135, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 01/68637, WO 01/68096, WO 02/08211, WO 03/020710, WO 03/022825, WO 03/022830, WO 03/022286, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 489 423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595, EP 869 121 and EP 1 070 703, and the contents of these patent applications, particularly the compounds described in claim 1 and the named examples, are incorporated herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepines Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and / or 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl β-D-glucopyranosiduronic acid (EP 864 582)

A further suitable compound possessing IBAT inhibitory activity is S-8921 (EP 597 107)

A further suitable IBAT inhibitor is the compound.



WO 99/32478

Other particular suitable compound possessing IBAT inhibitory activity include 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N*'-(carboxymethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N*'-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N*'-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine, 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,

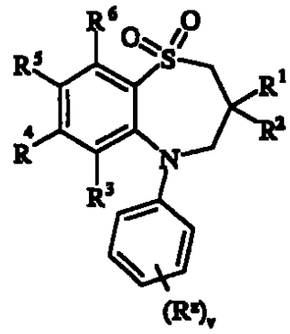
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-(5-carboxypentyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-(2-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-(*R*)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-(*R*)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(*R*)-α-(*N'*-{(*R*)-1-[*N''*-(*R*)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-((ethoxy)(methyl)phosphoryl-methyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(*R*)-α-(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(*R*)-α-(*N'*-{2-[(methyl)(ethyl) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(*R*)-α-(*N'*-{2-[(methyl)(hydroxy) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine,

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

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

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

Additional suitable IBAT inhibitors for combination with compounds of the present invention are those described in WO 03/020710 Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula (AI)



(AI)

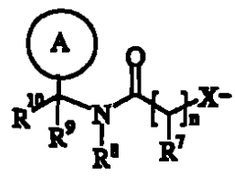
wherein

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^5 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 (AIA)



(AIA)

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_{1-6}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, 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^{17},

X is -O-, -N(R^8)-, -S(O)$_b$- or -CH(R^8)-, wherein R^8 is hydrogen or C_{1-6}alkyl and b is 0-2,

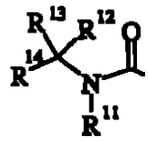
Ring A is aryl or heteroaryl, wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18},

R^7 is hydrogen, C_{1-6}alkyl, carbocyclyl or heterocyclyl, wherein R^7 is optionally substituted on carbon by one or more substituents selected from R^{19}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{20},

R^8 is hydrogen or C_{1-6}alkyl,

R^9 is hydrogen or C_{1-6}alkyl,

R^{10} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1\ 10}$alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkanoyl, $C_{1\ 10}$alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N,N*-($C_{1\ 10}$alkyl)$_2$amino, *N,N,N*-($C_{1\ 10}$alkyl)$_3$ammonio, $C_{1\ 10}$alkanoylamino, *N*-($C_{1\ 10}$alkyl)carbamoyl, *N,N*-($C_{1\ 10}$alkyl)$_2$carbamoyl, $C_{1\ 10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1\ 10}$alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-($C_{1\ 10}$alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, $C_{1\ 10}$alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclyl$C_{1\ 10}$alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{21}-($C_{1\ 10}$alkylene)$_q$- or heterocyclyl-($C_{1\ 10}$alkylene)$_r$-R^{22}-($C_{1\ 10}$alkylene)$_s$-, wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{23}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{24}, or R^{10} is a group of formula (AIB)



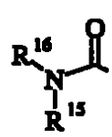
(AIB)

wherein

R^{11} is hydrogen or C_{1-6}alkyl,

R^{12} and R^{13} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkyl$S(O)_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, carbocyclyl or heterocyclyl, wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{26},

R^{14} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N N*-(C_{1-10}alkyl)$_2$amino, *N,N,N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkyl$S(O)_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{27}-(C_{1-10}alkylene)$_q$- or heterocyclyl-(C_{1-10}alkylene)$_r$-R^{28}-(C_{1-10}alkylene)$_s$-, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{30}, or R^{14} is a group of formula (AIC)



(AIC)

R^{15} is hydrogen or C_{1-6}alkyl,

R^{16} is hydrogen or C_{1-6}alkyl, wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31},

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

R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} or R^{31} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, *N,N,N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{32}-(C_{1-10}alkylene)$_q$- or heterocyclyl-(C_{1-10}alkylene)$_r$-R^{33}-(C_{1-10}alkylene)$_s$-, wherein R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} or R^{31} may be independently optionally substituted on carbon by one or more R^{34}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{35},

R^{21}, R^{22}, R^{27}, R^{28}, R^{32} or R^{33} are independently selected from -O-, -NR^{36}-, -S(O)$_x$-, -NR^{36}C(O)NR^{36}-, -NR^{36}C(S)NR^{36}-, -OC(O)N=C-, -NR^{36}C(O)- or -C(O)NR^{36}-, wherein R^{36} is selected from hydrogen or C_{1-6}alkyl, and x is 0-2,

p, q, r and s are independently selected from 0-2,

R^{34} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl, *N,N*-dimethylsulphamoyl, *N*-methylsulphamoylamino and *N,N*-dimethylsulphamoylamino,

R^{20}, R^{24}, R^{26}, R^{30} or R^{35} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl,

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

A particular IBAT inhibitor is selected from any one of Examples 1-44 of WO 03/020710, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-44 are incorporated herein by reference. Claims 1-

10 of WO 03/020710 are also incorporated herein by reference. A particular IBAT inhibitor selected from WO 03/020710 is selected from any one of

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

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,

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

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

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

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

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(1-*t*-butoxycarbonylpiperidin-4-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,

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

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

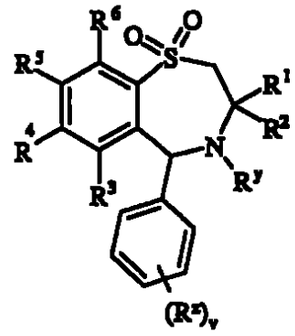
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(2-aminoethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,

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

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

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

Additional suitable IBAT inhibitors for combination with compounds of the present invention are those described in WO 03/022825 Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula (BI)



(BI)

wherein

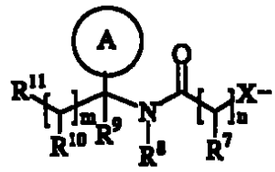
One of R^1 and R^2 are selected from hydrogen or C_{1-6}alkyl and the other is selected from C_{1-6}alkyl,

R^7 is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-4}alkoxy and C_{1-6}alkanoyloxy,

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 (BIA)



(BIA)

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},

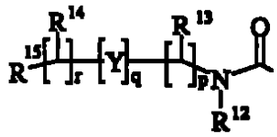
R^7 is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, wherein R^7 is optionally substituted by one or more substituents selected from R^{18},

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 (BIB)



(BIB)

wherein

Y is –N(R^z)-, -N(R^z)C(O)-, -O-, and -S(O)a-, wherein a is 0-2 and R^z is hydrogen or C_{1-4}alkyl,

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

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

R^{15} is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from C_{1-6}alkyl,

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

q is 0-1,

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

m is 0-2, wherein the values of R^{16} may be the same or different;

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

R^{16}, R^{17} and R^{18} are independently selected from halo, nitro, cyano, hydroxy, amino, 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}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl and *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, wherein R^{16}, R^{17} and R^{18} may be independently optionally substituted on carbon by one or more R^{21},

R^{19} and R^{20} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^b), wherein R^a and R^b are independently selected from C_{1-6}alkyl, wherein R^{19} and R^{20} may be independently optionally substituted on carbon by one or more R^{22},

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

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

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

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

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

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

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

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

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

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

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

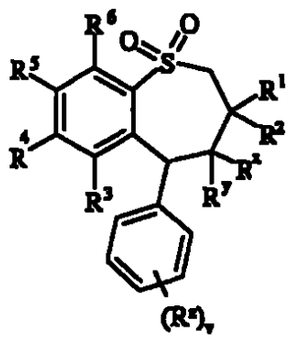
3,5-*trans*-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine ammonia salt,

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

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

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

Additional suitable IBAT inhibitors for combination with compounds of the present invention are those described in WO 03/022830 Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula (CI)



(CI)

wherein.

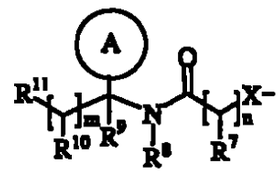
One of R^1 and R^2 are selected from hydrogen or C_{1-6}alkyl and the other is selected from C_{1-6}alkyl,

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,

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 (CIA)



(CIA)

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},

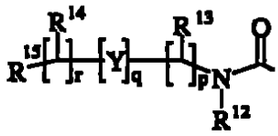
R^7 is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, wherein R^7 is optionally substituted by one or more substituents selected from R^{18},

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 (CIB)



(CIB)

wherein

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

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

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

R^{15} is carboxy, sulpho sulphino, phosphono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^e) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from C_{1-6}alkyl,

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

q is 0-1,

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

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

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

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

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

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

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

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

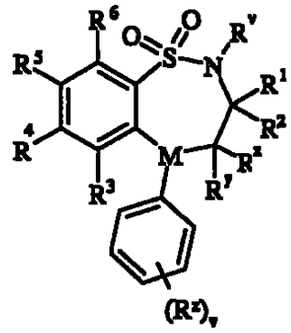
1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine

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

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

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

Additional suitable IBAT inhibitors for combination with compounds of the present invention are those described in WO 03/022286 Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula (DI)



(DI)

wherein

R^7 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,

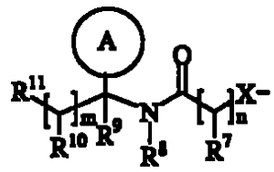
R^z and R^7 are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2,

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 (DIA)



(DIA)

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},

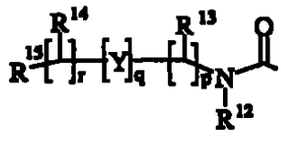
R^7 is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, wherein R^7 is optionally substituted by one or more substituents selected from R^{18},

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

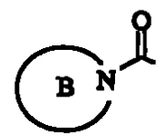
R^9 is hydrogen or C_{1-4}alkyl,

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 (DIB) or (DIC)



(DIB)



(DIC)

wherein

Y is –N(R^n)-, -N(R^n)C(O)-, -N(R^n)C(O)(CR^sR^t)$_v$N(R^n)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 C_{1-4}alkyl optionally substituted by R^{26} and R^n is hydrogen or C_{1-4}alkyl,

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

R^{13} and R^{14} are independently selected from hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, and when q is 0, R^{14} may additionally be selected from hydroxy; wherein R^{13} and R^{14} may be independently optionally substituted by one or more substituents selected from R^{20},

R^{15} is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^a)(OR^f), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^f) wherein R^a and R^f are independently selected from C_{1-6}alkyl,

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

q is 0-1,

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

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

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

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

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

R^{19}, R^{20}, R^{24} and R^{26} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, benzyloxycarbonylamino, sulpho, sulphino, amidino, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^b), wherein R^a and R^b are independently selected from C_{1-6}alkyl, wherein R^{19}, R^{20}, R^{24} and R^{26} may be independently optionally substituted on carbon by one or more R^{22},

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

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

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

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

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

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

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

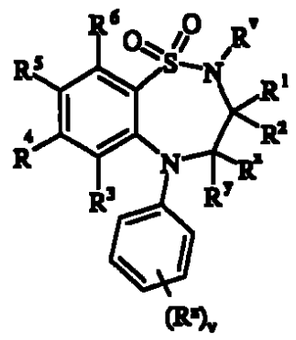
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,

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

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

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, and
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula (EI)



(EI)

wherein

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

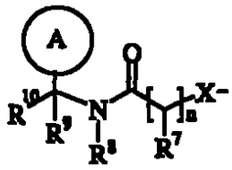
One of R^1 and R^2 are selected from hydrogen or C_{1-6}alkyl and the other is selected from C_{1-6}alkyl,

R^z 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,

R^5 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 (EIA)



(EIA)

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_{1-6}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, 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^{17},

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,

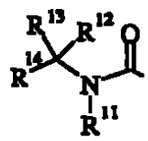
Ring A is aryl or heteroaryl, wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18},

R^7 is hydrogen, C_{1-6}alkyl, carbocyclyl or heterocyclyl, wherein R^7 is optionally substituted on carbon by one or more substituents selected from R^{19}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{20},

R^8 is hydrogen or C_{1-6}alkyl,

R^9 is hydrogen or C_{1-6}alkyl,

R^{10} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1\ 10}$alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkanoyl, $C_{1\ 10}$alkanoyloxy, *N*-($C_{1\ 10}$alkyl)amino, *N*,*N*-($C_{1\ 10}$alkyl)$_2$amino, *N N*,*N*-($C_{1\ 10}$alkyl)$_3$ammonio, $C_{1\ 10}$alkanoylamino, *N*-($C_{1\ 10}$alkyl)carbamoyl, *N*,*N*-($C_{1\ 10}$alkyl)$_2$carbamoyl, $C_{1\ 10}$alkyl*S*(O)$_a$ wherein a is 0 to 2, *N*-($C_{1\ 10}$alkyl)sulphamoyl, *N*,*N*-($C_{1\ 10}$alkyl)$_2$sulphamoyl, *N*-($C_{1\ 10}$alkyl)sulphamoylamino, *N*,*N*-($C_{1\ 10}$alkyl)$_2$sulphamoylamino, $C_{1\ 10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1\ 10}$alkyl, heterocyclyl, heterocyclyl$C_{1\ 10}$alkyl, carbocyclyl-($C_{1\ 10}$alkylene)$_p$-R^{21}-($C_{1\ 10}$alkylene)$_q$- or heterocyclyl-($C_{1\ 10}$alkylene)$_r$-R^{22}-($C_{1\ 10}$alkylene)$_s$-, wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{23}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{24}, or R^{10} is a group of formula (EIB)



(EIB)

wherein

R^{11} is hydrogen or C_{1-6}alkyl,

R^{12} and R^{13} are independently selected from hydrogen, halo, carbamoyl, sulphamoyl, $C_{1\ 10}$alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $C_{1\ 10}$alkanoyl, *N*-($C_{1\ 10}$alkyl)carbamoyl,

N,N-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, carbocyclyl or heterocyclyl, wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{26},

R^{14} is selected from hydrogen, halo, carbamoyl, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkanoyl, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N N*-(C_{1-10}alkyl)$_2$sulphamoylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{27}-(C_{1-10}alkylene)$_q$- or heterocyclyl-(C_{1-10}alkylene)$_r$-R^{28}-(C_{1-10}alkylene)$_s$-, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{30}, or R^{14} is a group of formula (EIC)



(EIC)

R^{15} is hydrogen or C_{1-6}alkyl,

R^{16} is hydrogen or C_{1-6}alkyl, wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31},

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

R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} or R^{31} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, *N,N,N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_p$-R^{32}-(C_{1-10}alkylene)$_q$- or

heterocyclyl-(C_{1-10}alkylene)$_r$-R^{33}-(C_{1-10}alkylene)$_r$-, wherein R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} or R^{31} may be independently optionally substituted on carbon by one or more R^{34}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{35},

R^{21}, R^{22}, R^{27}, R^{28}, R^{32} or R^{33} are independently selected from -O-, -NR^{36}-, -$S(O)_x$-, -$NR^{36}C(O)NR^{36}$-, -$NR^{36}C(S)NR^{36}$-, -OC(O)N=C-, -$NR^{36}C(O)$- or -$C(O)NR^{36}$-, wherein R^{36} is selected from hydrogen or C_{1-6}alkyl, and x is 0-2,

p, q, r and s are independently selected from 0-2,

R^{34} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl, *N,N*-dimethylsulphamoyl, *N*-methylsulphamoylamino and *N N*-dimethylsulphamoylamino,

R^{20}, R^{24}, R^{26}, R^{30} or R^{35} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl,

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

Suitable IBAT inhibitors having the above structure are selected from any one of

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

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

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

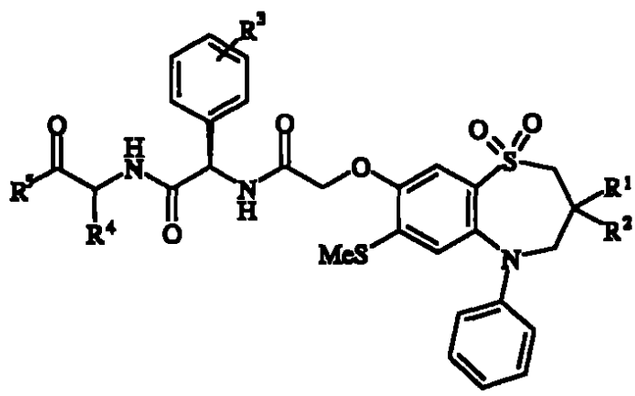
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N*-{2-(S)-[*N*-(carbamoylmethyl)carbamoyl]pyrrolidin-1-ylcarbonylmethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine,

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

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

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

Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula (FI)



(FI)

wherein

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

R^3 is hydrogen, hydroxy or halo,

R^4 is C_{1-4}alkyl optionally substituted by hydroxy, methoxy and methylS(O)a wherein a is 0-2

R^5 is hydroxy or HOC(O)CH(R^6)NH-,

R^6 is selected from hydrogen and C_{1-3}alkyl optionally substituted by hydroxy, methoxy and methylS(O)a wherein a is 0-2,

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; with the proviso that when R^1 and R^2 are both butyl, R^5 is hydroxy and R^4 is methylthiomethyl, methylsulphinylmethyl, methylthiomethyl, hydroxymethyl, methoxymethyl, R^3 is not hydrogen, and with the proviso that when R^1 and R^2 are both butyl, R^5 is HOC(O)CH(R^6)NH-, R^6 is hydroxymethyl and R^4 is hydroxymethyl, R^3 is not hydrogen.

Suitable IBAT inhibitors having the above structure are selected from any one of

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxybutyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-mesylethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1 1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-mesylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxyethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-

methylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,

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

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

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

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

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

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

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

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

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

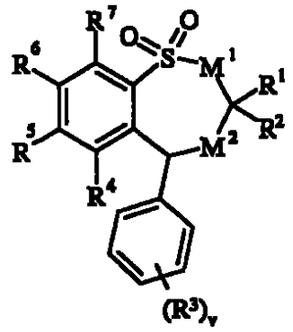
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-mesylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine,

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

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

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

Further suitable IBAT inhibitors are those having the structure (GI)



(GI)

wherein

M^1 is $-CH_2-$ or $-NR^{21}-$,

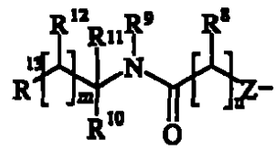
M^2 is $-CR^{22}R^{23}-$ or $-NR^{24}-$, provided that if M^1 is $-NR^{21}-$, M^2 is $-CR^{22}R^{23}-$,

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

R^3 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^5 and R^6 is a group of formula (GIA)



(GIA)

R^4 and R^7 and the other of R^5 and R^6 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^4 and R^7 and the other of R^5 and R^6 may be optionally substituted on carbon by one or more R^{25},

Z 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,

R^8 is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, wherein R^8 may be optionally substituted on carbon by one or more substituents selected from R^{26}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{27},

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

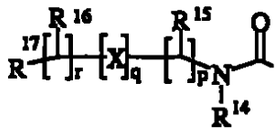
R^{10} and R^{11} are independently selected from hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, or R^{10} and R^{11} together form C_{2-6}alkylene, wherein R^{10} and R^{11} or R^{10} and R^{11} together may be independently optionally substituted on carbon by one or more substituents selected from R^{28}, and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{29},

R^{12} is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, wherein R^{12} may be optionally substituted on carbon by one or more substituents selected from R^{30}, and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{31},

R^{13} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1\ 10}$alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkoxycarbonyl, $C_{1\ 10}$alkanoyl, $C_{1\ 10}$alkanoyloxy, *N*-($C_{1\ 10}$alkyl)amino, *N,N*-($C_{1\ 10}$alkyl)$_2$amino, *N,N,N*-($C_{1\ 10}$alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-($C_{1\ 10}$alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1\ 10}$alkyl)sulphamoyl, *N,N*-($C_{1\ 10}$alkyl)$_2$sulphamoyl, *N*-($C_{1\ 10}$alkyl)sulphamoylamino, *N,N*-($C_{1\ 10}$alkyl)$_2$sulphamoylamino, $C_{1\ 10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1\ 10}$alkyl, heterocyclic group, heterocyclyl$C_{1\ 10}$alkyl, carbocyclyl-($C_{1\ 10}$alkylene)$_e$-R^{32}-($C_{1\ 10}$alkylene)$_f$- or heterocyclyl-($C_{1\ 10}$alkylene)$_g$-R^{33}-($C_{1\ 10}$alkylene)$_h$-, wherein R^{13} may be optionally substituted

239

on carbon by one or more substituents selected from R^{36}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{37}, or R^{13} is a group of formula (GIB)



(GIB)

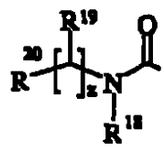
wherein

X is $-N(R^{38})-$, $-N(R^{38})C(O)-$, -O-, and $-S(O)_a-$, wherein a is 0-2 and R^{38} is hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen or C_{1-4}alkyl,

R^{15} and R^{16} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, 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, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, carbocyclyl or heterocyclic group, wherein R^{15} and R^{16} may be independently optionally substituted on carbon by one or more substituents selected from R^{41}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{42},

R^{17} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1\ 10}$alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkanoyl, $C_{1\ 10}$alkanoyloxy, *N*-($C_{1\ 10}$alkyl)amino, *N,N*-($C_{1\ 10}$alkyl)$_2$amino, $C_{1\ 10}$alkanoylamino, *N*-($C_{1\ 10}$alkyl)carbamoyl, $C_{1\ 10}$alkoxycarbonyl, *N,N*-($C_{1\ 10}$alkyl)$_2$carbamoyl, $C_{1\ 10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1\ 10}$alkyl)sulphamoyl, *N,N*-($C_{1\ 10}$alkyl)$_2$sulphamoyl, *N*-($C_{1\ 10}$alkyl)sulphamoylamino, *N,N*-($C_{1\ 10}$alkyl)$_2$sulphamoylamino, carbocyclyl, carbocyclyl$C_{1\ 10}$alkyl, heterocyclic group, heterocyclyl$C_{1\ 10}$alkyl, carbocyclyl-($C_{1\ 10}$alkylene)$_s$-R^{43}-($C_{1\ 10}$alkylene)$_t$- or heterocyclyl-($C_{1\ 10}$alkylene)$_s$-R^{44}-($C_{1\ 10}$alkylene)$_u$-, wherein R^{17} may be optionally substituted on carbon by one or more substituents selected from R^{47}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{48}, or R^{17} is a group of formula (GIC)



(GIC)

wherein

R^{18} is selected from hydrogen or C_{1-6}alkyl,

R^{19} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, 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, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, carbocyclyl or heterocyclic group, where R^{19} may be independently optionally substituted on carbon by one or more substituents selected from R^{31}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{32},

R^{20} is selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyamnocarbonyl, $C_{1\ 10}$alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $C_{1\ 10}$alkoxy, C_{1-10}alkoxycarbonyl, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-($C_{1\ 10}$alkyl)amino, *N,N*-($C_{1\ 10}$alkyl)$_2$amino, *N,N,N*-($C_{1\ 10}$alkyl)$_3$ammonio, $C_{1\ 10}$alkanoylamino, *N*-($C_{1\ 10}$alkyl)carbamoyl, *N,N*-($C_{1\ 10}$alkyl)$_2$carbamoyl, $C_{1\ 10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1\ 10}$alkyl)sulphamoyl, *N,N*-($C_{1\ 10}$alkyl)$_2$sulphamoyl, *N*-($C_{1\ 10}$alkyl)sulphamoylamino, *N,N*-($C_{1\ 10}$alkyl)$_2$sulphamoylamino, $C_{1\ 10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1\ 10}$alkyl, heterocyclic group, heterocyclyl$C_{1\ 10}$alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{33}-($C_{1\ 10}$alkylene)$_f$- or heterocyclyl-($C_{1\ 10}$alkylene)$_g$-R^{34}-($C_{1\ 10}$alkylene)$_h$-, wherein R^{20} may be independently optionally substituted on carbon by one or more R^{37}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{38},

p is 1-3, wherein the values of R^{15} may be the same or different,

q is 0-1,

r is 0-3, wherein the values of R^{16} may be the same or different,

m is 0-2, wherein the values of R^{12} may be the same or different;

n is 1-2, wherein the values of R^{8} may be the same or different;

z is 0-3, wherein the values of R^{19} may be the same or different;

R^{21} is selected from hydrogen or C_{1-6}alkyl,

R^{22} and R^{23} 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,

R^{24} is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-4}alkoxy and C_{1-6}alkanoyloxy,

R^{25} is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl and *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, wherein R^{25}, may be independently optionally substituted on carbon by one or more R^{67},

R^{26}, R^{28}, R^{30}, R^{36}, R^{41}, R^{47}, R^{51} and R^{57} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1\ 10}$alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkanoyl, $C_{1\ 10}$alkanoyloxy, $C_{1\ 10}$alkoxycarbonyl, *N*-($C_{1\ 10}$alkyl)amino, *N,N*-($C_{1\ 10}$alkyl)$_2$amino, *N,N,N*-(C_{1-10}alkyl)$_3$ammonio, $C_{1\ 10}$alkanoylamino, *N*-($C_{1\ 10}$alkyl)carbamoyl, *N,N*-($C_{1\ 10}$alkyl)$_2$carbamoyl, $C_{1\ 10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-($C_{1\ 10}$alkyl)sulphamoylamino, *N,N*-($C_{1\ 10}$alkyl)$_2$sulphamoylamino, $C_{1\ 10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1\ 10}$alkyl, heterocyclic group, heterocyclyl$C_{1\ 10}$alkyl, carbocyclyl-($C_{1\ 10}$alkylene)$_e$-R^{59}-($C_{1\ 10}$alkylene)$_f$- or heterocyclyl-($C_{1\ 10}$alkylene)$_g$-R^{60}-($C_{1\ 10}$alkylene)$_h$-, wherein R^{26}, R^{28}, R^{30}, R^{36}, R^{41}, R^{47}, R^{51} and R^{57} may be independently optionally substituted on carbon by one or more R^{63}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{64},

R^{27}, R^{29}, R^{31}, R^{37}, R^{42}, R^{48}, R^{52}, R^{58} and R^{64} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, benzyl, phenethyl, benzoyl, phenylsulphonyl and phenyl,

R^{32}, R^{33}, R^{43}, R^{44}, R^{53}, R^{54}, R^{59} and $R^{60}$are independently selected from -O-, -NR^{65}-, -S(O)$_x$-, -NR^{65}C(O)NR^{66}-, -NR^{65}C(S)NR^{66}-, -OC(O)N=C-, -NR^{65}C(O)- or -C(O)NR^{65}-, wherein R^{65} and R^{66} are independently selected from hydrogen or C_{1-6}alkyl, and x is 0-2,

R^{63} and R^{67} re independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, 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, and

e, f, g and h are independently selected from 0-2,

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

Additional suitable IBAT inhibitors having the above structure are selected from any one of:

(+/-)-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine,

(+/-)-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine,

1,1-dioxo-3-ethyl-3-butyl-4-hydroxy-5-phenyl-7-(*N*-{α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-2-fluorobenzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiapine, or

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(*N*-{1-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-1-(cyclohexyl)methyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine.

Compounds of formula (AI), (BI), (CI), (DI), (EI), (FI) and (GI) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may be prepared by processes known in the art.

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

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

Therefore in an additional feature of the invention, there is provided a method for producing a cholesterol lowering effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a

compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

42

amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

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

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

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

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

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

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

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

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

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

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

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

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula

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

In another aspect of the invention, 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 nicotinic acid derivative or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof As used herein "nicotinic acid derivative" means a compounds comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure Examples of nicotinic acid derivatives include nicotinic acid, niceritrol, nicofuranose, NIASPAN® and acipimox

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

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

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

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

£43

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thus in a further feature of the invention, there is provided a compound of formula (IV), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

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

pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier

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

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

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

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

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

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

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

146

Examples

The invention will now be illustrated in the following non limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise stated:

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

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

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

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

(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic resonance chemical shift values were measured in deuterated $CDCl_3$ (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer unless otherwise stated data was recorded at 400MHz; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; ABq, AB quartet; ABd, AB doublet, ABdd, AB doublet of doublets; dABq, doublet of AB quartets; LCMS were recorded on a Waters ZMD, LC column xTerra MS C_8(Waters), detection with a HP 1100 MS-detector diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-detector diode array equipped; unless otherwise stated the mass ion quoted is (MH^+); unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Cromasil C_8, 7 μm, (Akzo Nobel); MeCN and de-ionised water 10 mM ammonium acetate as mobile phases, with suitable composition;

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

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

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

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

Example 1

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(*N*-{(R)-α-[*N*-(*t*-butoxycarbonylmethyl)carbamoyl]benzyl}carbamoylmethoxy)phenyl]azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxy phenyl)azetidin-2-one (Method 1, 20 mg, 0 043 mmol), *tert*-butyl *N*-[(2*R*)-2-amino-2-phenylethanoyl]glycinate (Method 4, 14 mg, 0 047 mmol) and 2,6-lutidine (25 µl, 0 21 mmol) were added to DCM (2 ml) and the mixture was stirred for 5 minutes. TBTU (18 mg, 0 056 mmol) was added and the mixture was stirred for 4 hours. at room temperature. The reaction mixture was purified by column chromatography using DCM/EtOAc (10/2) as eluent to give 17 mg (56 %) of the title compound M/z 712.4 (m-H)

Example 2

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(*N*-{(R)-α-[*N*-(carboxymethyl) carbamoyl]benzyl}carbamoylmethoxy)phenyl]azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(*N*-{(R)-α-[*N*-(*t*-butoxycarbonylmethyl)carbamoyl]benzyl}carbamoylmethoxy)phenyl]azetidin-2-one (Example 1, 17 mg, 0 024 mmol) was added to formic acid (1 ml) and the mixture was stirred for 2.5 hours. at room temperature The solvent was evaporated under reduced pressure and methanol (1 ml) and triethylamine (75 µl) were added to the residue. The mixture was stirred for 4 5 hours at room temperature and the solvents were evaporated under reduced pressure. The residue was solved in MeCN/water (50/50) (3 ml) and acetic acid (1 ml) The mixture was lyophilised to obtain 13 mg (83%) of the title compound. NMR (300 MHz, DMSO-d_6)·

147

1 65-1 85 (m, 4H), 3 05 (bs, 1H), 3.5-3 7 (m, 3H), 4 45-4 55 (m, 1H), 4 6 (d, 2H), 4 85 (m, 1H), 5 55 (d, 1H), 6.9 (d, 1H), 7 05-7.4 (m, 17H), 8 4-8 55 (m, 2H), m/z 656.2 (m-H)

Example 3

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyll-4-{4-[*N*-((2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoylmethoxylphenyl}azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxy phenyl)azetidin-2-one (Method 1, 40 mg, 0 086 mmol), D-glucamine (16 mg, 0 09 mmol) and 2,6-lutidine (50 µl, 0.42 mmol) were added to DCM (3 ml) and 2 drops of DMF TBTU (36 mg, 0 11 mmol) was added and the mixture was stirred at room temperature for 2 hours The solvents were evaporated under reduced pressure and the residue was purified twice by preparative HPLC using MeCN /ammonium acetate buffer (45 55) as eluent. The collected fractions were lyophilised to obtain 16 mg (30%) of the title compound NMR (300 MHz, CD_3OD) 1 8-2 0 (m, 4H), 3 15-3.2 (m, 1H), 3 4-4 0 (m, 8H), 4 6 (s, 2H), 4 7-4 8 (m, 1H), 4 9 (bs, 1H), 7 0-7 5 (m, 12H), m/z 629 2 (m-H)

Example 4

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

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxy phenyl)azetidin-2-one (Method 1, 40 mg, 0 086 mmol), *tert*-butyl *N*-[(2*R*)-2-amino-2-phenylethanoyl]-*O*-(*tert*-butyl)-L-serinate (Method 6, 33 mg, 0 095 mmol) and 2,6-lutidine (50 µl, 0.42 mmol) were added to DCM (3 ml) TBTU (36 mg, 0 11 mmol) was added and the mixture was stirred at room temperature for 7 hours The solvents were evaporated under reduced pressure to give a mixture containing the title compound. M/z 798 4 (M-H)

Example 5

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

The 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(t-butoxycarbonyl)-2-(t-butoxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy] phenyl} azetidin-2-one prepared in Example 4 was added to formic acid (3 ml) and the mixture was

stirred for 5 days at room temperature. The solvent was evaporated under reduced pressure and methanol (4 ml) and triethylamine (0.4 ml) were added to the residue. The mixture was stirred for 24 hours at room temperature and the solvents were evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (40:60) as eluent. The collected fractions were lyophilised to obtain 12 mg (20%, 2 steps) of the title compound. NMR (300 MHz, CD_3OD) 1.8-1.95 (m, 4H), 3.1 (bs, 1H), 3.7-3.8 (m, 2H), 4.35 (bs, 1H), 4.55-4.7 (m, 3H), 4.8 (s, 1H), 5.65 (s, 1H), 6.95-7.4 (m, 17H), m/z 686.3 $(m-H)^-$

Example 6

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-{*N*-[(R)-α-(*t*-butoxycarbonyl)benzyl]carbamoylmethoxy}phenyl}azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 1, 40 mg, 0.086 mmol), *tert*-butyl (2*R*)-amino(phenyl)acetate (20 mg, 0.095 mmol) and 2,6-lutidine (50 µl, 0.42 mmol) were added to DCM (3 ml). TBTU (36 mg, 0.11 mmol) was added and the mixture was stirred at room temperature for 5 hours. The solvent was evaporated under reduced pressure and was co-evaporated with toluene. The residue was purified by column chromatography using DCM/EtOAc (10/2) as eluent to give the title compound. M/z 655.3 (m-H)

Example 7

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(R)-α-(carboxy)benzyl]carbamoylmethoxy}phenyl)azetidin-2-one

The 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-{*N*-[(R)-α-(*t*-butoxycarbonyl)benzyl]carbamoylmethoxy}phenyl}azetidin-2-one prepared in Example 6 was added to formic acid (3 ml) and the mixture was stirred for 12 hours at room temperature. The solvent was evaporated under reduced pressure and was co-evaporated with toluene. Methanol (3 ml) and triethylamine (0.1 ml) were added to the residue and the mixture was stirred for 4 hours at room temperature. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (50:50) as eluent. The collected fractions were lyophilised to obtain 17 mg (33%, 2 steps) of the title compound. NMR (300 MHz, CD_3OD) 1.8-2.0 (m, 4H), 3.05-3.15 (m, 1H), 4.5-4.7 (m, 3H), 4.8 (bs, 1H), 5.35 (d, 1H), 6.95-7.45 (m, 17H), m/z 599.5 (m-H)

Example 8

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(*t*-butoxycarbonylmethyl)carbamoylmethoxy]phenyl}azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxy phenyl)azetidin-2-one (Method 1, 40 mg, 0 086 mmol), glycine tert-butylester (18 mg, 0 091 mmol) and 2,6-lutidine (50 µl, 0.42 mmol) were added to DCM (3 ml) TBTU (36 mg, 0 11 mmol) was added and the mixture was stirred at room temperature for 20 hours The solvent was evaporated under reduced pressure. The residue was purified by column chromatography using DCM/EtOAc (10/4) as eluent to give the title compound. M/z 579.2 (m-H)

Example 9

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one

The 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(*t*-butoxycarbonylmethyl)carbamoylmethoxy]phenyl}azetidin-2-one prepared in Example 8 was added to formic acid (3 ml) and the mixture was stirred for 4 hours at room temperature The solvent was evaporated under reduced pressure and was co-evaporated with toluene. Methanol (3 ml) and triethylamine (0 1 ml) were added to the residue and mixture was stirred for 20 hours at room temperature The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (45 55) as eluent. The collected fractions were lyophilised to obtain 14 mg (31%, 2 steps) of the title compound. NMR (300 MHz, CD_3OD) 1 8-2 0 (m, 4H), 3 05-3 15 (m, 1H), 3 85 (s, 2H), 4 55 (s, 2H), 4 6-4 7 (m, 1H), 4 8 (bs, 1H), 6 95-7 35 (m, 12 H), m/z 523 1 (m-H)

Example 10

1-(4-Fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-{4-[*N*-(carboxymethyl)carbamoyl methoxy]phenyl}azetidin-2-one

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(carboxymethoxy) phenyl]azetidin-2-one (Method 8, 0 050 g, 0 110 mmol), *tert*-butyl glycinate hydrochloride (0 022 g, 0 131 mmol) and *N*-methylmorpholine (0 050 ml, 0 454 mmol) in DCM (3 ml) was stirred at room temperature for 5 minutes, after which TBTU (0 046 g, 0 143 mmol) was added After 78 hours the conversion to the ester (m/z 567.2) was completed and the solvent was removed under reduced pressure. The residue was dissolved in formic acid (3 ml) and the

solution was stirred for 20 hours The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. The fractions were freeze-dried and the title compound was obtained as a white solid (0 056 g, ~quantitative yield) NMR (CD_3OD, 400 MHz) 2.25-2.40 (m, 2H), 3 25-3.35 (m, 1H), 3 90 (s, 2H), 4 05-4.20 (m, 2H), 4 50 (s, 2H), 5 00 (d, 1H), 6 80-7 05 (m, 8H), 7.25-7.40 (m, 4H), m/z 511 1

Example 11

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

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(carboxymethoxy) phenyl]azetidin-2-one (Method 8, 0 070 g, 0 154 mmol), *tert*-butyl D-tyrosinate (0 044 g, 0 185 mmol) and *N*-methylmorpholine (0 051 ml, 0.463 mmol) in DCM (5 ml) was stirred at room temperature for 5 minutes, after which TBTU (0 065 g, 0 202 mmol) was added. After 20 hours, the conversion to the ester (m/z: 673.4) was complete and the solvent was removed under reduced pressure The residue was dissolved in formic acid (5 ml) and the solution was stirred for 24 hours The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. The fractions were freeze-dried and the title compound was obtained as a white solid (0.052 g; 55 %) NMR (CD_3OD, 400 MHz) 2 25-2 40 (m, 2H), 2 85-3 15 (m, 2H), 3 25-3.40 (m, 1H), 4 05-4 20 (m, 2H), 4.35-4 50 (m, 2H), 4 55-4 65 (m, 1H), 5.00 (d, 1H), 6 55-6.65 (m, 2H), 6 80-7.05 (m, 10H), 7.25-7 35 (m, 4H), m/z 615 2 (M-H)

Example 12

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

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(carboxymethoxy) phenyl]azetidin-2-one (Method 8, 0 070 g, 0 154 mmol), *tert*-butyl *O*-(*tert*-butyl)-D-serinate hydrochloride (0 047 g, 0 185 mmol) and *N*-methylmorpholine (0 068 ml, 0 617 mmol) in DCM (5 ml) was stirred at room temperature for 5 minutes, after which TBTU (0 065 g, 0.202 mmol) was added. After 20 hours, the conversion to the ester (m/z 653 4) was completed and TFA (1 5 ml) was added to the reaction mixture. After 24 hours the solvent was removed under reduced pressure and the residue was purified by preparative HPLC, using a gradient of

49

20-50% MeCN in 0 1M ammonium acetate buffer as eluent. The fractions were freeze-dried and the title compound was obtained as a white solid (0 074 g, 89 %) M/z 541 1 NMR (CD_3OD, 400 MHz) 2.25-2 40 (m, 2H), 3 25-3 35 (m, 1H), 3 80-3 95 (m, 2H), 4 05-4 20 (m, 2H), 4 40 (t, 1H), 4 55 (s, 2H), 5 00 (d, 1H), 6 80-6 90 (m, 2H), 6 90-7 05 (m, 6H), 7 25-7.40 (m, 4H)

Example 13

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

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(carboxymethoxy)phenyl]azetidin-2-one (Method 8, 0 070 g, 0 154 mmol), *tert*-butyl D-leucinate hydrochloride (0 042 g, 0 188 mmol) and *N*-methylmorpholine (0 068 ml, 0 617 mmol) in DCM (5 ml) was stirred at room temperature for 5 minutes, after which TBTU (0 065 g, 0 202 mmol) was added. After 20 hours, the conversion to the ester (m/z 623 3) was complete and the solvent was removed under reduced pressure The residue was dissolved in formic acid (5 ml) and the solution was stirred for 20 hours The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. The fractions were freeze-dried and the title compound was obtained as a white solid (0 080 g, 91 %) NMR (DMSO, 400 MHz) 0 75-0 85 (m, 6H), 1.45-1 60 (m, 3H), 2 15-2.30 (m, 2H), 3 20-3 30 (m, 1H), 4 00-4.25 (m, 3H), 4 50 (ABq, 2H), 5 05 (d, 1H), 6 85-6 95 (m, 4H), 7 00-7 25 (m, 6H), 7 30-7.40 (m, 2H), 8 05 (t, 1H), m/z 567.3

Example 14

1-(4-Fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-(4-{*N*-[(S)-1-(carboxy)-3-(carbamoyl)propyl]carbamoylmethoxy}phenyl)azetidin-2-one

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(carboxymethoxy)phenyl]azetidin-2-one (Method 8, 0 070 g, 0 154 mmol), *tert*-butyl L-glutaminate hydrochloride (0 044 g, 0 184 mmol) and *N*-methylmorpholine (0 068 ml, 0 617 mmol) in DCM (5 ml) was stirred at room temperature for 5 minutes, after which TBTU (0 065 g, 0.202 mmol) was added. After 20 hours, the conversion to the ester (m/z 638.3) was complete and the solvent was removed under reduced pressure The residue was dissolved in formic acid (5 ml) and the solution was stirred for 20 hours The solvent was removed under reduced

pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. The fractions were freeze-dried and the title compound was obtained as a white solid (0 088 g; 98 %) NMR (CD_3OD, 400 MHz) 1 90-2.40 (m, 6H), 3.25-3 35 (m, 1H), 4.05-4.20 (m, 2H), 4.30-4 40 (m, 1H), 4 50 (s, 2H), 5 00 (d, 1H), 6 80-7 05 (m, 8H), 7.25-7 40 (m, 4H), m/z. 582.2.

Example 15

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

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(carboxymethoxy) phenyl]azetidin-2-one (Method 8, 0 051 g, 0 113 mmol), *tert*-butyl *N*-[(2*R*)-2-amino-2-phenylethanoyl]-*O*-(*tert*-butyl)-L-serinate (Method 6, 0 047 g, 0 134 mmol) and *N*-methylmorpholine (0 050 ml, 0 454 mmol) in DCM (5 ml) was stirred at room temperature for 10 minutes, after which TBTU (0 065 g, 0.202 mmol) was added. After 18 hours, the conversion to the ester (m/z 786 5) was complete and TFA (1 5 ml) was added to the reaction mixture. After 24 hours the solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 30-50% MeCN in 0.1M ammonium acetate buffer as eluent. The fractions were freeze-dried and the title compound was obtained as a white solid (0 057 g; 75 %) NMR (CD_3OD, 400 MHz) 2.25-2.40 (m, 2H), 3.25-3.35 (m, 1H), 3 65-3 85 (m, 2H), 4.05-4 20 (m, 2H), 4.30-4.40 (m, 1H), 4.50-4 65 (m, 2H), 5 00 (d, 1H), 5 65 (s, 1H), 6.80-7 05 (m, 8H), 7 20-7.45 (m, 9H), m/z 674 2

Example 16

1-(4-Fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-{4-[*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]phenyl}azetidin-2-one

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(carboxymethoxy) phenyl]azetidin-2-one (Method 8, 0 050 g, 0 110 mmol), (R)-α-{*N*-[(S)-1-(*t*-butoxycarbonyl)propyl]carbamoyl}-4-hydroxybenzylamine (Method 11 of WO 03/022286, 0 046 g, 0 133 mmol) and *N*-methylmorpholine (0 049 ml, 0 445 mmol) in DCM (5 ml) was stirred at room temperature for 10 minutes, after which TBTU (0 046 g, 0 143 mmol) was added. After 20 hours, the conversion to the ester (m/z 744 5) was completed and the solvent was removed under reduced pressure The residue was dissolved in formic acid (3 ml) and the solution was stirred for 24 hours before the solvent again was removed under reduced

pressure The residue was purified by preparative HPLC using a gradient of 30-50% MeCN in 0 1M ammonium acetate buffer as eluent. The fractions were freeze-dried and the title compound was obtained as a white solid (0 052 g, 69 %) NMR (CD_3OD, 400 MHz) 0 70-0 80 (m, 3H), 1 55-1 70 (m, 1H), 1 75-1 90 (m, 1H), 2 25-2.40 (m, 2H), 3 25-3 35 (m, 1H), 4 05-4 20 (m, 2H), 4 20-4 30 (m, 1H), 4 55 (ABq, 2H), 5 00 (d, 1H), 5 50 (d, 1H), 6 65-6 75 (m, 2H), 6 80-7 05 (m, 8H), 7 15-7 40 (m, 6H), m/z 688.2.

Example 17

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

A solution of 3-(R)-4-(R)-1-(phenyl)-3-(phenylethylsulphanyl)-4-[4-(carboxymethoxy)phenyl]azetidin-2-one (Method 9, 0 050 g, 0 115 mmol), *tert*-butyl *N*-[(2*R*)-2-amino-2-phenylethanoyl]-*O*-(*tert*-butyl)-L-serinate (Method 6, 0 049 g, 0 140 mmol) and *N*-methylmorpholine (0 050 ml, 0 454 mmol) in DCM (5 ml) was stirred at room temperature for 10 minutes, after which TBTU (0 075 g, 0 234 mmol) was added. After 18 hours, the conversion to the ester (m/z 766 5) was complete and TFA (1.5 ml) was added to the reaction mixture After 24 hours the solvent was removed under reduced pressure and the residue was purified by preparative HPLC, using a gradient of 30-50% MeCN in 0 1M ammonium acetate buffer as eluent. The fractions were freeze-dried and the title compound was obtained as a white solid (0 052 g; 69 %) NMR (CD_3OD, 400 MHz) 2 85-3 00 (m, 4H), 3 65-3 85 (m, 2H), 4 00-4 05 (m, 1H), 4 35-4 40 (m, 1H), 4 60 (ABq, 2H), 4 85 (d, 1H), 5 65 (s, 1H), 6.95-7.45 (m, 19H), m/z 654.2

Example 18

3-(R)-4-(R)-1-(Phenyl)-3-(phenylethylsulphanyl)-4-{4-[*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]phenyl}azetidin-2-one

A solution of 3-(R)-4-(R)-1-(phenyl)-3-(phenylethylsulphanyl)-4-[4-(carboxymethoxy)phenyl]azetidin-2-one (Method 9, 0 050 g, 0 110 mmol), (R)-α-{*N*-[(S)-1-(*t*-butoxycarbonyl)propyl]carbamoyl}-4-hydroxybenzylamine (Method 11 of WO 03/022286, 0 048 g, 0 139 mmol) and *N*-methylmorpholine (0 051 ml, 0 463 mmol) in DCM (5 ml) was stirred at room temperature for 10 minutes, after which TBTU (0 075 g, 0 234 mmol) was added After 20 hours, the conversion to the ester (m/z 724 4) was completed and the solvent was removed under reduced pressure The residue was dissolved in formic acid (3 ml) and the

solution was stirred for 24 hours The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 30-50% MeCN in 0 1M ammonium acetate buffer as eluent. The fractions were freeze-dried and the title compound was obtained as a white solid (0 037 g; 48 %) M/z. 668 1 NMR (CD_3OD, 400 MHz) 0 65-0 80 (m, 3H), 1.50-1 70 (m, 1H), 1 75-1 90 (m, 1H), 2.85-3 00 (m, 4H), 4 00-4 05 (m, 1H), 4 20-4 30 (m, 1H), 4 55 (ABq, 2H), 4 85 (d, 1H), 4.45-4 55 (m, 1H), 6 65-6 75 (m, 2H), 6.95-7.40 (m, 16H)

Example 19

3-(R)-4-(R)-1-(Phenyl)-3-(phenylethylsulphinyl)-4-{4-[*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]phenyl}azetidin-2-one

To a solution of 3-(R)-4-(R)-1-(phenyl)-3-(phenylethylsulphanyl)-4-{4-[*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]phenyl} azetidin-2-one (Example 18, 0 026 g, 0 039 mmol) in DCM (3 ml) was added a solution of MCPBA in DCM in portions until the reaction was complete (LC/MS) (Approximately 0.015 g 70-75% *m*-CPBA was added) The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. After freeze-drying, the title compound was obtained as a white solid (0 018 g; 67 %) NMR (CD_3OD, 400 MHz) (NB diastereomeric mixture at the sulphinyl) 0 65-0 80 (m, 6H), 1.55-1 70 (m, 2H), 1 75-1 90 (m, 2H), 2.95-3 35 (m, 7H), 3 75-3 90 (m, 1H), 4 20-4 30 (m, 2H), 4 40-4 50 (m, 1H), 4 50-4 65 (m, 5H), 5 30 (d, 1H), 5 45-5 55 (m, 2H), 5 65 (d, 1H), 6 65-6 80 (m, 4H), 6 95-7 10 (m, 6H), 7 15-7 35 (m, 22H), 7 35-7.50 (m, 4H); m/z. 684.4

Example 20

3-(R)-4-(R)-1-(Phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one

A solution of 3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-[4-(carboxymethoxy)phenyl]azetidin-2-one (Method 10; 0 110 g, 0 236 mmol), *tert*-butyl glycinate hydrochloride (0 067 g, 0.400 mmol) and *N*-methylmorpholine (0 12 ml, 1 09 mmol) in DCM (5 ml) was stirred at room temperature for 5 minutes, after which TBTU (0 130 g, 0.4049 mmol) was added. After 66 hours the conversion to the ester (m/z. 579 2) was complete and the solvent was removed under reduced pressure The residue was

dissolved in formic acid (3 ml) and the solution was stirred at 40°C for 4 hours The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. A white solid was obtained after freeze-drying (0 035g; 28 %) M/z 521 12 [M-1]

Example 21

3-(R)-4-(R)-1-(Phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-[4-(*N*-{*N*-[(R)-1-(*t*-butoxycarbonyl)-2-(*t*-butoxy)ethyl]carbamoylmethyl}carbamoylmethoxy)phenyl]azetidin-2-one

A solution of 3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one (Example 20, 0 020 g, 0 038 mmol), *tert*-butyl *O*-(*tert*-butyl)-D-serinate hydrochloride (0 012 g, 0 047 mmol) and *N*-methylmorpholine (0 013 ml, 0 118 mmol) in DCM (3 ml) was stirred at room temperature for 10 minutes, after which TBTU (0 016 g, 0 050 mmol) was added. After 66 hours the solvent was removed under reduced pressure and the residue was purified by flash chromatography using heptane.EtOAc (1 2) as eluent to give the title compound (0 020 g; 74 %) NMR (400 MHz) 1 15 (s, 9H), 1 45 (s, 9H), 3.50-3 55 (m, 1H), 3 75-3 85 (m, 1H), 4 00-4 25 (m, 5H), 4 50 (s, 2H), 4 55-4 65 (m, 1H), 4 85 (d, 1H), 6 90-7 00 (m, 2H), 7 00-7 40 (m, 9H), 7 90-8 05 (m, 2H), m/z. 722 1

Example 22

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

To a solution of 3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-[4-(*N*-{*N*-[(R)-1-(*t*-butoxycarbonyl)-2-(*t*-butoxy)ethyl]carbamoylmethyl}carbamoylmethoxy) phenyl]azetidin-2-one (Example 21, 0 020 g, 0 146 mmol) in DCM (4 ml) was added TFA (1.5 ml) After 18 hours the solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer, as eluent. After freeze-drying, the title compound was obtained as a white solid (0 017 g, ~quantitative) NMR (CD_3COOH, 400 MHz) δ 3 95 (dd, 1H), 4 10 (dd, 1H), 4.15-4 35 (m, 5H), 4 65 (s, 2H), 4 70-4 80 (m, 1H), 5 05 (d, 1H), 6.90-7 45 (m, 11H), 7 95-8 10 (m, 2H), m/z 610.2

Example 23

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

A solution of 3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-[4-(carboxymethoxy)phenyl]azetidin-2-one (Method 10; 0 015 g, 0 032 mmol), *tert*-butyl *N*-[(2*R*)-2-amino-2-phenylethanoyl]-*O*-(*tert*-butyl)-L-serinate (Method 6, 0 017 g, 0 049 mmol) and *N*-methylmorpholine (0 011 ml, 0 100 mmol) in DCM (3 ml) was stirred at room temperature for 10 minutes, after which TBTU (0 016 g, 0 50 mmol) was added. After 19 hours the conversion to the ester (m/z. 798 80) was complete and TFA (1 5 ml)was added to the solution. After 7 hours the solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. After freeze-drying the title compound was obtained as a white solid (0.016 g; 72 %) NMR (CD_3COOH, 400 MHz) 3.85 (dd, 1H), 4 05 (dd, 1H), 4.20-4.30 (m, 3H), 4.60-4 80 (m, 3H), 5 00 (d, 1H), 5 90-6.00 (m, 1H), 6 90-7.50 (m, 16H), 8 00-8 10 (m, 2H), m/z. 686 6.

Example 24

3-(R)-4-(R)-1-(Phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one

To a stirring solution of 3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one (Example 20, 0.010 g, 0.019 mmol) in MeOH (1 ml) was added sodium borohydride (0 001 g, 0 026 mmol) After 10 minutes water (1 ml) was added and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. After freeze-drying the title compound was obtained as a white solid (0 008 g; 80 %) M/z 525 1 NMR (CD_3COOD, 400 MHz) 3 00-3 20 (m, 2H), 4 05-4 15 (m, 1H), 4.20 (s, 2H), 4.70 (s, 2H), 4 85-5 00 (m, 2H), 6.95-7 10 (m, 5H), 7 20-7.45 (m, 8H)

52

Example 25

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

To a stirred solution of 3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-[4-(*N*-{*N*-[(R)-1-(carboxy)-2-(hydroxy)ethyl]carbamoylmethyl}carbamoylmethoxy) phenyl]azetidin-2-one (Example 22, 0.015 g, 0 025 mmol) in MeOH (2 ml) was added sodium borohydride (0 003 g, 0 079 mmol) After 5 minutes water (1 ml) was added and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a gradient of 20-40% MeCN in 0 1M ammonium acetate buffer as eluent. After freeze-drying the title compound was obtained as a white solid (0 010 g; 66 %) NMR (CD_3COOD, 400 MHz) 2 95-3.20 (m, 2H), 3 95 (dd, 1H), 4 05-4 15 (m, 2H), 4.25 (ABq, 2H), 4 70 (s, 2H), 4 70-4 80 (m, 1H), 4 85-5 00 (m, 2H), 6 95-7 10 (m, 5H), 7 20-7 45 (m, 8H)

Example 26

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

To a solution of 3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-(4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy] phenyl}azetidin-2-one (Example 23, 0.019 g, 0 028 mmol) in MeOH (3 ml) was added sodium borohydride (0 005 g, 0 073 mmol) After 10 minutes 0 1M ammonium acetate buffer was added (aq, 1 ml) and the solvent was removed under reduced pressure The residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. After freeze-drying, the title compound was obtained as a white solid (0 008 g, 81 %) NMR (CD_3COOD, 400 MHz) 3 00-3.20 (m, 2H), 3 85 (dd, 1H), 4 00-4 15 (m, 2H), 4 65-4 80 (m, 3H), 4 85-5 00 (m, 2H), 5 95 (s 1H), 6.95-7 10 (m, 5H), 7 20-7 50 (m, 13H), m/z 688 21

Example 27

3-(R)-4-(R)-1-(Phenyl)-3-(thien-3-ylcarbonylmethylsulphanyl)-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one

A solution of 3-(R)-4-(R)-1-(phenyl)-3-(thien-3-ylcarbonylmethylsulphanyl)-4-[4-(carboxymethoxy)phenyl]azetidin-2-one (Method 11, 0 039 g, <0 086 mmol), *tert*-butyl

glycinate hydrochloride (0.020 g, 0 119 mmol) and *N*-methylmorpholine (0 035 ml, 0 318 mmol) in DCM (3 ml) was stirred at room temperature for 10 minutes, after which TBTU (0 042 g, 0 131 mmol) was added. After 22 hours the solvent was removed under reduced pressure and the residue was purified by flash chromatography using heptane.EtOAc (1 1) as eluent. This gave 0 035 g of a colourless oil (m/z 567 1) This oil was dissolved in formic acid (3 ml) and the solution was stirred at room temperature for 18 hours The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. After freeze-drying, the title compound was obtained as a white solid (0 019 g; 43 %) NMR (CD_3COOD, 400 MHz) 4 15 (ABq, 2H), 4 20 (s, 2H), 4.25 (d, 1H), 4 70 (s, 2H), 5 05 (d, 1H), 6 95-7 15 (m, 4H), 7.20-7 30 (m, 4H), 7 35-7 45 (m, 2H), 7 75-7.90 (m, 2H), m/z. 511 0

Example 28

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

A solution of 3-(R)-4-(R)-1-(phenyl)-3-(thien-3-ylcarbonylmethylsulphanyl)-4-[4-(carboxymethoxy) phenyl]azetidin-2-one (Method 11, 0 039 g, <0 086 mmol), *tert*-butyl *N*-[(2*R*)-2-amino-2-phenylethanoyl]-*O*-(*tert*-butyl)-L-serinate (Method 6, 0 042g) and *N*-methylmorpholine (0.022 ml) in DCM (4 ml) was stirred at room temperature for 10 minutes, after which TBTU (0.042 g) was added. After 22 hours the solvent was removed under reduced pressure and the residue was purified by flash chromatography using heptane.EtOAc (1 1) as eluent to give a colourless oil (0 050 g) M/z 786 6 This oil was dissolved in DCM (4 ml) and TFA (1.5 ml) was added. After 19 hours, the solvent was removed under reduced pressure and the residue was purified twice by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. After freeze-drying, the title compound was obtained as a white solid (0 019 g, 33 %) NMR (CD_3COOD, 400 MHz) 3 85 (dd, 1H), 4 05 (dd, 1H), 4 15 (ABq, 2H), 4 20-4.30 (m, 1H), 4 60-4 75 (m, 3H), 5.05 (d, 1H), 5 90 (s, 1H), 6.95-7 15 (m, 4H), 7 20-7 50 (m, 11H), 7 75-7 85 (m, 2H), m/z 674 3

53

Example 29

3-(R)-4-(R)-1-(Phenyl)-3-[2-(thien-3-yl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one

To a solution of 3-(R)-4-(R)-1-(phenyl)-3-(thien-3-ylcarbonylmethylsulphanyl)-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one (Example 27, 0 012 g, 0 024 mmol) in MeOH (3 ml) was added sodium borohydride (0 006 g, 0 159 mmol) After 10 minutes 0 1M ammonium acetate buffer (aq, 1 ml) was added and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent After freeze-drying the title compound was obtained as a white solid (0 010 g; 80 %) NMR (CD_3COOD, 400 MHz) δ 3 10-3 30 (m, 2H), 4 15 (dd, 1H), 4 20 (s, 2H), 4 70 (s 2H), 4 95 (dd, 1H), 5.20 (dt, 1H), 6 90-7 10 (m, 5H), 7.20-7 35 (m, 5H), 7 40-7.45 (m, 2H), m/z. 511 3 (M-1)

Example 30

3-(R)-4-(R)-1-(Phenyl)-3-[2-(thien-3-yl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one

To a solution of 3-(R)-4-(R)-1-(phenyl)-3-(thien-3-ylcarbonylmethylsulphanyl)-4-{4-[*N*-(α-(R)-{*N*-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy] phenyl}azetidin-2-one (Example 28, 0 019 g, 0 028 mmol) in MeOH (3 ml) was added sodium borohydride (0 005 g, 0 132 mmol) After 10 minutes 0 1M ammonium acetate buffer (aq, 1 ml) was added and the solvent was removed under reduced preasure The residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent. After freeze-drying, the title compound was obtained as a white solid (0 015 g; 79 %) NMR (CD_3COOD, 400 MHz) 3 05-3 30 (m, 2H), 3 85 (dd, 1H), 4 05 (dd, 1H), 4 15 (dd, 1H), 4 65-4 75 (m, 3H), 4 90 (dd, 1H), 5 15-5.25 (m, 1H), 5.95 (s, 1H), 6 90-7 10 (m, 5H), 7 20-7 50 (m, 12H), m/z 674 16 (M-H)

Example 31

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

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenylthio)ethyl]-4-[4-(carboxymethoxy)phenyl]azetidin-2-one (Method 17, 0 100 g, 0.213 mmol), *tert*-butyl *N*-

[(2*R*)-2-amino-2-phenylethanoyl]-*O*-(*tert*-butyl)-L-serinate (Method 6, 0 150g, 0.428 mmol) and *N*-methylmorpholine (0 070 ml, 0 635 mmol) in DCM (4 ml) was stirred at room temperature for 10 minutes, after which TBTU (0 140 g, 0.436 mmol) was added. After 19 hours the solvent was removed under reduced pressure and the residue was purified by flash chromatography using heptane:EtOAc (2:1) as eluent to give a colourless oil (0 149 g; 87 %). NMR (400 MHz) 0 90 (s, 9H), 1.45 (s, 9H), 2 05-2 30 (m, 2H), 2 95-3 15 (m, 2H), 3.20-3 25 (m, 1H), 3.30-3 35 (m, 1H), 3 65 (dd, 1H), 4.40-4 60 (m, 3H), 4 60 (d, 1H), 5 50 (dd, 1H), 6 50 (dd, 1H), 6 85-7 00 (m, 6H), 7 15-7.40 (m, 11H), 7 90 (dd, 1H), m/z. 802.8

Example 32

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

To a solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenylthio)ethyl]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(*t*-butoxycarbonyl)-2-(*t*-butoxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy] phenyl}azetidin-2-one (Example 31, 0 149 g, 0 186 mmol) in DCM (3 ml) was added TFA (1.5 ml) After 20 hours, the solvent was removed under reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer, as eluent. After freeze-drying, the title compound was obtained as a white solid (0 098 g; 77 %) NMR (400 MHz) 2 00-2 25 (m, 2H), 2.85-3 10 (m, 2H), 3 10-3 20 (m, 1H), 3 35-3 45 (m, 1H), 3 75-3 85 (m, 1H), 4 15-4.45 (m, 3H), 4.55 (d, 1H), 5 70 (d, 1H), 6 70-7 00 (m, 6H), 7 10-7.35 (m, 11H), 7.45-7 55 (m, 1H), 8 45-8.55 (m, 1H), m/z. 690 5

Example 33

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

Example 34

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

To a stirring suspension of 1-(4-fluorophenyl)-3-[2-(4-fluorophenylthio)ethyl]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy] phenyl}azetidin-2-one (Example 32, 0 070 g, 0 102 mmol) in DCM (5 ml) was added meta-chloroperoxybenzoic acid (0 035 g, 70-75%) After 20 hours, the solvent was removed under

reduced pressure and the residue was purified by preparative HPLC using a gradient of 20-40% MeCN in 0 1M ammonium acetate buffer as eluent. After freeze-drying, 1-(4-fluorophenyl)-3-[2-(4-fluorophenylsulphinyl)ethyl]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one (0 022 g, 30 %) NMR (CD_3COOD, 400 MHz) 2 15-2.45 (m, 2H), 3 10-3 35 (m, 3H), 3 85 (dd, 1H), 4 05 (dd, 1H), 4 65-4 75 (m, 3H), 4 80-4.90 (m, 1H), 5 90 (s 1H), 6 95-7 05 (m, 4H), 7.25-7 50 (m, 11H), 7 70-7 80 (m, 2H), m/z 706.2, and 1-(4-fluorophenyl)-3-[2-(4-fluorophenylsulphonyl) ethyl]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl) carbamoylmethoxy]phenyl}azetidin-2-one (0 043 g; 59 %) NMR (CD_3COOD, 400 MHz) 2.25-2.40 (m, 2H), 3 25 (dt, 1H), 3.35-3 55 (m, 2H), 3 85 (dd, 1H), 4 05 (dd, 1H), 4 65-4 75 (m, 3H), 4 85 (d, 1H), 5 95 (s, 1H), 6 95-7 05 (m, 4H), 7 20-7 50 (m, 11H), 7 95-8 05 (m, 2H), m/z 722 1 were obtained as a white solids

Example 35

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(S)-α-(carboxy)benzyl]carbamoylmethoxy}phenyl)azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 49mg, 0 105mmol) was dissolved in a solution of N-methylmorpholine (35µl, 0 318mmol) in 2ml DCM. (S)-Phenylglycine methyl ester hydrochloride (25mg, 0 124mmol) and TBTU (40mg, 0 125mmol) were added and the mixture was stirred at ambient temperature over night. The solution was diluted with 4ml DCM and washed with 1%$NaHCO_3$, 0 1M $KHSO_4$ and brine The organic phase was dried and evaporated to give the ester M/z 615 THF (2ml), water (0 5ml) and LiOH (ca 10mg, 0 418mmol) were added and the mixture was stirred over night. The solvent was removed and the residue was purified using preparative HPLC on a C8-column. A gradient from 20 to 50% MeCN in 0 1M ammonium acetate buffer was used as the mobile phase. Lyophilisation yielded a white solid. Mass 40mg (63%) M/z 601 NMR (400MHz, CD_3OD) 1 75-2 06 (m, 4H), 3 06-3 13 (m, 1H), 4 47-4 67 (m, 3H), 4 79-4 82 (m, 1H), 5 24 (d, 1H), 6.90-7 06 (m, 6H), 7 12-7 40 (m, 11H)

Example 36

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)carbamoyl]4-hydroxybenzyl}carbamoylmethoxy)phenyl]azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl) azetidin-2-one (Method 2, 49mg, 0 105mmol) was dissolved in a solution of N-methylmorpholine (40µl, 0.318mmol) in 2ml DCM. *tert*-Butyl (2*S*)-2-{[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino}butanoate hydrochloride (Method 14, 43mg, 0 125mmol) and TBTU (40mg, 0 125mmol) were added. The mixture was stirred over night at ambient temperature. Additionally 10mg (0 029mmol) of the dipeptide was added and after 2 hours the solution was diluted with 4ml DCM and washed with 1%$NaHCO_3$, 0 1M $KHSO_4$ and brine The organic phase was dried and evaporated to give the ester M/z 758 Formic acid (1 5ml) was added and the mixture was stirred over night Additionally 1ml formic acid was added. After 3 hours the formic acid was removed and MeOH (2ml) together with Et_3N (40µl, 0.288mmol) were added and the mixture was stirred over night. The mixture was concentrated under reduced pressure and purified using preparative chromatography A gradient from 20% to 80% MeCN in 0 1M ammonium acetate buffer was used as eluent. Lyophilisation yielded 42mg (57%) NMR (400MHz, DMSO-d_6)· 0.65-0 72 (m, 3H), 1 53-1 67 (m, 1H), 1 74-2.04 (m, 5H), 3 06-3 14 (m, 1H), 4 18-4.23 (m, 1H), 4.50-4 66 (m, 3H), 4.77-4 82 (m, 1H), 5.46 (d, 1H), 6 72 (t, 2H), 6 93-7 06 (m, 6H), 7 18-7.36 (m, 8H), m/z 702

Example 37

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(2-hydroxyethyl) carbamoylmethoxy]phenyl}azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 20mg, 0 043mmol) was dissolved in a solution of N-methylmorpholine (10µl, 0 091mmol) in 2ml DCM. 2-Aminoethanol (4µl, 0 066mmol) and TBTU (16mg, 0 050mmol) were added and the mixture was stirred for 3 hours Additional 2-aminoethanol (3µl) was added. The mixture was stirred for 2.5 days then concentrated and purified using preparative chromatography A gradient from 20% to 50% MeCN in 0 1M ammonium acetate buffer was used as eluent. Lyophilisation yielded 10mg (45%) NMR (400MHz, CD_3OD) 1 75-2 06 (m, 4H), 3 05-3 12 (m, 1H), 3 38 (t, 2H), 3 61 (t, 2H), 4.51 (d, 2H), 4.57-4.66 (m, 1H), 4 77-4 83 (m, 1H), 6 93-7 07 (m, 6H), 7.22-7.37 (m, 6H), m/z. 511

55

Example 38

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(2-methoxyethyl) carbamoylmethoxy]phenyl}azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 20mg, 0 043mmol) was dissolved in a solution of N-methylmorpholine (10µl, 0 091mmol) in 2ml DCM 2-Methoxyethylamine (5µl, 0 058mmol) and TBTU (16mg, 0 050mmol) were added and the mixture was stirred for 3 hours at ambient temperature The mixture was concentrated and purified using preparative chromatography A gradient from 20% to 50% MeCN in 0 1M ammonium acetate buffer was used as eluent. Lyophilisation yielded 5mg (22%) NMR (400 MHz, CD_3OD) 1 75-2.05 (m, 4H), 3 05-3 15 (m, 1H), 3 29 (s, 3H), 3.40-3 44 (m, 4H), 4 5 (d, 2H), 4 57-4 66 (m, 1H), 4 78-4 82 (m, 1H), 6 92-7 06 (m, 6H), 7 22-7 37 (m, 6H), m/z 525

Example 39

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(2-sulphoethyl) carbamoylmethoxy]phenyl}azetidin-2-one

TBTU (26 mg, 0 081 mmol) was added to a mixture of 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 29 mg, 0 062 mmol), taurine (24 mg, 0 19 mmol) and triethylamine (25 mg, 0 25 mmol) in MeCN (1 ml) After 1 hour DMF (1 ml) was added and the MeCN was removed in vacuo at 50°C After 4 days at room temperature the mixture was purified by preparative HPLC using a gradient of MeCN/ammonium acetate buffer to give the title compound (2 mg, 6%) NMR (CD_3OD, 400 MHz) 7 40-7 20 (m, 6H), 7.05-6 95 (m, 6H), 4 8 (m, 1H), 4 7-4.55 (m, 1H), 4 5 (s, 2H), 3 75 (t, 2H), 3 1 (m, 1H), 2 95 (t, 2H), 2 0-1 8 (m, 4H)

Example 40

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(S)-1-(*t*-butoxycarbonyl)ethyl]carbamoylmethoxy}phenyl)azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 30 mg, 0 064 mmol), *tert*-butyl L-alaninate hydrochloride (40 mg, 0 22 mmol), triethyl amine (0 036 ml, 0 26 mmol) and TBTU (35 mg, 0 11 mmol) were mixed (in that order) in MeCN (1 ml) After 4 hours the mixture was diluted with toluene and the solution was washed with hydrochloric acid (2M) and

sodium hydrogen carbonate solution The solvent was removed *in vacuo* and the residue was purified by preparative HPLC using a gradient of MeCN/ammonium acetate buffer to give the title compound (20 mg, 52%) NMR (CD_3OD, 500 MHz) 7 40-6 90 (m), 4 8 (m), 4 7-4.3 (m), 3 95 (q), 3.2 (q), 3 1 (m), 2-1 8 (m), 1 5-1.3 (m), m/z 595 60 $(M+H)^+$ and 593 53 (M-H)

Example 41

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

A solution of 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(S)-1-(*t*-butoxycarbonyl)ethyl]carbamoylmethoxy}phenyl)azetidin-2-one (Example 40; 20 mg, 0 034 mmol) in formic acid (1 ml) was kept at room temperature overnight. The formic acid was removed *in vacuo* and the residue was dissolved in methanol (4ml) Aqueous ammonia (25%, 0 2 ml) was added and after 1 hour at room temperature the mixture was purified by preparative HPLC using a gradient of MeCN/ammonium acetate buffer to give the title compound (5 mg, 28%) NMR (CD_3OD, 400 MHz) 7.4-7 2 (m, 6H), 7 1-6 9 (m, 6H), 4,8 (m, 1H), 4 7-4 6 (m, 1H), 4 5 (s, 2H), 4 3 (q, 1H), 3 1 (m, 1H), 2-1 7 (m, 4H), 1.4 (dd, 3H), m/z 539 51 $(M+H)^+$ and 537 50 (M-H)

Example 42

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)phenyl]azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 28 mg, 0 06 mmol), 2-{[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino}ethanesulfonic acid (30 mg, 0 11 mmol), triethylamine (24 mg, 0.24 mmol), and TBTU (29 mg, 0 09 mmol) were mixed in DMF (1 5 ml) After stirring overnight the reaction mixture was purified by preparative HPLC using a gradient of MeCN/ammonium acetate buffer to give the title compound (18 mg, 42%) NMR (CD_3OD, 400 MHz) 7 4-7 1 (m), 7 1-6 9 (m), 5.4 (m), 4 8 (m), 4.7-4.5 (m), 3 65-3.55 (m), 3 15-3 05 (m), 3-2 8 (m), 2-1 7 (m), m/z 724.46 $(M+H)^+$ and 722.54 (M-H)

56

Example 43

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-((S)-1-{*N*-[(S)-1-(*t*-butoxycarbonyl)ethyl]carbamoyl}ethyl)carbamoylmethoxy]phenyl}azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 30 mg, 0 064 mmol), *tert*-butyl L-alanyl-L-alaninate (25 mg, 0 12 mmol), triethylamine (0 036 ml, 0.26 mmol) and TBTU (31 mg, 0 10 mmol) were mixed (in that order) in DMF (1 5 ml) After 16 hours the mixture was diluted with toluene and the solution was washed with water, hydrochloric acid (2M), water and sodium hydrogen carbonate solution and water Addition of IPA and removal of the solvents *in vacuo* gave the title compound. M/z 666 57 $(M+H)^+$ and 664 68 (M-H)

Example 44

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-((S)-1-{*N*-[(S)-1-(carboxy)ethyl]carbamoyl}ethyl)carbamoylmethoxy]phenyl}azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-((S)-1-{*N*-[(S)-1-(*t*-butoxycarbonyl)ethyl]carbamoyl}ethyl)carbamoylmethoxy]phenyl} azetidin-2-one (Example 43, 54 mg, 0 081 mmol) was dissolved in formic acid (2 ml) After 16 hours the formic acid was removed *in vacuo* and the residue was dissolved in methanol (4 ml) and aqueous ammonia (25%, 0 2 ml) After 6 hours the mixture was purified by preparative HPLC using a gradient of MeCN/ammonium acetate buffer to give the title compound (15 mg, 30%) NMR (CD_3OD, 400 MHz) 7 4-7 2 (m, 6H), 7 1-6 9 (m, 6H), 4 8 (m, 1H), 4 7-4 5 (m, 1H), 4 5 (s, 2H), 4 45 (q, 1H), 4.3-4 2 (m, 1H), 3 2 (q, 1H), 3 1-3.0 (m, 1H), 2-1 8 (m, 4H), 1 4-1 2 (dd, 6H), m/z 610 57 $(M+H)^+$ and 608.53 (M-H)

Example 45

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[*N*-(methoxycarbonylmethyl)carbamoylmethyl]carbamoylmethoxy}phenyl)azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl) azetidin-2-one (Method 2, 30 mg, 0 064 mmol), methyl glycylglycinate (19 mg, 0 13 mmol), triethyl amine (0 036 ml, 0 26 mmol) and TBTU (31 mg, 0 10 mmol) were mixed (in that order) in DMF (1.5 ml) After 16 hours the mixture was diluted with toluene and the solution was washed with water, hydrochloric acid (2M), water

and sodium hydrogen carbonate solution and water Addition of IPA and removal of the solvents in vacuo gave the title compound. M/z 596.50 $(M+H)^+$ and 594 45 (M-H)

Example 46

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[*N*-(carboxymethyl) carbamoylmethyl]carbamoylmethoxy}phenyl)azetidin-2-one

A solution of 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[*N*-(methoxycarbonylmethyl)carbamoylmethyl]carbamoylmethoxy}phenyl)azetidin-2-one (Example 45, 44 mg, 0 074 mmol) in THF (4 ml) was added to a stirred solution of lithium hydroxide (10 mg, 0.43 mmol) in water (2 ml) After 16 hours the mixture was carefully neutralized with hydrochloric acid. Purification by preparative HPLC using a gradient of MeCN/ammonium acetate buffer gave the title compound (17 mg, 40%) NMR (CD_3OD, 400 MHz) 7.4-7 2 (m, 6H), 7 1-6 9 (m, 6H), 4 8 (m, 1H), 4 7-4 6 (m, 1H), 4 6 (s, 2H), 3 95 (s, 2H), 3 8 (s, 2H), 3 1-3.05 (m, 1H), 2-1.8 (m, 4H)

Example 47

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(S)-1,3-bis-(ethoxycarbonyl)propyl]carbamoylmethoxy}phenyl)azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 30 mg, 0 064 mmol), diethyl L-glutamate (19 mg, 0 093 mmol), triethylamine (0 036 ml, 0.26 mmol) and TBTU (31 mg, 0 10 mmol) were mixed (in that order) in DMF (1.5 ml) After 16 hours the mixture was diluted with toluene and the solution was washed with water, hydrochloric acid (2M), water and sodium hydrogen carbonate solution and water Addition of IPA and removal of the solvents in vacuo gave the title compound. M/z 653 56 $(M+H)^+$ and 651.60 (M-H)

Example 48

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(S)-1,3-bis-(carboxy) propyl]carbamoylmethoxy}phenyl)azetidin-2-one

To a solution of 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(S)-1,3-bis-(ethoxycarbonyl)propyl]carbamoylmethoxy}phenyl)azetidin-2-one (Example 47, 30 mg, 0.046 mmol) in ethanol (4 ml) was added 3 75 M sodium hydroxide solution (0.05 ml, 0 19 mmol) After 16 hours more 3 75M sodium hydroxide solution (0 05 ml, 0 19 mmol) was

added. The ethanol was removed *in vacuo* and THF (2.5 ml) and water (1 5 ml) were added. After 24 hours the reaction mixture was purified by preparative HPLC using a gradient of MeCN/ammonium acetate buffer to give the title compound (11 mg, 40%) NMR (CD_3OD, 400 MHz) 7 5-6 9 (m), 5-4 8 (m), 4 75-4 6 (m), 4 5 (s), 4 45 (m), 4 4-4-3 (br s), 3 1-3 05 (m), 2.3-2 1 (m), 2-1 8 (m), m/z 597 52 $(M+H)^+$ and 595.49 (M-H)

Example 49

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(S)-1-(*t*-butoxycarbonyl)-5-(*t*-butoxycarbonylamino)pentyl]carbamoylmethoxy}phenyl)azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 30 mg, 0 064 mmol), *tert*-butyl N^6-(*tert*-butoxycarbonyl)-L-lysinate (39 mg, 0 13 mmol), triethyl amine (0 036 ml, 0.26 mmol) and TBTU (31 mg, 0 096 mmol) were mixed in DMF (1.50 ml) The mixture was stirred for 16 hours and then diluted with water and toluene The organic phase was washed with hydrochloric acid, water, sodium bicarbonate solution and then water IPA was added to the organic phase and the solvents were removed in vacuo to give the title compound (39 mg, 81%) M/z 752 68 $(M+H)^+$ and 750 79 (M-H)

Example 50

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(S)-1-(carboxy)-5-(amino)pentyl]carbamoylmethoxy}phenyl)azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(S)-1-(*t*-butoxycarbonyl)-5-(*t*-butoxycarbonylamino)pentyl]carbamoylmethoxy}phenyl)azetidin-2-one (Example 49, 39 mg, 0 052 mmol) was kept in formic acid (2 ml) for 64 hours The acid was removed in vacuo and the residue was dissolved in methanol (4 ml) and aqueous ammonia (25%, 0.4 ml) After 16 hours the solvent was removed in vacuo and the residue was purified by preparative HPLC using a gradient of MeCN/ammonium acetate buffer to give the title compound (7 mg, 23%) NMR (CD_3OD, 400 MHz) 7 4-7 2 (m, 6H), 7 05-6 95 (m, 6H), 4 8 (m, 1H), 4 65-4 6 (m, 1H), 4 5 (s, 2H), 4 35-4-3 (m, 1H), 3 1-3 05 (m, 1H), 2.9-2 8 (m, 2H), 2-1 6 (m, 6H), 1 5-1 2 (m, 4H)

Example 51

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[2-(*t*-butoxycarbonyl)ethyl]carbamoylmethoxy}phenyl)azetidin-2-one

A mixture of 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl) azetidin-2-one (Method 2, 47 mg, 0 101 mmol), *tert*-butyl β-alaninate (48 mg, 0 33 mmol) triethylamine (0 07 ml, 0.5 mmol), and TBTU (42 mg, 0 13 mmol) were mixed in DMF (1 ml) and left overnight. The mixture was diluted with diethyl ether and washed with potassium hydrogen sulphate solution and sodium carbonate solution The organic phase was dried (magnesium sulphate) and the solvent was removed *in vacuo* to give the title compound (38 mg, 64%) M/z 595 54 $(M+H)^+$ and 593 61 (M-H)

Example 52

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

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[2-(*t*-butoxycarbonyl)ethyl]carbamoylmethoxy}phenyl)azetidin-2-one (Example 51, 38 mg, 0 064 mmol) was dissolved in formic acid (2 ml) After 16 hours the acid was removed *in vacuo* with the aid of MeCN After complete removal of the solvents the residue was dissolved in methanol (5 ml) and aqueous ammonia (25%, 1 ml) Hydrolysis was complete in 2 hours and purification by HPLC using a gradient of MeCN/ammonium acetate buffer gave the title compound (20 mg, 59%) NMR (CD_3OD, 400 MHz) 7.4-7 2 (m, 6H), 7 1-6.9 (m, 6H), 4 8 (m, 1H), 4 7-4 6 (m, 1H), 4 5 (s, 2H), 3.5 (t, 2H), 3 1-3 05 (m, 1H), 2.4 (t, 2H), 2-1 8 (m, 4H), m/z 539.42 $(M+H)^+$ and 537 50 $(M-H)^-$

Example 53

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(R)-1-(*t*-butoxycarbonyl)ethyl]carbamoylmethoxy}phenyl)azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl)azetidin-2-one (Method 2, 30 mg, 0 064 mmol), *tert*-butyl D-alaninate hydrochloride (50 mg, 0.28 mmol), triethylamine (0 05 ml, 0 36 mmol) and TBTU (31 mg, 0 096 mmol) were stirred in DMF (1 ml) for 3 hours The mixture was diluted with toluene and washed with water, hydrochloric acid, water, sodium bicarbonate solution and

water IPA was added to the organic phase and the solvents were removed *in vacuo* to give 30 mg (79%) of the title compound. M/z 595 48 $(M+H)^+$ and 593.56 (M-H)

Example 54

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

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(R)-1-(*t*-butoxycarbonyl)ethyl]carbamoylmethoxy}phenyl)azetidin-2-one (Example 54, 30 mg, 0 05 mmol) was dissolved in formic acid (2 ml) After 16 hours the acid was removed in vacuo and the residue was dissolved in methanol (3 ml) and aqueous ammonia (25%, 0.2 ml) The progress was followed by HPLC and after completion the mixture was purified by HPLC using a gradient of MeCN/ammonium acetate buffer to give the title compound (17 mg, 63%) NMR (CD_3OD, 400 MHz) 7 4-7 2 (m, 6H), 7 1-6 9 (m, 6H), 4 8 (m, 1H), 4 7-4 6 (m, 1H), 4 5 (s, 2H), 4.3-4.2 (s, 1H), 3 1-3 05 (m, 1H), 2 2-1 8 (m, 4H), 1 5-1 4 (m, 3H)

Preparation of Starting Materials

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

Method 1

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-*t*-butoxycarbonylmethoxyphenyl)azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl) azetidin-2-one (*J Med Chem* 1998, *41*, 973-980; 50 mg, 0 122 mmol), tert-butylbromoacetate (24 µl, 0 165 mmol), sodium carbonate (80 mg, 0 76 mmol) and a catalytic amount of caesium carbonate were added to MeCN (3 ml) and the mixture was stirred for 1 5 hours at 50°C The solids were filtered off and the solvent was evaporated under reduced pressure. Purification of the residue by column chromatography using DCM/EtOAc (100/7) as eluent gave 35 mg, (55 %) of the title compound. NMR (300 MHz) 1 45 (s, 9H), 1 8-2 1 (m, 4H), 2.25-2.3 (m, 1H), 3 05-3 15 (m, 1H), 4 5 (s, 2H), 4 55-4 6 (m, 1H), 4 75 (bs, 1H), 6.9-7.3 (m, 12H), m/z 524 3

Method 2

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-carboxymethoxyphenyl) azetidin-2-one

1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-*t*-butoxycarbonyl methoxyphenyl)azetidin-2-one (Method 1, 50 mg, 0 096 mmol) was added to formic acid (3 ml) and the mixture was stirred for 1 5 hours at room temperature. The solvent was evaporated under reduced pressure and methanol (3 ml) and triethylamine (150 µl) were added to the residue The mixture was stirred for 2 hours. at room temperature and the solvents were evaporated under reduced pressure The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (35 65) as eluent. The collected fractions were lyophilised to obtain 32 mg (56%) of the title compound. NMR (300 MHz, CD_3OD) 1 8-1 95 (m, 4H), 3 1 (bs, 1H), 4.4 (s, 2H), 4 55-4 65 (m, 1H), 4 8 (bs, 1H), 6 9-7 35 (m, 12H); m/z 466 1 (m-H)

Method 3

tert-Butyl *N*-((2*R*)-2-{[(benzyloxy)carbonyl]amino}-2-phenylethanoyl)glycinate

(2*R*)-{[(benzyloxy)carbonyl]amino}(phenyl)acetic acid (Z-(R)-Phg-OH) (10 g, 35 0 mmol) and *tert*-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 minutes at 0°C TBTU (12.4 g, 38 6 mmol) was added and stirring was continued 1 hours 30 minutes at 0°C and 3 hours 45 minutes at room temperature. The reaction mixture was washed with water (2 x 100 ml), dried (magnesium sulphate) and purified with flash chromatography (DCM.EtOAc 7 1→5 1) to give the title compound (13 g, 94 %) NMR (500 MHz) 1.45 (s, 9 H), 3 84 (d, 1 H), 4.00 (dd, 1 H), 5 10 (m, 2 H), 5.28 (br s, 1 H), 6.13 (br s, 1 H), 6.23 (br s, 1 H), 7 30-7.44 (m, 10 H)

Method 4

tert-Butyl *N*-[(2*R*)-2-amino-2-phenylethanoyl]glycinate

tert-Butyl *N*-((2*R*)-2-{[(benzyloxy)carbonyl]amino}-2-phenylethanoyl)glycinate (Method 3, 12.8 g, 32 2 mmol) was dissolved in EtOH (99%, 200 ml) and toluene (50 ml) Pd/C (10%, 0 65 g) was added and hydrogenation was performed at atmospheric pressure for 5 hours 30 minutes 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 %)

59
89

NMR (600 MHz) 1 45 (s, 9 H), 3 93 (m, 2 H), 4 54 (s, 1 H), 7.31-7.42 (m, 5 H), 7 51 (br s, 1 H)

Method 5

tert-Butyl *N*-((2*R*)-2-{[(benzyloxy)carbonyl]amino}-2-phenylethanoyl)-*O*-(*tert*-butyl)-L-serinate

(2*R*)-{[(Benzyloxy)carbonyl]amino}(phenyl)acetic acid (Z-(R)-Phg-OH) (2.0 g, 7 0 mmol) and *tert*-butyl *O*-(*tert*-butyl)-L-serinate (2 0 g, 7 9 mmol) and 2 6-lutidine were dissolved in DCM (30 ml) After stirring 5 minutes at 0°C TBTU (2.5 g, 7 8 mmol) was added and stirring was continued 30 minutes at 0°C and 4 hours 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, CD_3OD) 1 05 (s, 9H), 1.45 (s, 9H), 3.4-3 8 (m, 2H), 4 5 (bs, 1H), 4 85 (s, 2H), 5 1 (s, 2H), 5 4 (s, 1H), 7 25-7 5 (m, 10 H)

Method 6

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

tert-Butyl *N*-((2*R*)-2-{[(benzyloxy)carbonyl]amino}-2-phenylethanoyl)-*O*-(*tert*-butyl)-L-serinate (Method 5, 3 3 g, 6 8 mmol) was dissolved in EtOH (95%, 30 ml) and a cat amount of Pd/C (5%)(50% in water) was added and hydrogenation was performed at atmospheric preasure for 3 hours at room temperature. The reaction mixture was filtered through diatomaceous earth and the solvent was evaporated to give the title compound (2.35 g, 98 %) NMR (500 MHz, CD_3OD) 1 1 (s, 9H), 1.45 (s, 9H), 3.45-3 8 (m, 2H), 4 5 (t, 1H), 4 55 (s, 1H), 4 85 (s, 2H), 7 3-7.5 (m, 5H)

Method 7

1-(4-Fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(*t*-butoxycarbonylmethoxy) phenyl]azetidin-2-one

A mixture of 1-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-(4-hydroxyphenyl)azetidin-2-one (Prepared according to Bioorg. Med. Chem. Lett 1996, 6, 1271-1274, 1 00 g, 2.53 mmol), *t*-butyl bromoacetate (0.42 ml, 2 79 mmol) and caesium carbonate (1 00 g, 3 07 mmol) in MeCN (10 ml) was stirred at 40°C for 90 minutes. The suspension was filtered and the solid material was washed with MeCN (5 ml) and EtOAc (5

ml) The filtrate was concentrated and the residue was purified by flash chromatography using a mixture of hexane and EtOAc (7 2) as eluent. The title compound was obtained as a colourless oil (1.045 g; 81 %) NMR (600 MHz) 1.45 (s, 9H), 2.25-2.45 (m, 2H), 3.20-3 30 (m, 1H), 4 00-4-10 (m, 1H), 4 10-4.20 (m, 1H), 4 50 (s, 2H), 4 80 (d, 1H), 6 75-7 00 (m, 8H), 7 20-7.30 (m, 4H), m/z. 501 2

Method 8

1-(4-Fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(carboxymethoxy)phenyl]azetidin-2-one

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)ethyl]-4-[4-(*t*-butoxycarbonylmethoxy)phenyl]azetidin-2-one (Method 7, 1.045 g, 2.051 mmol) in formic acid (4 ml) was stirred at room temperature for 22 hours The solvent was removed under reduced pressure and the residue was dissolved in DCM (10 ml) The organic layer was successively washed with a saturated solution of sodium hydrogen carbonate (aq, 5 ml), water (5 ml) and brine (5 ml), dried and concentrated to give the title compound as a white solid (0 941 g, ~quantitative yield) NMR (400 MHz) 2.25-2.45 (m, 2H), 3 20-3.30 (m, 1H), 4.00-4 20 (m, 2H), 4 65 (s, 2H), 4 80 (d, 1H), 6 75-6.80 (m, 2H), 6 85-7 00 (m, 6H), 7 20-7 30 (m, 4H), m/z 454.0

Method 9

3-(R)-4-(R)-1-(Phenyl)-3-(phenylethylsulphanyl)-4-[4-(carboxymethoxy)phenyl]azetidin-2-one

3-(R)-4-(R)-1-(Phenyl)-3-(phenylethylsulphanyl)-4-[4-(*t*-butoxycarbonylmethoxy) phenyl]azetidin-2-one (Method 15, 220 mg) was stirred in formic acid (2 ml) for 20 hours at ambient temperature. The formic acid was then evaporated. Toluene was added and evaporated twice to give the title compound (180 mg) NMR 400 MHz, CD_3OD) 2.86-3 00 (m, 4H), 4.03 (d, 1H), 4 66 (s, 2H), 4.87 (d, 1H), 6 93-7 35 (m, 14H).

Method 10

3-(R)-4-(R)-1-(Phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-[4-(carboxymethoxy)phenyl] azetidin-2-one

A solution of 3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-(4-hydroxyphenyl)azetidin-2-one (synthesized according to WO 96/16037, 0 100 g, 0.245

160

mmol), caesium carbonate (0 040 g, 0.123 mmol) and t-butyl bromoacetate (0 019 ml, 0 129 mmol) in MeCN (0 5 ml) was stirred at room temperature for 10 minutes, after which more caesium carbonate (0 040 g, 0 123 mmol) and t-butyl bromoacetate (0 019 ml, 0 129 mmol) were added. After 7 hours water (5 ml) and AcOH (0 05 ml) were added to the reaction mixture and the organic solvent was removed under reduced pressure The water layer was extracted twice with DCM (2x5 ml) and the combined organic layers were washed with brine, dried over magnesium sulphate and concentrated. The residue was purified twice by flash chromatography using heptane EtOAc (3 1) as eluent, which gave a colourless oil (0 066 g) M/z 522.1 This oil was dissolved in formic acid (3ml) and the solution was stirred at room temperature for 18 hours The solvent was removed under reduced pressure and the residue was purified by preparative HPLC, using a gradient of 20-50% MeCN in 0 1M ammonium acetate buffer as eluent The title compound was obtained as a white solid (0 025 g, 22 %) NMR (CD_3COOD, 400 MHz) 4.20 (d, 1H), 4.25 (s, 2H), 4 70 (s, 2H), 5 00 (d, 1H), 6 90-7 10 (m, 2H), 7 00-7 40 (m, 9H), 8 00-8 10 (m, 2H), m/z 465 9

Method 11

3-(R)-4-(R)-1-(Phenyl)-3-(thien-3-ylcarbonylmethylsulphanyl)-4-[4-(carboxymethoxy) phenyl]azetidin-2-one

A solution of 3-(R)-4-(R)-1-(phenyl)-3-(thien-3-ylcarbonylmethylsulphanyl)-4-(4-hydroxyphenyl)azetidin-2-one (synthesized according to WO 96/16037, 0 100 g, 0.253 mmol), caesium carbonate (0 043 g, 0 132 mmol) and t-butyl bromoacetate (0 019 ml, 0 126 mmol) in MeCN (6 ml) was stirred at room temperature for 10 minutes, after which more caesium carbonate (0 040 g, 0 123 mmol) and t-butyl bromoacetate (0 019 ml, 0 126 mmol) were added. After 7 hours water (7 ml) and AcOH (0.05 ml) were added and the solvent was removed under reduced pressure. The water layer was extracted twice with DCM (2x3 ml) and the combined organic layers were washed with brine, dried over magnesium sulphate and concentrated. The residue was purified by flash chromatography using heptane.EtOAc (3 1) as eluent, which gave 0 103 g of a colourless oil (m/z 510 1) This oil was dissolved in formic acid (3ml) and the solution was stirred for 18 hours at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in DCM The solution was washed two times with water and one time with brine, dried over magnesium sulphate and concentrated This gave a colourless oil which was used without further purification (0 079 g) M/z 453 9

Method 12

1-(4-Fluorophenyl)-3-(2-chloroethyl)-4-(4-hydroxyphenyl)azetidin-2-one

A stirring mixture of 1-(4-fluorophenyl)-3-(2-chloroethyl)-4-[4-(benzyloxy)phenyl] azetidin-2-one (prepared according to Bioorg. Med. Chem. Lett 1996, 6, 1271-1274, 2 00 g, 4 88 mmol), $Pd(OH)_2/C$ (0 500 g, 20%) and cyclohexene (6 ml) in MeOH (60 ml) was heated to 70°C After 2 hours, the reaction mixture was cooled to room temperature and was filtered through diatomaceous earth The solvent was removed under reduced pressure to give the title compound (1.57 g, ~quantitative yield) No further purification was necessary NMR (CD_3OD, 400 MHz) 2.20-2.40 (m, 2H), 3 20-3 40 (m, 1H), 3 70 (t, 2H), 4 85 (d, 1H), 6.75-6 80 (m, 2H), 6 90-7 00 (m, 2H), 7 15-7.30 (m, 4H), m/z 320 0

Method 13

1-(4-Fluorophenyl)-3-[2-(4-fluorophenylthio)ethyl]-4-(4-hydroxyphenyl)azetidin-2-one

To a stirring solution of 1-(4-fluorophenyl)-3-(2-chloroethyl)-4-(4-hydroxyphenyl) azetidin-2-one (Method 12, 0 750 g, 2.35 mmol) in MeCN (10 ml) was added 4-fluorothiophenol (0.500 ml, 4.60 mmol) and triethylamine (0 500 ml, 3.59 mmol) at room temperature. After 20 hours there were still start material left (approximately 20 %, LC/MS) and more 4-fluorothiophenol (0 250 ml, 2 30 mmol) and triethylamine (0 170 ml, 1.22 mmol) were added. After 24 hours, the solvent was removed under reduced preasure and the residue was partitioned between water (20 ml) and EtOAc (20 ml) The organic layer was washed with brine (5 ml), dried over magnesium sulphate and concentrated. The residue was refluxed in heptane for 30 minutes before the title compound was filtered off as a grey solid (0 946 g; 98 %) NMR (CD_3OD, 400 MHz) 2.00-2 20 (m, 2H), 3 05 (t, 2H), 3 25 (dt, 1H), 4.75 (d, 1H), 6.75-6 80 (m, 2H), 6 90-7 05 (m, 4H), 7 15-7 40 (m, 6H); m/z 412 0

Method 14

tert-Butyl (2*S*)-2-{[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino}butanoate hydrochloride

tert-butyl (2*S*)-2-{[(2*R*)-2-{[(benzyloxy)carbonyl]amino}-2-(4-hydroxyphenyl)acetyl] amino}butanoate (Method 18, 47g, 106 2mmol) was dissolved in 400ml 95.5% ethanol Pd/C (5%, 3 0g) was added and the mixture was hydrogenated under $H_2(g)$ at 1bar pressure at ambient temperature. The hydrogenation was terminated after 20 hours and the catalyst was filtered off on SiO_2 and washed with ethanol The filtrate was concentrated and the residue (ca 35g) was dissolved in 300ml MeCN Pyridine hydrochloride (14g) was added and the mixture

was left to crystallize for 2 5 days The formed salt was filtered off and washed with 2 x 50ml MeCN The solid was dried under vacuum at 40°C to yield 29 6 g (81%) of a white crystalline product NMR (300MHz, DMSO-d_6) 0 64 (t, 3H), 1 39 (s, 9H), 1.40-1 70 (m, 2H), 3 98-4 04 (m, 1H), 4 90 (brs, 1H), 6 78 (d, 2H), 7 32 (d, 2H), 8 63 (brs, 3H), 8 79 (d, 1H), 9 83 (brs, 1H)

Method 15

3-(R)-4-(R)-1-(Phenyl)-3-(phenylethylsulphanyl)-4-[4-(*t*-butoxycarbonylmethoxy)phenyl] azetidin-2-one

A mixture of 3-(R)-4-(R)-1-(phenyl)-3-(phenylethylsulphanyl)-4-(4-hydroxyphenyl) azetidin-2-one (synthesized according to WO 96/16037, 0 5g, 1,33 mmol), t-butyl bromoacetate (0.31g, 1 58mmol), sodium carbonate (0.56g, 5.28mmol) and cesium carbonate (0 12g, 0 36mmol) in MeCN was stirred at 50°C overnight The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography (EtOAc isohexane, 1 6) to give the title compound 220 mg (33%) M/z 490 1

Method 16

1-(4-Fluorophenyl)-3-[2-(4-fluorophenylthio)ethyl]-4-[4-(*t*-butoxycarbonylmethoxy)phenyl] azetidin-2-one

A suspension of 1-(4-fluorophenyl)-3-[2-(4-fluorophenylthio)ethyl]-4-(4-hydroxyphenyl)azetidin-2-one (Method 13, 0 800g, 1 944 mmol), *t*-butyl bromoacetate (0 32 ml, 2 17 mmol) and caesium carbonate (0 700 g, 2 15 mmol) in MeCN (15 ml) was stirred at room temperature for 2 hours The solvent was removed under reduced pressure and the residue was partitioned between water (20 ml) and DCM (20 ml) The water layer was extracted once more with DCM (10 ml) and the combined organic layers were washed with brine, dried over magnesium sulphate and concentrated. The residue was purified by flash chromatography using heptane.EtOAc (4 1) as eluent. The title compound was obtained as a colourless oil (0 884 g; 87 %) NMR (400 MHz) 1.45 (s, 9H), 2 00-2.30 (m, 2H), 2.90-3 10 (m, 2H), 3 15-3 25 (m, 1H), 4 50 (s, 2H), 4 60 (d, 1H), 6 85-7 00 (m, 6H), 7 15-7 35 (m, 6H), m/z 526.2

Method 17

1-(4-Fluorophenyl)-3-[2-(4-fluorophenylthio)ethyl]-4-[4-(carboxymethoxy)phenyl]azetidin-2-one

A solution of 1-(4-fluorophenyl)-3-[2-(4-fluorophenylthio)ethyl]-4-[4-(t-butoxycarbonylmethoxy)phenyl]azetidin-2-one (Method 16, 0 880 g, 1 67 mmol) in formic acid (5 ml) was stirred at room temperature for 19 hours The solvent was removed under reduced preasure and the residue was dissolved in DCM (25 ml) The organic layer was washed twice with water (1x10 ml and 1x5 ml) and once with brine (5 ml), dried over magnesium sulphate and concentrated. This gave the title compound as a colourless oil (0 800 g, ~quantitative yield). NMR (CD_3COOD, 400 MHz) 2.10-2 30 (m, 2H), 3 10 (dt, 2H), 3 30-3.40 (m, 1H), 4.75 (s, 2H), 4 80 (d, 1H), 6 95-7 05 (m, 6H), 7 25-7 40 (m, 6H), m/z. 470 2

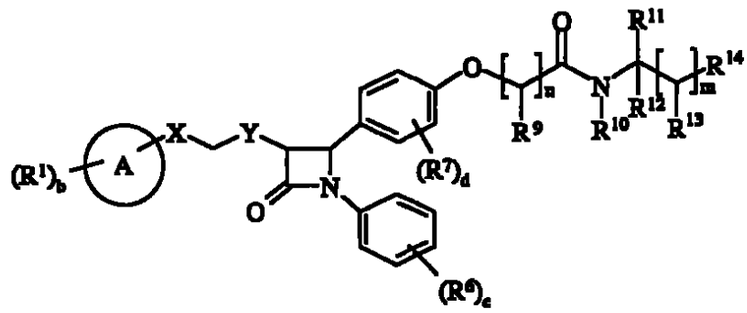
Method 18

tert-Butyl (2*S*)-2-{[(2*R*)-2-{[(benzyloxy)carbonyl]amino}-2-(4-hydroxyphenyl)acetyl]amino} butanoate

(R)-N-Benzyloxycarbonyl-4-hydroxyphenylglycine (J Chem. Soc. Perkin Trans 1, EN, 7, 1991, 1629-1635, 24.9g, 82.6mmol), (S)-2-aminobutyric acid *t*-butyl ester hydrochloride (18 6g, 95 0mmol) and *N*-methylmorpholine (23.0g, 227 4mmol) were dissolved in 220 ml DMF TBTU (33 7g, 105 0mmol) was added in portions over 10min. The reaction mixture was stirred for 1 hour at ambient temperature. Approximately 100ml solvent was evaporated from the solution Water (250ml) was added to the remaining solution, which caused the product to precipitate. The mixture was left overnight then the solid was filtered off and washed with 30% methanol (200ml) and hexane (100ml) The solid was dispersed in 100ml t-butyl methyl ether and stirred for 1 hour The solid was filtered off, washed with t-butyl methyl ether (100ml) and dried under vacuum at 40°C to yield 34 7g (95%) NMR (300MHz, DMSO-d_6) 0 71 (t, 3H), 1.37 (s, 9H), 1.40-1 70 (m, 2H), 3 91-4.01 (m, 1H), 5.02 (d, 2H), 5.23 (d, 1H), 6.67 (d, 2H), 7.22 (d, 2H), 7.27-7.36 (m, 5H), 7 67-7 74 (m, 1H), 8 32 (d, 1H), 9.37 (brs, 1H)

Claims

1 A compound of formula (I)



(I)

wherein

Ring A is selected from phenyl or thienyl,

X is selected from $-CR^2R^3-$, $-O-$, $-NR^x-$ and $-S(O)_a-$, wherein R^x is hydrogen or C_{1-6}alkyl, and a is 0-2,

Y is selected from $-CR^4R^5-$, $-O-$, $-NR^x-$ and $-S(O)_a-$, wherein R^x is hydrogen or C_{1-6}alkyl, and a is 0-2, wherein there is at least one $-CR^2R^3-$ or $-CR^4R^5-$ group,

R^1 is independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy and C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, wherein R^1 is independently optionally substituted on carbon by one or more halo, C_{1-6}alkoxy and hydroxy;

b is 0-3, wherein the values of R^1 may be the same or different,

R^2 and R^3 are independently selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy and C_{1-6}alkanoyloxy, wherein R^2 and R^3 may be independently optionally substituted on carbon by one or more halo or hydroxy; or R^2 and R^3 together form an oxo group,

R^4 and R^5 are independently selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy and C_{1-6}alkanoyloxy; or R^4 and R^5 together form an oxo group,

R^6 is independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, formyl, carbamoyl, carbamoyloxy, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkenyloxy, 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, C_{1-6}alkanoyl-*N*-(C_{1-6}alkyl)amino, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)carbamoyloxy, *N,N*-(C_{1-6}alkyl)$_2$carbamoyloxy, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino,

C_{1-6}alkoxycarbonyl-*N*-(C_{1-6}alkyl)amino, C_{1-6}alkoxycarbonyloxy, C_{1-6}alkoxycarbonylamino, ureido, *N'*-(C_{1-6}alkyl)ureido, *N*-(C_{1-6}alkyl)ureido, *N',N'*-(C_{1-6}alkyl)$_2$ureido, *N'*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkyl)ureido, *N',N'*-(C_{1-6}alkyl)$_2$-*N*-(C_{1-6}alkyl)ureido, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenyl, wherein R^7 is independently optionally substituted on carbon by one or more halo, C_{1-6}alkoxy, hydroxy, amino, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl-*N*-(C_{1-6}alkyl)amino, phenyl, phenoxy, benzoyl, phenylC_{1-6}alkyl and phenylC_{1-6}alkoxy;

c is 0-5, wherein the values of R^6 may be the same or different,

R^7 is 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,

d is 0-4, wherein the values of R^7 may be the same or different,

R^9 is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, wherein R^9 may be optionally substituted on carbon by one or more substituents selected from R^{23}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{24},

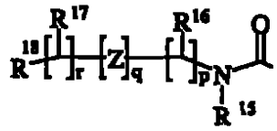
R^{10} is hydrogen or C_{1-4}alkyl,

R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, or R^{11} and R^{12} together form C_{2-6}alkylene, wherein R^{11} and R^{12} or R^{11} and R^{12} together may be independently optionally substituted on carbon by one or more substituents selected from R^{25}, and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{26},

R^{13} is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl, wherein R^{13} may be optionally substituted on carbon by one or more substituents selected from R^{27}, and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{28},

R^{14} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkoxycarbonyl, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino,

N,N-(C_{1-10}alkyl)$_2$amino, *N,N N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{29}-(C_{1-10}alkylene)$_f$-, heterocyclyl-(C_{1-10}alkylene)$_g$-R^{30}-(C_{1-10}alkylene)$_h$-, carboxy, sulpho, sulphino, phosphono, -P(O)(OR^{31})(OR^{32}), -P(O)(OH)(OR^{31}), -P(O)(OH)(R^{31}) or -P(O)(OR^{31})(R^{32}) wherein R^{31} and R^{32} are independently selected from C_{1-6}alkyl, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{34}, or R^{14} is a group of formula (IA)



(IA)

wherein

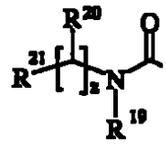
Z is –N(R^{35})-, -N(R^{35})C(O)-, -O-, and -S(O)$_a$-, wherein a is 0-2 and R^{35} is hydrogen or C_{1-4}alkyl,

R^{15} is hydrogen or C_{1-4}alkyl,

R^{16} and R^{17} are independently selected from hydrogen, 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, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, -P(O)(OR^{36})(OR^{37}), -P(O)(OH)(OR^{36}), -P(O)(OH)(R^{36}) or -P(O)(OR^{36})(R^{37}), wherein R^{36} and R^{37} are independently selected from C_{1-6}alkyl, wherein R^{16} and R^{17} may be independently optionally substituted on carbon by one or more substituents selected from R^{38}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{39},

R^{18} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl,

$C_{1\text{-}10}$alkoxy, $C_{1\text{-}10}$alkanoyl, $C_{1\text{-}10}$alkanoyloxy, *N*-($C_{1\text{-}10}$alkyl)amino, *N,N*-($C_{1\text{-}10}$alkyl)$_2$amino, $C_{1\text{-}10}$alkanoylamino, *N*-($C_{1\text{-}10}$alkyl)carbamoyl, $C_{1\text{-}10}$alkoxycarbonyl, *N N*-($C_{1\text{-}10}$alkyl)$_2$carbamoyl, $C_{1\text{-}10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1\text{-}10}$alkyl)sulphamoyl, *N,N*-($C_{1\text{-}10}$alkyl)$_2$sulphamoyl, *N*-($C_{1\text{-}10}$alkyl)sulphamoylamino, *N,N*-($C_{1\text{-}10}$alkyl)$_2$sulphamoylamino, carbocyclyl, carbocyclyl$C_{1\text{-}10}$alkyl, heterocyclyl, heterocyclyl$C_{1\text{-}10}$alkyl, carbocyclyl-($C_{1\text{-}10}$alkylene)$_e$-R^{40}-($C_{1\text{-}10}$alkylene)$_f$- or heterocyclyl-($C_{1\text{-}10}$alkylene)$_g$-R^{41}-($C_{1\text{-}10}$alkylene)$_h$-, carboxy, sulpho, sulphino, phosphono, -P(O)(OR^{42})(OR^{43}), -P(O)(OH)(OR^{42}), -P(O)(OH)(R^{42}) or -P(O)(OR^{42})(R^{43}) wherein R^{42} and R^{43} are independently selected from $C_{1\text{-}6}$alkyl, wherein R^{18} may be optionally substituted on carbon by one or more substituents selected from R^{44}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{45}, or R^{18} is a group of formula (IB)



(IB)

wherein

R^{19} is selected from hydrogen or $C_{1\text{-}4}$alkyl,

R^{20} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$alkanoyl, $C_{1\text{-}6}$alkanoyloxy, *N*-($C_{1\text{-}6}$alkyl)amino, *N,N*-($C_{1\text{-}6}$alkyl)$_2$amino, $C_{1\text{-}6}$alkanoylamino, *N*-($C_{1\text{-}6}$alkyl)carbamoyl, *N,N*-($C_{1\text{-}6}$alkyl)$_2$carbamoyl, $C_{1\text{-}6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1\text{-}6}$alkoxycarbonyl, *N*-($C_{1\text{-}6}$alkyl)sulphamoyl, *N,N*-($C_{1\text{-}6}$alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, -P(O)(OR^{46})(OR^{47}), -P(O)(OH)(OR^{46}), -P(O)(OH)(R^{46}) or -P(O)(OR^{46})(R^{47}), wherein R^{46} and R^{47} are independently selected from $C_{1\text{-}6}$alkyl, where R^{20} may be independently optionally substituted on carbon by one or more substituents selected from R^{48}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{49},

R^{21} is selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1\text{-}10}$alkyl, $C_{2\text{-}10}$alkenyl, $C_{2\text{-}10}$alkynyl, $C_{1\text{-}10}$alkoxy, $C_{1\text{-}10}$alkoxycarbonyl, $C_{1\text{-}10}$alkanoyl, $C_{1\text{-}10}$alkanoyloxy, *N*-($C_{1\text{-}10}$alkyl)amino, *N,N*-($C_{1\text{-}10}$alkyl)$_2$amino, *N,N,N*-($C_{1\text{-}10}$alkyl)$_3$ammonio, $C_{1\text{-}10}$alkanoylamino,

N-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{50}-(C_{1-10}alkylene)$_f$-, heterocyclyl-(C_{1-10}alkylene)$_g$-R^{51}-(C_{1-10}alkylene)$_h$-, carboxy, sulpho, sulphino, phosphono, -P(O)(OR^{52})(OR^{53}), -P(O)(OH)(OR^{52}), -P(O)(OH)(R^{52}) or -P(O)(OR^{53})(R^{53}) wherein R^{52} and R^{53} are independently selected from C_{1-6}alkyl, wherein R^{21} may be independently optionally substituted on carbon by one or more R^{54}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{55},

p is 1-3, wherein the values of R^{16} may be the same or different;

q is 0-1,

r is 0-3, wherein the values of R^{17} may be the same or different,

m is 0-2, wherein the values of R^{13} may be the same or different,

n is 1-2, wherein the values of R^{9} may be the same or different,

z is 0-3, wherein the values of R^{20} may be the same or different,

R^{23}, R^{25}, R^{27}, R^{33}, R^{38}, R^{44}, R^{48} and R^{54} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, C_{1-10}alkoxycarbonyl, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, *N,N,N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclyl, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{56}-(C_{1-10}alkylene)$_f$-, heterocyclyl-(C_{1-10}alkylene)$_g$-R^{57}-(C_{1-10}alkylene)$_h$-, carboxy, sulpho, sulphino, amidino, phosphono, -P(O)(OR^{58})(OR^{59}), -P(O)(OH)(OR^{58}), -P(O)(OH)(R^{58}) or -P(O)(OR^{59})(R^{59}), wherein R^{58} and R^{59} are independently selected from C_{1-6}alkyl, wherein R^{23}, R^{25}, R^{27}, R^{33}, R^{38}, R^{44}, R^{48} and R^{54} may be independently optionally substituted on carbon by one or more R^{60}, and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{61},

R^{24}, R^{26}, R^{28}, R^{34}, R^{39}, R^{45}, R^{49}, R^{55} and R^{61} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, benzyl, phenethyl, benzoyl, phenylsulphonyl and phenyl,

R^{29}, R^{30}, R^{40}, R^{41}, R^{50}, R^{51}, R^{56} and R^{57} are independently selected from -O-, -NR^{62}-, -$S(O)_x$-, -$NR^{62}C(O)NR^{63}$-, -$NR^{62}C(S)NR^{63}$-, -OC(O)N=C-, -$NR^{62}C(O)$- or -$C(O)NR^{62}$-, wherein R^{62} and R^{63} are independently selected from hydrogen or C_{1-6}alkyl, and x is 0-2,

R^{68} is 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, and

e, f, g and h are independently selected from 0-2,

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

2 A compound of formula (I) according to claim 1 wherein X is selected from -CH_2-, -CH(OH)-, -C(O)-, -O- -S-, -S(O)-and -$S(O)_2$-, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

3 A compound of formula (I) according to either of claims 1 or 2 wherein Y is -CH_2-, -S- or -S(O)-, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

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

5 A compound of formula (I) according to any one of claims 1 to 4 wherein b is 0-1, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

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

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

8 A compound of formula (I) according to any one of claims 1 to 7 wherein d is 0, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

9 A compound of formula (I) according to any one of claims 1 to 8 wherein R^9 is hydrogen, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

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

11 A compound of formula (I) according to any one of claims 1 to 10 wherein R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl or carbocyclyl, wherein R^{11} and R^{12} may be independently optionally substituted on carbon by one or more substituents selected from R^{25}, wherein R^{25} is selected from hydroxy, amino, carbamoyl, $C_{1\ 10}$alkoxycarbonyl, $C_{1\ 10}$alkoxycarbonylamino, carbocyclyl or carboxy; wherein R^{25} may be optionally substituted on carbon by one or more R^{60}, wherein R^{60} is hydroxy, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

12. A compound of formula (I) according to any one of claims 1 to 11 wherein R^{13} is hydrogen, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

13 A compound of formula (I) according to any one of claims 1 to 12 wherein R^{14} is hydroxy, C_{1-10}alkyl, $C_{1\ 10}$alkoxy, $C_{1\ 10}$alkoxycarbonyl, carboxy or sulpho, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, or R^{14} is a group of formula (IA) (as depicted above) wherein.

R^{15} is hydrogen,

R^{16} and R^{17} are independently selected from hydrogen, carboxy, C_{1-6}alkyl and C_{1-6}alkoxycarbonyl,

R^{18} is selected from hydroxy, C_{1-10}alkyl, C_{1-10}alkoxy, C_{1-10}alkoxycarbonyl, carboxy and sulpho,

p is 1,

q is 0,

r is 0 or 1,

m is 0 or 1,

n is 1, and

R^{33} is hydroxy;

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

14 A compound of formula (I) according to any one of claims 1 to 13 wherein m is 0 or 1, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

15 A compound of formula (I) according to any one of claims 1 to 14 wherein n is 1, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

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

Ring A is selected from phenyl or thienyl,

X is selected from $-CH_2-$, -CH(OH)-, -C(O)-, -O- -S-, -S(O)-and $-S(O)_2-$,

Y is $-CH_2-$, -S- or -S(O)-,

R^1 is fluoro,

b is 0-1,

R^6 is fluoro,

c is 0-1,

d is 0;

R^9 is hydrogen,

R^{10} is hydrogen,

One of R^{11} and R^{12} is hydrogen and the other is selected from hydrogen, methyl, hydroxymethyl, 2-carbamoylethyl, 2-(ethoxycarbonyl)ethyl, 2-carboxyethyl, 4-(*t*-butoxycarbonylamino)butyl, 4-aminobutyl, isobutyl, phenyl, 4-hydroxyphenyl and 4-hydroxybenzyl,

R^{13} is hydrogen,

R^{14} is hydroxy, pentyl, methoxy, ethoxycarbonyl, *t*-butoxycarbonyl, carboxy or sulpho, wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{33}, or R^{14} is a group of formula (IA) (as depicted above) wherein

R^{15} is hydrogen,

R^{16} and R^{17} are independently selected from hydrogen, carboxy, C_{1-6}alkyl and *t*-butoxycarbonyl,

R^{18} is selected from hydroxy, methyl, *t*-butoxy, ethoxycarbonyl *t*-butoxycarbonyl, carboxy and sulpho,

p is 1,

q is 0,

r is 0 or 1,

m is 0 or 1,

n is 1, and

R^{33} is hydroxy;

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

17 A compound of formula (I) (as depicted in claim 1) selected from

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

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[(R)-α-(carboxy) benzyl]carbamoylmethoxy}phenyl)azetidin-2-one,

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one,

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{*N*-[*N*-(carboxymethyl) carbamoylmethyl]carbamoylmethoxy}phenyl)azetidin-2-one,

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(2-hydroxyethyl) carbamoylmethoxy]phenyl}azetidin-2-one,

1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-{4-[*N*-(2-methoxyethyl) carbamoylmethoxy]phenyl}azetidin-2-one,

3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one,

3-(R)-4-(R)-1-(phenyl)-3-[2-(4-fluorophenyl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl)carbamoylmethoxy]phenyl}azetidin-2-one,

3-(R)-4-(R)-1-(phenyl)-3-[2-(thuen-3-yl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-(carboxymethyl) carbamoylmethoxy]phenyl}azetidin-2-one;

3-(R)-4-(R)-1-(phenyl)-3-[2-(thuen-3-yl)-2-hydroxyethylsulphanyl]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one,

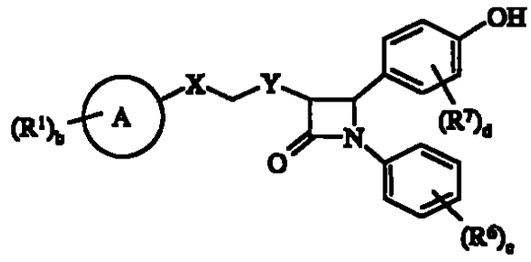
3-(R)-4-(R)-1-(phenyl)-3-(4-fluorobenzoylmethylsulphanyl)-4-(4-[*N*-((R)-α-{*N*-[(S)-1-(carboxy)-2-(hydroxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy]phenyl}azetidin-2-one, and

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

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

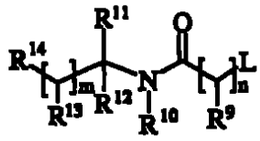
18 A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in claim 1) comprises of

Process 1) reacting a compound of formula (II)



(II)

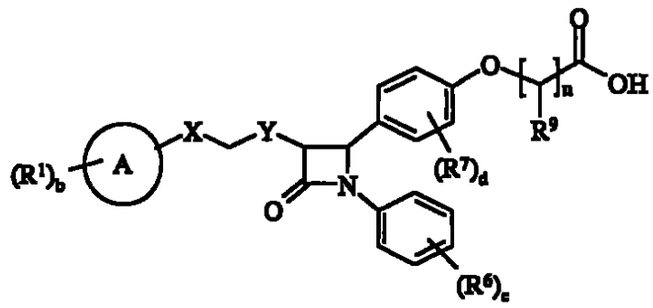
with a compound of formula (III)



(III)

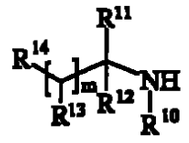
wherein L is a displaceable group,

Process 2) reacting an acid of formula (IV)



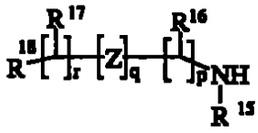
(IV)

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



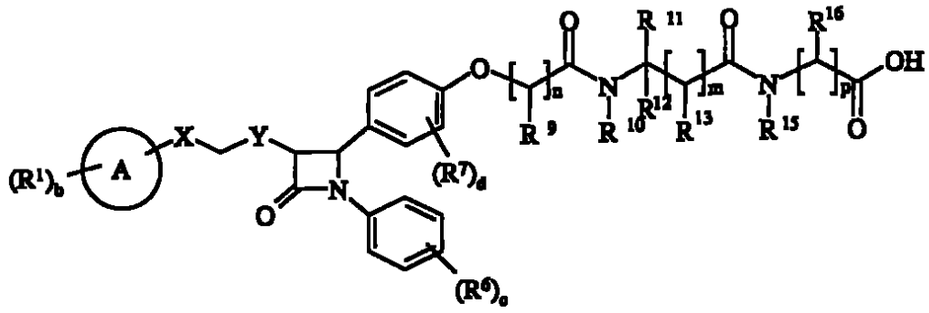
(V)

Process 3). for compounds of formula (I) wherein R^{14} is a group of formula (IA), reacting a compound of formula (VI) wherein R^{14} is carboxy, or an activated derivative thereof, with an amine of formula (VI)



(VI)

Process 4) for compounds of formula (I) wherein R^{14} is a group of formula (IA), Z is $-N(R^{35})C(O)-$ and q is 1, reacting an acid of formula (VII)



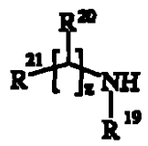
(VII)

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



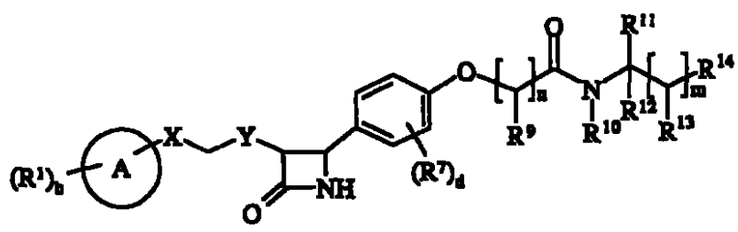
(VIII)

Process 5). for compounds of formula (I) wherein R^{14} is a group of formula (IA) and R^{18} is a group of formula (IB), reacting an acid of formula (I) wherein R^{14} is a group of formula (IA) and R^{18} is carboxy, or an activated derivative thereof, with an amine of formula (IX)



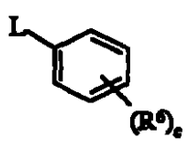
(IX)

Process 6) reacting a compound of formula (X)



(X)

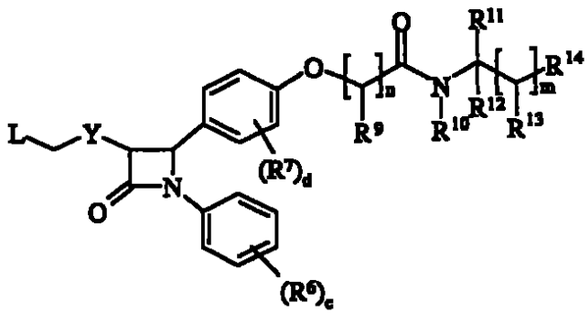
with a compound of formula (XI)



(XI)

wherein L is a displaceable group,

Process 7). for compounds of formula (I) wherein X is selected from -O-, $-NR^2-$ and $-S(O)_a-$ wherein a is 0, reacting a compound of formula (XII)



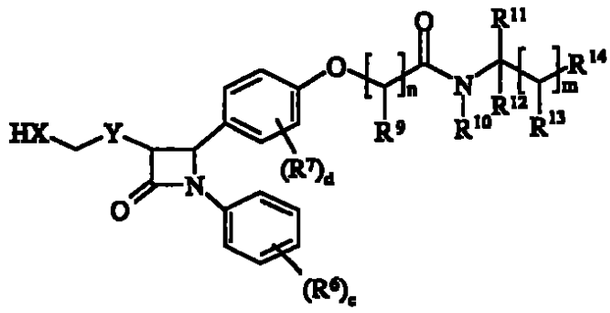
(XII)

wherein L is a displaceable group, with a compound of formula (XIII)



(XIII)

Process 8) for compounds of formula (I) wherein X is selected from -O-, -NR^2- and -$S(O)_a$- wherein a is 0, reacting a compound of formula (XIV)



(XIV)

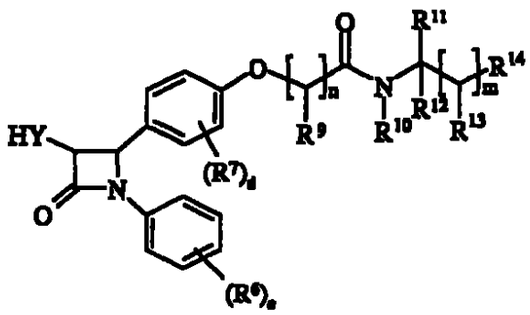
with a compound of formula (XV)



(XV)

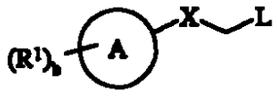
wherein L is a displaceable group,

Process 9) for compounds of formula (I) wherein Y is selected from -O-, -NR^2- and -$S(O)_a$- wherein a is 0, reacting a compound of formula (XVI)



(XVI)

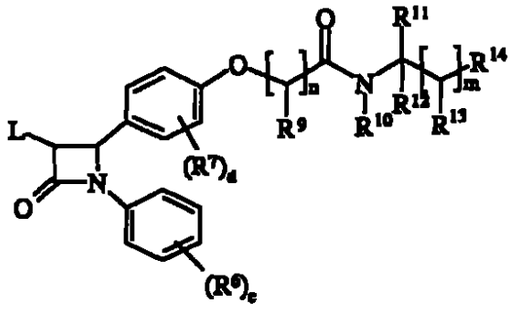
with a compound of formula (XVII)



(XVII)

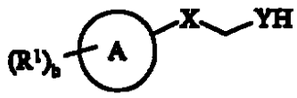
wherein L is a displaceable group,

Process 10) for compounds of formula (I) wherein Y is selected from -O-, $-NR^5-$ and $-S(O)_a-$ wherein a is 0, reacting a compound of formula (XVIII)



(XVIII)

wherein L is a displaceable group, with a compound of formula (XIX)



(XIX)

Process 11). for compounds of formula (I) wherein X or Y is $-S(O)_a-$ and a is 1 or 2, oxidizing a compound of formula (I) wherein X or Y is $-S(O)_a-$ and a is 0 (for compounds of formula (I) wherein and a is 1 or 2) or a is 1 (for compounds of formula (I) wherein and a is 2);

and thereafter if necessary or desirable.

69

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

ii) removing any protecting groups,

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

iv) separating two or more enantiomers

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 1-16, in association with a pharmaceutically-acceptable diluent or carrier

20 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 1-16, for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man

21 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 1-16, for use as a medicament.

22 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 1-16, in the production of a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man

23 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 1-16, in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man

24 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 1-16, in the manufacture of a medicament for use in the production of a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man

25 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 1-16, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

26 A method for producing a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16

27 A method of treating hyperlipidaemic 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, as claimed in any one of claims 1-16

28 A combination of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-16, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

29 A combination according to claim 28 wherein the HMG Co-A reductase inhibitors is selected from fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, pitvastatin, mevastatin and rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof

30 A pharmaceutical composition which comprises a combination according to either of claims 28 or 29, in association with a pharmaceutically acceptable diluent or carrier

31 The use of a combination according to either of claims 28 or 29, in the production of a cholesterol lowering effect in a warm-blooded animal, such as man.

32 The use of a combination according to either of claims 28 or 29, in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man

33 The use of a combination according to either of claims 28 or 29, in the manufacture of a medicament for use in the production of a cholesterol lowering effect.

34 The use of a combination according to either of claims 28 or 29, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions

35 A method for producing a cholesterol absorption inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a combination according to either of claims 28 or 29

36 A method of treating hyperlipidaemic 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 combination according to either of claims 28 or 29

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/02811

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D205/08 C07D409/12 A61K31/397 A61P3/06 A61P9/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02 50060 A (AVANTIS PHARMA DEUTSCHLAND GMB) 27 June 2002 (2002-06-27) cited in the application claims, examples	1,18-36
Y	WO 02 50068 A (AVENTIS PHARMA GMBH) 27 June 2002 (2002-06-27) cited in the application claims, examples	1,18-36
A	WO 02 50027 A (AVENTIS PHARMA GMBH) 27 June 2002 (2002-06-27) cited in the application claims	1,18-36
A	WO 02 18432 A (AVENTIS PHARMA GMBH) 7 March 2002 (2002-03-07) claims	1,18-36

-/-

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2003	26/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/02811

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 02 066464 A (NODA ATSUSHI ,OHNO AKIRA (JP), YOKOTA MASAYUKI (JP), KOTOBUKI PHAR) 29 August 2002 (2002-08-29) cited in the application claims, examples	1,18-36

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/02811

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

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

1 [X] Claims Nos..
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23,27,28,32,35,36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition

2. [ ] Claims Nos..
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos..
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1 [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos..

4 [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos..

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 03/02811

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0250060	A	27-06-2002	DE	10064402 A1	27-06-2002
			AU	1917302 A	01-07-2002
			AU	3168802 A	01-07-2002
			EE	200300237 A	15-08-2003
			EE	200300238 A	15-08-2003
			WO	0250068 A1	27-06-2002
			WO	0250060 A1	27-06-2002
			US	2002128252 A1	12-09-2002
			US	2002128253 A1	12-09-2002
WO 0250068	A	27-06-2002	DE	10064402 A1	27-06-2002
			AU	1917302 A	01-07-2002
			AU	3168802 A	01-07-2002
			EE	200300237 A	15-08-2003
			EE	200300238 A	15-08-2003
			WO	0250068 A1	27-06-2002
			WO	0250060 A1	27-06-2002
			US	2002128252 A1	12-09-2002
			US	2002128253 A1	12-09-2002
WO 0250027	A	27-06-2002	DE	10064398 A1	27-06-2002
			DE	10152981 A1	08-05-2003
			AU	1609702 A	01-07-2002
			CA	2431983 A1	27-06-2002
			EE	200300236 A	15-08-2003
			WO	0250027 A1	27-06-2002
			US	2002137689 A1	26-09-2002
WO 0218432	A	07-03-2002	DE	10042447 A1	28-03-2002
			AU	1044602 A	13-03-2002
			BR	0113533 A	15-07-2003
			CA	2420652 A1	26-02-2003
			WO	0218432 A2	07-03-2002
			EP	1315749 A2	04-06-2003
			NO	20030905 A	26-02-2003
			US	2002039774 A1	04-04-2002
WO 02066464	A	29-08-2002	WO	02066464 A1	29-08-2002

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

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación Internacional
15 de Enero de 2004 (15 01.2004)

PCT

(10) Número de Publicación Internacional
WO 2004/005247 A1

(51) Clasificación Internacional de Patentes[7] C07D 205/08, 409/12 A61K 31/397 A61P 3/06 9/10

(21) No. Solicitud Internacional PCT/GB2003/002811

(22) Fecha de Presentación Internacional
1 de Julio de 2003 (01 07 2003)

(25) Idioma de Presentación Inglés

(26) Idioma de Publicación Inglés

(30) Datos relativos a la Prioridad
0215579.4 5 de Julio de 2002 (05 07 2002) GB

(71) Solicitante *(para todos los países destinatarios con excepción de MG, US)*: ASTRAZENECA AB [SE/SE] Sodertalje S-151 85 (SE)

(71) Solicitante *(para MG únicamente)*: ASTRAZENECA UK LIMITED [GB/GB] 15 Stanhope Gate London, Greater London W1K 1LN (GB).

(72) Inventores, e
(75) Inventores/Solicitantes *(para US únicamente)*: STARKE, Ingemar [SE/SE] AstraZeneca R & D Molndal S-431 83 Molndal (SE) DAHLSTROM, Mikael, Ulf, Johan [FI/SE] AstraZeneca R & D Molndal, S-431 83 Molndal (SE) LINDQVIST, Ann-Margret [SE/SE] AstraZeneca R & D Molndal S-431 83 Molndal (SE) NORDBERG, Mats, Peter [SE/SE] AstraZeneca R & D Molndal S-431 83 Molndal (SE) SKJARET, Tore [NO/SE] AstraZeneca R & D Molndal S-431 83 Molndal (SE) LEMURELL, Malin, Anita [SE/SE] AstraZeneca R & D Molndal S-431 83 Molndal (SE)

(74) Agente: ASTRAZENECA, Global Intellectual Property Mereside Alderley Park, Macclesfield Cheshire SK10 4TG (GB)

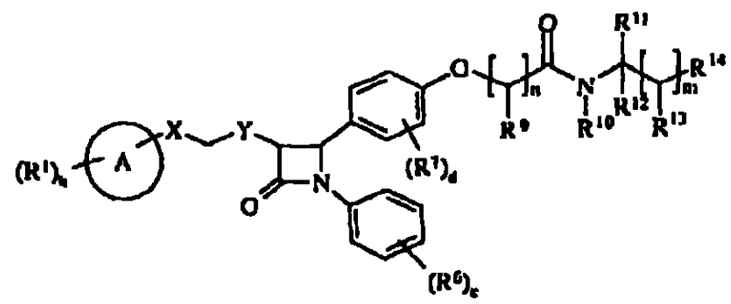
(81) Países designados *(nacional)*: AE AG, AL AM AT AU AZ, BA, BB BG, BR BY BZ CA, CH CN CO CR, CU, CZ, DE, DK, DM DZ, EC EE, ES, FI, GB, GD GE GH GM, HR HU ID, IL, IN IS JP KE, KG, KP KR KZ, LC LK, LR, LS, LT LU LV MA, MD MG MK, MN MW MX, MZ NI NO NZ, OM PG, PH, PL, PT RO RU SC, SD SE, SG, SK, SL,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

(84) Países designados *(regional)*: Patente ARIPO (GH, GM KE, LS MW MZ, SD, SL, SZ, TZ, UG ZM, ZW), Patente Euroasiática (AM, AZ, BY KG KZ, MD, RU, TJ, TM), Patente Europea (AT BE, BG CH CY CZ DE DK, EE, ES, FI FR GB GR, HU IE, IT LU MC, NL, PT RO, SE, SI SK, TR) Patente OAPI (BF BJ CF CG, CI, CM, GA, GN GQ GW ML, MR NE, SN TD TG).

Publicado
— *con informe internacional de búsqueda*

Para códigos de dos letras y otras abreviaturas remítase a las Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT

(54) Título: DERIVADOS DE DIFENILAZETIDINONA PARA TRATAR TRASTORNOS DEL METABOLISMO DE LÍPIDOS



(I)

(57) Extracto: Se describen compuestos de fórmula (I) (en donde grupos variables son como se definen allí) sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales y profármacos, y su uso como inhibidores de la absorción del colesterol para el tratamiento de hiperlipidemia. Se describen asimismo procesos para su manufactura y composiciones farmacéuticas que los contienen.

WO 2004/005247 A1

DERIVADOS DE DIFENILAZETIDINONA PARA TRATAR TRASTORNOS DEL METABOLISMO DE LÍPIDOS

Esta invención se refiere a derivados de 2-azetidinona, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales y profarmacos Estas 2-azetidinonas poseen actividad inhibidora de absorción de colesterol y, en consecuencia, son utiles en el tratamiento de estados patológicos asociados con afecciones hiperlipidémicas Por lo tanto, son de utilidad en métodos de tratamiento de un animal de sangre caliente, tal como el hombre La invencion se refiere igualmente a procesos para la manufactura de dichos derivados de 2-azetidinona, a composiciones farmacéuticas que los contienen y a su uso en la manufactura de medicamentos para inhibir la absorción del colesterol en un animal de sangre caliente, tal como el hombre Un aspecto adicional de esta invencion se relaciona con el uso de los compuestos de la invención en el tratamiento de afecciones dislipidémicas

La arteriopatía coronaria ateroesclerotica es una causa importante de muerte y morbilidad en el mundo occidental, asi como de una significativa disminución de recursos para el cuidado de la salud Es bien conocido que las afecciones hiperlipidémicas asociadas con concentraciones elevadas de colesterol total y colesterol de lipoproteína de baja densidad (LDL) son los principales riesgos de la enfermedad ateroesclerotica cardiovascular (por ejemplo, "Coronary Heart Disease Reducing the Risk, a Worldwide View" Assman G , Carmena R. Cullen P *et al*, Circulation 1999, 100, 1930-1938 y "Diabetes and Cardiovascular Disease A Statement for Healthcare Professionals from the American Heart Association" Grundy S , Benjamin I , Burke G , *et al*, Circulation, 1999, 100, 1134-46)

La concentracion de colesterol en el plasma depende del balance integrado de rutas endógenas y exógenas del metabolismo del colesterol En la ruta endógena, el colesterol es sintetizado por el higado y tejidos extrahepáticos y entra en la circulación en forma de lipoproteínas o es secretado en la bilis En la ruta exógena el colesterol de fuentes dietéticas y

biliares es absorbido en el intestino y entra en la circulacion como un componente de quilomicrones La alteracion de una cualquiera de las rutas afectara la concentración en el plasma del colesterol

Sin embargo, no es claro el mecanismo preciso por el cual el colesterol es absorbido del intestino La hipótesis original ha sido que el colesterol cruza el intestino mediante difusion no especifica Pero estudios mas recientes sugieren que hay transportadores especificos involucrados en la absorción intestinal del colesterol (Véase, por ejemplo, New molecular targets for cholesterol-lowering therapy Izzat, N N, Deshazer, M E and Loose-Mitchell D S JPET 293 315-320, 2000)

Se ha establecido una clara asociación entre la reducción del colesterol total y el colesterol (LDL) y la disminución en los casos de arteriopatía coronaria, y se emplean varias clases de agentes farmaceuticos para controlar el colesterol sérico Las principales opciones para regular el colesterol en el plasma incluyen (i) bloquear la síntesis del colesterol por agentes tales como inhibidores de HMG-CoA reductasa, por ejemplo estatinas tales como simvastatina y fluvastatina, las cuales, mediante la regulación por incremento de receptores de LDL, promoveran la eliminación del colesterol del plasma, (ii) bloquear la reabsorción de acido biliar por agentes específicos resultante en una excreción mayor de acido biliar y síntesis de ácidos biliares del colesterol con agentes tales como secuestrantes de acidos biliares, tales como resinas por ejemplo colestiramina y colestipol, y (iii) bloquear la absorción intestinal de colesterol mediante inhibidores selectivos de la absorción del colesterol Asimismo se han empleado agentes que elevan la lipoproteina de alta densidad (HDL) tales como fibratos y análogos del ácido nicotinico

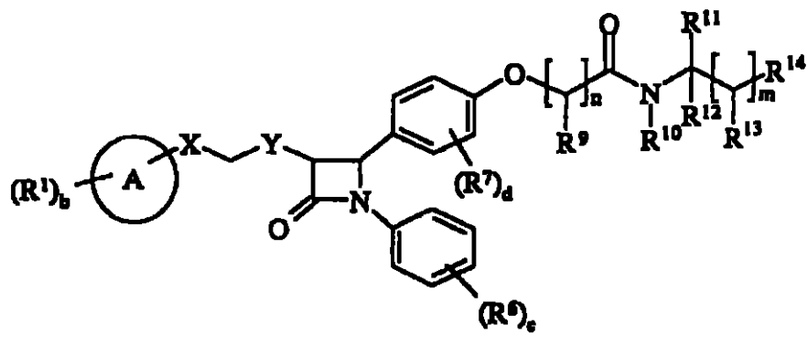
Incluso con la diversa gama actual de agentes terapeuticos, una significativa proporción de la población hipercolesterolémica es incapaz de alcanzar niveles de colesterol tomados como objetivo, o las interacciones de los medicamentos o la seguridad de los mismos impiden el uso a largo plazo necesario para alcanzar los niveles tomados como objetivo Por lo tanto, existe aun una necesidad de desarrollar agentes adicionales que sean

mas eficaces y mejor tolerados

Se han descrito compuestos que poseen tal actividad inhibidora de la absorcion de colesterol, vease, por ejemplo, los compuestos descritos en WO 93/02048, WO 94/17038, WO 95/08532, WO 95/26334, WO 95/35277, WO 96/16037, WO 96/19450, WO 97/16455, WO 02/50027, WO 02/50060, WO 02/50068, WO 02/50090, WO 02/66464, US 5756470, US 5767115 y US RE37721

La presente invención se basa en el descubrimiento de que ciertos compuestos de benzotiazepina y benzotiadiazepina inhiben sorpresivamente la absorcion del colesterol Se espera que tales propiedades sean utiles en el tratamiento de estados patológicos asociados con afecciones hiperlipidémicas Los compuestos de la presente invencion no se divulgan en ninguna de las solicitudes mencionadas, y nosotros hemos descubierto sorpresivamente que estos compuestos poseen perfiles metabólicos y toxicologicos benéficos, eficaces, que los hacen particularmente apropiados para administracion *in vivo* a un animal de sangre caliente tal como el hombre En particular, ciertos compuestos de la presente invencion tienen un bajo grado de absorción comparados con los compuestos del arte previo, conservando al mismo tiempo su capacidad de inhibir la absorción del colesterol

Por consiguiente se provee un compuesto de fórmula (I)



(I)

en donde

Anillo A se selecciona de fenilo o tienilo,

X se selecciona de $-CR^2R^3-$, $-O-$, $-NR^x-$ y $-S(O)_a-$, en donde R^x es hidrogeno o C_{1-6}alquilo, y a es 0-2,

Y se selecciona de $-CR^4R^5-$, -O-, $-NR^z-$ y $-S(O)_a-$, en donde R^z es hidrogeno o C_{1-6}alquilo, y a es 0-2, en donde hay por lo menos un grupo $-CR^2R^3-$ o $-CR^4R^5-$,

R^1 se selecciona independientemente de halo, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxi y C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, en donde R^1 se sustituye independientemente de manera opcional en carbono por uno o mas halo, C_{1-6}alcoxi e hidroxi,

b es 0-3, en donde los valores de R^1 pueden ser los mismos o diferentes,

R^2 y R^3 se seleccionan independientemente de hidrogeno, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxi y C_{1-6}alcanoiloxi, en donde R^2 y R^3 pueden sustituirse independientemente de manera opcional por uno o más halo o hidroxi, o R^2 y R^3 juntos forman un grupo oxo,

R^4 y R^5 se seleccionan independientemente de hidrógeno, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxi y C_{1-6}alcanoiloxi, o R^4 y R^5 juntos forman un grupo oxo,

R^6 se selecciona independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, formilo, carbamoilo, carbamoiloxi, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alqueniloxi, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, C_{1-6}alcanoil-*N*-(C_{1-6}alquil)amino, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)carbamoiloxi, *N*,*N*-(C_{1-6}alquil)$_2$carbamoiloxi, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, C_{1-6}alcoxicarbonil-*N*-(C_{1-6}alquil)amino, C_{1-6}alcoxicarboniloxi, C_{1-6}alcoxicarbonilamino, ureido, *N'*-(C_{1-6}alquil)ureido, *N*-(C_{1-6}alquil)ureido, *N'*,*N'*-(C_{1-6}alquil)$_2$ureido, *N'*-(C_{1-6}alquil)-*N*-(C_{1-6}alquil)ureido, *N'*,*N'*-(C_{1-6}alquil)$_2$-*N*-(C_{1-6}alquil)ureido, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo y fenilo, en donde R^7 se sustituye independientemente de manera opcional en carbono por uno o más halo, C_{1-6}alcoxi, hidroxi, amino, carboxi, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alcanoilamino, C_{1-6}alcanoil-*N*-(C_{1-6}alquil)amino, fenilo, fenoxi, benzoilo, fenilC_{1-6}alquilo y

fenilC$_{1-6}$alcoxi,

c es 0-5, en donde los valores de R^6 pueden ser los mismos o diferentes,

R^7 se selecciona independientemente de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carboxi, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxicarbonilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, *N*-metilcarbamoilo, *N,N*-dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, *N*-metilsulfamoilo y *N,N*-dimetilsulfamoilo,

d es 0-4, en donde los valores de R^7 pueden ser los mismos o diferentes,

R^9 es hidrogeno, C$_{1-4}$alquilo, carbociclilo o heterociclilo, en donde R^9 puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{23}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{24},

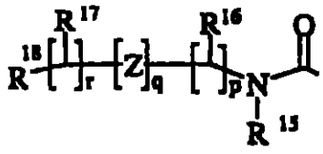
R^{10} es hidrogeno o C$_{1-4}$alquilo,

R^{11} y R^{12} se seleccionan independientemente de hidrogeno, C$_{1-4}$alquilo, carbociclilo o heterociclilo, ó R^{11} y R^{12} forman conjuntamente C$_{2-6}$alquileno, en donde R^{11} y R^{12} o R^{11} y R^{12} conjuntamente pueden sustituirse independientemente de manera opcional por uno o más sustituyentes seleccionados de R^{25}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrógeno puede sustituirse de manera opcional por uno o más R^{26},

R^{13} es hidrógeno, C$_{1-4}$alquilo, carbociclilo o heterociclilo, en donde R^{13} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{27}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrógeno puede sustituirse de manera opcional por uno o más R^{28},

R^{14} es hidrogeno, halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C$_{1-10}$alquilo, C$_{2-10}$alquenilo,

$C_{2\ 10}$alquinilo, C_{1-10}alcoxi, $C_{1\ 10}$alcoxicarbonilo, C_{1-10}alcanoilo, $C_{1\ 10}$alcanoiloxi, *N*-(C_{1-10}alquil)amino, *N*,*N*-(C_{1-10}alquil)$_2$amino, *N*,*N*,*N*-(C_{1-10}alquil)$_3$ammonio, $C_{1\ 10}$alcanoilamino, *N*-($C_{1\ 10}$alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil) sulfamoilo, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilamino, $C_{1\ 10}$alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-($C_{1\ 10}$alquilen)$_e$-R^{29}-(C_{1-10}alquilen)$_f$-, heterociclil-(C_{1-10}alquilen)$_g$-R^{30}-(C_{1-10}alquilen)$_h$-, carboxi, sulfo, sulfino, fosfono, -P(O)(OR^{31})(OR^{32}), -P(O)(OH)(OR^{31}), -P(O)(OH)(R^{31}) ó -P(O)(OR^{31})(R^{32}), en donde R^{31} y R^{32} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{33}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{34}, ó R^{14} es un grupo de fórmula (IA)



(IA)

en donde

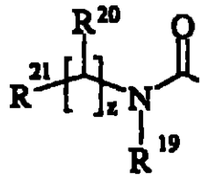
Z es -N(R^{35})-, -N(R^{35})C(O)-, -O-, y -S(O)$_a$-, en donde a es 0-2 y R^{35} es hidrógeno o C_{1-4}alquilo,

R^{15} es hidrógeno o C_{1-4}alquilo,

R^{16} y R^{17} se seleccionan independientemente de hidrogeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, $C_{1\ 6}$alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, carbociclilo, heterociclilo, sulfo, sulfino, amidino, fosfono, -P(O)(OR^{36})(OR^{37}), -P(O)(OH)(OR^{36}), -P(O)(OH)(R^{36}) ó -P(O)(OR^{36})(R^{37}), en donde R^{36} y R^{37} se seleccionan

independientemente de C_{1-6}alquilo, en donde R^{16} y R^{17} pueden sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{38}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{39},

R^{18} se selecciona de hidrogeno halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, $C_{1\ 10}$alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-($C_{1\ 10}$alquil)amino, *N*,*N*-(C_{1-10}alquil)$_2$amino, $C_{1\ 10}$alcanoilamino, *N*-($C_{1\ 10}$alquil)carbamoilo, $C_{1\ 10}$alcoxicarbonilo, *N*,*N*-($C_{1\ 10}$alquil)$_2$carbamoilo, $C_{1\ 10}$alquilS(O)$_a$ en donde a es 0 a 2, *N*-($C_{1\ 10}$alquil)sulfamoilo, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N*,*N*-(C_{1-10}alquil)$_2$ sulfamoilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_e$-R^{40}-($C_{1\ 10}$alquilen)$_f$ o heterociclil-(C_{1-10}alquilen)$_g$-R^{41}-(C_{1-10}alquilen)$_h$-, carboxi, sulfo, sulfino, fosfono, -P(O)(OR^{42})(OR^{43}), -P(O)(OH)(OR^{42}), -P(O)(OH)(R^{42}) ó -P(O)(OR^{42})(R^{43}) en donde R^{42} y R^{43} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{18} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{44}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{45}, ó R^{18} es un grupo de formula (IB)



(IB)

en donde

R^{19} se selecciona de hidrógeno o C_{1-4}alquilo,

R^{20} se selecciona de hidrógeno halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino,

R^{63} se seleccionan independientemente de hidrogeno o C_{1-6}alquilo, y x es 0-2,

R^{60} se selecciona de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carboxi, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxicarbonilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, *N*-metilcarbamoilo, *N,N*-dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, *N*-metilsulfamoilo y *N,N*-dimetilsulfamoilo, y

e, f, g y h se seleccionan independientemente de 0-2,

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

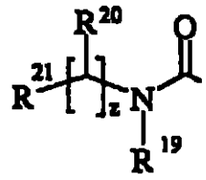
En esta especificacion el termino "alquilo" incluye los dos grupos alquilo de cadena recta y ramificada, pero referencias a grupos alquilo individuales tales como "propilo" son específicos de la version de cadena recta unicamente Por ejemplo, "C_{1-10}alquilo", "C_{1-6}alquilo" y "C_{1-4}alquilo" incluyen propilo, isopropilo y *t*-butilo Sin embargo, referencias a grupos alquilo individuales tales como 'propilo' son especificos de la versión de cadena recta unicamente y referencias a grupos alquilo individuales de cadena ramificada tales como 'isopropilo' son especificos de la versión de cadena ramificada unicamente Una convención similar se aplica a otros radicales, por ejemplo "fenilC_{1-6}alquilo" incluiria bencilo, 1-feniletilo y 2-feniletilo El término "halo" se refiere a fluoro, cloro, bromo y yodo

Donde sustituyentes opcionales se escogen de "uno o más" grupos hay que entender que esta definicion incluye todos los sustituyentes que se escogen de uno de los grupos especificados o los sustituyentes que se escogen de dos o mas de los grupos especificados

Un "heterociclilo" es un anillo mono o bicíclico saturado, parcialmente saturado o insaturado, que contiene 3-12 atomos de los cuales por lo menos un atomo se escoge de nitrogeno, azufre u oxigeno que, a menos que se especifique lo contrario, puede enlazarse con carbono o nitrogeno, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente

independientemente de C_{1-6}alquilo, en donde R^{16} y R^{17} pueden sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{38}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{39},

R^{18} se selecciona de hidrógeno halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, $C_{1\ 10}$alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-($C_{1\ 10}$alquil)amino, *N*,*N*-($C_{1\ 10}$alquil)$_2$amino, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, C_{1-10}alcoxicarbonilo, *N*,*N*-($C_{1\ 10}$alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N*,*N*-(C_{1-10}alquil)$_2$ sulfamoilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_e$-R^{40}-($C_{1\ 10}$alquilen)$_f$ o heterociclil-($C_{1\ 10}$alquilen)$_g$-R^{41}-(C_{1-10}alquilen)$_h$-, carboxi, sulfo, sulfino, fosfono, -P(O)(OR^{42})(OR^{43}), -P(O)(OH)(OR^{42}), -P(O)(OH)(R^{42}) ó -P(O)(OR^{42})(R^{43}) en donde R^{42} y R^{43} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{18} puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{44}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{45}, o R^{18} es un grupo de formula (IB)



(IB)

en donde

R^{19} se selecciona de hidrógeno o C_{1-4}alquilo,

R^{20} se selecciona de hidrógeno halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino,

781

N,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, carbociclilo, heterociclilo, sulfo, sulfino, amidino, fosfono, -P(O)(OR^{46})(OR^{47}), -P(O)(OH)(OR^{46}), -P(O)(OH)(R^{46}) o -P(O)(OR^{46})(R^{47}), en donde R^{46} y R^{47} se seleccionan independientemente de C_{1-6}alquilo, donde R^{20} puede sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{48}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{49},

R^{21} se selecciona de halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcoxicarbonilo, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-(C_{1-10}alquil)amino, *N*,*N*-(C_{1-10}alquil)$_2$amino, *N*,*N*,*N*-(C_{1-10}alquil)$_3$amonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil) sulfamoilamino, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilamino, C_{1-10}alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_e$-R^{50}-(C_{1-10}alquilen)$_f$, heterociclil-(C_{1-10}alquilen)$_g$-R^{51}-(C_{1-10}alquilen)$_h$-, carboxi, sulfo, sulfino, fosfono, -P(O)(OR^{52})(OR^{53}), -P(O)(OH)(OR^{52}), -P(O)(OH)(R^{52}) o -P(O)(OR^{53})(R^{53}) en donde R^{52} y R^{53} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{21} puede sustituirse independientemente de manera opcional por uno o más R^{54}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{55},

p es 1-3, en donde los valores de R^{16} pueden ser los mismos o diferentes,

q es 0-1,

r es 0-3, en donde los valores de R^{17} pueden ser los mismos o diferentes,

m es 0-2, en donde los valores de R^{13} pueden ser los mismos o diferentes,

n es 1-2, en donde los valores de R^{9} pueden ser los mismos o diferentes,

z es 0-3, en donde los valores de R^{20} pueden ser los mismos o diferentes,

R^{23}, R^{25}, R^{27}, R^{33}, R^{38}, R^{44}, R^{48} y R^{54} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, $C_{2\ 10}$alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, C_{1-10}alcoxicarbonilo, *N*-$C_{1\ 10}$alquil)amino, *N*,*N*-($C_{1\ 10}$alquil)$_2$amino, *N*,*N*,*N*-(C_{1-10}alquil)$_3$amonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-($C_{1\ 10}$alquil)sulfamoilamino, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilamino, $C_{1\ 10}$alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-($C_{1\ 10}$alquilen)$_e$-R^{56}-($C_{1\ 10}$alquilen)$_f$, heterociclil-(C_{1-10}alquilen)$_g$-R^{57}-($C_{1\ 10}$alquilen)$_h$-, carboxi, sulfo, sulfino, amidino, fosfono, -P(O)(OR^{58})(OR^{59}), -P(O)(OH)(OR^{58}), -P(O)(OH)(R^{58}) o -P(O)(OR^{59})(R^{59}), en donde R^{58} y R^{59} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{23}, R^{25}, R^{27}, R^{33}, R^{38}, R^{44}, R^{48} y R^{54} pueden sustituirse independientemente de manera opcional por uno o mas R^{60}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{61},

R^{24}, R^{26}, R^{28}, R^{34}, R^{39}, R^{45}, R^{49}, R^{55} y R^{61} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, sulfamoilo, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, $C_{1\ 6}$alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, bencilo, fenetilo, benzoilo, fenilsulfonilo y fenilo,

R^{29}, R^{30}, R^{40}, R^{41}, R^{50}, R^{51}, R^{56} y R^{57} se seleccionan independientemente de -O-, -NR^{62}-, -S(O)$_x$-, -NR^{62}C(O)NR^{63}-, -NR^{62}C(S)NR^{63}-, -OC(O)N=C-, -NR^{62}C(O)- o -C(O)NR^{62}-, en donde R^{62} y

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

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

Un ejemplo de "$C_{1\ 10}$alcanoiloxi" y "C_{1-6}alcanoiloxi" es acetoxi Ejemplos de "C_{1-10}alcoxicarbonilo" y "C_{1-6}alcoxicarbonilo" incluyen

metoxicarbonilo, etoxicarbonilo, *n*- y *t*-butoxicarbonilo Ejemplos de "C_{1-10}alcoxi" y "C_{1-6}alcoxi" incluyen metoxi, etoxi y propoxi Ejemplos de "C_{1-10}alcanoilamino" y "C_{1-6}alcanoilamino" incluyen formamido, acetamido y propionilamino Ejemplos de "C_{1-6}alcanoil-*N*-(C_{1-6}alquil)amino" incluyen acetil-*N*-metilamino y propionil-*N*-etil-amino Ejemplos de "C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2" y "C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2" incluyen metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo y etilsulfonilo Ejemplos de "C_{1-10}alcanoilo" y "C_{1-6}alcanoilo" incluyen C_{1-3}alcanoilo, propionilo y acetilo Ejemplos de "*N*-(C_{1-10}alquil)amino" y "*N*-(C_{1-6}alquil)amino" incluyen metilamino y etilamino Ejemplos de "*N*,*N*-(C_{1-10}alquil)$_2$amino" y "*N*,*N*-(C_{1-6}alquil)$_2$amino" incluyen di-*N*-metilamino, di-(*N*-etil)amino y *N*-etil-*N*-metilamino Ejemplos de "C_{2-10}alquenily" y "C_{2-6}alquenily" son vinilo, alilo y 1-propenilo Ejemplos de "C_{2-10}alquinilo" y "C_{2-6}alquinily" son etinilo, 1-propinilo y 2-propinilo Ejemplos de "C_{2-6}alquileno" son etileno, propileno y butileno Ejemplos de "C_{2-6}alqueniloxi" son viniloxi, aliloxi y 1-propeniloxi Ejemplos de "*N*-(C_{1-10}alquil)sulfamoilo" y "*N*-(C_{1-6}alquil)sulfamoilo" son *N*-(C_{1-3}alquil)sulfamoilo, *N*-(metil)sulfamoilo y *N*-(etil)sulfamoilo Ejemplos de "*N*-(C_{1-10}alquil)$_2$sulfamoilo" y "*N*-(C_{1-6}alquil)$_2$sulfamoilo" son *N*,*N*-(dimetil)sulfamoilo y *N*-(metil)-*N*-(etil)sulfamoilo Ejemplos de "*N*-(C_{1-10}alquil)carbamoilo" y "*N*-(C_{1-6}alquil)carbamoilo" son metilaminocarbonilo y etilaminocarbonilo Ejemplos de "*N*,*N*-(C_{1-10}alquil)$_2$carbamoilo" y "*N*,*N*-(C_{1-6}alquil)$_2$carbamoilo" son dimetilaminocarbonilo y metiletilaminocarbonilo Ejemplos de "*N*-(C_{1-10}alquil)carbamoilo" y "*N*-(C_{1-6}alquil)carbamoiloxi" son metilaminocarboniloxi y etilaminocarboniloxi Ejemplos de "*N*,*N*-C_{1-10}alquil)$_2$carbamoilo" y "*N*,*N*-(C_{1-6}alquil)$_2$carbamoiloxi" son dimetilaminocarboniloxi y metiletilaminocarboniloxi Ejemplos de "C_{1-6}alquilsulfonil" son mesilo y etilsulfonilo Ejemplos de "C_{1-10}alquilsulfonilamino" y "C_{1-6}alquilsulfonilamino" son mesilamino y etilsulfonilamino Ejemplos de "C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino" son mesil-*N*-metilamino y etilsulfonil-*N*-propilamino Ejemplos de "*N'*-(C_{1-6}alquil)ureido" son *N'*-metilureido y

N-*i*-propilureido Ejemplos de "*N*-(C_{1-6}alquil)ureido" son *N*-metilureido y *N*-*i*-propilureido Ejemplos de "*N',N'*-(C_{1-6}alquil)$_2$ureido" son *N',N'*-dimetilureido y *N'*-metil-*N'*-etilureido Ejemplos de "*N'*-(C_{1-6}alquil)-*N*-(C_{1-6}alquil)ureido" son *N',N'*-dimetilureido y *N'*-metil-*N*-etilureido Ejemplos de *N',N'*-(C_{1-6}alquil)$_2$-*N*-(C_{1-6}alquil)ureido" son *N',N'*-dimetil-*N*-metilureido y *N'*-metil-*N'*-etil-*N*-*t*-butilureido Ejemplos de "*N,N,N*-(C_{1-10}alquil)$_3$ammonio" son trimetilamino y metildietilamino Ejemplos de "C_{1-10}alcoxicarbonilamino" y "C_{1-6}alcoxicarbonilamino" son metoxicarbonilamino y *t*-butoxicarbonilamino Ejemplos de "*N*-(C_{1-10}alquil)sulfamoilamino" son *N*-metilsulfamoilamino y *N*-etilsulfamoilamino Ejemplos de "*N,N*-(C_{1-10}alquil)$_2$sulfamoilamino" son *N,N*-dimetilsulfamoilamino y *N*-metil-N-etilsulfamoilamino Ejemplos de "carbociclilC_{1-10}alquilo" incluyen bencilo y fenetilo Ejemplos de "heterociclilC_{1-10}alquilo" incluyen 2-morfolinopropilo y piridilmetilo Ejemplos de "fenilC_{1-6}alcoxi" incluyen 2-feniletoxi y 2-fenilpropoxi

Una sal apropiada, farmaceuticamente aceptable de un compuesto de la invencion, u otros compuestos divulgados aqui, es, por ejemplo, una sal de adicion de ácido de un compuesto de la invención, que es suficientemente básica, por ejemplo, una sal de adición de acido con, por ejemplo, un ácido orgánico o inorgánico, por ejemplo ácido clorhidrico, bromhídrico, sulfurico, fosfórico, trifluoroacético, cítrico, acetato o acido maleico Adicionalmente, una sal apropiada, farmaceuticamente aceptable de un compuesto de la invención, que es suficientemente ácida es una sal de metal alcalino, por ejemplo una sal de sodio o potasio, una sal de metal alcalinoterreo, por ejemplo una sal de calcio o magnesio, una sal de amonio o una sal con una base organica que suministre un catión fisiológicamente aceptable, por ejemplo una sal con metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina

Los compuestos de la formula (I), u otros compuestos divulgados aqui, pueden administrarse en la forma de un profarmaco que se descompone en el cuerpo humano o animal para producir un compuesto de la formula (I) Ejemplos de profarmacos incluyen ésteres hidrolizables *in*

vivo y amidas hidrolizables *in vivo* de un compuesto de la formula (I)

Un éster hidrolizable *in vivo* de un compuesto de la fórmula (I), u otros compuestos divulgados aquí, que contienen un grupo carboxi o hidroxi es, por ejemplo, un éster farmacéuticamente aceptable que se hidroliza en el cuerpo humano o animal para producir el ácido original o alcohol Ésteres apropiados farmacéuticamente aceptables para carboxi incluyen C_{1-6}alcoximetil ésteres por ejemplo metoximetilo, C_{1-6}alcanoiloximetil esteres por ejemplo pivaloiloximetilo, ftalidil esteres, C_{3-8}cicloalcoxicarboniloxiC_{1-6}alquil ésteres por ejemplo 1-ciclohexilcarboniloxietilo, 1,3-dioxolen-2-onilmetil ésteres por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo, y C_{1-6} alcoxicarboniloxietil esteres por ejemplo 1-metoxicarboniloxietilo, y pueden formarse en cualquier grupo carboxi en los compuestos de esta invencion

Un ester hidrolizable *in vivo* de un compuesto de la formula (I), u otros compuestos divulgados aquí, que contienen un grupo hidroxi incluye ésteres inorgánicos tales como ésteres de fosfato y α-aciloxialquil eteres y compuestos relacionados los cuales, como resultado de la hidrolisis *in vivo* del éster se descomponen para producir el grupo hidroxi original Ejemplos de α-aciloxialquil eteres incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi Una selección de grupos formadores de éster hidrolizable *in vivo* para hidroxi incluyen alcanoilo, benzoilo, fenilacetilo y benzoilo sustituido y fenilacetilo, alcoxicarbonilo (para producir ésteres de alquil carbonato), dialquilcarbamoilo y *N*-(dialquilaminoetil)-*N*-alquilcarbamoilo (para producir carbamatos), dialquilaminoacetilo y carboxiacetilo Ejemplos de sustituyentes en benzoilo incluyen morfolino y piperazino enlazados desde un átomo de nitrógeno del anillo mediante un grupo metileno a la posición 3 ó 4 del anillo benzoilo

Un valor apropiado para una amida hidrolizable *in vivo* de un compuesto de la fórmula (I), u otros compuestos divulgados aquí, que contienen un grupo carboxi es, por ejemplo, una *N*-C_{1-6}alquilo o *N*,*N*-di-C_{1-6}alquil amida tales como *N*-metil, *N*-etil, *N*-propil, *N*,*N*-dimetil, *N*-etil-*N*-metil o *N*,*N*-dietil amida.

Algunos compuestos de la fórmula (I) pueden centros quirales y/o centros isoméricos geométricos (E- y Z-isomeros), y hay que entender que la invención abarca la totalidad de tales, diastereoisomeros e isomeros geometricos, ópticos que poseen actividad inhibidora de absorción de colesterol

La invención se refiere a cualquiera y todas las formas tautomericas de los compuestos de la fórmula (I) que poseen actividad inhibidora de absorción de colesterol

Hay que entender igualmente que ciertos compuestos de la formula (I) pueden existir en formas solvatadas y no solvatadas tales como, por ejemplo, formas hidratadas Hay que entender que la invencion abarca la totalidad de tales formas solvatadas que poseen actividad inhibidora de absorción de colesterol

Valores particulares son como sigue Tales valores pueden usarse donde sea apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas mas arriba en el texto o mas adelante

Anillo A se selecciona de tienilo

Anillo A se selecciona de fenilo

X es $-CR^2R^3-$

X es -O-

X es $-NR^x-$, en donde R^x es hidrógeno o C_{1-6}alquilo

X es $-S(O)_a-$, en donde a es 0-2

X es $-CR^2R^3-$ en donde uno de R^2 y R^3 es hidrogeno y el otro es hidroxi

X es $-CH_2-$

X es -CH(OH)-

X es -C(O)-

X es -S-

X es -S(O)-

X es $-S(O)_2-$

X se selecciona de $-CR^2R^3-$, -O- y $-S(O)_a-$, en donde a es 0-2

X se selecciona de $-CR^2R^3-$, -O- y $-S(O)_a-$, en donde a es 0-2, y R^2 y

R^3 se seleccionan independientemente de hidrógeno e hidroxi, ó R^2 y R^3 juntos forman un grupo oxo

X se selecciona de $-CH_2-$, -CH(OH)-, -C(O)-, -O- -S-, -S(O)- y $-S(O)_2-$

Y es $-CR^4R^5-$

Y es -O-

Y es $-NR^z-$, en donde R^z es hidrogeno o C_{1-6}alquilo

Y es $-S(O)_a-$, en donde a es 0-2

Y es $-CR^4R^5-$ en donde R^4 y R^5 son ambos hidrogeno

Y es $-CH_2-$

Y es -S-

Y es -S(O)-

Y se selecciona de $-CR^4R^5-$ y $-S(O)_a-$, a es 0 ó 1

Y se selecciona de $-CR^4R^5-$ y $-S(O)_a-$, a es 0 ó 1, en donde R^4 y R^5 son ambos hidrógeno

Y es $-CH_2-$, -S- ó -S(O)-

X es $-CR^2R^3-$ y Y es $-CR^4R^5-$ en donde uno de R^2 y R^3 es hidrogeno y el otro es hidroxi, y en donde R^4 y R^5 son ambos hidrógeno

X es $-CH_2-$ y Y es -S-

X es -C(O)- y Y es -S-

X es $-CH_2-$ y Y es -S(O)-

X es -C(O)- y Y es -S(O)-

X es $-CH_2-$ y Y es $-S(O)_2-$

X es -C(O)- y Y es $-S(O)_2-$

X es -O- y Y es $-CH_2-$

X es -CHOH- y Y es $-S(O)_a-$, en donde a es 0-2

X es -CHOH- y Y es -S-

X es -CHOH- y Y es -S(O)-

X es -CHOH- y Y es $-S(O)_2-$

R^1 es halo

R^1 es fluoro

R^1 es 4-fluoro si el anillo A es fenilo

b es 0-2, en donde los valores de R^1 pueden ser los mismos o diferentes

b es 0-1

b es 1

b es 0

b es 1, en donde el sustituyente es *para* al grupo X si el anillo A es fenilo

R^2 y R^3 se seleccionan independientemente de hidrógeno e hidroxi, o R^2 y R^3 juntos forman un grupo oxo

R^2 y R^3 se seleccionan independientemente de hidrogeno e hidroxi

Uno de R^2 y R^3 es hidrógeno y el otro es hidroxi

R^4 y R^5 son ambos hidrógeno

R^6 es halo ó C_{1-6}alcoxi

R^6 es halo

R^6 es fluoro o metoxi

R^6 es fluoro

R^6 es 4-fluoro o 4-metoxi

R^6 es 4-fluoro

c es 0-2, en donde los valores de R^6 pueden ser los mismos o diferentes

c es 0-1

c es 1

c es 0

c es 1, en donde el sustituyente es *para* al nitrógeno del anillo azetidin-2-ona

R^7 es halo, metoxi o etoxi

R^7 es fluoro o metoxi

d es 0-2, en donde los valores de R^7 pueden ser los mismos o diferentes

d es 0-1

d es 0

R^9 es hidrogeno

R^{10} es hidrógeno

R^{11} y R^{12} se seleccionan independientemente de hidrogeno carbociclilo

R^{11} y R^{12} se seleccionan independientemente de hidrogeno o fenilo

Uno de R^{11} y R^{12} es hidrogeno y el otro es fenilo, o los dos R^{11} y R^{12} son hidrógeno

R^{11} y R^{12} se seleccionan independientemente de hidrógeno, C_{1-4}alquilo o carbociclilo, en donde R^{11} y R^{12} pueden sustituirse independientemente de manera opcional por uno o más sustituyentes seleccionados de R^{25}

R^{11} y R^{12} se seleccionan independientemente de hidrógeno, metilo, etilo, butilo, isobutilo o fenilo, en donde R^{11} y R^{12} pueden sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{25}

R^{11} y R^{12} se seleccionan independientemente de hidrógeno, C_{1-4}alquilo o carbociclilo, en donde R^{11} y R^{12} pueden sustituirse independientemente de manera opcional por uno o más sustituyentes seleccionados de R^{25}, en donde R^{25} se selecciona de hidroxi, amino, carbamoilo, C_{1-10}alcoxicarbonilo, C_{1-10}alcoxicarbonilamino, carbociclilo o carboxi, en donde R^{25} puede sustituirse de manera opcional en carbono por uno o más R^{60}, en donde R^{60} es hidroxi

R^{11} y R^{12} se seleccionan independientemente de hidrógeno, metilo, etilo, butilo, isobutilo o fenilo, en donde R^{11} y R^{12} pueden sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{25}, en donde R^{25} se selecciona de hidroxi, amino, carbamoilo, etoxicarbonilo, *t*-butoxicarbonilamino, fenilo o carboxi, en donde R^{25} puede sustituirse de manera opcional en carbono por uno o más R^{60}, en donde R^{60} es hidroxi

R^{11} y R^{12} se seleccionan independientemente de hidrógeno, metilo, hidroximetilo, 2-carbamoiletilo, 2-(etoxicarbonil)etilo, 2-carboxietilo, 4-(*t*-butoxicarbonilamino)butilo, 4-aminobutilo, isobutilo, fenilo, 4-hidroxifenilo y 4-hidroxibencilo

Uno de R^{11} y R^{12} es hidrógeno y el otro se selecciona de hidrógeno

metilo, hidroximetilo, 2-carbamoiletilo, 2-(etoxicarbonil)etilo, 2-carboxietilo, 4-(*t*-butoxicarbonilamino)butilo, 4-aminobutilo, isobutilo, fenilo, 4-hidroxifenilo y 4-hidroxibencilo

R^{13} es hidrógeno

R^{14} es $C_{1\ 10}$alquilo, C_{1-10}alcoxicarbonilo o carboxi, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{33}, ó R^{14} es un grupo de formula (IA) como se describe más arriba

R^{14} es C_{1-6}alquilo, C_{1-6}alcoxicarbonilo o carboxi, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o más hidroxi, ó R^{14} es un grupo de fórmula (IA) como se describe más arriba.

R^{14} es 1,2,3,4,5-pentahidroxipentilo, *t*-butoxicarbonilo o carboxi, ó R^{14} es un grupo de fórmula (IA) como se describe más arriba

R^{14} es hidroxi, C_{1-10}alquilo, C_{1-10}alcoxi, $C_{1\ 10}$alcoxicarbonilo, carboxi o sulfo, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{33}, ó R^{14} es un grupo de fórmula (IA) (como se describe más arriba)

R^{14} es hidroxi, pentilo, metoxi, etoxicarbonilo, *t*-butoxicarbonilo, carboxi o sulfo, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{33}, ó R^{14} es un grupo de fórmula (IA) (como se describe mas arriba)

R^{15} es hidrógeno

R^{16} y R^{17} se seleccionan independientemente de hidrogeno, carboxi o C_{1-6}alcoxicarbonilo

R^{16} y R^{17} se seleccionan independientemente de hidrogeno, carboxi o *t*-butoxicarbonilo

Uno de R^{16} y R^{17} es hidrogeno, y el otro es hidrógeno, carboxi o *t*-butoxicarbonilo

R^{16} y R^{17} se seleccionan independientemente de hidrogeno, carboxi, C_{1-6}alquilo y C_{1-6}alcoxicarbonilo

R^{16} y R^{17} se seleccionan independientemente de hidrogeno, carboxi, C_{1-6}alquilo y *t*-butoxicarbonilo

93

R^{18} se selecciona de hidroxi, $C_{1\ 10}$alcoxi, C_{1-10}alcoxicarbonilo o carboxi

R^{18} se selecciona de hidroxi, C_{1-6}alcoxi, C_{1-6}alcoxicarbonilo o carboxi

R^{18} se selecciona de hidroxi, *t*-butoxi, *t*-butoxicarbonilo o carboxi

R^{18} se selecciona de hidroxi, C_{1-10}alquilo, $C_{1\ 10}$alcoxi, $C_{1\ 10}$alcoxicarbonilo, carboxi y sulfo

R^{18} se selecciona de hidroxi, metilo, *t*-butoxi, etoxicarbonilo, *t*-butoxicarbonilo, carboxi y sulfo

p es 1

q es 0

r es 0 ó 1

m es 0

m es 1

m es 0 ó 1

n es 1

R^{14} es hidroxi, C_{1-10}alquilo, C_{1-10}alcoxi, C_{1-10}alcoxicarbonilo, carboxi o sulfo, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{33}, ó R^{14} es un grupo de fórmula (IA) (como se describe más arriba) en donde

R^{15} es hidrógeno,

R^{16} y R^{17} se seleccionan independientemente de hidrogeno, carboxi, C_{1-6}alquilo y C_{1-6}alcoxicarbonilo,

R^{18} se selecciona de hidroxi, C_{1-10}alquilo, C_{1-10}alcoxi, C_{1-10}alcoxicarbonilo, carboxi y sulfo,

p es 1,

q es 0,

r es 0 o 1,

m es 0 ó 1,

n es 1, y

R^{33} es hidroxi

R^{14} es hidroxi, pentilo, metoxi, etoxicarbonilo, *t*-butoxicarbonilo, carboxi o sulfo, en donde R^{14} puede sustituirse de manera opcional en

carbono por uno o más sustituyentes seleccionados de R^{33}, o R^{14} es un grupo de formula (IA) (como se describe más arriba) en donde

R^{15} es hidrógeno,

R^{16} y R^{17} se seleccionan independientemente de hidrógeno, carboxi, C_{1-6}alquilo y *t*-butoxicarbonilo,

R^{18} se selecciona de hidroxi, metilo, *t*-butoxi, etoxicarbonilo, *t*-butoxicarbonilo, carboxi y sulfo,

p es 1,

q es 0,

r es 0 ó 1,

m es 0 ó 1,

n es 1, y

R^{33} es hidroxi

R^{25} se selecciona de hidroxi, amino, carbamoilo, C_{1-10}alcoxicarbonilo, $C_{1\ 10}$alcoxicarbonilamino, carbociclilo o carboxi, en donde R^{25} puede sustituirse de manera opcional en carbono por uno o mas R^{60}

R^{25} se selecciona de hidroxi, amino, carbamoilo, etoxicarbonilo, *t*-butoxicarbonilamino, fenilo o carboxi, en donde R^{25} puede sustituirse de manera opcional en carbono por uno o más R^{60}

R^{25} se selecciona de hidroxi, amino, carbamoilo, C_{1-10}alcoxicarbonilo, C_{1-10}alcoxicarbonilamino, carbociclilo o carboxi, en donde R^{25} puede sustituirse de manera opcional en carbono por uno o mas R^{60}, en donde R^{60} es hidroxi

R^{25} se selecciona de hidroxi, amino, carbamoilo, etoxicarbonilo, *t*-butoxicarbonilamino, fenilo o carboxi, en donde R^{25} puede sustituirse de manera opcional en carbono por uno o mas R^{60}, en donde R^{60} es hidroxi

R^{33} es hidroxi

R^{60} es hidroxi

La cadena lateral R^{14}-$[C(R^{13})]_m$-$C(R^{11})(R^{12})$-$N(R^{10})$-C(O)-$[C(R^9)]_n$-O- es *N*-(2-sulfoetil)carbamoilmetoxi,

N-(carboximetil)carbamoilmetoxi,

N-(2-hidroxietil)carbamoilmetoxi,

95

N-(2-metoxıetıl)carbamoılmetoxı,

N-[2-(carboxı)etıl]carbamoılmetoxı,

N-[(S)-1-(carboxı)etıl]carbamoılmetoxı,

N-[(R)-1-(carboxı)etıl]carbamoılmetoxı,

N-[(S)-α-(carboxı)bencıl]carbamoılmetoxı,

N-[(R)-α-(carboxı)bencıl]carbamoılmetoxı,

N-(*t*-butoxıcarbonılmetıl)carbamoılmetoxı,

N-[2-(*t*-butoxıcarbonıl)etıl]carbamoılmetoxı,

N-[(S)-1,3-bıs-(carboxı)propıl]carbamoılmetoxı,

N-((R)-1-carboxı-3-metılbutıl)carbamoılmetoxı,

N-[(S)-1-(*t*-butoxıcarbonıl)etıl]carbamoılmetoxı,

N-[(R)-1-(*t*-butoxıcarbonıl)etıl]carbamoılmetoxı,

N-[(R)-α-(*t*-butoxıcarbonıl)bencıl]carbamoılmetoxı,

N-[(S)-1-(carboxı)-5-(amıno)pentıl]carbamoılmetoxı,

N-[(R)-1-(carboxı)-2-(hıdroxı)etıl]carbamoılmetoxı,

N-[(S)-1,3-bıs-(etoxıcarbonıl)propıl]carbamoılmetoxı,

N-[(R)-α-(carboxı)-4-(hıdroxı)bencıl]carbamoılmetoxı,

N-[*N*-(carboxımetıl)carbamoılmetıl]carbamoılmetoxı,

N-[(S)-1-(carboxı)-3-(carbamoıl)propıl]carbamoılmetoxı,

N-{(R)-α-[*N*-(carboxımetıl)carbamoıl]bencıl}carbamoılmetoxı,

N-[*N*-(metoxıcarbonılmetıl)carbamoılmetıl]carbamoılmetoxı,

N-((S)-1-{*N*-[(S)-1-(carboxı)etıl]carbamoıl}etıl)carbamoılmetoxı,

N-((2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahıdroxıhexıl)carbamoılmetoxı,

N-{(R)-α-[*N*-(*t*-butoxıcarbonılmetıl)carbamoıl]bencıl}carbamoılmetoxı,

N-{(R)-α-[*N*-(2-sulfoetıl)carbamoıl]-4-hıdroxıbencıl}carbamoılmetoxı,

N-{*N*-[(R)-1-(carboxı)-2-(hıdroxı)etıl]carbamoılmetıl}carbamoılmetoxı,

N-[(S)-1-(*t*-butoxıcarbonıl)-5-(*t*-butoxıcarbonılamıno)pentıl]
carbamoılmetoxı,

N-((S)-1-{*N*-[(S)-1-(*t*-butoxıcarbonıl)etıl]carbamoıl}etıl)carbamoılmetoxı,

N-{(R)-α-[*N*-((S)-1-carboxıpropıl)carbamoıl]4-hıdroxıbencıl}
carbamoılmetoxı,

N-((R)-α-{*N*-[(S)-1-(carboxı)-2-(hıdroxı)etıl]carbamoıl}bencıl)

r es 0 ó 1,

m es 0,

n es 1,

R^{33} es hidroxi,

o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco

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

Anillo A se selecciona de fenilo,

X es $-CR^2R^3-$ y Y es $-CR^4R^5-$ en donde uno de R^2 y R^3 es hidrógeno y el otro es hidroxi, y en donde R^4 y R^5 son ambos hidrógeno,

R^1 es 4-fluoro,

b es 1,

R^6 es 4-fluoro,

c es 1,

d es 0,

R^9 es hidrógeno,

R^{10} es hidrógeno,

Uno de R^{11} y R^{12} es hidrógeno y el otro es fenilo o los dos R^{11} y R^{12} son hidrogeno,

R^{11} es 1,2,3,4,5-pentahidroxipentilo, *t*-butoxicarbonilo o carboxi, o R^{14} es un grupo de fórmula (IA) como se describe más arriba,

R^{15} es hidrógeno,

Uno de R^{16} y R^{17} es hidrogeno, y el otro es hidrógeno, carboxi o *t*-butoxicarbonilo,

R^{18} se selecciona de hidroxi, *t*-butoxi, *t*-butoxicarbonilo o carboxi,

p es 1,

q es 0,

r es 0 ó 1,

m es 0,

n es 1,

R^{33} es hidroxi,

95

N-(2-metoxıetıl)carbamoılmetoxı,

N-[2-(carboxı)etıl]carbamoılmetoxı,

N-[(S)-1-(carboxı)etıl]carbamoılmetoxı,

N-[(R)-1-(carboxı)etıl]carbamoılmetoxı,

N-[(S)-α-(carboxı)bencıl]carbamoılmetoxı,

N-[(R)-α-(carboxı)bencıl]carbamoılmetoxı,

N-(*t*-butoxıcarbonılmetıl)carbamoılmetoxı,

N-[2-(*t*-butoxıcarbonıl)etıl]carbamoılmetoxı,

N-[(S)-1,3-bıs-(carboxı)propıl]carbamoılmetoxı,

N-((R)-1-carboxı-3-metılbutıl)carbamoılmetoxı,

N-[(S)-1-(*t*-butoxıcarbonıl)etıl]carbamoılmetoxı,

N-[(R)-1-(*t*-butoxıcarbonıl)etıl]carbamoılmetoxı,

N-[(R)-α-(*t*-butoxıcarbonıl)bencıl]carbamoılmetoxı,

N-[(S)-1-(carboxı)-5-(amıno)pentıl]carbamoılmetoxı,

N-[(R)-1-(carboxı)-2-(hıdroxı)etıl]carbamoılmetoxı,

N-[(S)-1,3-bıs-(etoxıcarbonıl)propıl]carbamoılmetoxı,

N-[(R)-α-(carboxı)-4-(hıdroxı)bencıl]carbamoılmetoxı,

N-[*N*-(carboxımetıl)carbamoılmetıl]carbamoılmetoxı,

N-[(S)-1-(carboxı)-3-(carbamoıl)propıl]carbamoılmetoxı,

N-{(R)-α-[*N*-(carboxımetıl)carbamoıl]bencıl}carbamoılmetoxı,

N-[*N*-(metoxıcarbonılmetıl)carbamoılmetıl]carbamoılmetoxı,

N-((S)-1-{*N*-[(S)-1-(carboxı)etıl]carbamoıl}etıl)carbamoılmetoxı,

N-((2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahıdroxıhexıl)carbamoılmetoxı,

N-{(R)-α-[*N*-(*t*-butoxıcarbonılmetıl)carbamoıl]bencıl}carbamoılmetoxı,

N-{(R)-α-[*N*-(2-sulfoetıl)carbamoıl]-4-hıdroxıbencıl}carbamoılmetoxı,

N-{*N*-[(R)-1-(carboxı)-2-(hıdroxı)etıl]carbamoılmetıl}carbamoılmetoxı,

N-[(S)-1-(*t*-butoxıcarbonıl)-5-(*t*-butoxıcarbonılamıno)pentıl]
carbamoılmetoxı,

N-((S)-1-{*N*-[(S)-1-(*t*-butoxıcarbonıl)etıl]carbamoıl}etıl)carbamoılmetoxı,

N-{(R)-α-[*N*-((S)-1-carboxıpropıl)carbamoıl]4-hıdroxıbencıl}
carbamoılmetoxı,

N-((R)-α-{*N*-[(S)-1-(carboxı)-2-(hıdroxı)etıl]carbamoıl}bencıl)

96

carbamoilmetoxi,

N-{*N*-[(R)-1-(*t*-butoxicarbonil)-2-(*t*-butoxi)etil]carbamoilmetil} carbamoilmetoxi, o

N-((R)-α-{*N*-(S)-[1-(*t*-butoxicarbonil)-2-(*t*-butoxi)etil]carbamoil}bencil) carbamoilmetoxi

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

Anillo A es fenilo,

X es $-CR^2R^3-$,

Y es $-CR^4R^5-$,

R^1 es halo,

b es 1,

Uno de R^2 y R^3 es hidrógeno y el otro es hidroxi,

R^4 y R^5 son ambos hidrógeno,

R^6 es halo,

c es 1,

d es 0,

R^9 es hidrógeno,

R^{10} es hidrógeno,

R^{11} y R^{12} se seleccionan independientemente de hidrogeno o carbociclilo,

R^{14} es C_{1-10}alquilo, C_{1-10}alcoxicarbonilo o carboxi, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{33}, ó R^{14} es un grupo de fórmula (IA) como se describe más arriba,

R^{15} es hidrogeno,

R^{16} y R^{17} se seleccionan independientemente de hidrógeno, carboxi o C_{1-6}alcoxicarbonilo,

R^{18} se selecciona de hidroxi, C_{1-10}alcoxi, $C_{1\ 10}$alcoxicarbonilo o carboxi,

p es 1,

q es 0,

98

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

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

Anillo A se selecciona de fenilo o tienilo,

X se selecciona de $-CR^2R^3-$, -O- y $-S(O)_a-$, en donde a es 0-2, y R^2 y R^3 se seleccionan independientemente de hidrógeno e hidroxi, ó R^2 y R^3 juntos forman un grupo oxo,

Y se selecciona de $-CR^4R^5-$ y $-S(O)_a-$, a es 0 ó 1, en donde R^4 y R^5 son ambos hidrógeno,

R^1 es halo,

b es 0-1,

R^6 es halo,

c es 0-1,

d es 0,

R^9 es hidrógeno,

R^{10} es hidrógeno,

R^{11} y R^{12} se seleccionan independientemente de hidrógeno, C_{1-4}alquilo o carbociclilo, en donde R^{11} y R^{12} pueden sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{25}, en donde R^{25} se selecciona de hidroxi, amino, carbamoilo, $C_{1\ 10}$alcoxicarbonilo, $C_{1\ 10}$alcoxicarbonilamino, carbociclilo o carboxi, en donde R^{25} puede sustituirse de manera opcional en carbono por uno o mas R^{60}, en donde R^{60} es hidroxi,

R^{13} es hidrógeno,

R^{14} es hidroxi, C_{1-10}alquilo, C_{1-10}alcoxi, C_{1-10}alcoxicarbonilo, carboxi o sulfo, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{33}, o R^{14} es un grupo de formula (IA) (como se describe mas arriba) en donde

R^{15} es hidrogeno,

R^{16} y R^{17} se seleccionan independientemente de hidrogeno, carboxi, C_{1-6}alquilo y C_{1-6}alcoxicarbonilo,

R^{18} se selecciona de hidroxi, C_{1-10}alquilo, $C_{1\ 10}$alcoxi, $C_{1\ 10}$alcoxicarbonilo, carboxi y sulfo,

p es 1,

q es 0,

r es 0 o 1,

m es 0 ó 1,

n es 1, y

R^{33} es hidroxi,

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

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

Anillo A se selecciona de fenilo o tienilo,

X se selecciona de $-CH_2-$, -CH(OH)-, -C(O)-, -O- -S-, -S(O)- y $-S(O)_2-$,

Y es $-CH_2-$, -S- o -S(O)-,

R^1 es fluoro,

b es 0-1,

R^6 es fluoro,

c es 0-1,

d es 0,

R^9 es hidrogeno,

R^{10} es hidrógeno,

Uno de R^{11} y R^{12} es hidrógeno y el otro se selecciona de hidrogeno metilo, hidroximetilo, 2-carbamoiletilo, 2-(etoxicarbonil)etilo, 2-carboxietilo, 4-(*t*-butoxicarbonilamino)butilo, 4-aminobutilo, isobutilo, fenilo, 4-hidroxifenilo y 4-hidroxibencilo,

R^{13} es hidrógeno,

R^{14} es hidroxi, pentilo, metoxi, etoxicarbonilo, *t*-butoxicarbonilo, carboxi o sulfo, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{33}, o R^{14} es un grupo de formula (IA) (como se describe mas arriba) en donde

100

R^{15} es hidrógeno,

R^{16} y R^{17} se seleccionan independientemente de hidrogeno, carboxi, C_{1-6}alquilo y *t*-butoxicarbonilo,

R^{18} se selecciona de hidroxi, metilo, *t*-butoxi, etoxicarbonilo, *t*-butoxicarbonilo, carboxi y sulfo,

p es 1,

q es 0,

r es 0 o 1,

m es 0 ó 1,

n es 1, y

R^{33} es hidroxi,

o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

En otro aspecto de la invención, compuestos preferidos de la invención son uno cualquiera de los ejemplos o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

En otro aspecto de la invencion, compuestos preferidos de la invención son

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona,

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(R)-α-(carboxi)bencil]carbamoilmetoxi}fenil)azetidin-2-ona,

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona,

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[*N*-(carboximetil)carbamoilmetil]carbamoilmetoxi}fenil)azetidin-2-ona,

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(2-hidroxietil)carbamoilmetoxi]fenil}azetidin-2-ona,

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(2-metoxietil)carbamoilmetoxi]fenil}azetidin-2-ona,

3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-{4-[*N*-

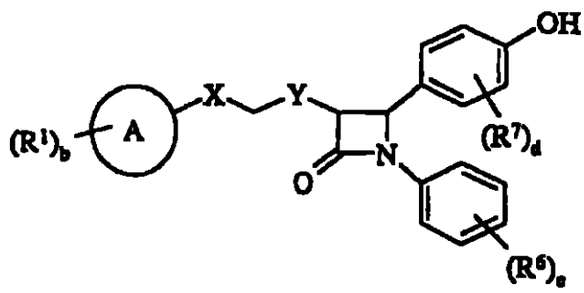
101

(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona,
3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona,
3-(R)-4-(R)-1-(fenil)-3-[2-(tien-3-il)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona,
3-(R)-4-(R)-1-(fenil)-3-[2-(tien-3-il)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona,
3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-(4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona, y
3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona,
o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Aspectos preferidos de la invención son los que se relacionan con el compuesto de fórmula (I) o su sal farmaceuticamente aceptable

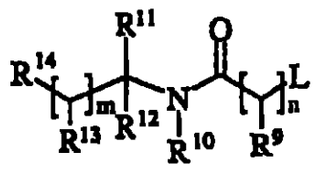
Otro aspecto de la presente invención provee un proceso para preparar un compuesto de formula (I) o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, proceso que (en donde hay grupos variables, a menos que se especifique lo contrario, como se define en la fórmula (I)), comprende

Proceso 1) hacer reaccionar un compuesto de fórmula (II)



(II)

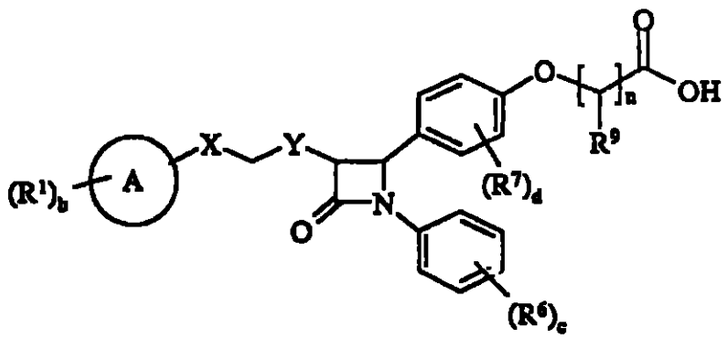
con un compuesto de fórmula (III)



(III)

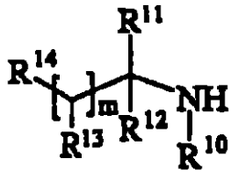
en donde L es un grupo desplazable,

Proceso 2) hacer reaccionar un ácido de fórmula (IV)



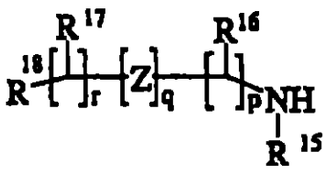
(IV)

o su derivado activado, con una amina de fórmula (V)



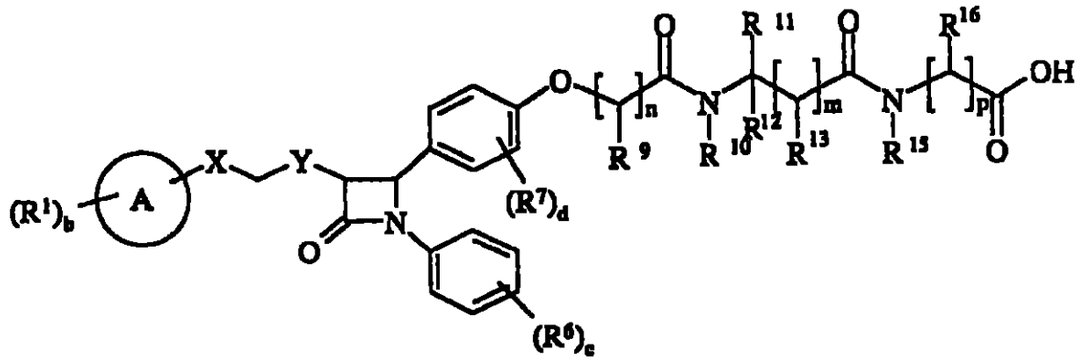
(V)

Proceso 3) para compuestos de fórmula (I) en donde R^{14} es un grupo de fórmula (IA), hacer reaccionar un compuesto de fórmula (VI) en donde R^{14} es carboxi, o su derivado activado, con una amina de fórmula (VI)



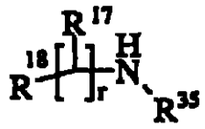
(VI)

Proceso 4) para compuestos de formula (I) en donde R^{14} es un grupo de fórmula (IA), Z es $-N(R^{35})C(O)-$ y q es 1, hacer reaccionar un ácido de fórmula (VII)



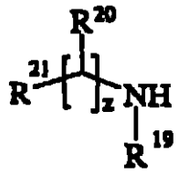
(VII)

(o su derivado activado, con una amina de fórmula (VIII)



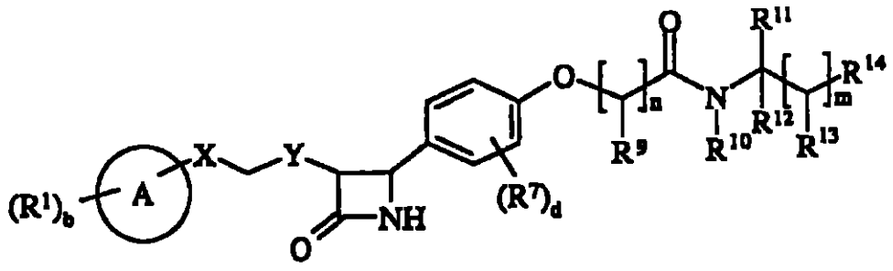
(VIII)

Proceso 5) para compuestos de fórmula (I) en donde R^{14} es un grupo de formula (IA) y R^{18} es un grupo de fórmula (IB), hacer reaccionar un ácido de fórmula (I) en donde R^{14} es un grupo de fórmula (IA) y R^{18} es carboxi, o su derivado activado, con una amina de fórmula (IX)



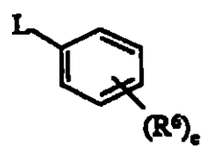
(IX)

Proceso 6) hacer reaccionar un compuesto de fórmula (X):



(X)

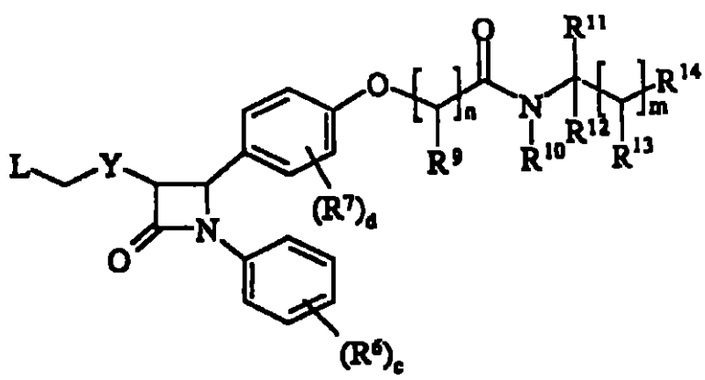
con un compuesto de fórmula (XI)



(XI)

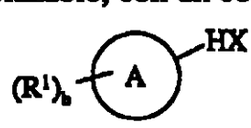
en donde L es un grupo desplazable,

Proceso 7) para compuestos de formula (I) en donde X se selecciona de -O-, $-NR^x-$ y $-S(O)_a$ en donde a es 0, hacer reaccionar un compuesto de fórmula (XII)



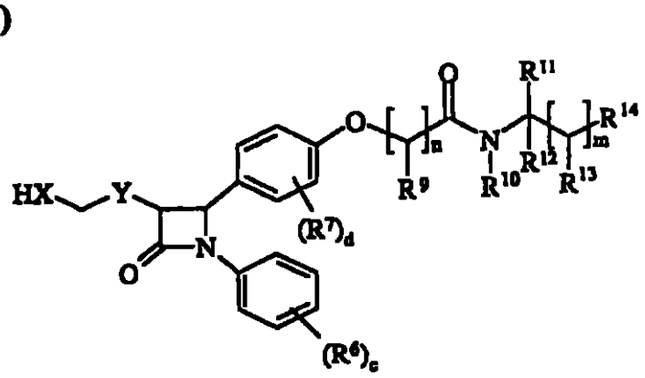
(XII)

en donde L es un grupo desplazable, con un compuesto de fórmula (XIII)



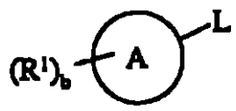
(XIII)

Proceso 8) para compuestos de fórmula (I) en donde X se selecciona de -O-, $-NR^x-$ y $-S(O)_a-$ en donde a es 0, hacer reaccionar un compuesto de formula (XIV)



(XIV)

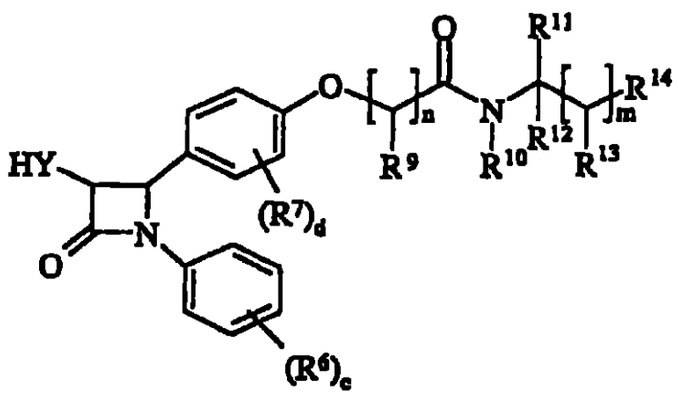
con un compuesto de fórmula (XV)



(XV)

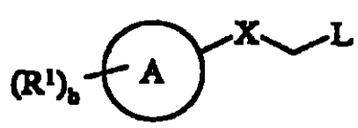
en donde L es un grupo desplazable,

Proceso 9) para compuestos de fórmula (I) en donde Y se selecciona de -O-, $-NR^z-$ y $-S(O)_a$ en donde a es 0, hacer reaccionar un compuesto de fórmula (XVI)



(XVI)

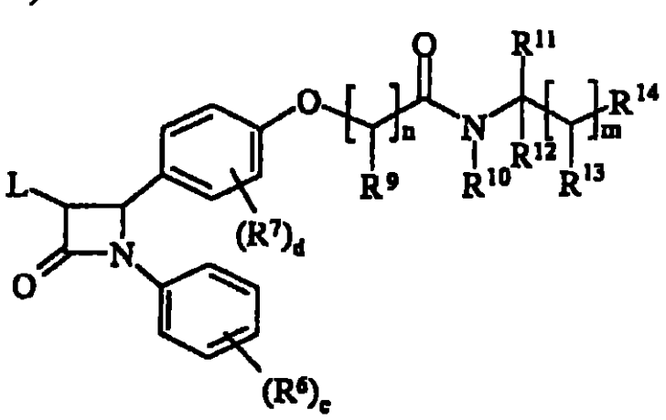
con un compuesto de fórmula (XVII)



(XVII)

en donde L es un grupo desplazable,

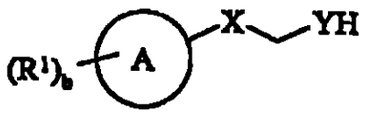
Proceso 10) para compuestos de formula (I) en donde Y se selecciona de -O-, $-NR^z-$ y $-S(O)_a-$ en donde a es 0, hacer reaccionar un compuesto de fórmula (XVIII)



(XVIII)

106

en donde L es un grupo desplazable, con un compuesto de formula (XIX)



(XIX)

Proceso 11) para compuestos de fórmula (I) en donde X o Y es $-S(O)_a-$ y a es 1 ó 2, oxidar un compuesto de fórmula (I) en donde X o Y es $-S(O)_a-$ y a es 0 (para compuestos de formula (I) en donde a es 1 ó 2) o a es 1 (para compuestos de formula (I) en donde y a es 2),

y posteriormente, si es necesario o deseable,

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

ii) retirar cualesquiera grupos protectores,

iii) formar una sal farmaceuticamente aceptable, solvato, solvato de tal sal o un profarmaco, o

iv) separar dos o más enantiomeros

L es un grupo desplazable, valores apropiados para L son por ejemplo, un halógeno o grupo sulfoniloxi, por ejemplo un grupo cloro, bromo, metanosulfoniloxi o tolueno-4-sulfoniloxi

Condiciones especificas de reacción para las reacciones anteriores son como sigue

Proceso 1) Alcoholes de formula (II) pueden hacerse reaccionar con compuestos de fórmula (III) en la presencia de una base por ejemplo una base inorgánica tal como carbonato de sodio, o una base orgánica tal como una base de Hünig, en la presencia de un disolvente apropiado tal como acetonitrilo, diclorometano o tetrahidrofurano a una temperatura en el rango de 0°C a reflujo, preferiblemente a reflujo o cerca de él

Compuestos de formula (II) en donde X es $-CR^2R^3-$, Y se selecciona de $-CR^4R^5-$, R^2 y R^3 juntos forman un grupo oxo y R^4 y R^5 son ambos hidrogeno, pueden prepararse de acuerdo con el siguiente esquema

dimetilacetamida, diclorometano, benceno, tetrahidrofurano y dimetilformamida La reacción de acoplamiento puede realizarse convenientemente a una temperatura en el rango de -40 a 40°C

Derivados apropiados de ácido activado incluyen halogenuros de ácido, por ejemplo cloruros de ácido, y esteres activos, por ejemplo pentafluorofenil esteres La reacción de estos tipos de compuestos con aminas es bien conocida en el arte, por ejemplo pueden hacerse reaccionar en la presencia de una base, tal como las descritas anteriormente, y en un disolvente apropiado, tal como los ya descritos La reacción puede llevarse convenientemente a cabo a una temperatura en el rango de -40 a 40°C

Acidos de fórmula (IV) y (VII) pueden prepararse de compuestos de fórmula (II) haciéndolos reaccionar con la cadena lateral, apropiada, protegida de manera opcional, usando las condiciones del *Proceso 1*).

Aminas de fórmula (V), (VI), (VIII) y (IX) son compuestos disponibles en el comercio, o se conocen en la literatura, o pueden prepararse por procesos estándar conocidos en el arte

Proceso 6) Compuestos de formula (X) pueden hacerse reaccionar con compuestos de fórmula (XI) en la presencia de una base, por ejemplo una base inorgánica tal como carbonato de sodio, o una base organica tal como una base de Hunigs, en la presencia de un disolvente apropiado tal como acetonitrilo, diclorometano, DMF o tetrahidrofurano a una temperatura en el rango de 0°C a reflujo, preferiblemente a reflujo o cerca de el Alternativamente, esta reacción puede llevarse a cabo usando química de metal de transición conocida por la persona experta, por ejemplo química de cobre o paladio

Compuestos de fórmula (X) pueden prepararse de acuerdo con Esquema 1 con un sustituto apropiado para el compuesto (IIb), por ejemplo bencilamina, seguida por debencilación en un punto apropiado en el esquema sintetico

Compuestos de fórmula (XI) son compuestos disponibles en el comercio, o se conocen en la literatura, o pueden prepararse por procesos estandar conocidos en el arte

109

Proceso 7), *Proceso 8*), *Proceso 9*) y *Proceso 10*) Estos compuestos pueden hacerse reaccionar juntos en la presencia de una base por ejemplo una base inorganica tal como carbonato de sodio, o una base organica tal como una base de Hunigs, en la presencia de un disolvente apropiado tal como acetonitrilo, diclorometano, o tetrahidrofurano a una temperatura en el rango de 0°C a reflujo, preferiblemente a reflujo o cerca de el

Compuestos de fórmula **(XII)**, **(XIV)**, **(XVI)** y **(XVIII)** pueden prepararse de acuerdo con Esquema 1 con un sustituto apropiado para el compuesto **(IId)**.

Compuestos de fórmula **(XIII)**, **(XV)**, **(XVII)** y **(XIX)** son compuestos disponibles en el comercio, o se conocen en la literatura, o pueden prepararse por procesos estandar conocidos en el arte

Proceso 11) Estos compuestos pueden oxidarse bajo condiciones estandar de oxidación de azufre, por ejemplo usando peróxido de hidrogeno y ácido trifluoroacético a una temperatura en el rango de 0°C a reflujo, preferiblemente a temperatura de la sala o cerca de ella.

Se observará que algunos de los diferentes sustituyentes del anillo en los compuestos de la presente invención pueden introducirse por reacciones estándar de sustitución aromática o generarse por modificaciones convencionales del grupo funcional ya sea antes o inmediatamente despues de los procesos mencionados más arriba, y como tales se incluyen en el aspecto de los procesos de la invención Tales reacciones y modificaciones incluyen, por ejemplo, la introducción de un sustituyente por medio de una reaccion de sustitución aromatica, reducción de sustituyentes, alquilación de sustituyentes y oxidación de sustituyentes Los reactivos y condiciones de reaccion para tales procedimientos son bien conocidos en el arte quimico Ejemplos particulares de reacciones de sustitución aromática incluyen la introduccion de un grupo nitro usando acido nitrico concentrado, la introduccion de un grupo acilo usando, por ejemplo, un halogenuro de acilo y un acido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts, la introduccion de un grupo alquilo usando un halogenuro de alquilo y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones

110

de Friedel Crafts, y la introduccion de un grupo halogeno Ejemplos particulares de modificaciones incluyen la reduccion de un grupo nitro a un grupo amino mediante, por ejemplo, hidrogenación catalitica con un catalizador de niquel o tratamiento con hierro en la presencia de ácido clorhidrico con calentamiento, oxidación de alquiltio en alquilsulfinilo o alquilsulfonilo

Se apreciará igualmente que en algunas de las reacciones mencionadas aquí puede ser necesario/deseable proteger cualesquiera grupos sensibles en los compuestos Los casos en donde la protección es necesaria o deseable y los métodos apropiados para la proteccion son conocidos por los expertos en el arte Grupos protectores convencionales pueden usarse se acuerdo con la practica estandar (para efectos de ilustración véase T W Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999) Por lo tanto, si los reactivos incluyen grupos tales como amino, carboxi o hidroxi, puede ser deseable proteger el grupo en algunas de las reacciones mencionadas aqui

Un grupo protector adecuado para un grupo amino o alquilamino es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como un grupo acetilo, un grupo alcoxicarbonilo, por ejemplo un grupo metoxicarbonilo, etoxicarbonilo o t-butoxicarbonilo, un grupo arilmetoxicarbonilo, por ejemplo benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo Las condiciones de desproteccián para los anteriores grupos protectores varian necesariamente con la eleccion del grupo protector Así, por ejemplo, un grupo acilo tal como un grupo alcanoilo o alcoxicarbonilo o un grupo aroilo pueden retirarse por ejemplo, mediante hidrólisis con una base adecuada tal como un hidróxido de metal alcalino, por ejemplo hidróxido de litio o sodio Alternativamente un grupo acilo tal como un grupo *t*-butoxicarbonilo puede retirarse, por ejemplo, mediante tratamiento con un ácido adecuado tal como acido clorhidrico, sulfurico o fosforico o ácido trifluoroacético, y un grupo arilmetoxicarbonilo tal como un grupo benciloxicarbonilo puede retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbón, o

mediante tratamiento con un ácido de Lewis por ejemplo tris(trifluoroacetato) de boro Un grupo protector alternativo adecuado para un grupo amino primario es, por ejemplo, un grupo ftaloilo que puede retirarse mediante tratamiento con una alquilamina, por ejemplo dimetilaminopropilamina, o con hidrazina.

Un grupo protector adecuado para un grupo hidroxi es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como acetilo, un grupo aroilo, por ejemplo benzoilo, o un grupo arilmetilo, por ejemplo bencilo Las condiciones de desprotección para los grupos protectores anteriores variaran necesariamente con la elección del grupo protector Así, por ejemplo, un grupo acilo tal como un alcanolilo o un grupo aroilo pueden retirarse, por ejemplo, mediante hidrolisis con una base apropiada tal como un hidroxido de metal alcalino, por ejemplo hidroxido de litio o de sodio Alternativamente, un grupo arilmetilo tal como un grupo bencilo pueden retirarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbón

Un grupo protector adecuado para un grupo carboxi, por ejemplo, un grupo esterificante, por ejemplo un grupo metilo o etilo que puede retirarse, por ejemplo, mediante hidrólisis con una base tal como hidróxido de sodio, o por ejemplo un grupo *t*-butilo que puede retirarse, por ejemplo, mediante tratamiento con un acido, por ejemplo un ácido organico tal como ácido trifluoroacético, o por ejemplo un grupo bencilo que puede retirarse, por ejemplo, mediante hidrogenacion sobre un catalizador tal como paladio sobre carbón

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

Como ya se afirmó anteriormente en el texto, los compuestos definidos en la presente invencion poseen actividad inhibidora de absorcion del colesterol Estas propiedades pueden avaluarse, por ejemplo, usando la siguiente prueba biológica

Analisis *in vivo* de los inhibidores de absorcion del colesterol

112

Ratones hembra C57BL/6 se mantuvieron en una dieta regular de comida y se albergaron en jaulas individuales para recoger las heces Se hizo ayunar a los ratones durante 3 y luego se alimentaron mediante sonda gastrica con vehiculo o compuesto Media hora después los ratones se recibieron colesterol radiomarcado a traves de la sonda gastrica Dos o seis horas después de la administración de ^{14}C-colesterol con sonda gástrica, se tomaron muestras de sangre de la cola y se preparó el plasma para determinar la cantidad de colesterol que se había absorbido 24 horas después de la administración de ^{14}C-colesterol con sonda gástrica, los ratones se desangraron hasta morir y se preparó el plasma para análisis Se recogieron las heces durante 24 horas para evaluar la eficiencia de la absorción

Referencias

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

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

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

Absorción

La absorción de los compuestos de formula (I) se evaluo en un modelo de células Caco-2 (Gastroenterology 1989, 96, 736)

Los siguientes datos muestran que el Ejemplo 24 exhibe una absorción mucho más baja comparada con el ezetimibe (US RE37721)

Compuesto	Ejemplo 24	Ezetimibe
Coeficiente de partición aparente, P_{app} [cm/s]	$0\ 24 \times 10^{-06}$	21×10^{-06}

113

De acuerdo con un aspecto adicional de la invencion se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define mas arriba en el texto en asociación con un diluyente o vehículo farmacéuticamente aceptables

La composicion puede estar en una forma apropiada para administracion oral, por ejemplo como una tableta o cápsula, para inyección parenteral (incluida intravenosa, subcutanea, intramuscular, intravascular o infusion) como una solución estéril, suspension o emulsión, para administracion local como un ungüento o crema o para administración rectal como un supositorio

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

El compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, se administrarán normalmente a un animal de sangre caliente en una dosis unitaria en el rango de aproximadamente 0 02-100 mg/kg, preferiblemente 0 02 -50 mg/kg, y esta proporciona normalmente una dosis terapéuticamente eficaz Una forma de dosis unitaria tal como una tableta o cápsula contendrá usualmente, por ejemplo 1-250 mg de ingrediente activo Preferiblemente se emplea una dosis diaria en el rango de 1-50 mg/kg, particularmente 0 1-10 mg/kg En otro aspecto se emplea una dosis diaria en el rango de 0 01-20 mg/kg No obstante, la dosis diaria variará necesariamente dependiendo del anfitrion tratado, la via particular de administración, y la gravedad de la enfermedad que se esta tratando En consecuencia, la posologia optima puede determinarse por el profesional medico que este tratando un paciente particular

De acuerdo con un aspecto adicional de la presente invención se provee un compuesto de la formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto para uso en un método de tratamiento terapeutico o profiláctico de un animal de sangre caliente, tal como el hombre

114

Hemos descubierto que los compuestos definidos en la presente invencion, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, son inhibidores efectivos de la absorcion del colesterol y, en consecuencia, son de utilidad en el tratamiento de estados patológicos asociados con afecciones hiperlipidémicas

Por consiguiente, de acuerdo con este aspecto de la invencion se provee un compuesto de la fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco, como se define más arriba en el texto para uso como un medicamento

De acuerdo con otra característica de la invencion se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define mas arriba en el texto en la manufactura de un medicamento para uso en la produccion de un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre

De acuerdo con otra caracteristica de la invencion se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto en la producción de un efecto inhibidor de absorcion de colesterol en un animal de sangre caliente, tal como el hombre

En este caso, donde se especifica la producción de un efecto inhibidor de absorcion de colesterol o un efecto reductor del colesterol, convenientemente éste se refiere al tratamiento de afecciones hiperlipidemicas en un animal de sangre caliente, tal como el hombre Adicionalmente se refiere al tratamiento de afecciones dislipidemicas y trastornos tales como hiperlipidemia, hipertrigliceridemia, hiperbetalipoproteinemia (LDL alta), hiperprebetalipoproteinemia (VLDL alta), hiperquilomicronemia, hipolipoproteinemia, hipercolesterolemia, hiperlipoproteinemia e hipoalfalipoproteinemia (HDL baja) en un animal de sangre caliente, tal como el hombre Más aun, se refiere al tratamiento de diferentes afecciones clínicas tales como ateroesclerosis, arteriosclerosis, arritmia, afecciones hipertrombóticas, disfuncion vascular, disfunción

endotelial, insuficiencia cardíaca, cardiopatias coronarias, enfermedades cardiovasculares, infarto del miocardio, angina pectoris, enfermedades vasculares periféricas, inflamación de tejidos cardiovasculares tales como corazon, válvulas, vasculatura, arterias y venas, aneurismas, estenosis, restenosis, placas vasculares, estrias adiposas vasculares, leucocitos, monocitos y/o infiltracion de macrófagos, engrosamiento de la capa intima, adelgazamiento de la media, trauma infeccioso y quirurgico y trombosis vascular, apoplejía y ataques isquémicos transitorios en un animal de sangre caliente, tal como el hombre Se refiere asimismo al tratamiento de ateroesclerosis, cardiopatias coronarias, infarto del miocardio, angina pectoris, enfermedades vasculares periféricas, apoplejía y ataques isquémicos transitorios en un animal de sangre caliente, tal como el hombre

La produccion de un efecto inhibidor de absorción de colesterol o un efecto reductor del colesterol se refiere tambien a un metodo de tratar y/o prevenir lesiones ateroescleroticas, un método de prevenir la ruptura de placas y un método de promover la regresión de la lesión Más aun, se refiere a un metodo de inhibir la acumulación de monocitos-macrófago en lesiones ateroescleróticas, un metodo de inhibir la expresión de metaloproteinasas de matriz en lesiones ateroescleróticas, un metodo de inhibir la desestabilización de lesiones ateroescleroticas, un método para prevenir la ruptura de placas ateroescleróticas y un método de trata angina inestable

La producción de un efecto inhibidor de absorción de colesterol o un efecto reductor del colesterol se relaciona igualmente con un método de tratar sitosterolemia.

Ademas, los compuestos de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco pueden ser útiles en el tratamiento o prevencion de la Enfermedad de Alzheimer (véase por ejemplo WO 02/096415) Por lo tanto, en un aspecto adicional de la invención, se provee un compuesto de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, para

uso en el tratamiento o prevención de la Enfermedad de Alzheimer

Compuestos de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco pueden tener asimismo utilidad en el tratamiento o prevención de la inflamación vascular (vease por ejemplo WO 03/026644) Por lo tanto en un aspecto adicional de la invencion, se provee un compuesto de fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, para uso en el tratamiento o prevención de la inflamación vascular

De acuerdo con una caracteristica adicional de este aspecto de la invencion se provee un método para producir un efecto inhibidor de absorcion de colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

La actividad inhibidora de absorción de colesterol definida más arriba en el texto puede aplicarse como terapia unica o puede incluir, aparte de un compuesto de la invención, uno o más de otras sustancias y/o tratamientos Tal tratamiento conjunto puede lograrse mediante la administración simultanea, consecutiva o separada de los componentes individuales del tratamiento De acuerdo con este aspecto de la invencion se provee un producto farmacéutico que comprende un compuesto de la formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto, y una sustancia adicional inhibidora de la absorcion de colesterol, como se define más arriba en el texto, y un agente hipolipidémico adicional para el tratamiento conjunto de hiperlipidemia.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, pueden administrarse en asociación con inhibidores de biosíntesis de colesterol, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos Inhibidores apropiados de biosíntesis de colesterol incluyen inhibidores de HMG Co-A reductasa, inhibidores de la

117

síntesis de escualeno e inhibidores de escualeno epoxidasa Un inhibidor apropiado de la síntesis de escualeno es esqualestatina 1 y un inhibidor apropiado de escualeno epoxidasa es NB-598

En este aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, pueden administrarse en asociación con un inhibidor de HMG Co-A reductasa, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos Inhibidores apropiados de HMG Co-A reductasa, sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos son estatinas son bien conocidos en el arte Estatinas particulares son fluvastatina, lovastatina, pravastatina, simvastatina, atorvastatina, cerivastatina, bervastatina, dalvastatina, mevastatin y rosuvastatina, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco Otra estatina particular es pitvastatina, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco Una estatina particular es atorvastatina, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco Una estatina más particular es sal de calcio de atorvastatina Otra estatina particular es rosuvastatina, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco Una estatina particular preferible es sal de calcio de rosuvastatina

Por lo tanto en una característica adicional de la invención, se provee una combinacion de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco y un inhibidor de HMG Co-A reductasa, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco

Por lo tanto en una característica adicional de la invención, se provee un método para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, en administración simultánea, consecutiva o separada con una cantidad eficaz de un inhibidor de HMG Co-A reductasa, o su sal

118

farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco

De acuerdo con un aspecto adicional de la invencion se provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, y un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmaceuticamente aceptables

De acuerdo con un aspecto adicional de la presente invencion se provee un estuche que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

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

a) un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una primera presentacion farmacéutica unitaria,

b) un inhibidor de HMG Co-A reductasa, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, en una segunda presentación farmaceutica unitaria, y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda

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

a) un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, conjuntamente con un diluyente o vehículo farmaceuticamente aceptables, en una primera presentación farmacéutica unitaria,

b) un inhibidor de HMG Co-A reductasa, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, en una segunda presentación farmacéutica unitaria, y

c) medios de envase para contener dichas presentaciones farmacéuticas

119

primera y segunda

De acuerdo con otra caracteristica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, en la manufactura de un medicamento para uso en la produccion de un efecto reductor del colesterol

De acuerdo con un aspecto adicional de la presente invención se provee un tratamiento de combinacion que comprende la administracion de una cantidad eficaz de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehiculo farmacéuticamente aceptables, con la administracion simultánea, consecutiva o separada de una cantidad eficaz de un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, de manera opcional conjuntamente con un diluyente o vehiculo farmaceuticamente aceptables a un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento terapéutico

De acuerdo con otro aspecto adicional de la presente invención se provee un tratamiento de combinacion que comprende la administración de una cantidad eficaz de un compuesto de la formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehiculo farmaceuticamente aceptables, con la administracion simultanea, consecutiva o separada de un inhibidor de metaloproteinasa de matriz

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco, pueden administrarse en asociacion con un inhibidor de transporte de acido bilial en el íleon (IBAT) o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco Se han descrito compuestos apropiados que poseen tal actividad inhibidora IBAT, vease, por ejemplo, los compuestos hipolipidémicos descritos en 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 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/66533, WO 02/50051 y EP 0 864 582, y el compuesto descrito en estas solicitudes de patente, particularmente la reivindicacion 1, se incorporan aquí por referencia

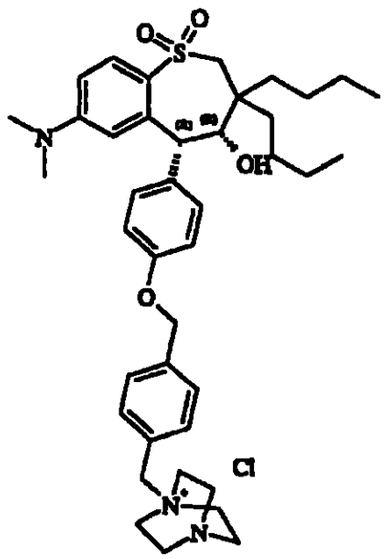
Otros compuestos apropiados que poseen actividad inhibidora IBAT se han descrito en WO 94/24087, WO98/07749, WO 98/56757, WO 99/32478, WO 99/35135, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 01/68637, WO 01/68096, WO 02/08211, WO 03/020710, WO 03/022825, WO 03/022830, WO 03/022286, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 489 423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595, EP 869 121 y EP 1 070 703, y los contenidos de estas solicitudes de patente, particularmente los compuestos descritos en la reivindicacion 1 y los ejemplos designados, se incorporan aqui por referencia

Clases particulares de inhibidores IBAT, apropiadas para uso en la presente invención son benzotiepinas Otras clases apropiadas de inhibidores IBAT son las 1,2-benzotiazepinas, 1,4-benzotiazepinas y/o 1,5-benzotiazepinas Otra clase apropiada de inhibidores IBAT son las 1,2,5-benzotiadiazepinas

Un compuesto particular apropiado, que posee actividad inhibidora IBAT es ácido (3*R*,5*R*)-3-butil-3-etil-1,1-dioxido-5-fenil-2,3,4,5-tetrahidro-1,4-benzothiazepin-8-il β-D-glucopiranosidurónico (EP 864 582)

Otro compuesto apropiado que posee actividad inhibidora IBAT es S-8921 (EP 597 107)

Otro inhibidor IBAT apropiado es el compuesto



WO 99/32478

Otros compuestos particulares que poseen actividad inhibidora IBAT incluyen

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N'*-(carboximetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(carboximetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N'*-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N'*-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

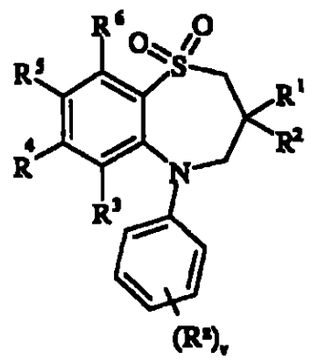
1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-carboxietil)

carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-carboxietil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(5-carboxipentil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-carboxietil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-(2-sulfoetil)carbamoil]-2-fluorobencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hidroxi-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hidroxi-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hidroxi-1-carboxietil)carbamoil]-2-hidroxietil}carbamoil)bencil] carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-(carboximetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{α-[*N'*-((etoxi)(metil) fosforil-metil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{2-[(hidroxi) (metil)fosforil]etil}carbamoil)bencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-metiltio-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{2-[(metil)(etil) fosforil]etil}carbamoil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5-

123

tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N'*-{2-[(metil)(hidroxi)fosforil]etil}carbamoil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[(R)-*N'*-(2-metilsulfinil-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina, y
1,1-dioxo-3,3-dibutil-5-fenil-7-metoxi-8-[*N*-{(R)-α-[*N'*-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina,
o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

Inhibidores IBAT adicionales apropiados para combinacion con compuestos de la presente invención son los descritos en WO 03/020710 Otros compuestos apropiados que poseen actividad inhibidora IBAT tienen la siguiente estructura de formula (AI)



(AI)

en donde

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

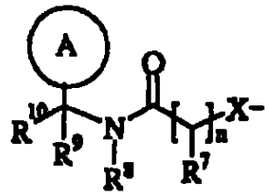
R^z se selecciona de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo,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

124

$_6$alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo y *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo,

v es 0-5,

uno de R^4 y R^5 es un grupo de fórmula (AIA)



(AIA)

R^3 y R^6 y el otro de R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo y *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, en donde R^3 y R^6 y el otro de R^4 y R^5 puede sustituirse de manera opcional en carbono por uno o más R^{17},

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

Anillo A es arilo o heteroarilo, en donde Anillo A se sustituye de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{18},

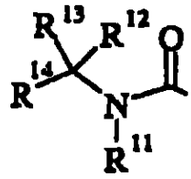
R^7 es hidrógeno, C_{1-6}alquilo, carbociclilo o heterociclilo, en donde R^7 se sustituye de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{19}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{20},

R^8 es hidrogeno o C_{1-6}alquilo,

R^9 es hidrógeno o C_{1-6}alquilo,

R^{10} es hidrógeno, halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-(C_1

$_{10}$alquil)amino, *N,N*-($C_{1\ 10}$alquil)$_2$amino, *N,N,N*-(C_{1-10}alquil)$_3$amonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N,N*-(C_{1-10}alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-($C_{1\ 10}$alquil)sulfamoilo, *N,N*-($C_{1\ 10}$alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N,N*-($C_{1\ 10}$alquil)$_2$ sulfamoilamino, C_{1-10}alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_p$-R^{21}-(C_{1-10}alquilen)$_q$- o heterociclil-($C_{1\ 10}$alquilen)$_r$-R^{22}-(C_{1-10}alquilen)$_s$-, en donde R^{10} se sustituye de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{23}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{24}, o R^{10} es un grupo de fórmula (AIB)



(AIB)

en donde

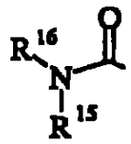
R^{11} es hidrógeno o C_{1-6}alquilo,

R^{12} y R^{13} se seleccionan independientemente de hidrogeno, halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, C_{1-10}alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, $C_{1\ 10}$alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-(C_{1-10}alquil)amino, *N,N*-(C_{1-10}alquil)$_2$amino, $C_{1\ 10}$alcanoilamino, *N*-($C_{1\ 10}$alquil)carbamoilo, *N,N*-(C_{1-10}alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N,N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-($C_{1\ 10}$alquil)sulfamoilamino, *N,N*-(C_{1-10}alquil)$_2$sulfamoilamino, carbociclilo o heterociclilo, en donde R^{12} y R^{13} pueden sustituirse independientemente de manera opcional por uno o más sustituyentes seleccionados de R^{25}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{26},

R^{14} se selecciona de hidrógeno halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, $C_{1\ 10}$alquilo, C_{2-}

126

$_{10}$alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-($C_{1\ 10}$alquil)amino, *N*,*N*-($C_{1\ 10}$alquil)$_2$amino, *N*,*N*,*N*-(C_{1-10}alquil)$_3$ammonio, C_{1-10}alcanoilamino, *N*-($C_{1\ 10}$alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$ carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-($C_{1\ 10}$alquil)sulfamoilamino, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilamino, C_{1-10}alcoxicarbonilamino, carbociclilo, carbociclil C_{1-10}alquilo, heterociclilo, heterociclil$C_{1\ 10}$alquilo, carbociclil-($C_{1\ 10}$alquilen)$_p$-R^{27}-(C_{1-10}alquilen)$_q$- o heterociclil-(C_{1-10}alquilen)$_r$-R^{28}-(C_{1-10}alquilen)$_s$-, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{29}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{30}, o R^{14} es un grupo de formula (AIC)



(AIC)

R^{15} es hidrógeno o C_{1-6}alquilo,

R^{16} es hidrogeno o C_{1-6}alquilo, en donde R^{16} puede sustituirse de manera opcional en carbono por uno o más grupos seleccionados de R^{31},

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

R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} ó R^{31} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, $C_{2\ 10}$alquinilo, $C_{1\ 10}$alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-(C_{1-10}alquil)amino, *N*,*N*-($C_{1\ 10}$alquil)$_2$amino, *N*,*N*,*N*-(C_{1-10}alquil)$_3$ammonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, $C_{1\ 10}$alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilamino, C_{1-10}alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-($C_{1\ 10}$alquilen)$_p$-R^{32}-($C_{1\ 10}$alquilen)$_q$- o

heterociclil-(C_{1-10}alquilen)$_r$-R^{33}-(C_{1-10}alquilen)$_s$-, en donde R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} ó R^{31} pueden sustituirse independientemente de manera opcional por uno o mas R^{34}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{35},

R^{21}, R^{22}, R^{27}, R^{28}, R^{32} ó R^{33} se seleccionan independientemente de -O-, -NR^{36}-, -$S(O)_x$-, -$NR^{36}C(O)NR^{36}$-, -$NR^{36}C(S)NR^{36}$-, -OC(O)N=C-, -$NR^{36}C(O)$- ó -$C(O)NR^{36}$-, en donde R^{36} se selecciona de hidrógeno o C_{1-6}alquilo, y x es 0-2,

p, q, r y s se seleccionan independientemente de 0-2,

R^{34} se selecciona de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, *N*-metilcarbamoilo, *N,N*-dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, *N*-metilsulfamoilo, *N,N*-dimetilsulfamoilo, *N*-metilsulfamoilamino y *N,N*-dimetilsulfamoilamino,

R^{20}, R^{24}, R^{26}, R^{30} ó R^{35} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

Un inhibidor IBAT particular se selecciona de uno cualquiera de Ejemplos 1-44 de WO 03/020710, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, y los compuestos de Ejemplos 1-44 se incorporan aquí por referencia Igualmente, las reivindicaciones 1-10 de WO 03/020710 se incorporan aquí por referencia. Un inhibidor IBAT particular seleccionado de WO 03/020710 se selecciona de uno cualquiera de

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

128

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-((S)-1-carbamoil-2-hidroxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-(R)-α-[*N'*-(hidroxicarbamoil-metil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N'*-[2-(*N'*-pirimidin-2-ilureido)etil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N'*-[2-(*N'*-piridin-2-ilureido)etil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(1-*t*-butoxicarbonilpiperidin-4-ilmetil)carbamoil]bencil} carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2,3-dihidroxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-[*N*-((R)-α-{*N'*-[2-(3,4-dihidroxifenil)-2-metoxietil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,5-benzotiazepina

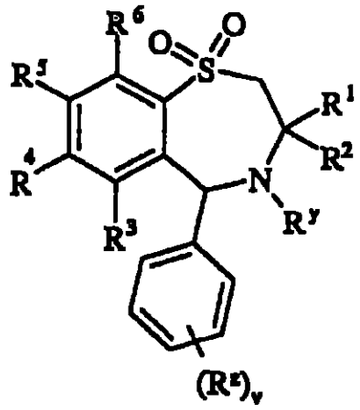
1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-aminoetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5 -benzotiazepina,

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(piperidin-4-ilmetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina, o

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-*N*,*N*-dimetilaminosulfamoiletil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco

Inhibidores IBAT adicionales apropiados para combinacion con compuestos de la presente invención son los descritos en WO 03/022825 Otros compuestos apropiados que poseen actividad inhibidora IBAT tienen la siguiente estructura de fórmula (BI)



(BI)

en donde

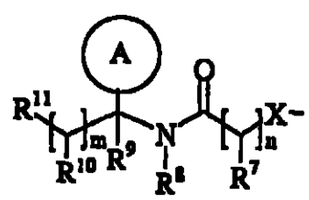
Uno de R^1 y R^2 se seleccionan de hidrógeno o C_{1-6}alquilo y el otro se selecciona de C_{1-6}alquilo,

R^y se selecciona de hidrogeno hidroxi, C_{1-6}alquilo, C_{1-4}alcoxi y C_{1-6}alcanoiloxi,

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

v es 0-5,

uno de R^4 y R^5 es un grupo de fórmula (BIA)



(BIA)

130

R^3 y R^6 y el otro de R^4 y R^5 se seleccionan independientemente de hidrogeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N*,*N*-(C_{1-4}alquil)$_2$amino, C_{1-4}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, en donde R^3 y R^6 y el otro de R^4 y R^5 puede sustituirse de manera opcional en carbono por uno o mas R^{16},

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

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

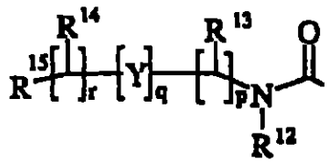
R^7 es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo, en donde R^7 se sustituye de manera opcional por uno o mas sustituyentes seleccionados de R^{18},

R^8 es hidrógeno o C_{1-4}alquilo,

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

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

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



(BIB)

en donde

Y es -N(R^x)-, -N(R^x)C(O)-, -O-, y -S(O)$_a$-, en donde a es 0-2 y R^x es

hidrogeno o C_{1-4}alquilo,

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

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

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

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

q es 0-1,

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

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

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

R^{16}, R^{17} y R^{18} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N*,*N*-(C_{1-4}alquil)$_2$amino, C_{1-4}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, en donde R^{16}, R^{17} y R^{18} pueden sustituirse independientemente de manera opcional por uno o más R^{21},

R^{19} y R^{20} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N*,*N*-(C_{1-4}alquil)$_2$amino, C_{1-4}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a

132

es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo, *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, carbociclilo, heterociclilo, sulfo, sulfino, amidino, fosfono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) o -P(O)(OR^a)(R^b), en donde R^a y R^b se seleccionan independientemente de C_{1-6}alquilo, en donde R^{19} y R^{20} pueden sustituirse independientemente de manera opcional por uno o mas R^{22},

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

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Un inhibidor IBAT particular se selecciona de uno cualquiera de Ejemplos 1-7 de WO 03/022825, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco, y los compuestos de Ejemplos 1-7 se incorporan aqui por referencia. De igual manera, las reivindicaciones 1-8 de WO 03/022825 se incorporan aqui por referencia Un inhibidor IBAT particular, seleccionado de WO 03/022825 se selecciona de uno cualquiera de

1,1-dioxo-3(R)-3-butil-3-etil-5-(R)-5-fenil-8-[*N*-((R)-α-carboxibencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,4-benzotiazepina,

1,1-dioxo-3(S)-3-butil-3-etil-5-(S)-5-fenil-8-[*N*-((R)-α-carboxibencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,4-benzotiazepina,

1,1-dioxo-3(R)-3-butil-3-etil-5-(R)-5-fenil-8-(*N*-{(R)-α-[*N*-(carboximetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina,

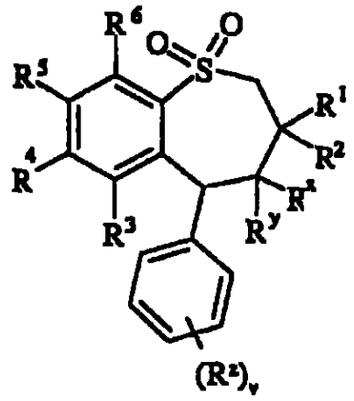
1,1-dioxo-3(S)-3-butil-3-etil-5-(S)-5-fenil-8-(*N*-{(R)-α-[*N*-(carboximetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina,

3,5-*trans*-1,1-dioxo-3-etil-3-butil-5-fenil-7-bromo-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-

133

benzotiazepina,
3,5-*trans*-1,1-dioxo-3-(S)-3-etil-3-butil-4-hidroxi-5-(S)-5-fenil-7-bromo-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina
3,5-*trans*-1,1-dioxo-3-(R)-3-etil-3-butil-4-hidroxi-5-(R)-5-fenil-7-bromo-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina,
3,5-*trans*-1,1-dioxo-3-etil-3-butil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina,
3,5-*trans*-1,1-dioxo-3-etil-3-butil-5-fenil-7-metiltio-8-(*N*-{(R)-α-*N*-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina sal de amoníaco,
1,1-dioxo-3-(S)-3-etil-3-butil-5-(S)-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil)carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina sal dietilamina, y
1,1-dioxo-3-(R)-3-etil-3-butil-5-(R)-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina sal dietilamina,
o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Inhibidores IBAT adicionales apropiados para combinación con compuestos de la presente invencion son los descritos en WO 03/022830 Otros compuestos apropiados que poseen actividad inhibidora IBAT tienen la siguiente estructura de fórmula (CI)



(CI)

en donde

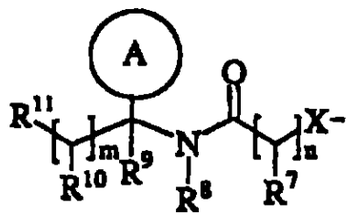
Uno de R^1 y R^2 se seleccionan de hidrogeno o C_{1-6}alquilo y el otro se selecciona de C_{1-6}alquilo,

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

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

v es 0-5,

uno de R^4 y R^5 es un grupo de fórmula (CIA)



(CIA)

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

135

C_{1-4}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, en donde R^3 y R^6 y el otro de R^4 y R^5 puede sustituirse de manera opcional en carbono por uno o más R^{16},

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

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

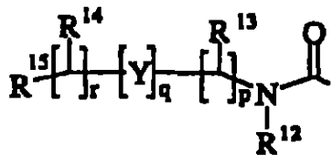
R^7 es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo, en donde R^7 se sustituye de manera opcional por uno o mas sustituyentes seleccionados de R^{18},

R^8 es hidrógeno o C_{1-4}alquilo,

R^9 es hidrógeno o C_{1-4}alquilo,

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

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



(CIB)

en donde

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

R^{12} es hidrógeno o C_{1-4}alquilo,

R^{13} y R^{14} se seleccionan independientemente de hidrogeno, C_{1-4}alquilo, carbociclilo o heterociclilo, en donde R^{13} y R^{14} pueden sustituirse

136

independientemente de manera opcional por uno o más sustituyentes seleccionados de R^{20},

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

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

q es 0-1,

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

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

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

R^{16}, R^{17} y R^{18} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-4}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, en donde R^{16}, R^{17} y R^{18} pueden sustituirse independientemente de manera opcional por uno o más R^{21},

R^{19} y R^{20} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N*,*N*-(C_{1-4}alquil)$_2$amino, C_{1-4}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo, *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, carbociclilo, heterociclilo, sulfo, sulfino, amidino, fosfono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) o -P(O)(OR^a)(R^b), en donde R^a y R^b se seleccionan independientemente de C_1

137

$_{6}$alquilo, en donde R^{19} y R^{20} pueden sustituirse independientemente de manera opcional por uno o más R^{22},

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

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Un inhibidor IBAT particular se selecciona de uno cualquiera de Ejemplos 1-4 de WO 03/022830, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y los compuestos de Ejemplos 1-4 se incorporan aquí por referencia. Asimismo las reivindicaciones 1-8 de WO 03/022830 se incorporan aquí por referencia. Un inhibidor IBAT particular seleccionado de WO 03/022830 se selecciona de uno cualquiera de

1,1-dioxo-3-butil-3-etil-4-hidroxi-5-fenil-7-(*N*-{(R)-α-[*N*-(carboximetil) carbamoil]bencil}carbamoilmetiltio)-2,3,4,5-tetrahidrobenzotiepina,

1,1-dioxo-3-butil-3-etil-4-hidroxi-5-fenil-7-(*N*-{(R)-α-[*N*-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetiltio)-2,3,4,5-tetrahidrobenzotiepina sal de amonfaco,

1,1-dioxo-3-butil-3-etil-4-hidroxi-5-fenil-7-{*N*-[α-(carboxi)-2-fluorobencil] carbamoilmetiltio}-2,3,4,5-tetrahidrobenzotiepina, y

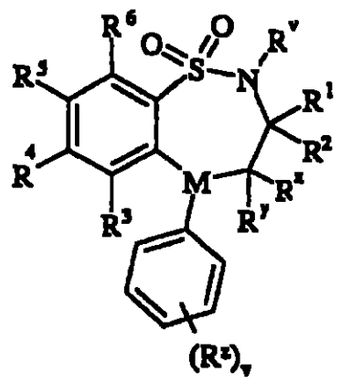
1,1-dioxo-3-butil-3-etil-4-hidroxi-5-fenil-7-{*N*-[1-(carboxi)-1-(tien-2-il) metil]carbamoilmetiltio}-2,3,4,5-tetrahidrobenzotiepina

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Inhibidores IBAT adicionales apropiados para combinación con compuestos de la presente invención son los descritos en WO 03/022286 Otros compuestos apropiados que poseen actividad inhibidora IBAT tienen

138

la siguiente estructura de fórmula (DI)



(DI)

en donde

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

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

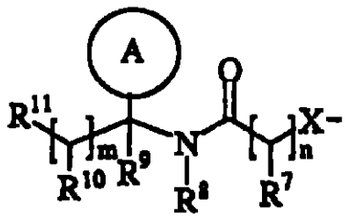
R^x y R^y se seleccionan independientemente de hidrogeno, hidroxi, amino, mercapto, C_{1-6}alquilo, C_{1-6}alcoxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquilS(O)$_a$ en donde a es 0 – 2,

M se selecciona de -*N*- ó -CH-,

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

v es 0-5,

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



(DIA)

R^3 y R^6 y el otro de R^4 y R^5 se seleccionan independientemente de

hidrogeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C1-4alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N*,*N*-(C_{1-4}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, en donde R^3 y R^6 y el otro de R^4 y R^5 puede sustituirse de manera opcional en carbono por uno o más R^{16},

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

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

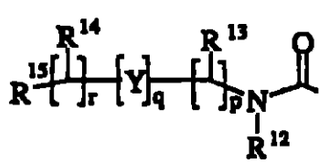
R^7 es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo, en donde R^7 se sustituye de manera opcional por uno o más sustituyentes seleccionados de R^{18},

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

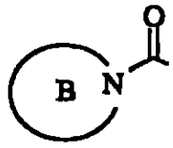
R^9 es hidrogeno o C_{1-4}alquilo,

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

R^{11} es carboxi, sulfo, sulfino, fosfono, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) ó -P(O)(OR^c)(R^d) en donde R^c y R^d se seleccionan independientemente de C_{1-6}alquilo, ó R^{11} es un grupo de formula **(DIB)** o **(DIC)**



(DIB)



(DIC)

en donde

Y es -N(R^n)-, -N(R^n)C(O)-, -N(R^n)C(O)(C$R^s R^t$)$_v$N(R^n)C(O)-, -O-, y -S(O)$_a$-, en donde a es 0-2, v es 1-2, R^s y R^t se seleccionan

140

independientemente de hidrógeno o C_{1-4}alquilo sustituido de manera opcional por R^{26} y R^n es hidrógeno o C_{1-4}alquilo,

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

R^{13} y R^{14} se seleccionan independientemente de hidrogeno, C_{1-4}alquilo, carbociclilo o heterociclilo, y cuando q es 0, R^{14} puede seleccionarse adicionalmente de hidroxi, en donde R^{13} y R^{14} pueden sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{20},

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

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

q es 0-1,

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

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

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

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

R^{16}, R^{17} y R^{18} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N*,*N*-(C_{1-4}alquil)$_2$amino, C_{1-4}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N*,*N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}

141

$_4$alquil)sulfamoilo y *N*,*N*-(C_{1-4}alquil)$_2$sulfamoilo, en donde R^{16}, R^{17} y R^{18} pueden sustituirse independientemente de manera opcional por uno o mas R^{21},

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

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

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

R^{25} se selecciona de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo,

o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

Un inhibidor IBAT particular se selecciona de uno cualquiera de Ejemplos 1-39 de WO 03/022286, o su sal farmaceuticamente aceptable,

142

solvato, solvato de tal sal o profármaco, y los compuestos de Ejemplos 1-39 se incorporan aquí por referencia Las reivindicaciones 1-10 de WO 03/022286 se incorporan también aquí por referencia Un inhibidor IBAT particular seleccionado de WO 03/022286 se selecciona de uno cualquiera de

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxi-2-metiltio)etil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxi-2-(R)-hidroxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxi-2-metilpropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxibutil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,

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

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

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxi-2-(R)-hidroxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(2-sulfoetil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3 4,5-tetrahidro-1,2,5-benzotiadiazepina,

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

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

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-{(S)-1-[*N*-((S)-2-hidroxi-1-carboxietil)carbamoil]propil}carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,

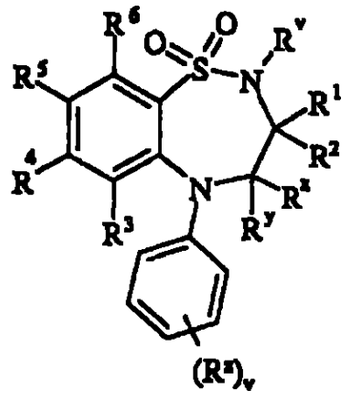
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxi-2-metilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina, y

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-((R)-α-carboxi-4-hidroxibencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,

o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

Otros compuestos apropiados que poseen actividad inhibidora IBAT tienen la siguiente estructura de fórmula (EI)



(EI)

en donde

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

Uno de R^1 y R^2 se seleccionan de hidrogeno o C_{1-6}alquil y el otro se selecciona de C_{1-6}alquilo,

R^x y R^y se seleccionan independientemente de hidrógeno, hidroxi, amino, mercapto, C_{1-6}alquilo, C_{1-6}alcoxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-}

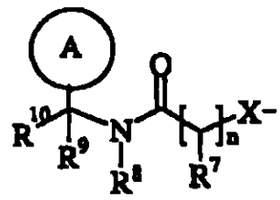
144

$_6$alquil)$_2$amino, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2,

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

v es 0-5,

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



(EIA)

R^3 y R^6 y el otro de R^4 y R^5 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo y *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, en donde R^3 y R^6 y el otro de R^4 y R^5 puede sustituirse de manera opcional en carbono por uno o mas R^{17},

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

Anillo A es arilo o heteroarilo, en donde Anillo A se sustituye de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{18},

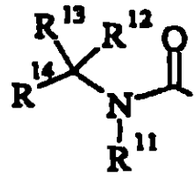
R^7 es hidrógeno, C_{1-6}alquilo, carbociclilo o heterociclilo, en donde R^7 se sustituye de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{19}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo

seleccionado de R^{20},

R^8 es hidrogeno o C_{1-6}alquilo,

R^9 es hidrógeno o C_{1-6}alquilo,

R^{10} es hidrógeno, halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, $C_{1\ 10}$alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, $C_{1\ 10}$alcanoiloxi, *N*-($C_{1\ 10}$alquil)amino, *N*,*N*-(C_{1-10}alquil)$_2$amino, *N*,*N*,*N*-(C_{1-10}alquil)$_3$ammonio, $C_{1\ 10}$alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilamino, C_{1-10}alcoxicarbonilamino, carbociclilo, carbociclil$C_{1\ 10}$alquilo, heterociclilo, heterociclil$C_{1\ 10}$alquilo, carbociclil-(C_{1-10}alquilen)$_p$-R^{21}-(C_{1-10}alquilen)$_q$- o heterociclil-($C_{1\ 10}$alquilen)$_r$-R^{22}-(C_{1-10}alquilen)$_s$-, en donde R^{10} se sustituye de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{23}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{24}, ó R^{10} es un grupo de formula (EIB)



(EIB)

en donde

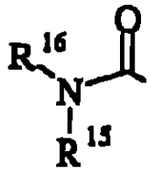
R^{11} es hidrógeno o C_{1-6}alquilo,

R^{12} y R^{13} se seleccionan independientemente de hidrógeno, halo, carbamoilo, sulfamoilo, C_{1-10}alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, $C_{1\ 10}$alcanoilo, *N*-($C_{1\ 10}$alky])carbamoilo, *N*,*N*-($C_{1\ 10}$alquil)$_2$carbamoilo, $C_{1\ 10}$alquilS(O)$_a$ en donde a es 0 a 2, *N*-($C_{1\ 10}$alquil)sulfamoilo, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilamino, carbociclilo o heterociclilo, en donde R^{12} y R^{13} pueden sustituirse independientemente de manera opcional por uno o mas

146

sustituyentes seleccionados de R^{25}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{26},

R^{14} se selecciona de hidrogeno halo, carbamoilo, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, $C_{2\ 10}$alquinilo, $C_{1\ 10}$alcanoilo, *N*-(C_{1-10}alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, $C_{1\ 10}$alquilS(O)$_a$ en donde a es 0 a 2, *N*-($C_{1\ 10}$alquil)sulfamoilo, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N*,*N*-($C_{1\ 10}$alquil)$_2$sulfamoilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_p$-R^{27}-($C_{1\ 10}$alquilen)$_q$- o heterociclil-(C_{1-10}alquilen)$_r$-R^{28}-(C_{1-10}alquilen)$_s$-, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{29}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{30}, ó R^{14} es un grupo de fórmula (EIC)



(EIC)

R^{15} es hidrogeno o C_{1-6}alquilo,

R^{16} es hidrógeno o C_{1-6}alquilo, en donde R^{16} puede sustituirse de manera opcional en carbono por uno o más grupos seleccionados de R^{31},

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

R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} o R^{31} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, $C_{2\ 10}$alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-($C_{1\ 10}$alquil)amino, *N*,*N*-(C_{1-10}alquil)$_2$amino, *N*,*N*,*N*-($C_{1\ 10}$alquil)$_3$ammonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-

147

$(C_{1-10}$alquil)sulfamoilamino, *N,N*-$(C_{1-10}$alquil$)_2$sulfamoilamino, C_{1-10}alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-$(C_{1-10}$alquilen$)_p$-R^{32}-$(C_{1-10}$alquilen$)_q$- o heterociclil-$(C_{1-10}$alquilen$)_r$-R^{33}-$(C_{1-10}$alquilen$)_s$-, en donde R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29} o R^{31} pueden sustituirse independientemente de manera opcional por uno o más R^{34}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{35},

R^{21}, R^{22}, R^{27}, R^{28}, R^{32} o R^{33} se seleccionan independientemente de -O-, -NR^{36}-, -$S(O)_x$-, -$NR^{36}C(O)NR^{36}$-, -$NR^{36}C(S)NR^{36}$-, -OC(O)N=C-, -$NR^{36}C(O)$- o -$C(O)NR^{36}$-, en donde R^{36} se selecciona de hidrogeno o C_{1-6}alquilo, y x es 0-2,

p, q, r y s se seleccionan independientemente de 0-2,

R^{34} se selecciona de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, *N*-metilcarbamoilo, *N,N*-dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, *N*-metilsulfamoilo, *N,N*-dimetilsulfamoilo, *N*-metilsulfamoilamino y *N,N*-dimetilsulfamoilamino,

R^{20}, R^{24}, R^{26}, R^{30} ó R^{35} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-$(C_{1-6}$alquil)carbamoilo, *N,N*-$(C_{1-6}$alquil)carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

Inhibidores IBAT apropiados que tienen la anterior estructura se seleccionan de uno cualquiera de

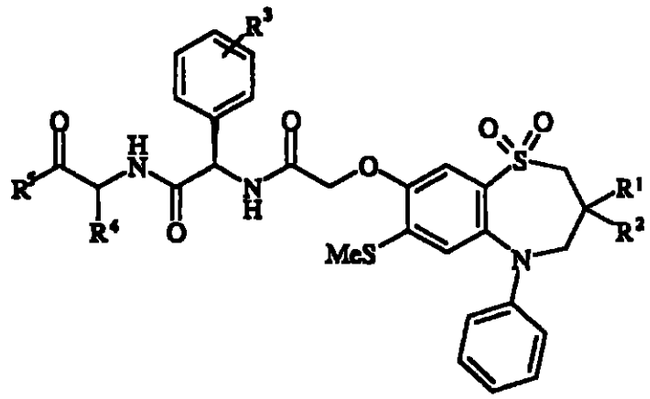
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,

1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]-4-hidroxibencil}

148

carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-[*N*-((R/S)-α-{*N*-[1-(R)-2-(S)-1-hidroxi-1-(3,4-dihidroxifenil)prop-2-il]carbamoil}bencil) carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina (los dos enantiómeros),
1,1-Dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{*N*-[(R)-α-(*N*-{2-(S)-[*N*-(carbamoilmetil)carbamoil]pirrolidin-1-ilcarbonilmetil}carbamoil) bencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,
1,1 -Dioxo-3,3 -dibutil-5-fenil-7-metiltio-8-[N-((R)-α-{*N*-[2-(3,4,5-trihidroxifenil)etil]carbamoil}bencil)carbamoilmetoxi]-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina, o
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N*-(2-(R)-3-(S)-4-(S)-5-(R)-3,4,5,6-tetrahidroxitetrahidropiran-2-ilmetil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina,
o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Otros compuestos apropiados que poseen actividad inhibidora IBAT tienen la siguiente estructura de fórmula (FI)



(FI)

en donde

R^1 y R^2 se seleccionan independientemente de C_{1-4}alquilo,

R^3 es hidrógeno, hidroxi o halo,

R^4 es C_{1-4}alquil sustituido de manera opcional por hidroxi, metoxi y

metilS(O)$_a$ en donde a es 0-2

R^5 es hidroxi o HOC(O)CH(R^6)NH-,

R^6 se selecciona de hidrogeno y C_{1-3}alquilo sustituido de manera opcional por hidroxi, metoxi y metilS(O)$_a$ en donde a es 0-2,

o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco, con la salvedad que cuando R^1 y R^2 son ambos butilo, R^5 es hidroxi y R^4 es metiltiometilo, metilsulfinilmetilo, metiltiometilo, hidroximetilo, metoximetilo, R^3 no es hidrógeno, y con la salvedad que cuando R^1 y R^2 son ambos butilo, R^5 es HOC(O)CH(R^6)NH-, R^6 es hidroximetilo y R^4 es hidroximetilo, R^3 no es hidrogeno

Inhibidores IBAT apropiados que tienen la anterior estructura se seleccionan de uno cualquiera de

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxietil) carbamoil]bencil]}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxibutil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metilbutil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-metilbutil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-hidroxipropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-

mesiletil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-metilsulfonilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-mesilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxietil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxibutil) carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((S)-1-carboxi-2-metilpropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metilbutil)carbamoil]-4-hidroxibencil} carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

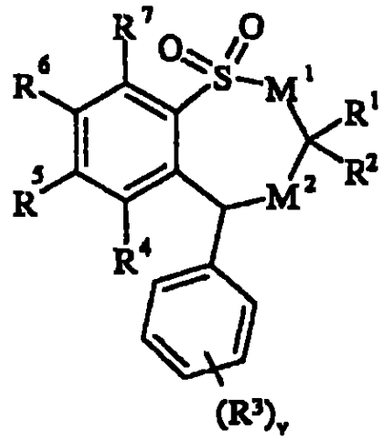
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-metilbutil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-hidroxietil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-hidroxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metiltioetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metilsulfiniletil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-mesiletil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-2-metoxietil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-metiltiopropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((S)-1-carboxi-3-metilsulfonilpropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxi-3-mesilpropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxipropil)carbamoil]-4-hidroxibenzil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina, o
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina,
o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Otros inhibidores IBAT apropiados son los que tienen la estructura (GI)



(GI)

en donde

M^1 es $-CH_2-$ ó $-NR^{21}-$,

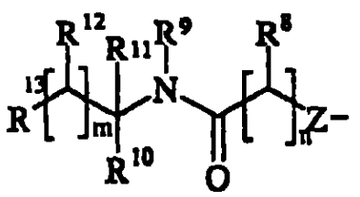
M^2 es $-CR^{22}R^{23}-$ ó $-NR^{24}-$, con la condicion que si M^1 es $-NR^{21}-$, M^2 es $-CR^{22}R^{23}-$,

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

R^3 se selecciona de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo y *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo,

v es 0-5,

uno de R^5 y R^6 es un grupo de fórmula (GIA)



(GIA)

R^4 y R^7 y el otro de R^5 y R^6 se seleccionan independientemente de hidrogeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi,

C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N,N*-(C_{1-4}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N,N*-(C_{1-4}alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-4}alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N,N*-(C_{1-4}alquil)$_2$sulfamoilo, en donde R^4 y R^7 y el otro de R^5 y R^6 puede sustituirse de manera opcional en carbono por uno o más R^{25},

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

R^8 es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo, en donde R^8 puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{26}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{27},

R^9 es hidrógeno o C_{1-4}alquilo,

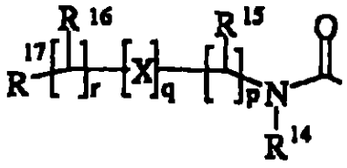
R^{10} y R^{11} se seleccionan independientemente de hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo, o R^{10} y R^{11} forman conjuntamente C_{2-6}alquileno, en donde R^{10} y R^{11} ó R^{10} y R^{11} conjuntamente pueden sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{28}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrógeno puede sustituirse de manera opcional por uno o más R^{29},

R^{12} es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo, en donde R^{12} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{30}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrógeno puede sustituirse de manera opcional por uno o más R^{31},

R^{13} es hidrógeno, halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, $C_{1\ 10}$alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcoxicarbonilo, C_{1-10}alcanoilo, $C_{1\ 10}$alcanoiloxi, *N*-($C_{1\ 10}$alquil)amino, *N,N*-($C_{1\ 10}$alquil)$_2$amino, *N,N,N*-($C_{1\ 10}$alquil)$_3$ammonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N,N*-($C_{1\ 10}$alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1}

154

$_{10}$alquil)sulfamoilo, *N,N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-(C_1 $_{10}$alquil)sulfamoilamino, *N,N*-(C_1 $_{10}$alquil)$_2$sulfamoilamino, C_1 $_{10}$alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, un grupo heterociclico, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_e$-R^{32}-(C_{1-10}alquilen)$_f$ o heterociclil-(C_1 $_{10}$alquilen)$_g$-R^{33}-(C_{1-10}alquilen)$_h$-, en donde R^{13} puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{36}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{37}, ó R^{13} es un grupo de fórmula (GIB)



(GIB)

en donde

X es -N(R^{38})-, -N(R^{38})C(O)-, -O-, y -S(O)$_a$-, en donde a es 0-2 y R^{38} es hidrógeno o C_{1-4}alquilo,

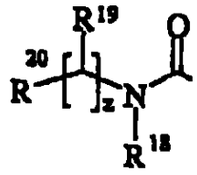
R^{14} es hidrógeno o C_{1-4}alquilo,

R^{15} y R^{16} se seleccionan independientemente de hidrogeno, halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_1 $_6$alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_1 $_6$alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, carbociclilo o grupo heterociclico, en donde R^{15} y R^{16} pueden sustituirse independientemente de manera opcional por uno o más sustituyentes seleccionados de R^{41}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{42},

R^{17} se selecciona de hidrogeno halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-

155

$(C_{1\ 10}alquil)amino$, N,N-$(C_{1-10}alquil)_2amino$, $C_{1-10}alcanoilamino$, N-$(C_{1-10}alquil)carbamoilo$, $C_{1-10}alcoxicarbonilo$, N,N-$(C_{1\ 10}alquil)_2carbamoilo$, $C_{1\ 10}alquilS(O)_a$ en donde a es 0 a 2, N-$(C_{1-10}alquil)sulfamoilo$, N,N-$(C_{1-10}alquil)_2sulfamoilo$, N-$(C_{1-10}alquil)sulfamoilamino$, N,N-$(C_{1\ 10}alquil)_2sulfamoilamino$, carbociclilo, carbociclil$C_{1-10}alquilo$, un grupo heterocíclico, heterociclil$C_{1\ 10}alquilo$, carbociclil-$(C_{1\ 10}alquilen)_e$-R^{43}-$(C_{1\ 10}alquilen)_f$ o heterociclil-$(C_{1-10}alquilen)_g$-R^{44}-$(C_{1-10}alquilen)_h$-, en donde R^{17} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{47}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{48}, ó R^{17} es un grupo de fórmula (GIC)



(GIC)

en donde

R^{18} se selecciona de hidrógeno o $C_{1-4}alquilo$,

R^{19} se selecciona de hidrógeno halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, $C_{1-6}alquilo$, $C_{2-6}alquenilo$, $C_{2-6}alquinilo$, $C_{1-6}alcoxi$, $C_{1-6}alcanoilo$, $C_{1-6}alcanoiloxi$, N-$(C_{1-6}alquil)amino$, N,N-$(C_{1\ 6}alquil)_2amino$, $C_{1-6}alcanoilamino$, N-$(C_{1-6}alquil)carbamoilo$, N,N-$(C_{1-6}alquil)_2carbamoilo$, $C_{1-6}alquilS(O)_a$ en donde a es 0 a 2, $C_{1\ 6}alcoxicarbonilo$, N-$(C_{1-6}alquil)sulfamoilo$, N,N-$(C_{1-6}alquil)_2sulfamoilo$, carbociclilo o un grupo heterocíclico, donde R^{19} pueden sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{51}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{52},

R^{20} se selecciona de halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, $C_{1\ 10}alquilo$, $C_{2-10}alquenilo$, $C_{2\ 10}alquinilo$, $C_{1-10}alcoxi$, $C_{1-10}alcoxicarbonilo$, $C_{1-10}alcanoilo$, C_{1-}

156

$_{10}$alcanoiloxi, *N*-(C_{1-10}alquil)amino, *N,N*-($C_{1\ 10}$alquil)$_2$amino, *N,N,N*-(C_{1-10}alquil)$_3$ammonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N,N*-($C_{1\ 10}$alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N,N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-($C_{1\ 10}$alquil)sulfamoilamino, *N,N*-(C_{1-10}alquil)$_2$sulfamoilamino, $C_{1\ 10}$alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, un grupo heterociclico, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_e$-R^{53}-($C_{1\ 10}$alquilen)$_f$- o heterociclil-(C_{1-10}alquilen)$_g$-R^{54}-(C_{1-10}alquilen)$_h$-, en donde R^{20} pueden sustituirse independientemente de manera opcional por uno o más R^{57}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{58},

p es 1-3, en donde los valores de R^{15} pueden ser los mismos o diferentes,

q es 0-1,

r es 0-3, en donde los valores de R^{16} pueden ser los mismos o diferentes,

m es 0-2, en donde los valores de R^{12} pueden ser los mismos o diferentes,

n es 1-2, en donde los valores de R^{8} pueden ser los mismos o diferentes,

z es 0-3, en donde los valores de R^{19} pueden ser los mismos o diferentes,

R^{21} se selecciona de hidrógeno o C_{1-6}alquilo,

R^{22} y R^{23} se seleccionan independientemente de hidrogeno, hidroxi, amino, mercapto, C_{1-6}alquilo, C_{1-6}alcoxi, *N*-(C_{1-6}alquil)amino, *N,N*-($C_{1\ 6}$alquil)$_2$amino, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2,

R^{24} se selecciona de hidrógeno hidroxi, C_{1-6}alquilo, C_{1-4}alcoxi y $C_{1\ 6}$alcanoiloxi,

R^{25} se selecciona de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, *N*-(C_{1-4}alquil)amino, *N,N*-(C_{1}

157

$_4$alquil)$_2$amino, C_{1-4}alcanoilamino, *N*-(C_{1-4}alquil)carbamoilo, *N,N*-(C_1 $_4$alquil)$_2$carbamoilo, C_{1-4}alquilS(O)$_a$ en donde a es 0 a 2, C_1-$_4$alcoxicarbonilo, *N*-(C_{1-4}alquil)sulfamoilo y *N,N*-(C_{1-4}alquil)$_2$sulfamoilo, en donde R^{25}, pueden sustituirse independientemente de manera opcional por uno o más R^{67},

R^{26}, R^{28}, R^{30}, R^{36}, R^{41}, R^{47}, R^{51} y R^{57} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, $C_{1\ 10}$alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, C_1-$_{10}$alcoxicarbonilo, *N*-($C_{1\ 10}$alquil)amino, *N,N*-($C_{1\ 10}$alquil)$_2$amino, *N,N,N*-(C_1 $_{10}$alquil)$_3$ammonio, C_{1-10}alcanoilamino, *N*-($C_{1\ 10}$alquil)carbamoilo, *N,N*-(C_1 $_{10}$alquil)$_2$carbamoilo, $C_{1\ 10}$alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_1 $_{10}$alquil)sulfamoilo, *N,N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-(C_1-$_{10}$alquil)sulfamoilamino, *N,N*-(C_{1-10}alquil)$_2$sulfamoilamino, C_1-$_{10}$alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, un grupo heterociclico, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_e$-R^{59}-(C_1 $_{10}$alquilen)$_f$- o heterociclil-($C_{1\ 10}$alquilen)$_g$-R^{60}-(C_{1-10}alquilen)$_h$-, en donde R^{26}, R^{28}, R^{30}, R^{36}, R^{41}, R^{47}, R^{51} y R^{57} pueden sustituirse independientemente de manera opcional por uno o más R^{63}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{64},

R^{27}, R^{29}, R^{31}, R^{37}, R^{42}, R^{48}, R^{48}, R^{58} y R^{64} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, sulfamoilo, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_1-$_6$alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_1-$_6$alquil)$_2$carbamoilo, bencilo, fenetilo, benzoilo, fenilsulfonilo y fenilo,

R^{32}, R^{33}, R^{43}, R^{44}, R^{53}, R^{54}, R^{59} y R^{60} se seleccionan independientemente de -O-, -NR^{65}-, -$S(O)_x$-, -$NR^{65}C(O)NR^{66}$-, -$NR^{65}C(S)NR^{66}$-, -OC(O)N=C-, -$NH^{65}C(O)$- ó -$C(O)NR^{65}$-, en donde R^{65} y R^{66} se seleccionan independientemente de hidrogeno o C_{1-6}alquilo, y x es 0-2,

R^{63} y R^{67} se seleccionan independientemente de halo, hidroxi, ciano,

158

carbamoilo, ureido, amino, nitro, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxicarbonilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, *N*-metilcarbamoilo, *N,N*-dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, *N*-metilsulfamoilo y *N,N*-dimetilsulfamoilo, y

e, f, g y h se seleccionan independientemente de 0-2,

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Mas inhibidores IBAT apropiados que tienen la anterior estructura se seleccionan de uno cualquiera de

(+/-)-trans-1,1-dioxo-3-etil-3-butil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil) carbamoil]bencil]}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina,

(+/-)-trans-1,1-dioxo-3-etil-3-butil-5-fenil-7-metiltio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil) carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,4-benzotiazepina,

1,1-dioxo-3-etil-3-butil-4-hidroxi-5-fenil-7-(*N*-{α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]-2-fluorobencil}carbamoilmetiltio)-2,3,4,5-tetrahidrobenzotiapina, o

1,1-dioxo-3-butil-3-etil-4-hidroxi-5-fenil-7-(*N*-{1-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]-1-(ciclohexil) metil}carbamoilmetiltio)-2,3,4,5-tetrahidrobenzotiepina.

Compuestos de formula **(AI), (BI), (CI), (DI), (EI), (FI)** y **(GI)** o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco pueden prepararse por procesos conocidos en el arte

En un aspecto particular de la invencion un inhibidor IBAT o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco es un inhibidor IBAT o su sal farmacéuticamente aceptable

Por lo tanto en una caracteristica adicional de la invencion, se provee una combinación de un compuesto de formula **(I)**, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco y un

159

inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

Por lo tanto, en una característica adicional de la invención, se provee un metodo para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en administración simultánea, consecutiva o separada con una cantidad eficaz de un inhibidor IBAT, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

De acuerdo con un aspecto adicional de la invencion se provee una composicion farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, y un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptables

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor IBAT, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco

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

a) un compuesto de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una primera presentación farmaceutica unitaria,

b) un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una segunda presentacion farmaceutica unitaria, y

c) medios de envase para contener dichas presentaciones farmaceuticas primera y segunda.

De acuerdo con un aspecto adicional de la presente invencion se

160

provee un estuche que comprende

a) un compuesto de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, junto con un diluyente o vehiculo farmacéuticamente aceptables, en una primera presentación farmacéutica unitaria,

b) un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una segunda presentación farmacéutica unitaria, y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un inhibidor IBAT, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso e la producción de un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre

De acuerdo con un aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad eficaz de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables, con la administración simultánea, consecutiva o separada de una cantidad eficaz de un inhibidor IBAT, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehiculo farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento terapeutico,

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, pueden administrarse en asociación con un agonista PPAR alfa y/o gamma, o sus sales farmaceuticamente aceptables, solvatos, solvatos de tales sales o profarmacos Agonistas PPAR alfa y/o gamma apropiados, sus sales

161

farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos son bien conocidos en el arte Estos incluyen los compuestos descritos en WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (en particular los compuestos descritos en las solicitudes de patente enumeradas en la página 634) y J Med Chem, 2000, 43, 527, que se incorporan todos aqui por referencia. Particularmente un agonista PPAR alfa y/o gamma se refiere a WY-14643, clofibrato, fenofibrato, bezafibrato, GW 9578, troglitazona, pioglitazona, rosiglitazona, eglitazona, proglitazona, NN622/Ragaglitazar, BMS 298585, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 y GW 2433 Particularmente un agonista PPAR alfa y/o gamma se refiere a ácido (S)-2-etoxi-3-[4-(2-{4-metanosulfoniloxifenil}etoxi)fenil]propanoico y sus sales farmacéuticamente aceptables

Por lo tanto, en una característica adicional de la invencion, se provee una combinación de un compuesto de fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco y un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Por lo tanto, en una característica adicional de la invencion, se provee un metodo para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de un compuesto de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en administración simultánea, consecutiva o separada con una cantidad eficaz de un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

De acuerdo con un aspecto adicional de la invencion se provee una composición farmaceutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, y un agonista PPAR alfa y/o gamma, o su sal

farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptables

De acuerdo con un aspecto adicional de la presente invencion se provee un estuche que comprende un compuesto de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, y un agonista PPAR alfa y/o gamma, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende

a) un compuesto de fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, en una primera presentación farmaceutica unitaria,

b) un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una segunda presentación farmacéutica unitaria, y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda

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

a) un compuesto de fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, junto con un diluyente o vehiculo farmacéuticamente aceptables, en una primera presentacion farmacéutica unitaria,

b) un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en una segunda presentación farmaceutica unitaria, y

c) medios de envase para contener dichas presentaciones farmacéuticas primera y segunda

De acuerdo con otra caracteristica de la invención se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un agonista PPAR alfa y/o gamma, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en producir un

efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre

De acuerdo con un aspecto adicional de la presente invencion se provee un tratamiento de combinación que comprende la administracion de una cantidad eficaz de un compuesto de la formula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco, de manera opcional conjuntamente con un diluyente o vehiculo farmacéuticamente aceptables, con la administracion simultánea, consecutiva o separada de una cantidad eficaz de un agonista PPAR alfa y/o gamma, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, de manera opcional conjuntamente con un diluyente o vehiculo farmaceuticamente aceptables a un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento terapéutico

En otro aspecto de la invención, el compuesto de formula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco, pueden administrarse en asociacion con un derivado de ácido nicotinico o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco Tal como se usa aquí "derivado de acido nicotinico" significa compuestos que comprenden una estructura piridin-3-carboxilato o una estructura pirazin-2-carboxilato Ejemplos de derivados de ácido nicotinico incluyen ácido nicotinico, niceritrol, nicofuranose, NIASPAN® y acipimox

Por lo tanto, en una caracteristica adicional de la invencion, se provee una combinación de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco y un derivado de ácido nicotinico o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

Por lo tanto, en una caracteristica adicional de la invención, se provee un método para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en administración simultanea, consecutiva o separada con

una cantidad eficaz de un derivado de ácido nicotinico, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

De acuerdo con un aspecto adicional de la invención se provee una composicion farmaceutica que comprende un compuesto de formula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, y un derivado de ácido nicotínico, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehiculo farmacéuticamente aceptables

De acuerdo con otra caracteristica de la invencion se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un derivado de ácido nicotinico, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en la produccion de un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre

En otro aspecto de la invención, el compuesto de formula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, pueden administrarse en asociación con un secuestrante de ácido biliar o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco Secuestrantes apropiados de ácidos biliares incluyen colestiramina, colestipol y clorhidrato de colesevelam

Por lo tanto, en una característica adicional de la invención, se provee una combinación de un compuesto de formula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco y un secuestrante de acido biliar o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

Por lo tanto, en una caracteristica adicional de la invención, se provee un metodo para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco en administracion simultánea, consecutiva o separada con

una cantidad eficaz de un secuestrante de ácido biliar, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un secuestrante de ácido biliar, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociacion con un diluyente o vehiculo farmaceuticamente aceptables

De acuerdo con otra caracteristica de la invencion se provee el uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un secuestrante de acido biliar, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, en la manufactura de un medicamento para uso en la produccion de un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre

De acuerdo con otro aspecto adicional de la presente invencion se provee un tratamiento de combinación que comprende la administración de una cantidad eficaz de un compuesto de la formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, de manera opcional conjuntamente con un diluyente o vehiculo farmacéuticamente aceptables, con la administración simultánea, consecutiva o separada de uno o mas de los siguientes agentes seleccionados del grupo X

- un compuesto antihipertensor (por ejemplo altiazida, benztiazida, captopril, carvedilol, clorotiazida sódica, clorhidrato de clonidina, ciclotiazida, delapril clorhidrato, dilevalol clorhidrato, doxazosina mesilato, fosinopril sódico, clorhidrato de guanfacina, metildopa, metoprolol succinato, moexipril clorhidrato, monatepil maleato, clorhidrato de pelanserina, clorhidrato de fenoxibenzemina, clorhidrato de prazosina, primidolol, quinapril clorhidrato, quinaprilat, ramipril, clorhidrato de terazosina, candesartán, candesartán cilexetil, telmisartán, bisalato de amlodipina, maleato de

amlodipina y bevantolol clorhidrato),

- un inhibidor de la enzima de conversión de angiotensina (por ejemplo alacepril, alatriopril, altiopril cálcico, ancovenina, benazepril, benazepril clorhidrato, benazeprilat, benzoilcaptopril, captopril, captopril-cisteina, captopril-glutation, ceranapril, ceranopril, ceranapril, cilazapril, cilazaprilat, delapril, delapril-diacido, enalapril, enalaprilat, enapril, epicaptopril, foroximitina, fosfenopril, fosenopril, fosenopril sodico, fosinopril, fosinopril sódico, fosinoprilat, ácido fosinoprílico, glicopril, hemorfin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, liciumina A, liciumina B, mixanpril, moexipril, moexiprilat, moveltipril, muraceina A, muraceína B, muraceína C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril clorhidrato, quinaprilat, ramipril, ramiprilat, spirapril, spirapril clorhidrato, spiraprilat, spiropril, spiropril clorhidrato, temocapril, temocapril clorhidrato, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril y zofenoprilat),
- un antagonista de receptor de angiotensina II (por ejemplo candesartán, candesartán cilexetil, losartán, valsartán, irbesartan, tasosartán, telmisartan y eprosartán),
- un bloqueador andrenergico (por ejemplo bretilio tosilato, dihidroergotamina mesilato, fentolamina mesilato, solipertina tartrato, clorhidrato de zolertina, carvedilol o labetalol clorhidrato), un bloqueador alfa andrenérgica (por ejemplo fenspiride clorhidrato, labetalol clorhidrato, proroxan y alfuzosin clorhidrato), un bloqueador beta andrenérgico (por ejemplo acebutolol, acebutolol clorhidrato, alprenolol clorhidrato, atenolol, bunolol clorhidrato, carteolol clorhidrato, celiprolol clorhidrato, cetamolol clorhidrato, cicloprolol clorhidrato, dexpropranolol clorhidrato, diacetolol clorhidrato, dilevalol clorhidrato, esmolol clorhidrato, exaprolol clorhidrato, flestolol sulfato, labetalol clorhidrato, levobetaxolol clorhidrato, levobunolol clorhidrato, metalol clorhidrato, metoprolol,

metoprolol tartrato, nadolol, pamatolol sulfato, penbutolol sulfato, practolol, propranolol clorhidrato, sotalol clorhidrato, timolol, timolol maleato, tiprenolol clorhidrato, tolamolol, bisoprolol, bisoprolol fumarato y nebivolol), o un bloqueador adrenergico alfa/beta mixto,

- un estimulante andrenérgico (por ejemplo un producto de combinacion de clorotiazida y metildopa, el producto de combinación de metildopa hidroclorotiazida y metildopa, clonidina clorhidrato, clonidina, el producto de combinación de clortalidona y clonidina clorhidrato y guanfacina clorhidrato),
- bloqueador de canal, por ejemplo un bloqueador de canales de calcio (por ejemplo clentiazem maleato, amlodipina besilato, isradipina, nimodipina, felodipina, nilvadipina, nifedipina, teludipina clorhidrato, diltiazem clorhidrato, belfosdil, verapamil clorhidrato o fostedil),
- un diuretico (por ejemplo el producto de combinación de hidroclorotiazida y espironolactona y el producto de combinacion de hidroclorotiazida y triamterene),
- agentes antianginales (por ejemplo amlodipina besilato, amlodipina maleato, betaxolol clorhidrato, bevantolol clorhidrato, butoprozina clorhidrato, carvedilol, cinepazet maleato, metoprolol succinato, molsidomine, monatepil maleato, primidolol, ranolazina clorhidrato, tosifeno o verapamil clorhidrato),
- vasodilatadores por ejemplo vasodilatadores coronarios (por ejemplo fostedil, azaclorzina clorhidrato, cromonar clorhidrato, clonitrato, diltiazem clorhidrato, dipiridamol, droprenilamina, eritritil tetranitrato, isosorbida dinitrato, isosorbida mononitrato, lidoflazina, mioflazina clorhidrato, mixidina, molsidomina, nicorandil, nifedipina, nisoldipina, nitroglicerina, oxprenolol clorhidrato, pentrinitrol, perhexilina maleato, prenilamina, propatil nitrato, terodilina clorhidrato, tolamolol y verapamil),
- anti-coagulantes (seleccionados de argatroban, bivalirudina, dalteparina sódica, desirudina, dicumarol, Iyapolato sódico,

nafamostat mesilato, fenprocoumon, tinzaparina sódica y warfarina sódica),

- agentes antitrombóticos (por ejemplo anagrelide clorhidrato, bivalirudina, cilostazol, dalteparina sódica, danaparoid sodico, dazoxiben clorhidrato, efegatran sulfato, enoxaparina sodica, fluretofen, ifetroban, ifetroban sódico, lamifiban, lotrafiban clorhidrato, napsagatran, orbofiban acetato, roxifiban acetato, sibrafiban, tinzaparina sódica, trifenagrel, abciximab y zolimomab aritox),
- antagonistas de receptor de fibrinógeno (por ejemplo roxifiban acetato, fradafiban, orbofiban, lotrafiban clorhidrato, tirofiban, xemilofiban, anticuerpo monoclonal 7E3 y sibrafiban)
- inhibidores plaquetarios (por ejemplo cilostezol, clopidogrel bisulfato, epoprostenol, epoprostenol sódico, ticlopidina clorhidrato, aspirina, ibuprofeno, naproxeno, sulindae, indometacina, mefenamato, droxicam, diclofenac, sulfinpirazona y piroxicam, dipiridamol),
- inhibidores de agregación plaquetaria (por ejemplo acadesine, beraprost, beraprost sódico, ciprostene cálcico, itezigrel, lifarizina, lotrafiban clorhidrato, orbofiban acetato, oxagrelate, fradafiban, orbofiban, tirofiban y xemilofiban)
- agentes hemorreológicos (por ejemplo pentoxifilina),
- inhibidores de coagulacion asociada con lipoproteina,
- inhibidores de Factor VIIa,
- inhibidores de Factor Xa,
- heparinas de bajo peso molecular (por ejemplo enoxaparina, nardroparina, dalteparina, certroparina, parnaparina, reviparina y tinzaparina),
- inhibidores de escualeno sintasa,
- inhibidores de escualeno epoxidasa,
- agonistas de receptor hepático X (LXR) por ejemplo GW-3965 y los descritos en WO00224632, WO00103705, WO02090375 y

WO00054759 (reivindicación 1 y los ejemplos mencionados de estas cuatro aplicaciones se incorporan aqui por referencia),

- inhibidores de proteína de transporte de triglicerídos microsomales por ejemplo implitapide y los descritos en WO03004020, WO03002533, WO02083658 y WO 00242291 (reivindicación 1 y los ejemplos mencionados de estas cuatro solicitudes se incorporan aqui por referencia),

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptables a un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento terapeutico

Por lo tanto, en una caracteristica adicional de la invencion, se provee una combinación de un compuesto de fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco, y un compuesto del Grupo X o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

Por lo tanto, en una característica adicional de la invención, se provee un método para producir un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco en administración simultánea, consecutiva o separada con una cantidad eficaz de un compuesto de Grupo X, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

De acuerdo con un aspecto adicional de la invención se provee una composición farmaceutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, y un compuesto de Grupo X, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptables

De acuerdo con otra caracteristica de la invención se provee el uso de un compuesto de la formula (I), o su sal farmacéuticamente aceptable,

170

solvato, solvato de tal sal o profármaco, y un compuesto de Grupo X, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en la producción de un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre

Además de su uso en la medicina terapeutica, los compuestos de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, son también útiles como herramientas farmacologicas en el desarrollo y estandarizacion de sistemas de análisis *in vitro* e *in vivo* para la evaluacion de los efectos de inhibidores de la absorcion del colesterol en animales de laboratorio tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la investigación de nuevos agentes terapéuticos

Muchos de los intermedios descritos aqui son novedosos y, por consiguiente, se proveen como una característica más de la invención Por ejemplo compuestos de formula (IV) muestran actividad inhibidora de absorción de colesterol cuando evaluan en el ensayo de prueba *in vitro* referenciado más arriba y, por lo tanto, se reivindican como una caracteristica adicional de la invención

Por consiguiente, en una caracteristica más de la invencion, se provee un compuesto de fórmula (IV), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

Por lo tanto de acuerdo con un aspecto adicional de la invencion se provee una composición farmaceutica que comprende un compuesto de fórmula (IV), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define mas arriba en el texto en asociación con un diluyente o vehículo farmacéuticamente aceptables

De acuerdo con un aspecto adicional de la presente invención se provee un compuesto de la fórmula (IV), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, como se define mas arriba en el texto para uso en un metodo de tratamiento profilactico o terapeutico de un animal de sangre caliente, tal como el hombre

Así, de acuerdo con este aspecto de la invencion se provee un

compuesto de la fórmula (IV), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco, como se define mas arriba en el texto para uso como un medicamento

De acuerdo con otra característica de la invencion se provee el uso de un compuesto de la fórmula (IV), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define mas arriba en el texto, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula (IV), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, como se define más arriba en el texto, en la manufactura de un medicamento para uso en el tratamiento de afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para producir un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (IV), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

De acuerdo con una característica adicional de este aspecto de la invención se provee un método de tratar afecciones hiperlipidemicas en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (IV), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

En la otra composicion farmacéutica ya mencionada, se aplican asimismo las caracteristicas proceso, metodo, uso y manufactura de medicamento, las incorporaciones alternativas y preferidas de los compuestos de la invencion descritos aqui

172

Ejemplos

La invencion se ilustrara ahora en los siguientes ejemplos no limitantes, en los cuales pueden utilizarse tecnicas estándar conocidas por el quimico experto, y tecnicas análogas a las descritas en estos ejemplos, donde se consideren apropiadas, y en las cuales, a menos que se afirme lo contrario

(i) las evaporaciones se llevaron a cabo por evaporacion rotatoria *in vacuo* y los procedimientos de preparación se realizaron luego del retiro de los solidos residuales tales como agentes de secamiento por filtracion,

(ii) todas las reacciones se llevaron a cabo bajo una atmosfera inerte a temperatura ambiente, típicamente en el rango de 18-25°C, con solventes de grado HPLC bajo condiciones anhidras, a menos que se indique lo contrario,

(iii) cromatografía de columna (por los procedimientos de destello) se realizo en gel de sílice 40-63 μm (Merck),

(iv) los rendimientos se dan para efectos de ilustración unicamente no son necesariamente el máximo alcanzable,

(v) las estructuras de los productos finales de la formula (I) se confirmaron generalmente por resonancia magnetica nuclear (generalmente de protones) (NMR) y tecnicas de espectros de masa, los valores de cambio quimico con resonancia magnética se midieron en CD3OD deuterado (a menos que se indique lo contrario) en la escala delta (ppm campo abajo de tetrametilsilano), a menos que se indique lo contrario, los datos de protones se citan, los espectros se registran en un espectrometro Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz o en Varian Inova-500 MHz, y los multiplos de picos se muestran como sigue s, singlete, d, doblete, dd, doble doblete, t, triplete, tt, triple triplete, q, cuartete, tq, triple cuartete, m, multiplete, br, amplio, LCMS se registraron en una Aguas ZMD, LC columna x Terra MS C8(Aguas), detección con un HP 1100 MS-detector equipado con arreglo de diodos, los espectros de masa (MS) (bucle) se registraron en VG Platform II (Fisons Instruments) con un HP-1100 MS-detector equipado con arreglo de diodos, a menos que

se indique lo contrario el ión de masa citado es (MH+),
(vi) a menos que se especifiquen más detalles en el texto, la cromatografía analítica de liquido de alto rendimiento (HPLC) se realizo en Prep LC 2000 (Aguas), Kromasil C_8, 7 µm, (Akzo Nobel), MeCN y agua deionizada 100 mM acetato de amonio como fases móviles, con la composicion adecuada,
(vii) en general los intermedios no se caracterizaron plenamente y la pureza se evaluo mediante cromatografía de capa delgada (TLC), HPLC, infra-rojo (IR), MS o análisis NMR,
(viii) donde se secaron las soluciones el agente de secamiento fue sulfato de sodio, y
(ix) las siguientes abreviaturas pueden usarse mas arriba o mas adelante en el texto -

DCM	diclorometano,
DMFN,	*N*,*N*-dimetilformamida,
TBTU	o-Benzotriazol-1-il-*N*,*N*,*N*',*N*'-tetrametiluronio-tetrafluoroborato,
EtOAc	acetato de etilo,
MeCN	acetonitrilo,
TFA	ácido trifluoroacético,
IPA	isopropanol,
DIPEA	di-isopropiletilamina, y
THF	tetrahidrofurano

Ejemplo 1

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-[4-(*N*-{(R)-α-[*N*-(*t*-butoxicarbonilmetil)carbamoil]bencil}carbamoilmetoxi)fenil]azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 1, 20 mg, 0 043 mmol), *tert*-butil *N*-[(2*R*)-2-amino-2-feniletanoil]glicinate (Método 4, 14 mg, 0 047 mmol) y 2,6-lutidina (25µl, 0 21 mmol) se agregaron a DCM (2 ml) y la

174

mezcla se agitó durante 5 minutos Se agregó TBTU (18 mg, 0 056 mmol) y la mezcla se agito durante 4 horas a la temperatura de la sala La mezcla de reaccion se purificó por cromatografía de columna usando DCM/EtOAc (10/2) como eluente para producir 17 mg (56 %) del compuesto del titulo M/z 712 4 $(m-H)^-$

Ejemplo 2

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-[4-(*N*-{(R)-α-[*N*-(carboximetil)carbamoil]bencil}carbamoilmetoxi)fenil]azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-[4-(*N*-{(R)-α-[*N*-(*t*-butoxicarbonilmetil)carbamoil]bencil}carbamoilmetoxi) fenil]azetidin-2-ona (Ejemplo 1, 17 mg, 0 024 mmol) se agregó a acido fórmico (1 ml) y la mezcla se agitó durante 2 5 horas a la temperatura de la sala. El disolvente se evaporo bajo presión reducida, y metanol (1 ml) y trietilamina (75µl) se agregaron al residuo La mezcla se agitó durante 4 5 horas a la temperatura de la sala y los disolventes se evaporaron bajo presión reducida. El residuo se disolvió en MeCN/agua (50/50) (3 ml) y acido acético (1 ml) La mezcla se liofilizó para obtener 13 mg (83%) del compuesto del titulo NMR (300 MHz, DMSO-d_6) 1 65-1 85 (m, 4H), 3 05 (bs, 1H), 3 5-3 7 (m, 3H), 4 45-4 55 (m, 1H), 4 6 (d, 2H), 4 85 (m, 1H), 5 55 (d, 1H), 6 9 (d, 1H), 7 05-7 4 (m, 17H), 8 4-8 55 (m, 2H), m/z 656 2 (m-H)

Ejemplo 3

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-((2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoilmetoxi] fenil}azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxi fenil)azetidin-2-ona (Método 1, 40 mg, 0 086 mmol), D-glucamina (16 mg, 0 09 mmol) y 2,6-lutidina (50 µl, 0 42 mmol) se agregaron a DCM (3 ml) y 2 gotas de DMF Se agregó TBTU (36 mg, 0 11 mmol) y la mezcla se agitó a la temperatura de la sala durante 2 horas Los

175

disolventes se evaporaron bajo presión reducida y el residuo se purifico dos veces por HPLC preparativa usando solución amortiguadora MeCN/amonio (45 55) como eluente Las fracciones recogidas se liofilizaron para obtener 16 mg (30%) del compuesto del título NMR (300 MHz, CD_3OD) 1 8-2 0 (m, 4H), 3 15-3 2 (m, 1H), 3 4-4 0 (m, 8H), 4 6 (s, 2H), 4 7-4 8 (m, 1H), 4 9 (bs, 1H), 7 0-7 5 (m, 12H), m/z 629 2 $(m-H)^-$

Ejemplo 4

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(*t*-butoxicarbonil)-2-(*t*-butoxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Metodo 1, 40 mg, 0 086 mmol), *tert*-butil *N*-[(2R)-2-amino-2-feniletanoil]-*O*-(*tert*-butil)-L-serinato (Metodo 6, 33 mg, 0 095 mmol) y 2,6-lutidina (50 µl, 0 42 mmol) se agregaron a DCM (3 ml) Se agregó TBTU (36 mg, 0 11 mmol) y la mezcla se agito a la temperatura de la sala durante 7 horas Los disolventes se evaporaron bajo presión reducida para producir una mezcla que contenía el compuesto del titulo M/z 798 4 $(M-H)^-$

Ejemplo 5

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil} azetidin-2-ona

La 1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(t-butoxicarbonil)-2-(t-butoxi)etil]carbamoil} bencil)carbamoilmetoxi]fenil}azetidin-2-ona preparada en Ejemplo 4 se agrego a ácido formico (3 ml) y la mezcla se agitó durante 5 días a la temperatura de la sala. El disolvente se evaporó bajo presión reducida, y metanol (4 ml) y trietilamina (0 4 ml) se agregaron al residuo La mezcla se agito durante 24 horas a la temperatura de la sala y los disolventes se evaporaron bajo presión reducida. El residuo se purificó por HPLC

176

preparativa usando solución amortiguadora MeCN/amonio (40 60) como eluente Las fracciones recogidas se liofilizaron para obtener 12 mg (20%, 2 pasos) del compuesto del título NMR (300 MHz, CD_3OD) 1 8-1 95 (m, 4H), 3 1 (bs, 1H), 3 7- 3 8 (m, 2H), 4 35 (bs, 1H), 4 55-4 7 (m, 3H), 4 8 (s, 1H), 5 65 (s, 1H), 6 95-7 4 (m, 17H), m/z 686 3 $(m-H)^-$

Ejemplo 6

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-{*N*-[(R)-α-(*t*-butoxicarbonil)bencil]carbamoilmetoxi}fenil}azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 1, 40 mg, 0 086 mmol *tert*-butil (2*R*)-amino(fenil) acetato (20 mg, 0 095 mmol) y 2,6-lutidina (50 µl, 0 42 mmol) se agregaron a DCM (3ml) Se agregó TBTU (36 mg, 0 11 mmol) y la mezcla se agito a la temperatura de la sala durante 5 horas El disolvente se evaporó bajo presión reducida y se co-evaporó con tolueno El residuo se purificó por cromatografía de columna usando DCM/EtOAc (10/2) como eluente para producir el compuesto del título M/z 655 3 (m-H)

Ejemplo 7

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(R)-α-(carboxi)bencil]carbamoilmetoxi}fenil)azetidin-2-ona

La 1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-{*N*-[(R)-α-(*t*-butoxicarbonil)bencil]carbamoilmetoxi}fenil}azetidin-2-ona preparada en Ejemplo 6 se agregó a ácido fórmico (3 ml) y la mezcla se agitó durante 12 horas a la temperatura de la sala. El disolvente se evaporo bajo presion reducida y se co-evaporó con tolueno Metanol (3 ml) y trietilamine (0 1 ml) se agregaron al residuo, y la mezcla se agitó durante 4 horas a la temperatura de la sala. Los disolventes se evaporaron bajo presion reducida y el residuo se purificó por HPLC preparativa usando solución amortiguadora MeCN/amonio (50 50) como eluente Las fracciones recogidas se liofilizaron para obtener 17 mg (33%, 2 pasos) del compuesto del titulo NMR (300 MHz, CD_3OD) 1 8-2 0 (m, 4H), 3 05-

177

3 15 (m, 1H), 4 5-4 7 (m, 3H), 4 8 (bs, 1H), 5 35 (d, 1H), 6 95-7 45 (m, 17H), m/z 599 5 (m-H)$^-$

Ejemplo 8

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(*t*-butoxicarbonilmetil)carbamoilmetoxi]fenil}azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Metodo 1, 40 mg, 0 086 mmol), glicina *tert*-butiléster (18 mg, 0 091 mmol) y 2,6-lutidina (50 µl, 0 42 mmol) se agregaron a DCM (3 ml) Se agrego TBTU (36 mg, 0 11 mmol) y la mezcla se agitó a la temperatura de la sala durante 20 horas El disolvente se evaporó bajo presión reducida El residuo se purifico por cromatografía de columna usando DCM/EtOAc (10/4) como eluente para producir el compuesto del titulo M/z 579 2 (m-H)$^-$

Ejemplo 9

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona

La 1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(*t*-butoxicarbonilmetil)carbamoilmetoxi]fenil}azetidin-2-ona preparada en Ejemplo 8 se agregó a ácido fórmico (3 ml), y la mezcla se agitó durante 4 horas a la temperatura de la sala. El disolvente se evaporó bajo presion reducida y se co-evaporo con tolueno Metanol (3 ml) y trietilamina (0 1 ml) se agregaron al residuo y la mezcla se agitó durante 20 horas a la temperatura de la sala. Los disolventes se evaporaron bajo presión reducida y el residuo se purifico por HPLC preparativa usando solución amortiguadora MeCN/amonio (45 55) como eluente Las fracciones recogidas se liofilizaron para obtener 14 mg (31%, 2 pasos) del compuesto del titulo NMR (300 MHz,CD_3OD) 1 8-2 0 (m, 4H), 3 05-3 15 (m, 1H), 3 85 (s, 2H), 4 55 (s, 2H), 4 6-4 7 (m, 1H), 4 8 (bs, 1H), 6 95-7 35 (m, 12H), m/z 523 1 (m-H)

178

Ejemplo 10

1-(4-Fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-{4-[*N*-(carboximetil) carbamoilmetoxi]fenil}azetidin-2-ona

Una solución de 1-(4-fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 8, 0 050 g, 0 110 mmol), *tert*-butil glicinato clorhidrato(0 022 g, 0 131 mmol) y *N*-metilmorfolina (0 050 ml, 0 454 mmol) en DCM (3 ml) se agitó a la temperatura de la sala durante 5 minutos, luego de lo cual se agregó TBTU (0 046 g, 0 143 mmol) Después de 78 horas la conversión en el éster (m/z 567 2) se completo y el disolvente se retiró bajo presión reducida. El residuo se disolvio en ácido fórmico (3 ml) y la solución se agitó durante 20 horas El disolvente se retiró bajo presion reducida y el residuo se purifico por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Las fracciones se secaron por congelamiento y el compuesto del titulo se obtuvo como un sólido blanco (0 056 g, ~ rendimiento cuantitativo) NMR (CD_3OD, 400 MHz) 2 25-2 40 (m, 2H), 3 25-3 35 (m, 1H), 3 90 (s, 2H), 4 05-4 20 (m, 2H), 4 50 (s, 2H), 5 00 (d, 1H), 6 80-7 05 (m, 8H), 7 25-7 40 (m, 4H), m/z 511 1

Ejemplo 11

1-(4-Fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-(4-{*N*-[(R)-α-(carboxi)-4-(hidroxi)bencil]carbamoilmetoxifenil)azetidin-2-ona

Una solución de 1-(4-fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(carboximetoxi)fenil] azetidin-2-ona (Método 8, 0 070 g, 0 154 mmol), *tert*-butil D-tirosinato (0 044 g, 0 185 mmol) y *N*-metilmorfolina (0 051 ml, 0 463 mmol) en DCM (5 ml) se agito a la temperatura de la sala durante 5 minutos, luego de lo cual se agregó TBTU (0 065 g, 0 202 mmol) Después de 20 horas, la conversion en el éster (m/z 673 4) se completó y el disolvente se retiró bajo presion reducida. El residuo se disolvió en ácido formico (5 ml) y la solución se agitó durante 24 horas El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora

de acetato de amonio como eluente Las fracciones se secaron por congelamiento y el compuesto del titulo se obtuvo como un sólido blanco (0 052 g, 55 %) NMR (CD_3OD, 400 MHz) 2 25-2 40 (m, 2H), 2 85-3 15 (m, 2H), 3 25-3 40 (m, 1H), 4 05-4 20 (m, 2H), 4 35-4 50 (m, 2H), 4 55-4 65 (m, 1H), 5 00 (d, 1H), 6 55-6 65 (m, 2H), 6 80-7 05 (m, 10H), 7 25-7 35 (m, 4H), m/z 615 2 (M-H)

Ejemplo 12

1-(4-Fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-(4-{*N*-[(R)-1-(carboxi)-2-(hidroxi)etil]carbamoilmetoxi}fenil)azetidin-2-ona

Una solución de 1-(4-fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 8, 0 070 g, 0 154 mmol), *tert*-butil *O*-(*tert*-butil)-D-serinato clorhidrato(0 047 g, 0 185 mmol) y *N*-metilmorfolina (0 068 ml, 0 617 mmol) en DCM (5 ml) se agitó a la temperatura de la sala durante 5 minutos, luego de lo cual se agregó TBTU (0 065 g, 0 202 mmol) Después de 20 horas, la conversión en el éster (m/z 653 4) se completó y se agregó TFA (1 5 ml) a la mezcla de reacción Después de 24 horas el disolvente se retiro bajo presión reducida y el residuo se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0 1M solucion amortiguadora de acetato de amonio como eluente Las fracciones se secaron por congelamiento y el compuesto del titulo se obtuvo como un solido blanco (0 074 g, 89%) M/z 541 1 NMR (CD_3OD, 400 MHz) 2 25-2 40 (m, 2H), 3 25-3 35 (m, 1H), 3 80-3 95 (m, 2H), 4 05-4 20 (m, 2H), 4 40 (t, 1H), 4 55 (s, 2H), 5 00 (d, 1H), 6 80-6 90 (m, 2H), 6 90-7 05 (m, 6H), 7 25-7 40 (m, 4H)

Ejemplo 13

1-(4-Fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-{4-[*N*-((R)-1-carboxi-3-metilbutil)carbamoilmetoxi]fenil}azetidin-2-ona

Una solución de 1-(4-fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 8, 0 070 g, 0 154 mmol), *tert*-butil D-leucinato clorhidrato (0 042 g, 0 188 mmol) y *N*-metilmorfolina

180

(0 068 ml, 0 617 mmol) en DCM (5 ml) se agitó a la temperatura de la sala durante 5 minutos, luego de lo cual se agregó TBTU (0 065 g, 0 202 mmol) Después de 20 horas, la conversión en el éster (m/z 623 3) se completo y el disolvente se retiró bajo presión reducida El residuo se disolvió en ácido fórmico (5 ml) y la solución se agito durante 20 horas El disolvente se retiro bajo presión reducida y el residuo se purifico por HPLC preparativa usando una gradiente de 20- 50% MeCN en 0 1M solucion amortiguadora de acetato de amonio como eluente Las fracciones se secaron por congelamiento y el compuesto del titulo se obtuvo como un solido blanco (0 080 g, 91 %) NMR (DMSO, 400 MHz) 0 75-0 85 (m, 6H), 1 45-1 60 (m, 3H), 2 15-2 30 (m, 2H), 3 20-3 30 (m, 1H), 4 00-4 25 (m, 3H), 4 50 (ABq, 2H), 5 05 (d, 1H), 6 85-6 95 (m, 4H), 7 00-7 25 (m, 6H), 7 30-7 40 (m, 2H), 8 05 (t, 1H), m/z 567 3

Ejemplo 14

1-(4-Fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-(4-{*N*-[(S)-1-(carboxi)-3-(carbamoil)propil]carbamoilmetoxi}fenil)azetidin-2-ona

Una solución de 1-(4-fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 8, 0 070 g, 0 154 mmol), *tert*-butil L-glutaminato clorhidrato(0 044 g, 0 184 mmol) y *N*-metilmorfolina (0 068 ml, 0 617 mmol) en DCM (5 ml) se agitó a la temperatura de la sala durante 5 minutos, luego de lo cual se agrego TBTU (0 065 g, 0 202 mmol) Después de 20 horas, la conversión en el éster (m/z 638 3) se completo y el disolvente se retiró bajo presión reducida El residuo se disolvió en ácido fórmico (5 ml) y la solución se agito durante 20 horas El disolvente se retiró bajo presión reducida y el residuo se purifico por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Las fracciones se secaron por congelamiento y el compuesto del titulo se obtuvo como un sólido blanco (0 088 g, 98 %) NMR (CD_3OD, 400 MHz) 1 90-2 40 (m, 6H), 3 25-3 35 (m, 1H), 4 05-4 20 (m, 2H), 4 30-4 40 (m, 1H), 4 50 (s, 2H), 5 00 (d, 1H), 6 80-7 05 (m, 8H), 7 25-7 40 (m, 4H), m/z 582 2

181

Ejemplo 15

1-(4-Fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona

Una solucion de 1-(4-fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 8, 0 051 g, 0 113 mmol), *tert*-butil *N*-[(2R)-2-amino-2-feniletanoil]-*O*-(*tert*-butil)-L-serinato (Método 6, 0 047 g, 0 134 mmol) y *N*-metilmorfolina (0 050 ml, 0 454 mmol) en DCM (5 ml) se agitó a la temperatura de la sala durante 10 minutos, luego de lo cual se agrego TBTU (0 065 g, 0 202 mmol) Después de 18 horas, la conversión en el éster (m/z 786 5) se completo y se agregó TFA (1 5 ml) a la mezcla de reacción Después de 24 horas el disolvente se retiro bajo presión reducida y el residuo se purificó por HPLC preparativa usando una gradiente de 30-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Las fracciones se secaron por congelamiento y el compuesto del título se obtuvo como un sólido blanco (0 057 g, 75 %) NMR(CD_3OD, 400 MHz) 2 25-2 40 (m, 2H), 3 25-3 35 (m, 1H), 3 65-3 85 (m, 2H), 4 05-4 20 (m, 2H), 4 30-4 40 (m, 1H), 4 50-4 65 (m, 2H), 5 00 (d, 1H), 5 65 (s, 1H), 6 80-7 05 (m, 8H), 7 20-7 45 (m, 9H), m/z 674 2

Ejemplo 16

1-(4-Fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-{4-[*N*-{(R)-α-[*N*-((S)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi]fenil} azetidin-2-ona

Una solución de 1-(4-fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 8, 0 050 g, 0 110 mmol), (R)-α-{*N*-[(S)-1-(*t*-butoxicarbonil)propil]carbamoil}-4-hidroxibencilamina (Método 11 de WO 03/022286, 0 046 g, 0 133 mmol) y *N*-metilmorfolina (0 049ml, 0 445 mmol) en DCM (5 ml) se agitó a la temperatura de la sala durante 10 minutos, luego de lo cual se agregó TBTU (0 046 g, 0 143 mmol) Después de 20 horas, la conversion en el ester (m/z 744 5) se

182

completo y el disolvente se retiró bajo presion reducida El residuo se disolvió en ácido formico (3 ml) y la solución se agitó durante 24 horas antes de retirar el disolvente de nuevo bajo presión reducida El residuo se purifico por HPLC preparativa usando una gradiente de 30-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Las fracciones se secaron por congelamiento y el compuesto del titulo se obtuvo como un sólido blanco (0 052 g, 69 %) NMR (CD_3OD, 400 MHz) 0 70-0 80 (m, 3H), 1 55-1 70 (m, 1H), 1 75-1 90 (m, 1H), 2 25-2 40 (m, 2H), 3 25-3 35 (m, 1H), 4 05-4 20 (m, 2H), 4 20-4 30 (m, 1H), 4 55 (ABq, 2H), 5 00 (d, 1H), 5 50 (d, 1H), 6 65-6 75 (m, 2H), 6 80-7 05 (m, 8H), 7 15-7 40 (m, 6H), m/z 688 2

Ejemplo 17

3-(R)-4-(R)-1-(Fenil)-3-(feniletilsulfanil)-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona

Una solucion de 3-(R)-4-(R)-1-(fenil)-3-(feniletilsulfanil)-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 9, 0 050 g, 0 115 mmol), *tert*-butil *N*-[(2*R*)-2-amino-2-feniletanoil]-*O*-(*tert*-butil)-L-serinato (Método 6, 0 049 g, 0 140 mmol) y *N*-metilmorfolina (0 050 ml, 0 454 mmol) en DCM (5 ml) se agitó a la temperatura de la sala durante 10 minutos, luego de lo cual se agregó TBTU (0 075 g, 0 234 mmol) Despues de 18 horas, la conversion en el éster (m/z 766 5) se completó y se agregó TFA (1 5 ml) a la mezcla de reacción Después de 24 horas el disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa, usando una gradiente de 30-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Las fracciones se secaron por congelamiento y el compuesto del título se obtuvo como un sólido blanco (0 052 g, 69%) NMR (CD_3OD, 400 MHz) 2 85-3 00 (m, 4H), 3 65-3 85 (m, 2H), 4 00-4 05 (m, 1H), 4 35-4 40 (m, 1H), 4 60 (ABq, 2H), 4 85 (d, 1H), 5 65 (s, 1H), 6 95-7 45 (m, 19H), m/z 654 2

Ejemplo 18

3-(R)-4-(R)-1-(Fenil)-3-(feniletilsulfanil)-4-{4-[*N*-{(R)-α-[*N*-((S)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi] azetidin-2-ona

Una solucion de 3-(R)-4-(R)-1-(fenil)-3-(feniletilsulfanil)-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Metodo 9, 0 050 g, 0 110 mmol), (R)-α-{*N*-[(S)-1-(*t*-butoxicarbonil)propil]carbamoil}-4-hidroxibencilamina (Método 11 de WO 03/022286, 0 048 g, 0 139 mmol) y *N*-metilmorfolina (0 051 ml, 0 463 mmol) en DCM (5 ml) se agitó a la temperatura de la sala durante 10 minutos, luego de lo cual se agregó TBTU (0 075 g, 0 234 mmol) Después de 20 horas, la conversión en el ester (m/z 724 4) se completo y el disolvente se retiro bajo presion reducida. El residuo se disolvió en ácido formico (3 ml) y la solución se agitó durante 24 horas El disolvente se retiró bajo presión reducida y el residuo se purifico por HPLC preparativa usando una gradiente de 30-50% MeCN en 0 1M solucion amortiguadora de acetato de amonio como eluente Las fracciones se secaron por congelamiento y el compuesto del título se obtuvo como un solido blanco (0 037 g, 48 %) M/z 668 1 NMR (CD_3OD, 400 MHz) 0 65-0 80 (m, 3H), 1 50-1 70 (m, 1H), 1 75-1 90 (m, 1H), 2 85-3 00 (m, 4H), 4 00-4 05 (m, 1H), 4 20-4 30 (m, 1H), 4 55 (ABq, 2H), 4 85 (d, 1H), 4 45-4 55 (m, 1H), 6 65-6 75 (m, 2H), 6 95-7 40 (m, 16H)

Ejemplo 19

3-(R)-4-(R)-1-(Fenil)-3-(feniletilsulfinil)-4-{4-[*N*-{(R)-α-[*N*-((S)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi]fenil}azetidin-2-ona

A una solución de 3-(R)-4-(R)-1-(fenil)-3- (feniletilsulfanil)-4-{4-[*N*-{(R)-α-[*N*-((S)-1-carboxipropil)carbamoil]-4-hidroxibencil} carbamoilmetoxi]fenil}azetidin-2-ona (Ejemplo 18, 0 026 g, 0 039 mmol) en DCM (3 ml) se agrego una solución de MCPBA en DCM en porciones hasta que la reaccion se completo (LC/MS) (Se agregó aproximadamente 0 015 g 70-75% *m*-CPBA) El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa usando una gradiente de 20-

184

50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Despues del secamiento por congelamiento, el compuesto del titulo se obtuvo como un sólido blanco (0 018 g, 67 %) NMR (CD_3OD, 400 MHz) (NB mezcla diastereomérica en el sulfinilo) 0 65- 0 80 (m, 6H), 1 55-1 70 (m, 2H), 1 75-1 90 (m, 2H), 2 95-3 35 (m, 7H), 3 75-3 90 (m, 1H), 4 20-4 30 (m, 2H), 4 40-4 50 (m, 1H), 4 50-4 65 (m,5H), 5 30 (d, 1H), 5 45-5 55 (m, 2H), 5 65 (d,1H), 6 65-6 80 (m, 4H), 6 95-7 10 (m, 6H), 7 15-7 35 (m, 22H), 7 35-7 50 (m, 4H), m/z 684 4

Ejemplo 20

3-(R)-4-(R)-1-(Fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona

Una solución de 3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 10, 0 110 g, 0 236 mmol), *tert*-butil glicinato clorhidrato (0 067 g, 0 400 mmol) y *N*-metilmorfolina (0 12 ml, 1 09 mmol) en DCM (5 ml) se agito a la temperatura de la sala durante 5 minutos, luego de lo cual se agregó TBTU (0 130 g, 0 4049 mmol) Después de 66 horas la conversion en el éster (m/z 579 2) se completo y el disolvente se retiró bajo presión reducida. El residuo se disolvió en ácido formico (3 ml) y la solucion se agitó a 40°C durante 4 horas El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Se obtuvo un sólido blanco después de secamiento por congelamiento (0 035g, 28 %) M/z 521 12 [M-1]

Ejemplo 21

3-(R)-4-(R)-1-(Fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-[4-(*N*-{*N*-[(R)-1-(*t*-butoxicarbonil)-2-(*t*-butoxi)etil]carbamoilmetil}carbamoilmetoxi)fenil] azetidin-2-ona

Una solución de 3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-{4-[*N*-carboximetil)carbamoilmetoxi]

185

fenil}azetidin-2-ona (Ejemplo 20, 0 020 g, 0 038 mmol), *tert*-butil *O*- (*tert*-butil)-D-serinato clorhidrato(0 012 g, 0 047 mmol) y *N*- metilmorfolina (0 013 ml, 0 118 mmol) en DCM (3 ml) se agitó a la temperatura de la sala durante 10 minutos, luego de lo cual se agregó TBTU (0 016 g, 0 050 mmol) Después de 66 horas el disolvente se retiro bajo presión reducida y el residuo se purificó por cromatografía de destello usando heptano EtOAc (1 2) como eluente para producir el compuesto del titulo (0 020 g, 74 %) NMR (400 MHz) 1 15 (s, 9H), 1 45 (s, 9H), 3 50-3 55 (m, 1H), 3 75-3 85 (m, 1H), 4 00- 4 25 (m,5H), 4 50 (s, 2H), 4 55-4 65 (m, 1H), 4 85 (d, 1H), 6 90-7 00 (m, 2H), 7 00-7 40 (m, 9H), 7 90-8 05 (m, 2H), m/z 722 1

Ejemplo 22

3-(R)-4-(R)-1-(Fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-[4-(*N*-{*N*-[(R)-1-(carboxi)-2-(hidroxi)etil]carbamoilmetil]carbamoilmetoxi) fenil]azetidin-2-ona

A una solución de 3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-[4-(*N*-{*N*-[(R)-1-(*t*-butoxicarbonil)-2-(*t*-butoxi)etil]carbamoilmetil}carbamoilmetoxi)fenil]azetidin-2-ona (Ejemplo 21, 0 020 g, 0 146 mmol) en DCM (4 ml) se agregó TFA (1 5 ml) Después de 18 horas el disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solucion amortiguadora de acetato de amonio, como eluente Despues de secamiento por congelamiento, el compuesto del titulo se obtuvo como un sólido blanco (0 017 g, ~ cuantitativo) NMR (CD_3COOH, 400 MHz) δ 3 95 (dd, 1H), 4 10 (dd, 1H), 4 15-4 35 (m, 5H), 4 65 (s, 2H), 4 70-4 80 (m, 1H), 5 05 (d, 1H), 6 90-7 45 (m, 11H), 7 95-8 10 (m, 2H), m/z 610 2

Ejemplo 23

3-(R)-4-(R)-1-(Fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-(4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil} azetidin-2-ona

186

Una solución de 3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 10, 0 015 g, 0 032 mmol), *tert*-butil *N*-[(2*R*)-2-amino-2-feniletanoil]-*O*-(*tert*-butil)-L-serinato (Método 6, 0 017 g, 0 049 mmol) y *N*-metilmorfolina (0 011 ml, 0 100 mmol) en DCM (3 ml) se agito a la temperatura de la sala durante 10 minutos, luego de lo cual se agregó TBTU (0 016 g, 0 50 mmol) Despues de 19 horas la conversion en el ester (m/z 798 80) se completó y se agregó TFA (1 5 ml) a la solucion Después de 7 horas el disolvente se retiró bajo presion reducida y el residuo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Después de secamiento por congelamiento el compuesto del título se obtuvo como un sólido blanco (0 016 g, 72 %) NMR (CD_3COOH, 400 MHz) 3 85 (dd, 1H), 4 05 (dd, 1H), 4 20-4 30 (m, 3H), 4 60-4 80 (m, 3H), 5 00 (d, 1H), 5 90-6 00 (m, 1H), 6 90-7 50 (m, 16H), 8 00-8 10 (m, 2H), m/z 686 6

Ejemplo 24

3-(R)-4-(R)-1-(Fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona

A una solución en agitación de 3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-{4-[*N*-(carboximetil) carbamoilmetoxi]fenil}azetidin-2-ona (Ejemplo 20, 0 010 g, 0 019 mmol) en MeOH (1 ml) se agrego borohidruro de sodio (0 001 g, 0 026 mmol) Despues de 10 minutos se agrego agua (1 ml) y el disolvente se retiró bajo presión reducida. El residuo se purifico por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Despues de secamiento por congelamiento el compuesto del titulo se obtuvo como un solido blanco (0 008 g, 80%) M/z 525 1 NMR (CD_3COOD, 400 MHz) 3 00-3 20 (m, 2H), 4 05-4 15 (m, 1H), 4 20 (s, 2H), 4 70 (s, 2H), 4 85-5 00 (m, 2H), 6 95-7 10 (m, 5H), 7 20-7 45 (m, 8H)

187

Ejemplo 25

3-(R)-4-(R)-1-(Fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-[4-(*N*-{*N*-[(R)-1-(carboxi)-2-(hidroxi)etil]carbamoilmetil}carbamoilmetoxi)fenil] azetidin-2-ona

A una solución agitada de 3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-[4-(*N*-{*N*-[(R)-1-(carboxi)-2-(hidroxi) etil]carbamoilmetil}carbamoilmetoxi)fenil]azetidin-2-ona (Ejemplo 22, 0 015 g, 0 025 mmol) en MeOH (2 ml) se agrego borohidruro de sodio (0 003 g, 0 079 mmol) Después de 5 minutos se agregó agua (1 ml) y el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa usando una gradiente de 20-40% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Despues de secar por congelamiento el compuesto del titulo se obtuvo como un solido blanco (0 010 g, 66 %) NMR (CD_3COOD, 400 MHz) 2 95-3 20 (m, 2H), 3 95 (dd, 1H), 4 05-4 15 (m, 2H), 4 25 (ABq, 2H), 4 70 (s, 2H), 4 70-4 80 (m, 1H), 4 85-5 00 (m, 2H), 6 95-7 10 (m, 5H), 7 20-7 45 (m, 8H)

Ejemplo 26

3-(R)-4-(R)-1-(Fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi)fenil}azetidin-2-ona

A una solución de 3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-(4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona (Ejemplo 23, 0 019 g, 0 028 mmol) en MeOH (3 ml) se agregó borohidruro de sodio (0 005 g, 0 073mmol) Después de 10 minutos se agrego 0 1M solucion amortiguadora de acetato de amonio (aq , 1 ml) y el disolvente se retiró bajo presión reducida. El residuo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solucion amortiguadora de acetato de amonio como eluente Después de secamiento por congelamiento, el compuesto del titulo se obtuvo como un solido blanco (0 008 g, 81 %) NMR (CD_3COOD, 400 MHz) 3 00-3 20 (m, 2H), 3 85

188

(dd, 1H), 4 00-4 15 (m, 2H), 4 65-4 80 (m, 3H), 4 85-5 00 (m, 2H), 5 95 (s, 1H), 6 95-7 10 (m, 5H), 7 20-7 50 (m, 13H), m/z 688 21

Ejemplo 27

3-(R)-4-(R)-1-(Fenil)-3-(tien-3-ilcarbonilmetilsulfanil)-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona

Una solución de 3-(R)-4-(R)-1-(fenil)-3-(tien-3-ilcarbonilmetilsulfanil)-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Metodo 11, 0 039 g, < 0 086 mmol), *tert*-butil glicinato clorhidrato (0 020 g, 0 119 mmol) y *N*-metilmorfolina (0 035 ml, 0 318 mmol) en DCM (3 ml) se agitó a la temperatura de la sala durante 10 minutos, luego de lo cual se agrego TBTU (0 042 g, 0 131 mmol) Después de 22 horas el disolvente se retiro bajo presión reducida y el residuo se purifico por cromatografía de destello usando heptano EtOAc (1 1) como eluente Esto produjo 0 035 g de un aceite incoloro (m/z 567 1) Este aceite se disolvio en acido fórmico (3 ml) y la solución se agitó a la temperatura de la sala durante 18 horas El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solucion amortiguadora de acetato de amonio como eluente Después de secamiento por congelamiento, el compuesto del titulo se obtuvo como un sólido blanco (0 019 g, 43 %) NMR (CD_3COOD, 400 MHz) 4 15 (ABq, 2H), 4 20 (s, 2H), 4 25 (d, 1H), 4 70 (s, 2H), 5 05 (d, 1H), 6 95-7 15 (m, 4H), 7 20-7 30 (m, 4H), 7 35-7 45 (m, 2H), 7 75-7 90 (m, 2H), m/z 511 0

Ejemplo 28

3-(R)-4-(R)-1-(fenil)-3-(tien-3-ilcarbonilmetilsulfanil)-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil} azetidin-2-ona

Una solución de 3-(R)-4-(R)-1-(fenil)-3-(tien-3-ilcarbonilmetilsulfanil)-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Metodo 11, 0 039 g, < 0 086 mmol), *tert*-butil *N*-[(2R)-2-amino-2-feniletanoil]-*O*-(*tert*-butil)-L-serinato (Método 6, 0 042g) y *N*- metilmorfolina (0 022 ml)

189

en DCM (4 ml) se agito a la temperatura de la sala durante 10 minutos, luego de lo cual se agregó TBTU (0 042 g) Después de 22 horas el disolvente se retiró bajo presión reducida y el residuo se purificó por cromatografía de destello usando heptano EtOAc (1 1) como eluente para producir un aceite incoloro (0 050 g) M/z 786 6 Este aceite se disolvio en DCM (4 ml) y se agregó TFA (1 5 ml) Después de 19 horas, el disolvente se retiró bajo presión reducida y el residuo se purificó dos veces por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Despues de secamiento por congelamiento, el compuesto del titulo se obtuvo como un solido blanco (0 019 g, 33 %) NMR (CD_3COOD, 400 MHz) 3 85 (dd, 1H), 4 05 (dd, 1H), 4 15 (ABq, 2H), 4 20-4 30 (m, 1H), 4 60-4 75 (m, 3H), 5 05 (d, 1H), 5 90 (s, 1H), 6 95-7 15 (m, 4H), 7 20-7 50 (m, 11H), 7 75-7 85 (m, 2H), m/z 674 3

Ejemplo 29

3-(R)-4-(R)-1-(Fenil)-3-[2-(tien-3-il)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona

A una solución de 3-(R)-4-(R)-1-(fenil)-3-(tien-3-ilcarbonilmetilsulfanil)-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil} azetidin-2-ona (Ejemplo 27, 0 012 g, 0 024 mmol) en MeOH (3 ml) se agrego borohidruro de sodio (0 006 g, 0 159 mmol) Después de 10 minutos se agregó 0 1M solucion amortiguadora de acetato de amonio (aq , 1 ml) y el disolvente se retiro bajo presion reducida El residuo se purifico por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente Despues de secamiento por congelamiento el compuesto del titulo se obtuvo como un sólido blanco (0 010 g, 80%) NMR (CD_3COOD, 400 MHz) δ 3 10-3 30 (m, 2H), 4 15 (dd, 1H), 4 20 (s, 2H), 4 70 (s, 2H), 4 95 (dd, 1H), 5 20 (dt, 1H), 6 90-7 10 (m, 5H), 7 20-7 35 (m, 5H), 7 40-7 45 (m, 2H), m/z 511 3 $(M-1)^-$

190

Ejemplo 30

3-(R)-4-(R)-1-(Fenil)-3-[2-(tien-3-il)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-((S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil)carbamoilmetoxi] fenil}azetidin-2-ona

A una solucion de 3-(R)-4-(R)-1-(fenil)-3-(tien-3-ilcarbonilmetilsulfanil)-4-{4-[*N*-(α-(R)-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil}azetidin-2-ona (Ejemplo 28, 0 019 g, 0 028 mmol) en MeOH (3 ml) se agrego borohidruro de sodio (0 005 g, 0 132 mmol) Después de 10 minutos se agrego 0 1M solución amortiguadora de acetato de amonio (aq , 1 ml) y el disolvente se retiró bajo presión reducida. El residuo se purifico por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solucion amortiguadora de acetato de amonio como eluente Después de secamiento por congelamiento, el compuesto del título se obtuvo como un sólido blanco (0 015 g, 79 %) NMR (CD_3COOD, 400 MHz) 3 05-3 30 (m, 2H), 3 85 (dd, 1H), 4 05 (dd, 1H), 4 15 (dd, 1H), 4 65-4 75 (m, 3H), 4 90 (dd, 1H), 5 15-5 25 (m, 1H), 5 95 (s, 1H), 6 90-7 10 (m, 5H), 7 20-7 50 (m, 12H), m/z 674 16 $(M-H)^-$

Ejemplo 31

1-(4-Fluorofenil)-3-[2-(4-fluorofeniltio)etil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(*t*-butoxicarbonil)-2-(*t*-butoxi)etil]carbamoil}bencil)carbamoilmetoxi]fenil} azetidin-2-ona

Una solucion de 1-(4-fluorofenil)-3-[2-(4-fluorofeniltio)etil]-4-[4-(carboximetoxi)fenil]azetidin-2-ona (Método 17, 0 100 g, 0 213 mmol), *tert*-butil *N*-[(2*R*)-2-amino-2-feniletanoil]-*O*-(*tert*-butil)-L-serinato (Metodo 6, 0 150g, 0 428 mmol) y *N*-metilmorfolina (0 070 ml, 0 635 mmol) en DCM (4ml) se agito a la temperatura de la sala durante 10 minutos, luego de lo cual se agrego TBTU (0 140 g, 0 436 mmol) Después de 19 horas el disolvente se retiró bajo presion reducida y el residuo se purifico por cromatografía de destello usando heptano EtOAc (2 1) como eluente para producir un aceite incoloro (0 149 g, 87 %) NMR (400 MHz) 0 90 (s, 9H),

191

1 45 (s, 9H), 2 05-2 30 (m, 2H), 2 95-3 15 (m, 2H), 3 20-3 25 (m, 1H), 3 30-3 35 (m, 1H), 3 65 (dd, 1H), 4 40-4 60 (m, 3H), 4 60 (d, 1H), 5 50 (dd, 1H), 6 50 (dd, 1H), 6 85-7 00 (m, 6H), 7 15-7 40 (m, 11H), 7 90 (dd, 1H), m/z 802 8

Ejemplo 32

1-(4-Fluorofenil)-3-[2-(4-fluorofeniltio)etil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil)carbamoilmetoxi] fenil}azetidin-2-ona

A una solucion de 1-(4-fluorofenil)-3-[2-(4-fluorofeniltio)etil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(*t*-butoxicarbonil)-2-(*t*-butoxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona (Ejemplo 31, 0 149 g, 0 186 mmol) en DCM (3 ml) se agrego TFA (1 5 ml) Después de 20 horas, el disolvente se retiro bajo presion reducida y el residuo se purifico por HPLC preparativa usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora de acetato de amonio, como eluente Despues de secamiento por congelamiento, el compuesto del título se obtuvo como un sólido blanco (0 098 g, 77 %) NMR (400 MHz) 2 00-2 25 (m, 2H), 2 85-3 10 (m, 2H), 3 10-3 20 (m, 1H), 3 35-3 45 (m, 1H), 3 75-3 85 (m, 1H), 4 15-4 45 (m, 3H), 4 55 (d, 1H), 5 70 (d, 1H), 6 70-7 00 (m, 6H), 7 10-7 35 (m, 11H), 7 45-7 55 (m, 1H), 8 45-8 55 (m, 1H), m/z 690 5

Ejemplo 33

1-(4-Fluorofenil)-3-[2-(4-fluorofenilsulfinil)etil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi)fenil}azetidin-2-ona

Ejemplo 34

1-(4-Fluorofenil)-3-[2-(4-fluorofenilsulfonil)etil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona

A una suspension en agitación de 1-(4-fluorofenil)-3-[2-(4-

192

fluorofenıltıo)etıl]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxı)-2-(hıdroxı)etıl] carbamoıl}bencıl)carbamoılmetoxı]fenıl}azetıdın-2-ona (Ejemplo 32, 0 070 g, 0 102 mmol) en DCM (5 ml) se agregó acido metacloroperoxıbenzoico (0 035 g, 70-75%) Después de 20 horas, el dısolvente se retıro bajo presión reducıda y el resıduo se purıfıcó por HPLC preparatıva usando una gradıente de 20-40% MeCN en 0 1M solucıón amortıguadora de acetato de amonıo como eluente Despues de secamıento por congelamıento, se obtuvıeron como sólıdos blancos 1-(4-fluorofenıl)-3-[2-(4-fluorofenılsulfınıl)etıl]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxı)-2-(hıdroxı)etıl] carbamoıl}bencıl)carbamoılmetoxı]fenıl}azetıdın-2-ona (0 022 g, 30 %) NMR (CD_3COOD, 400 MHz) 2 15-2 45 (m, 2H), 3 10-3 35 (m, 3H), 3 85 (dd, 1H), 4 05 (dd, 1H), 4 65-4 75 (m, 3H), 4 80-4 90 (m, 1H), 5 90 (s, 1H), 6 95-7 05 (m, 4H), 7 25-7 50 (m, 11H), 7 70-7 80 (m, 2H), m/z 706 2, y 1-(4-fluorofenıl)-3-[2-(4-fluorofenılsulfonıl)etıl]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxı)-2-(hıdroxı)etıl]carbamoıl}bencıl)carbamoılmetoxı]fenıl}azetıdın-2-ona (0 043 g, 59 %) NMR (CD_3COOD, 400 MHz) 2 25-2 40 (m, 2H), 3 25 (dt, 1H), 3 35-3 55 (m, 2H), 3 85 (dd, 1H), 4 05 (dd, 1H), 4 65-4 75 (m, 3H), 4 85 (d, 1H), 5 95 (s, 1H), 6 95-7 05 (m, 4H), 7 20-7 50 (m, 11H), 7 95-8 05 (m, 2H), m/z 722 1

Ejemplo 35

1-(4-Fluorofenıl)-3-[3-(4-fluorofenıl)-3-hıdroxıpropıl]-4-(4-{*N*-[(S)-α-(carboxı)bencıl]carbamoılmetoxı}fenıl)azetıdın-2-ona

1-(4-Fluorofenıl)-3-[3-(4-fluorofenıl)-3-hıdroxıpropıl]-4-(4-carboxımetoxıfenıl)azetıdın-2-ona (Metodo 2,49mg, 0 105mmol) se dısolvıo en una solucıón de N-metılmorfolına (35µl, 0 318mmol) en 2ml DCM Se agregaron (S)-fenılglıcına metıl ester clorhıdrato (25mg, 0 124mmol) y TBTU (40mg, 0 125mmol) y la mezcla se agıtó a temperatura ambiente de un día para otro La solucion se dıluyó con 4ml DCM y se lavo con 1% $NaHCO_3$, 0 1M $KHSO_4$ y salmuera La fase orgánica se secó y se evaporó LıOH (aprox 10mg, 0 418mmol) y la mezcla se agıto de un día para otro. Se retıró el dısolvente y el resıduo se purıfico

193

usando HPLC preparativa en una columna C8 Una gradiente de 20 a 50% MeCN en 0 1M solución amortiguadora de acetato de amonio se uso como la fase movil La liofilización produjo un sólido blanco Masa 40mg (63%) M/z 601 NMR (400MHz, CD_3OD) 1 75-2 06 (m, 4H), 3 06-3 13 (m, 1H), 4 47-4 67 (m, 3H), 4 79-4 82 (m, 1H), 5 24 (d, 1H), 6 90-7 06 (m, 6H), 7 12-7 40 (m, 11H)

Ejemplo 36

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-[4-(*N*-{(R)-α-[*N*-((S)-1-carboxipropil)carbamoil]4-hidroxibencil}carbamoilmetoxi)fenil] azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 2, 49mg, 0 105mmol) se disolvio en una solución de N-metilmorfolina (40µl, 0 318mmol) en 2ml DCM Se agregaron *tert*-butil (2*S*)-2-{[(2*R*)-2-amino-2-(4-hidroxifenil) acetil]amino}butanoato clorhidrato (Método 14, 43mg, 0 125mmol) y TBTU (40mg, 0 125mmol) La mezcla se agito de un dia para otro a temperatura ambiente Adicionalmente se agregaron 10mg (0 029mmol) del dipéptido y después de 2 horas la solución se diluyó con 4ml DCM y se lavó con 1 % $NaHCO_3$, 0 1M $KHSO_4$ y salmuera La fase organica se seco y se evaporó para producir el ester M/z 758 Se agrego acido formico (1 5ml) y la mezcla se agitó de un día para otro Adicionalmente se agregó 1ml de ácido fórmico Después de 3 horas se retiró el acido fórmico, y se agregaron MeOH (2ml) junto con Et_3N (40µl, 0 288mmol) y la mezcla se agito de un día para otro La mezcla se concentró bajo presión reducida y se purifico usando cromatografía preparativa Una gradiente de 20% a 80% MeCN en 0 1M solución amortiguadora de acetato de amonio se uso como eluente La liofilización produjo 42mg (57%) NMR (400MHz, DMSO-d_6) 0 65-0 72 (m, 3H), 1 53-1 67 (m, 1H), 1 74-2 04 (m, 5H), 3 06-3 14 (m, 1H), 4 18-4 23 (m, 1H), 4 50-4 66 (m, 3H), 4 77-4 82 (m, 1H), 5 46 (d, 1H), 6 72 (t, 2H), 6 93-7 06 (m, 6H), 7 18-7 36 (m, 8H), m/z 702

194

Ejemplo 37

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(2-hidroxietil)carbamoilmetoxi]fenil}azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 2, 20mg, 0 043mmol) se disolvio en una solucion de *N*-metilmorfolina (10µl, 0 091mmol) en 2ml DCM Se agregaron 2-aminoetanol (4µl, 0 066mmol) y TBTU (16mg, 0 050mmol) y la mezcla se agitó durante 3 horas Se agregó mas 2-aminoetanol (3µl) La mezcla se agitó durante 2 5 dias, luego se concentro y se purificó usando cromatografía preparativa Una gradiente de 20% a 50% MeCN en 0 1M solución amortiguadora de acetato de amonio se uso como eluente La liofilización produjo 10mg (45%) NMR (400MHz, CD_3OD) 1 75-2 06 (m, 4H), 3 05-3 12 (m, 1H), 3 38 (t, 2H), 3 61 (t, 2H), 4 51 (d, 2H), 4 57-4 66 (m, 1H), 4 77-4 83 (m, 1H), 6 93-7 07 (m, 6H), 7 22-7 37 (m, 6H), m/z 511

Ejemplo 38

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(2-metoxietil)carbamoilmetoxi]fenil}azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 2, 20mg, 0 043mmol) se disolvio en una solucion de N-metilmorfolina (10µl, 0 091mmol) en 2ml DCM Se agregaron 2-metoxietilamina (5µl 0 058mmol) y TBTU (16mg, 0 050mmol) y la mezcla se agitó durante 3 horas a temperatura ambiente La mezcla se concentró y se purificó usando cromatografía preparativa Una gradiente de 20% a 50% MeCN en 0 1M solucion amortiguadora de acetato de amonio se usó como eluente La liofilizacion produjo 5mg (22%) NMR (400 MHz, CD_3OD) 1 75-2 05 (m, 4H), 3 05-3 15 (m, 1H), 3 29 (s, 3H), 3 40-3 44 (m, 4H), 4 5 (d, 2H), 4 57-4 66 (m, 1H), 4 78- 4 82 (m, 1H), 6 92-7 06 (m, 6H), 7 22-7 37 (m, 6H), m/z 525

Ejemplo 39

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(2-sulfoetil)carbamoilmetoxilfenil}azetidin-2-ona

TBTU (26 mg, 0 081 mmol) se agregó a una mezcla de 1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil) azetidin-2-ona (Método 2, 29 mg, 0 062 mmol), taurina (24 mg, 0 19 mmol) y trietilamina (25 mg, 0 25 mmol) en MeCN (1 ml) Después de 1 hora se agregó DMF (1 ml) y el MeCN se retiró *in vacuo* a 50°C Despues de 4 dias a la temperatura de la sala la mezcla se purifico por HPLC preparativa usando una gradiente de solución amortiguadora MeCN/amonio para producir el compuesto del título (2 mg, 6%) NMR (CD_3OD, 400 MHz) 7 40-7 20 (m, 6H), 7 05-6 95 (m, 6H), 4 8 (m, 1H), 4 7-4 55 (m, 1H), 4 5 (s, 2H), 3 75 (t, 2H), 3 1 (m, 1H), 2 95 (t, 2H), 2 0-1 8 (m, 4H)

Ejemplo 40

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(S)-1-(*t*-butoxicarbonil)etil]carbamoilmetoxi}fenil)azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Metodo 2, 30 mg, 0 064 mmol), *tert*-butil L-alaninato clorhidrato (40 mg, 0 22 mmol), trietil amina (0 036 ml, 0 26 mmol) y TBTU (35 mg, 0 11 mmol) se mezclaron (en ese orden) en MeCN (1 ml) Después de 4 horas la mezcla se diluyó con tolueno y la solución se lavó con ácido clorhídrico (2M) y solución de bicarbonato de sodio El disolvente se retiró *in vacuo* y el residuo se purificó por HPLC preparativa usando una gradiente de Solucion amortiguadora MeCN/amonio para producir el compuesto del título (20 mg, 52%) NMR (CD_3OD, 500 MHz) 7 40-6 90 (m), 4 8 (m), 4 7-4 3 (m), 3 95 (q), 3 2 (q), 3 1 (m), 2-1 8 (m), 1 5-1 3 (m), m/z 595 60 (M+H)+ y 593 53 (M-H)

Ejemplo 41

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(S)-1-(carboxi)etil]carbamoilmetoxi}fenil)azetidin-2-ona

Una solución de 1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-

196

hidroxipropil]-4-(4-{*N*-[(S)-1-(*t*-butoxicarbonil)etil]carbamoilmetoxi}fenil) azetidin-2-ona (Ejemplo 40, 20 mg, 0 034 mmol) en ácido formico (1 ml) se mantuvo a la temperatura de la sala de un dia para otro El ácido fórmico se retiró *in vacuo* y el residuo se disolvió en metanol (4ml) Se agregó amoníaco acuoso (25%, 0 2 ml) y después de 1 hora a la temperatura de la sala la mezcla se purifico por HPLC preparativa usando una gradiente de solución amortiguadora MeCN/amonio para producir el compuesto del título (5 mg, 28%) NMR (CD_3OD, 400 MHz) 7 4-7 2 (m, 6H), 7 1-6 9 (m, 6H), 4,8 (m, 1H), 4 7-4 6 (m, 1H), 4 5 (s, 2H), 4 3 (q, 1H), 3 1 (m, 1H), 2-1 7 (m, 4H), 1 4 (dd, 3H), m/z 539 51 $(M+H)^+$ y 537 50 $(M-H)^-$

Ejemplo 42

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-[4-(*N*-{(R)-α-[*N*-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)fenil]azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 2, 28 mg, 0 06 mmol), acido 2-{[(2*R*)-2-amino-2-(4-hidroxifenil)acetil]amino}etanosulfónico (30 mg, 0 11 mmol), trietilamina (24 mg, 0 24 mmol), y TBTU (29 mg, 0 09 mmol) se mezclaron en DMF (1 5 ml) Después de agitar de un dia para otro, la mezcla de reaccion se purificó por HPLC preparativa usando una gradiente de solución amortiguadora MeCN/amonio para producir el compuesto del titulo (18 mg, 42%) NMR (CD_3OD, 400 MHz) 7 4-7 1 (m), 7 1-6 9 (m), 5 4 (m), 4 8 (m), 4 7-4 5 (m), 3 65-3 55 (m), 3 15-3 05 (m), 3-2 8 (m), 2-1 7 (m), m/z 724 46 $(M+H)^+$ y 722 54 $(M-H)^-$

Ejemplo 43

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-((S)-1-{*N*-[(S)-1-(*t*-butoxicarbonil)etil]carbamoil}etil)carbamoilmetoxi]fenil} azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Metodo 2, 30 mg, 0 064mmol), *tert*-

197

butil L-alanil-L-alaninato (25 mg, 0 12 mmol), trietilamina (0 036 ml, 0 26 mmol) y TBTU (31 mg, 0 10 mmol) se mezclaron (en ese orden) en DMF (1 5 ml) Después de 16 horas la mezcla se diluyo con tolueno y la solucion se lavó con agua, ácido clorhidrico (2M), agua y solución de bicarbonato de sodio La adición de IPA y el retiro de los disolventes *in vacuo* produjeron el compuesto del título M/z 66 57 $(M+H)^+$ y 664 68 (M-H)

Ejemplo 44

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-((S)-1-{*N*-[(S)-1-(carboxi)etil]carbamoil}etil)carbamoilmetoxi] fenil}azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-((S)-1-{*N*-[(S)-1-(*t*-butoxicarbonil)etil]carbamoil}etil)carbamoilmetoxi]fenil} azetidin-2-ona (Ejemplo 43, 54 mg, 0 081 mmol) se disolvió en ácido formico (2 ml) Despues de 16 horas el ácido fórmico se retiró *in vacuo* y el residuo se disolvió en metanol (4 ml) y amoniaco acuoso (25%, 0 2 ml) Despues de 6 horas la mezcla se purificó por HPLC preparativa usando una gradiente de solución amortiguadora MeCN/amonio para producir el compuesto del título (15 mg, 30%) NMR(CD_3OD, 400 MHz) 7 4-7 2 (m, 6H), 7 1-6 9 (m, 6H), 4 8 (m, 1H), 4 7-4 5 (m, 1H), 4 5 (s, 2H), 4 45 (q, 1H), 4 3-4 2 (m, 1H), 3 2 (q, 1H), 3 1-3 0 (m, 1H), 2-1 8 (m, 4H), 1 4-1 2 (dd, 6H), m/z 610 57 $(M+H)^+$ y 608 53 $(M-H)^-$

Ejemplo 45

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[*N*-(metoxicarbonilmetil)carbamoilmetil]carbamoilmetoxi}fenil)azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 2, 30 mg, 0 064 mmol), metil glicilglicinato (19 mg, 0 13 mmol), trietil amina (0 036 ml, 0 26 mmol) y TBTU (31 mg, 0 10 mmol) se mezclaron (en ese orden) en DMF (1 5 ml) Despues de 16 horas la mezcla se diluyo con tolueno y la solucion se lavó con agua, ácido clorhídrico (2M), agua y solución de bicarbonato de sodio La adición de IPA y el retiro de los disolventes *in vacuo* produjeron el

198

compuesto del título M/z 596 50 $(M+H)^+$ y 594 45 $(M-H)^-$

Ejemplo 46

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[*N*-(carboximetil)carbamoilmetil]carbamoilmetoxi}fenil)azetidin-2-ona

Una solución de 1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[*N*-(metoxicarbonilmetil)carbamoilmetil] carbamoilmetoxi}fenil)azetidin-2-ona (Ejemplo 45, 44 mg, 0 074 mmol) en THF (4 ml) se agregó a una solución agitada de hidróxido de litio (10 mg, 0 43 mmol) en agua (2 ml) Después de 16 horas la mezcla se neutralizó cuidadosamente con ácido clorhídrico La purificación por HPLC preparativa usando una gradiente de solución amortiguadora MeCN/amonio produjo el compuesto del título (17 mg, 40%) NMR (CD_3OD, 400 MHz) 7 4-7 2 (m, 6H), 7 1-6 9 (m, 6H), 4 8 (m, 1H), 4 7-4 6 (m, 1H), 4 6 (s, 2H), 3 95 (s, 2H), 3 8 (s, 2H), 3 1-3 05 (m, 1H), 2-1 8 (m, 4H)

Ejemplo 47

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(S)-1,3-bis-(etoxicarbonil)propil]carbamoilmetoxi}fenil)azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 2, 30 mg, 0 064 mmol), dietil L-glutamato (19 mg, 0 093 mmol), trietilamina (0 036 ml, 0 26 mmol) y TBTU (31 mg, 0 10 mmol) se mezclaron (en ese orden) en DMF (1 5 ml) Despues de 16 horas la mezcla se diluyo con tolueno y la solucion se lavó con agua, ácido clorhídrico (2M), agua y solución de bicarbonato de sodio La adicion de IPA y el retiro de los disolventes *in vacuo* produjeron el compuesto del título M/z 653 56 (M+H)+ y 651 60 $(M-H)^-$

Ejemplo 48

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(S)-1,3-bis-(carboxi)propil]carbamoilmetoxi}fenil)azetidin-2-ona

A una solucion de 1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-

199

hidroxipropil]-4-(4-{*N*-[(S)-1,3-bis-(etoxicarbonil)propil]carbamoilmetoxi} fenil)azetidin-2-ona (Ejemplo 47, 30 mg, 0 046 mmol) en etanol (4 ml) se agrego 3 75 M solucion de hidroxido de sodio (0 05 ml, 0 19 mmol) Despues de 16 horas se agregó mas 3 75M solución de hidroxido de sodio (0 05 ml, 0 19 mmol) El etanol se retiró *in vacuo* y se agregaron THF (2 5 ml) y agua (1 5 ml) Despues de 24 horas la mezcla de reaccion se purifico por HPLC preparativa usando una gradiente de solución amortiguadora MeCN/amonio para producir el compuesto del titulo (11 mg, 40%) NMR (CD_3OD, 400 MHz) 7 5-6 9 (m), 5-4 8 (m), 4 75-4 6 (m), 4 5 (s), 4 45 (m), 4 4-4-3 (br s), 3 1-3 05 (m), 2 3-2 1 (m), 2-1 8 (m), m/z 597 52 $(M+H)^+$ y 595 49 $(M-H)^-$

Ejemplo 49

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(S)-1-(*t*-butoxicarbonil)-5-(*t*-butoxicarbonilamino)pentil]carbamoilmetoxi]fenil) azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Metodo 2, 30 mg, 0 064 mmol), *tert*-butil N^6- (*tert*-butoxicarbonil)-L-lisinato (39 mg, 0 13 mmol), trietil amina (0 036 ml, 0 26 mmol) y TBTU (31 mg, 0 096 mmol) se mezclaron en DMF (1 50 ml) La mezcla se agitó durante 16 horas y luego se diluyó con agua y tolueno La fase orgánica se lavó con ácido clorhídrico, agua, solución de bicarbonato de sodio y luego agua IPA se agregó a la fase orgánica y los disolventes se retiraron *in vacuo* para producir el compuesto del titulo (39 mg, 81%) M/z 752 68 (M+H)+ y 750 79 $(M-H)^-$

Ejemplo 50

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(S)-1-(carboxi)-5-(amino)pentil]carbamoilmetoxi}fenil)azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4- {*N*-[(S)-1-(*t*-butoxicarbonil)-5-(*t*-butoxicarbonilamino)pentil]carbamoilmetoxi} fenil)azetidin-2-ona (Ejemplo 49, 39 mg, 0 052 mmol) se mantuvo en ácido

fórmico (2 ml) durante 64 horas El ácido se retiro *in vacuo* y el residuo se disolvió en metanol (4 ml) y amoníaco acuoso (25%, 0 4 ml) Despues de 16 horas el disolvente se retiro *in vacuo* y el residuo se purificó por HPLC preparativa usando una gradiente de solucion amortiguadora MeCN/amonio para producir el compuesto del titulo (7 mg, 23%) NMR (CD_3OD, 400 MHz) 7 4-7 2 (m, 6H), 7 05-6 95 (m, 6H), 4 8 (m, 1H), 4 65-4 6 (m, 1H), 4 5 (s, 2H), 4 35-4-3 (m,1H), 3 1-3 05 (m, 1H), 2 9-2 8 (m, 2H), 2-1 6 (m, 6H), 1 5-1 2 (m, 4H)

Ejemplo 51

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[2-(*t*-butoxicarbonil)etil]carbamoilmetoxi}fenil)azetidin-2-ona

Una mezcla de 1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 2, 47 mg, 0 101 mmol), *tert*-butil β-alaninato (48 mg, 0 33 mmol), trietilamina (0 07 ml, 0 5 mmol), y TBTU (42 mg, 0 13 mmol) se mezclaron en DMF (1 ml) y se dejaron de un día para otro La mezcla se diluyo con eter dietílico y se lavó con solucion de bisulfato de potasio y solución de carbonato de sodio La fase orgánica se secó (sulfato de magnesio) y el disolvente se retiro *in vacuo* para producir el compuesto del título (38 mg, 64%) M/z 595 54 $(M+H)^+$ y 593 61 $(M-H)^-$

Ejemplo 52

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropill-4-(4-{*N*-[2-(carboxi)etil]carbamoilmetoxi}fenil)azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[2-(*t*-butoxicarbonil)etil]carbamoilmetoxi}fenil)azetidin-2-ona (Ejemplo 51, 38 mg, 0 064 mmol) se disolvió en ácido fórmico (2 ml) Despues de 16 horas el ácido se retiró *in vacuo* con la ayuda de MeCN Después del retiro completo de los disolventes el residuo se disolvio en metanol (5 ml) y amoniaco acuoso (25%, 1 ml) La hidrolisis se completó en 2 horas y la purificación por HPLC usando una gradiente de solución amortiguadora

201

MeCN/amonio produjo el compuesto del titulo (20 mg, 59%) NMR (CD_3OD, 400 MHz) 7 4-7 2 (m, 6H), 7 1-6 9 (m, 6H), 4 8 (m, 1H), 4 7-4 6 (m, 1H), 4 5 (s, 2H), 3 5 (t, 2H), 3 1-3 05 (m, 1H), 2 4 (t, 2H), 2-1 8 (m, 4H), m/z 539 42 $(M+H)^+$ y 537 50 $(M-H)^-$

Ejemplo 53

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(R)-1-(*t*-butoxicarbonil)etil]carbamoilmetoxifenil)azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona (Método 2, 30 mg, 0 064 mmol), *tert*-butil D-alaninato clorhidrato (50 mg, 0 28 mmol), trietilamina (0 05 ml, 0 36 mmol) y TBTU (31 mg, 0 096 mmol) se agitaron en DMF (1 ml) durante 3 horas La mezcla se diluyó con tolueno y se lavó con agua, ácido clorhídrico, agua, solución de bicarbonato de sodio y agua. IPA se agrego a la fase organica y los disolventes se retiraron *in vacuo* para producir 30 mg (79%) del compuesto del titulo M/z 595 48 $(M+H)^+$ y 593 56 $(M-H)^-$

Ejemplo 54

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hedroxipropil]-4-(4-{*N*-[(R)-1-(carboxi)etil]carbamoilmetoxi}fenil)azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*- [(R)-1-(*t*-butoxicarbonil)etil]carbamoilmetoxi}fenil)azetidin-2-ona (Ejemplo 54, 30 mg, 0 05 mmol) se disolvió en ácido fórmico (2 ml) Después de 16 horas el ácido se retiro *in vacuo* y el residuo se disolvio en metanol (3 ml) y amoniaco acuoso (25%, 0 2 ml) Se siguió la evolución por HPLC y después de la conclusión la mezcla se purifico por HPLC usando una gradiente de solución amortiguadora MeCN/amonio para producir el compuesto del titulo (17 mg, 63%) NMR (CD_3OD, 400 MHz) 7 4-7 2 (m, 6H), 7 1-6 9 (m, 6H), 4 8 (m, 1H), 4 7-4 6 (m, 1H), 4 5 (s, 2H), 4 3-4 2 (s, 1H), 3 1-3 05 (m, 1H), 2 2-1 8 (m, 4H), 1 5-1 4 (m, 3H)

Preparación de los Materiales de Partida

Los materiales de partida para los Ejemplos anteriores se obtienen en el comercio o se preparan fácilmente por metodos estándar a partir de materiales conocidos Por ejemplo, las siguientes reacciones son una ilustracion, pero no una limitación, de algunos de los materiales de partida usados en las reacciones ya mencionadas

Método 1

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-*t*-butoxicarbonilmetoxifenil) azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-hidroxifenil)azetidin-2-ona (*J Med Chem* **1998**, *41*, 973-980, 50 mg, 0 122 mmol), tert-butilbromoacetato (24µl, 0 165 mmol), carbonato de sodio (80 mg, 0 76 mmol) y una cantidad catalitica de carbonato de cesio se agregaron a MeCN (3 ml) y la mezcla se agitó durante 1 5 horas a 50°C Los sólidos se extrajeron por filtración y el disolvente se evaporó bajo presion reducida La purificacion del residuo por cromatografía de columna usando DCM/EtOAc (100/7) como eluente produjo 35 mg, (55 %) del compuesto del título NMR (300 MHz) 1 45 (s, 9H), 1 8-2 1 (m, 4H), 2 25-2 3 (m, 1H), 3 05-3 15 (m, 1H), 4 5 (s, 2H), 4 55-4 6 (m, 1H), 4 75 (bs, 1H), 6 9-7 3 (m, 12H), m/z 524 3

Método 2

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-carboximetoxifenil)azetidin-2-ona

1-(4-Fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-*t*-butoxicarbonil metoxifenil)azetidin-2-ona (Método 1, 50 mg, 0 096 mmol) se agregó a ácido formico (3 ml) y la mezcla se agito durante 1 5 horas a la temperatura de la sala El disolvente se evaporó bajo presión reducida y metanol (3 ml) y trietilamina (150µl) se agregaron al residuo La mezcla se agito durante 2 horas a la temperatura de la sala y los disolventes se evaporaron bajo presión reducida. El residuo se purifico por HPLC preparativa usando solución amortiguadora MeCN/amonio (35 65) como

203

eluente Las fracciones recogidas se liofilizaron para obtener 32 mg (56%) del compuesto del título NMR (300 MHz, CD_3OD) 1 8-1 95 (m, 4H), 3 1 (bs, 1H), 4 4 (s, 2H), 4 55-4 65 (m, 1H), 4 8 (bs, 1H), 6 9-7 35 (m, 12H), m/z 466 1 $(m-H)^-$

Método 3

tert-Butil *N*-((2*R*)-2-{[(benciloxi)carbonil]amino}-2-feniletanoil)glicinato

Ácido (2R)-{[(benciloxi)carbonil]amino}(fenil)acético (Z-(R)-Phg-OH) (10 g, 35 0 mmol) y *tert*-butilglicina clorhidrato (6 3 g, 37 4 mmol) se disolvieron en DCM (200 ml) con 2,6-lutidina (8 2 ml, 70 4 mmol) Después de agitar 5 minutos a 0°C, se agrego TBTU (12 4 g, 38 6 mmol) y la agitación se continuó 1 hora 30 minutos a 0°C y 3 horas 45 minutos a la temperatura de la sala La mezcla de reaccion se lavó con agua (2 x 100ml), se secó (sulfato de magnesio) y se purifico con cromatografía de destello (DCM EtOAc 7 1→5 1) para producir el compuesto del título (13 g, 94 %) NMR (500 MHz) 1 45 (s, 9H), 3 84 (d, 1 H), 4 00 (dd, 1 H), 5 10 (m, 2H), 5 28 (br s, 1H), 6 13 (br s, 1 H), 6 23 (br s, 1 H), 7 30-7 44 (m, 10 H)

Método 4

tert-Butil *N*-[(2*R*)-2-amino-2-feniletanoil]glicinato

tert-Butil *N*-((2*R*)-2-{[(benciloxi)carbonil]amino}-2-feniletanoil) glicinato (Metodo 3, 12 8 g, 32 2 mmol) se disolvio en EtOH (99%, 200 ml) y tolueno (50 ml) Se agregó Pd/C(10%, 0 65 g) y se efectuó hidrogenación a presion atmosferica durante 5 horas 30 minutos a la temperatura de la sala La mezcla de reaccion se filtro a través de tierra de diatomeas y los disolventes se evaporaron para producir el compuesto del título (8 4 g, 99 %) NMR (600 MHz) 1 45 (s, 9 H), 3 93 (m, 2H), 4 54 (s, 1H), 7 31-7 42 (m, 5H), 7 51 (br s, 1H)

Método 5

tert-Butil *N*-((2R)-2-{[(benciloxi)carbonil]amino}-2-feniletanoil)-*O*-(*tert*-

204

butil)-L-serinato

Ácido (2*R*)-{[(benciloxi)carbonil]amino}(fenil) acético (Z-(R)-Phg-OH) (2 0 g, 7 0 mmol) y *tert*-butil *O*-(*tert*-butil)-L-serinato (2 0 g, 7 9 mmol) y 2 6-lutidina se disolvieron en DCM (30 ml) Después de agitar 5 minutos a 0°C se agregó TBTU (2 5 g, 7 8 mmol) y la agitación se continuo 30 minutos a 0°C y 4 horas a la temperatura de la sala La mezcla de reacción se lavó con agua (2 x 100 ml), se secó y se purifico con cromatografía de destello (DCM) para producir el compuesto del título (3 3g, 97 %) NMR (300 MHz, CD_3OD) 1 05 (s, 9H), 1 45 (s, 9H), 3 4-3 8 (m, 2H), 4 5 (bs, 1H), 4 85 (s, 2H), 5 1 (s, 2H), 5 4 (s, 1H), 7 25-7 5 (m, 10H)

Método 6

tert-Butil *N*-[(2R)-2-amino-2-feniletanoil]-*O*-(*tert*-butil)-L-serinato

tert-Butil *N*-((2*R*)-2-{[(benciloxi)carbonil]amino}-2-feniletanoil)-*O*-(*tert*-butil)-L-serinato (Método 5, 3 3 g, 6 8 mmol) se disolvió en EtOH (95%, 30 ml) y se agregó una cantidad catalítica de Pd/C (5%) (50% en agua) y se efectuó hidrogenación a presión atmosferica durante 3 horas a la temperatura de la sala La mezcla de reaccion se filtró a traves de tierra de diatomeas y el disolvente se evaporó para producir el compuesto del título (2 35 g, 98 %) NMR (500 MHz, CD_3OD) 1 1 (s, 9H), 1 45 (s, 9H), 3 45-3 8 (m, 2H), 4 5 (t, 1H), 4 55 (s, 1H), 4 85 (s, 2H), 7 3-7 5 (m, 5H)

Método 7

1-(4-Fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(*t*-butoxicarbonilmetoxi) fenil]azetidin-2-ona

Una mezcla de 1-(4-fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-(4-hidroxifenil)azetidin-2-ona (Preparada de acuerdo con Bioorg Med Chem Lett 1996, 6, 1271-1274, 1 00 g, 2 53 mmol), *t*-butil bromoacetato (0 42 ml, 2 79 mmol) y carbonato de cesio (1 00 g, 3 07 mmol) en MeCN (10 ml) se agito a 40°C durante 90 minutos Se filtró la suspensión y el material sólido se lavó con MeCN (5ml) y EtOAc (5 ml) El filtrado se concentró y el

residuo se purificó por cromatografía de destello usando una mezcla de hexano y EtOAc (7 2) como eluente El compuesto del título se obtuvo como un aceite incoloro (1 045 g, 81 %) NMR (600 MHz) 1 45 (s, 9H), 2 25-2 45 (m, 2H), 3 20-3 30 (m, 1H), 4 00-4-10 (m, 1H), 4 10-4 20 (m, 1H), 4 50 (s, 2H), 4 80 (d, 1H), 6 75-7 00 (m, 8H), 7 20-7 30 (m, 4H), m/z 501 2

Método 8

1-(4-Fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(carboximetoxi) fenil]azetidin-2-ona

Una solución de 1-(4-fluorofenil)-3-[2-(4-fluorofenoxi)etil]-4-[4-(*t*-butoxicarbonilmetoxi)fenil]azetidin-2-ona (Método 7, 1 045 g, 2 051 mmol) en ácido fórmico (4 ml) se agito a la temperatura de la sala durante 22 horas El disolvente se retiró bajo presión reducida y el residuo se disolvió en DCM (10 ml) La capa orgánica se lavó sucesivamente con una solucion de bicarbonato de sodio saturado (aq, 5 ml), agua (5 ml) y salmuera (5 ml), se secó y se concentró para producir el compuesto del título como un sólido blanco (0 941 g, ~rendimiento cuantitativo) NMR (400 MHz) 2 25-2 45 (m, 2H), 3 20-3 30 (m, 1H), 4 00- 4 20 (m, 2H), 4 65 (s, 2H), 4 80 (d, 1H), 6 75-6 80 (m, 2H), 6 85-7 00 (m, 6H), 7 20-7 30 (m, 4H), m/z 454 0

Método 9

3-(R)-4-(R)-1-(Fenil)-3-(feniletilsulfanil)-4-[4-(carboximetoxi)fenil] azetidin-2-ona

3-(R)-4-(R)-1-(Fenil)-3-(feniletilsulfanil)-4-[4-(*t*-butoxicarbonilmetoxi)fenil]azetidin-2-ona (Método 15, 220 mg) se agito en ácido fórmico (2 ml) durante 20 horas a temperatura ambiente Entonces se evaporó el acido fórmico Se agregó tolueno y se evaporo dos veces para producir el compuesto del título (180 mg) NMR 400 MHz, CD_3OD) 2 86-3 00 (m, 4H), 4 03 (d, 1H), 4 66 (s, 2H), 4 87 (d, 1H), 6 93-7 35 (m, 14H)

Métod 10

206

3-(R)-4-(R)-1-(Fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-[4-(carboximetoxi) fenil]azetidin-2-ona

Una solución de 3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-(4-hidroxifenil)azetidin-2-ona (sintetizada de acuerdo con WO 96/16037, 0 100 g, 0 245 mmol), carbonato de cesio (0 040 g, 0 123 mmol) y *t*-butil bromoacetato (0 019 ml, 0 129 mmol) en MeCN (0 5 ml) se agitó a la temperatura de la sala durante 10 minutos, luego de lo cual se agregaron más carbonato de cesio (0 040 g, 0 123 mmol) y *t*-butil bromoacetato (0 019 ml, 0 129 mmol) Después de 7 horas, se agregaron agua (5 ml) y AcOH (0 05 ml) a la mezcla de reacción y el disolvente orgánico se retiró bajo presión reducida La capa de agua se extrajo dos veces con DCM (2x5 ml) y las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio y se concentraron El residuo se purificó dos veces por cromatografía de destello usando heptano EtOAc (3 1) como eluente, lo cual produjo un aceite incoloro (0 066 g) M/z 522 1 Este aceite se disolvio en acido formico (3ml) y la solución se agitó a la temperatura de la sala durante 18 horas El disolvente se retiró bajo presión reducida y el residuo se purificó por HPLC preparativa, usando una gradiente de 20-50% MeCN en 0 1M solución amortiguadora de acetato de amonio como eluente El compuesto del titulo se obtuvo como un solido blanco (0 025 g, 22 %) NMR (CD_3COOD, 400 MHz) 4 20 (d, 1H), 4 25 (s, 2H), 4 70 (s, 2H), 5 00 (d, 1H), 6 90-7 10 (m, 2H), 7 00-7 40 (m, 9H), 8 00-8 10 (m, 2H), m/z 465 9

Método 11

3-(R)-4-(R)-1-(Fenil)-3-(tien-3-ilcarbonilmetilsulfanil)-4-[4-(carboximetoxi) fenil]azetidin-2-ona

Una solucion de 3-(R)-4-(R)-1-(fenil)-3-(tien-3-ilcarbonilmetilsulfanil)-4-(4-hidroxifenil)azetidin-2-ona (sintetizada de acuerdo con WO 96/16037, 0 100 g, 0 253 mmol), carbonato de cesio (0 043 g, 0 132 mmol) y *t*-butil bromoacetate (0 019 ml, 0 126 mmol) en MeCN (6 ml) se agito a la temperatura de la sala durante 10 minutos, luego

de lo cual se agregaron mas carbonato de cesio (0 040 g, 0 123 mmol) y *t*-butil bromoacetato (0 019 ml, 0 126 mmol) Después de 7 horas se agregaron agua (7 ml) y AcOH (0 05 ml), y el disolvente se retiro bajo presión reducida. La capa de agua se extrajo dos veces con DCM (2x3 ml) y las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magenesio y se concentraron El residuo se purifico por cromatografía de destello usando heptane EtOAc (3 1) como eluente, lo cual produjo 0 103 g de un aceite incoloro (m/z 510 1) Este aceite se disolvió en acido formico (3ml) y la solución se agitó durante 18 horas a la temperatura de la sala El disolvente se retiró bajo presión reducida y el residuo se disolvió en DCM La solucion se lavo dos veces con agua y una vez con salmuera, se secó sobre sulfato de magenesio y se concentro Esto produjo un aceite incoloro, el cual se usó sin más purificación (0 079 g) M/z 453 9

Método 12

1-(4-Fluorofenil)-3-(2-chloroetil)-4-(4-hidroxifenil)azetidin-2-ona

Una mezcla en agitación de 1-(4-fluorofenil)-3-(2-cloroetil)-4-[4-(benciloxi)fenil]azetidin-2-ona (preparada de acuerdo con Bioorg Med Chem Lett 1996, 6, 1271-1274, 2 00 g, 4 88 mmol), $Pd(OH)_2/C$ (0 500 g, 20%) y ciclohexeno (6 ml) en MeOH (60 ml) se calentó a 70°C Después de 2 horas, la mezcla de reacción se enfrió a la temperatura de la sala y se filtró a través de tierra de diatomeas El disolvente se retiro bajo presion reducida para producir el compuesto del título (1 57 g, ~ rendimiento cuantitativo) No fue necesaria más purificacion NMR (CD_3OD, 400 MHz) 2 20-2 40 (m, 2H), 3 20-3 40 (m, 1H), 3 70 (t, 2H), 4 85 (d, 1H), 6 75- 6 80 (m, 2H), 6 90-7 00 (m, 2H), 7 15-7 30 (m, 4H), m/z 320 0

Método 13

1-(4-Fluorofenil)-3-[2-(4-fluorofeniltio)etil]-4-(4-hidroxifenil)azetidin-2-ona

A una solución en agitacion de 1-(4-fluorofenil)-3-(2-chloroetil)-4-

(4-hidroxifenil)azetidin-2-ona (Método 12, 0 750 g, 2 35 mmol) en MeCN (10 ml) se agregaron 4-fluorotiofenol (0 500 ml, 4 60 mmol) y trietilamina (0 500 ml, 3 59 mmol) a la temperatura de la sala Despues de 20 horas quedaba todavía material (aproximadamente 20 %, LC/MS), y se agregaron más 4-fluorotiofenol (0 250 ml, 2 30 mmol) y trietilamina (0 170 ml, 1 22 mmol) Despues de 24 horas, el disolvente se retiró bajo presión reducida y el residuo se repartio en porciones entre agua (20 ml) y EtOAc (20 ml) La capa orgánica se lavó con salmuera (5 ml), se secó sobre sulfato de magenesio y se concentró El residuo se hizo refluir en heptano durante 30 minutos antes de extraer por filtracion el compuesto del titulo como un solido gris (0 946 g, 98 %) NMR (CD_3OD, 400 MHz) 2 00-2 20 (m, 2H), 3 05 (t, 2H), 3 25 (dt, 1H), 4 75 (d, 1H), 6 75-6 80 (m, 2H), 6 90-7 05 (m, 4H), 7 15-7 40 (m, 6H), m/z 412 0

Método 14

tert-Butil (2*S*)-2-{[(2*R*)-2-amino-2-(4-hidroxifenil)acetil]amino}butanoato clorhidrato

tert-butil (2*S*)-2-{[(2*R*)-2-{[(benciloxi)carbonil]amino}-2-(4-hidroxifenil)acetil]amino}butanoato (Metodo 18, 47g, 106 2mmol) se disolvió en 400ml 95 5% etanol Se agregó Pd/C (5%, 3 0g) y la mezcla se hidrogenó bajo H_2(g) a una presión de 1 bar a temperatura ambiente La hidrogenación se concluyo despues de 20 horas y el catalizador se extrajo por filtración en SiO_2 y se lavó con etanol El filtrado se concentro y el residuo (aprox 35g) se disolvió en 300ml MeCN Se agregó clorhidrato de piridina (14g) y la mezcla se dejó cristalizar durante 2 5 dias La sal formada se extrajo por filtración y se lavó con 2 x 50ml MeCN El sólido se secó bajo vacio a 40°C para producir 29 6 g (81%) de un producto blanco cristalino NMR (300MHz, DMSO-d_6) 0 64 (t, 3H), 1 39 (s, 9H), 1 40-1 70 (m, 2H), 3 98-4 04 (m, 1H), 4 90 (brs, 1H), 6 78 (d, 2H), 7 32 (d, 2H), 8 63 (brs, 3H), 8 79 (d, 1H), 9 83 (brs, 1H)

Métod 15

209

3-(R)-4-(R)-1-(Fenil)-3-(feniletilsulfanil)-4-[4-(*t*-butoxicarbonilmetoxi) fenil]azetidin-2-ona

Una mezcla de 3-(R)-4-(R)-1-(fenil)-3-(feniletilsulfanil)-4-(4-hidroxifenil)azetidin-2-ona (sintetizada de acuerdo con WO 96/16037, 0 5g, 1,33 mmol), *t*-butil bromoacetato (0 31g, 1 58mmol), carbonato de sodio (0 56g, 5 28mmol) y carbonato de cesio (0 12g, 0 36mmol) en MeCN se agitó a 50°C de un día para otro La mezcla de reaccion se filtró y el disolvente se retiró bajo presión reducida. El residuo se purifico por cromatografía (EtOAc isohexano, 1 6) para producir el compuesto del titulo 220 mg (33%) M/z 490 1

Método 16

1-(4-Fluorofenil)-3-[2-(4-fluorofeniltio)etil]-4-[4-(*t*-butoxicarbonilmetoxi) fenil]azetidin-2-ona

Una suspensión de 1-(4-fluorofenil)-3-[2-(4-fluorofeniltio)etil]-4-(4-hidroxifenil)azetidin-2-ona (Método 13, 0 800g, 1 944 mmol), *t*-butil bromoacetato (0 32 ml, 2 17 mmol) y carbonato de cesio (0 700 g, 2 15 mmol) en MeCN (15 ml) se agitó a la temperatura de la sala durante 2 horas El disolvente se retiró bajo presión reducida y el residuo se repartió en porciones entre agua (20 ml) y DCM (20ml) La capa de agua se extrajo una vez más con DCM (10 ml) y las capas organicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magenesio y se concentraron El residuo se purifico por cromatografía de destello usando heptano EtOAc (4 1) como eluente El compuesto del titulo se obtuvo como un aceite incoloro (0 884 g, 87 %) NMR (400 MHz) 1 45 (s, 9H), 2 00-2 30 (m, 2H), 2 90-3 10 (m, 2H), 3 15-3 25 (m, 1H), 4 50 (s, 2H), 4 60 (d, 1H), 6 85-7 00 (m, 6H), 7 15-7 35 (m, 6H), m/z 526 2

Método 17

1-(4-Fluorofenil)-3-[2-(4-fluorofeniltio)etil]-4-[4-(carboximetoxi)fenil] azetidin-2-ona

Una solucion de 1-(4-fluorofenil)-3-[2-(4-fluorofeniltio)etil]-4-[4-(*t*-

butoxicarbonilmetoxi)fenil]azetidin-2-ona (Método 16, 0 880 g, 1 67 mmol) en ácido fórmico (5 ml) se agitó a la temperatura de la sala durante 19 horas El disolvente se retiró bajo presión reducida y el residuo se disolvió en DCM (25 ml) La capa orgánica se lavo dos veces con agua (1x10 ml y 1x5 ml) y un vez con salmuera (5 ml), se secó sobre sulfato de magenesio y se concentro Esto produjo el compuesto del titulo como un aceite incoloro (0 800 g, ~ rendimiento cuantitativo) NMR (CD_3COOD, 400 MHz) 2 10-2 30 (m, 2H), 3 10 (dt, 2H), 3 30-3 40 (m, 1H), 4 75 (s, 2H), 4 80 (d, 1H), 6 95-7 05 (m, 6H), 7 25-7 40 (m, 6H), m/z 470 2

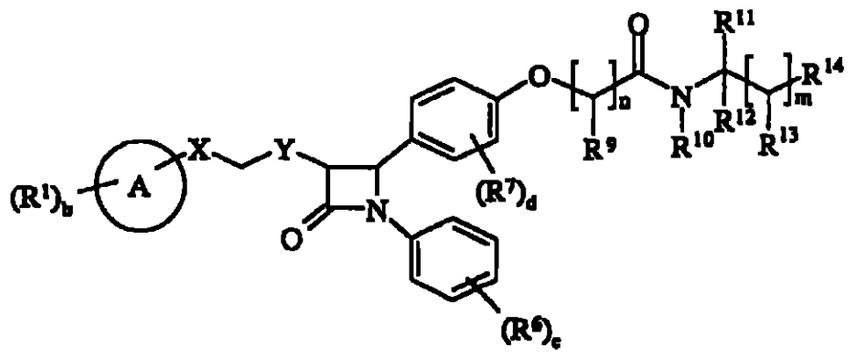
Método 18

tert-Butil (2*S*)-2-{[(2*R*)-2-{[(benciloxi)carbonil]amino}-2-(4-hidroxifenil) acetil]amino}butanoato

(R)-N-Benciloxicarbonil-4-hidroxifenilglicina (J Chem Soc Perkin Trans 1, EN, 7, 1991, 1629-1635, 24 9g, 82 6mmol), clorhidrato de t-butil ester de ácido (S)-2-aminobutírico (18 6g, 95 0mmol) y *N*-metilmorfolina (23 0g, 227 4mmol) se disolvieron en 220 ml DMF TBTU (33 7g, 105 0mmol) se agrego en porciones durante 10min La mezcla de reacción se agitó durante 1 hora a temperatura ambiente Aproximadamente 100ml de disolvente se evaporaron de la solución Se agregó agua (250ml) a la solución restante, lo cual hizo que el producto se precipitara La mezcla se dejó de un dia para otro, luego el solido se extrajo por filtración y se lavo con 30% metanol (200ml) y hexano (100ml) El sólido se dispersó en 100ml de t-butil metil eter y se agito durante 1 hora. El sólido se extrajo por filtración, se lavó con t-butil metil eter (100ml) y se secó bajo vacio a 40°C para producir 34 7g (95%) NMR (300MHz, DMSO-d_6) 0 71 (t, 3H), 1 37 (s, 9H), 1 40-1 70 (m, 2H), 3 91-4 01 (m, 1H), 5 02 (d, 2H), 5 23 (d, 1H), 6 67 (d, 2H), 7 22 (d, 2H), 7 27-7 36 (m, 5H), 7 67-7 74 (m, 1H), 8 32 (d, 1H), 9 37 (brs, 1H)

Reivindicaciones

1 Un compuesto (I)·



(I)

en donde

Anillo A se selecciona de fenilo o tienilo,

X se selecciona de $-CR^2R^3-$, -O-, $-NR^x-$ y $-S(O)_a-$, en donde R^x es hidrogeno o C_{1-6}alquilo, y a es 0-2,

Y se selecciona de $-CR^4R^5-$, -O-, $-NR^z-$ y $-S(O)_a-$, en donde R^z es hidrógeno o C_{1-6}alquilo, y a es 0-2, en donde hay por lo menos un grupo $-CR^2R^3-$ ó $-CR^4R^5-$,

R^1 se selecciona independientemente de halo, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxi y C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, en donde R^1 se sustituye independientemente de manera opcional en carbono por uno o mas halo, C_{1-6}alcoxi e hidroxi,

b es 0-3, en donde los valores de R^1 pueden ser los mismos o diferentes,

R^2 y R^3 se seleccionan independientemente de hidrógeno, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxi y C_{1-6}alcanoiloxi, en donde R^2 y R^3 pueden sustituirse independientemente de manera opcional por uno o más halo o hidroxi, ó R^2 y R^3 juntos forman un grupo oxo,

R^4 y R^5 se seleccionan independientemente de hidrógeno, hidroxi, C_{1-6}alquilo, C_{1-6}alcoxi y C_{1-6}alcanoiloxi, ó R^4 y R^5 juntos forman un grupo oxo,

R^6 se selecciona independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, formilo, carbamoilo, carbamoiloxi, mercapto, sulfamoilo,

C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alqueniloxi, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, C_{1-6}alcanoil-*N*-(C_{1-6}alquil)amino, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, *N*-(C_{1-6}alquil)carbamoiloxi, *N*,*N*-(C_{1-6}alquil)$_2$carbamoiloxi, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, C_{1-6}alcoxicarbonilamino, C_{1-6}alcoxicarbonil-*N*-(C_{1-6}alquil)amino, C_{1-6}alcoxicarboniloxi, C_{1-6}alcoxicarbonilamino, ureido, *N'*-(C_{1-6}alquil)ureido, *N*-(C_{1-6}alquil) ureido, *N'*,*N'*-(C_{1-6}alquil)$_2$ureido, *N'*-(C_{1-6}alquil)-*N*-(C_{1-6}alquil)ureido, *N'*,*N'*-(C_{1-6}alquil)$_2$-*N*-(C_{1-6}alquil)ureido, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo y fenilo, en donde R^7 se sustituye independientemente de manera opcional en carbono por uno o más halo, C_{1-6}alcoxi, hidroxi, amino, carboxi, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alcanoilamino, C_{1-6}alcanoil-*N*-(C_{1-6}alquil)amino, fenilo, fenoxi, benzoilo, fenilC_{1-6}alquilo y fenilC_{1-6}alcoxi,

c es 0-5, en donde los valores de R^6 pueden ser los mismos o diferentes,

R^7 se selecciona independientemente de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carboxi, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxicarbonilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, *N*-metilcarbamoilo, *N*,*N*-dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, *N*-metilsulfamoilo y *N*,*N*-dimetilsulfamoilo,

d es 0-4, en donde los valores de R^7 pueden ser los mismos o diferentes,

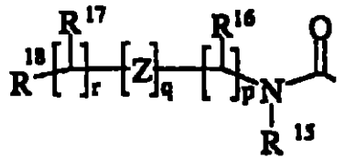
R^9 es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo, en donde R^9 puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{23}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{24},

R^{10} es hidrógeno o C_{1-4}alquilo,

R^{11} y R^{12} se seleccionan independientemente de hidrogeno, C_{1-4}alquilo, carbociclilo o heterociclilo, ó R^{11} y R^{12} forman conjuntamente C_{2-6}alquilen, en donde R^{11} y R^{12} ó R^{11} y R^{12} juntos pueden sustituirse independientemente de manera opcional por uno o mas sustituyentes seleccionados de R^{25}, y en donde, si dicho heterociclilo contiene una fraccion -NH-, ese nitrogeno puede sustituirse de manera opcional por uno o mas R^{26},

R^{13} es hidrógeno, C_{1-4}alquilo, carbociclilo o heterociclilo, en donde R^{13} puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{27}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrógeno puede sustituirse de manera opcional por uno o más R^{28},

R^{14} es hidrógeno, halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcoxicarbonilo, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-(C_{1-10}alquil)amino, *N*,*N*-(C_{1-10}alquil)$_2$amino, *N*,*N*,*N*-(C_{1-10}alquil)$_3$ammonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil) sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilamino, C_{1-10}alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_e$-R^{29}-(C_{1-10}alquilen)$_f$-, heterociclil-(C_{1-10}alquilen)$_g$-R^{30}-(C_{1-10}alquilen)$_h$-, carboxi, sulfo, sulfino, fosfono, -P(O)(OR^{31})(OR^{32}), -P(O)(OH)(OR^{31}), -P(O)(OH)(R^{31}) ó -P(O)(OR^{31})(R^{32}) en donde R^{31} y R^{32} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{14} puede sustituirse de manera opcional en carbono por uno o mas sustituyentes seleccionados de R^{33}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{34}, o R^{14} es un grupo de fórmula (IA)



(IA)

en donde

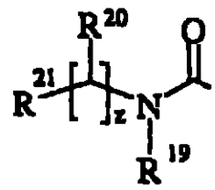
Z es -N(R^{35})-, -N(R^{35})C(O)-, -O-, y -S(O)$_a$-, en donde a es 0-2 y R^{35} es hidrógeno o C_{1-4}alquilo,

R^{15} es hidrógeno o C_{1-4}alquilo,

R^{16} y R^{17} se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, carbociclilo, heterociclilo, sulfo, sulfino, amidino, fosfono, -P(O)(OR^{36})(OR^{37}), -P(O)(OH)(OR^{36}), -P(O)(OH)(R^{36}) o -P(O)(OR^{36})(R^{37}), en donde R^{36} y R^{37} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{16} y R^{17} pueden sustituirse independientemente de manera opcional por uno o más sustituyentes seleccionados de R^{38}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrogeno puede sustituirse de manera opcional por un grupo seleccionado de R^{39},

R^{18} se selecciona de hidrógeno halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-(C_{1-10}alquil)amino, *N*,*N*-(C_{1-10}alquil)$_2$amino, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, C_{1-10}alcoxicarbonilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, C_{1-10}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-10}alquil)sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil)sulfamoilamino, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_e$-R^{40}-(C_{1-10}alquilen)$_f$ o

heterociclil-(C_{1-10}alquilen)$_g$-R^{41}-(C_{1-10}alquilen)$_h$-, carboxi, sulfo, sulfino, fosfono, -P(O)(OR^{42})(OR^{43}), -P(O)(OH)(OR^{42}), -P(O)(OH)(R^{42}) ó -P(O)(OR^{42})(R^{43}) en donde R^{42} y R^{43} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{18} puede sustituirse de manera opcional en carbono por uno o más sustituyentes seleccionados de R^{44}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{45}, o R^{18} es un grupo de fórmula **(IB)**



(IB)

en donde

R^{19} se selecciona de hidrogeno o C_{1-4}alquilo,

R^{20} se selecciona de hidrógeno halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, carbociclilo, heterociclilo, sulfo, sulfino, amidino, fosfono, -P(O)(OR^{46})(OR^{47}), -P(O)(OH)(OR^{46}), -P(O)(OH)(R^{46}) ó -P(O)(OR^{46})(R^{47}), en donde R^{46} y R^{47} se seleccionan independientemente de C_{1-6}alquilo, donde R^{20} pueden sustituirse independientemente de manera opcional por uno o más sustituyentes seleccionados de R^{48}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{49},

R^{21} se selecciona de halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, $C_{1\ 10}$alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcoxicarbonilo, C_{1-10}alcanoilo, C_{1-10}alcanoiloxi, *N*-(C_{1-10}alquil)amin , *N,N*-(C_{1-10}alquil)$_2$amino, *N,N,N*-(C_1

$_{10}$alquil)amonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, $C_{1\ 10}$alquilS(O)$_a$ en donde a es 0 a 2, *N*-($C_{1\ 10}$alquil)sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-(C_{1-10}alquil) sulfamoilamino, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilamino, $C_{1\ 10}$alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclil$C_{1\ 10}$alquilo, carbociclil-(C_{1-10}alquilen)$_c$-R^{50}-(C_{1-10}alquilen)$_f$, heterociclil-($C_{1\ 10}$alquilen)$_g$-R^{51}-(C_{1-10}alquilen)$_h$-, carboxi, sulfo, sulfino, fosfono, -P(O)(OR^{52})(OR^{53}), -P(O)(OH)(OR^{52}), -P(O)(OH)(R^{52}) o -P(O)(OR^{53})(R^{53}) en donde R^{52} y R^{53} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{21} pueden sustituirse independientemente de manera opcional por uno o más R^{54}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{55},

p es 1-3, en donde los valores de R^{16} pueden ser los mismos o diferentes,

q es 0-1,

r es 0-3, en donde los valores de R^{17} pueden ser los mismos o diferentes,

m es 0-2, en donde los valores de R^{13} pueden ser los mismos o diferentes,

n es 1-2, en donde los valores de R^{9} pueden ser los mismos o diferentes,

z es 0-3, en donde los valores de R^{20} pueden ser los mismos o diferentes,

R^{23}, R^{25}, R^{27}, R^{33}, R^{38}, R^{44}, R^{48} y R^{54} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carbamoilo, mercapto, sulfamoilo, hidroxiaminocarbonilo, C_{1-10}alquilo, C_{2-10}alquenilo, C_{2-10}alquinilo, C_{1-10}alcoxi, C_{1-10}alcanoilo, $C_{1\ 10}$alcanoiloxi, C_{1-10}alcoxicarbonilo, *N*-C_{1-10}alquil)amino, *N*,*N*-(C_{1-10}alquil)$_2$amino, *N*,*N*,*N*-(C_{1-10}alquil)$_3$amonio, C_{1-10}alcanoilamino, *N*-(C_{1-10}alquil)carbamoilo, *N*,*N*-(C_{1-10}alquil)$_2$carbamoilo, $C_{1\ 10}$alquilS(O)$_a$ en donde a es 0 a 2, *N*-($C_{1\ 10}$alquil)sulfamoilo, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilo, *N*-(C_{1-10}

217

$_{10}$alquil)sulfamoilamino, *N*,*N*-(C_{1-10}alquil)$_2$sulfamoilamino, C_{1-10}alcoxicarbonilamino, carbociclilo, carbociclilC_{1-10}alquilo, heterociclilo, heterociclilC_{1-10}alquilo, carbociclil-(C_{1-10}alquilen)$_e$-R^{56}-(C_{1-10}alquilen)$_f$, heterociclil-(C_{1-10}alquilen)$_g$-R^{57}-(C_{1-10}alquilen)$_h$-, carboxi, sulfo, sulfino, amidino, fosfono, -P(O)(OR^{58})(OR^{59}), -P(O)(OH)(OR^{58}), -P(O)(OH)(R^{58}) o -P(O)(OR^{59})(R^{59}), en donde R^{58} y R^{59} se seleccionan independientemente de C_{1-6}alquilo, en donde R^{23}, R^{25}, R^{27}, R^{33}, R^{38}, R^{44}, R^{48} y R^{54} pueden sustituirse independientemente de manera opcional por uno o mas R^{60}, y en donde, si dicho heterociclilo contiene un grupo -NH-, ese nitrógeno puede sustituirse de manera opcional por un grupo seleccionado de R^{61},

R^{24}, R^{26}, R^{28}, R^{34}, R^{39}, R^{45}, R^{49}, R^{55} y R^{61} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, sulfamoilo, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, bencilo, fenetilo, benzoilo, fenilsulfonilo y fenilo,

R^{29}, R^{30}, R^{40}, R^{41}, R^{50}, R^{51}, R^{56} y R^{57} se seleccionan independientemente de -O-, -NR^{62}-, -S(O)$_x$-, -NR^{62}C(O)NR^{63}-, -NR^{62}C(S)NR^{63}-, -OC(O)N=C-, -NR^{62}C(O)- ó -C(O)NR^{62}-, en donde R^{62} y R^{63} se seleccionan independientemente de hidrógeno o C_{1-6}alquilo, y x es 0-2,

R^{60} se selecciona de halo, hidroxi, ciano, carbamoilo, ureido, amino, nitro, carboxi, carbamoilo, mercapto, sulfamoilo, trifluorometilo, trifluorometoxi, metilo, etilo, metoxi, etoxi, vinilo, alilo, etinilo, metoxicarbonilo, formilo, acetilo, formamido, acetilamino, acetoxi, metilamino, dimetilamino, *N*-metilcarbamoilo, *N*,*N*-dimetilcarbamoilo, metiltio, metilsulfinilo, mesilo, *N*-metilsulfamoilo y *N*,*N*-dimetilsulfamoilo, y

e, f, g y h se seleccionan independientemente de 0-2,

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

2 Un compuesto de fórmula (I) de acuerdo con la reivindicación 1 en

248

donde X se selecciona de-CH_2-, -CH(OH)-,-C(O)-,-O- -S-, -S(O)- y -$S(O)_2$-, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco

3 Un compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 o 2 en donde Y es-CH_2-, -S- o -S(O)-, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

4 Un compuesto de formula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 3 en donde R^1 es halo, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

5 Un compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 4 en donde b es 0-1, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

6 Un compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 5 en donde R^6 es halo, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco

7 Un compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 6 en donde c es 0-1, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

8 Un compuesto de formula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 7 en donde d es 0, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

9 Un compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 8 en donde R^9 es hidrogeno, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

n es 1 , y

R^{33} es hidroxi, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

14 Un compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 13 en donde m es 0 o 1, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco

15 Un compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 14 en donde n es 1, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

16 Un compuesto de fórmula (I) (como se describe en la reivindicacion 1) en donde

Anillo A se selecciona de fenilo o tienilo,

X se selecciona de $-CH_2-$, -CH(OH)-, -C(O)-, -O- -S-, -S(O)- y $-S(O)_2-$,

Y es $-CH_2-$, -S- ó -S(O)-,

R^1 es fluoro,

b es 0-1,

R^6 es fluoro,

c es 0-1,

d es 0,

R^9 es hidrógeno,

R^{10} es hidrógeno,

uno de R^{11} y R^{12} es hidrogeno y el otro se selecciona de hidrógeno metilo, hidroximetilo, 2-carbamoiletilo, 2-(etoxicarbonil) etilo, 2-carboxietilo, 4-(*t*-butoxicarbonilamino)butilo, 4-aminobutilo, isobutilo, fenilo, 4-hidroxifenilo y 4-hidroxibencilo,

R^{13} es hidrógeno,

R^{14} es hidroxi, pentilo, metoxi, etoxicarbonilo, *t*-butoxicarbonilo, carboxi o sulfo, en donde R^{14} puede sustituirse de manera opcional en

carbono por uno o mas sustituyentes seleccionados de R^{33}, o R^{14} es un grupo de fórmula (IA) (como se describe más arriba) en donde

R^{15} es hidrógeno,

R^{16} y R^{17} se seleccionan independientemente de hidrogeno, carboxi, C_{1-6}alquilo y *t*-butoxicarbonilo,

R^{18} se selecciona de hidroxi, metilo, *t*-butoxi, etoxicarbonilo, *t*-butoxicarbonilo, carboxi y sulfo,

p es 1,

q es 0,

r es 0 ó 1,

m es 0 ó 1,

n es 1, y

R^{33} es hidroxi,

o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

17 Un compuesto de fórmula (I) (como se describe en la reivindicación 1) seleccionado de

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-((R)-α-{*N*-(S)-[1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona,

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[(R)-α-(carboxi)bencil]carbamoilmetoxi}fenil)azetidin-2-ona,

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona,

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-(4-{*N*-[*N*-(carboximetil)carbamoilmetil]carbamoilmetoxi}fenil)azetidin-2-ona,

1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(2-hidroxietil)carbamoilmetoxi]fenil}azetidin-2-ona,

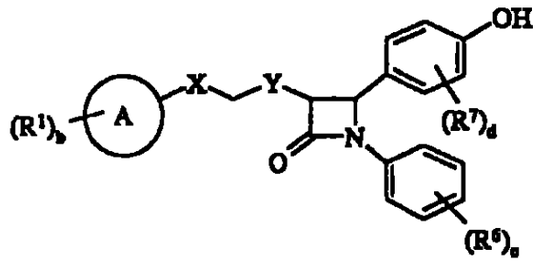
1-(4-fluorofenil)-3-[3-(4-fluorofenil)-3-hidroxipropil]-4-{4-[*N*-(2-metoxietil)carbamoilmetoxi]fenil}azetidin-2-ona,

3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-{4-[*N*-

(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona,
3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona,
3-(R)-4-(R)-1-(fenil)-3-[2-(tien-3-il)-2-hidroxietilsulfanil]-4-{4-[*N*-(carboximetil)carbamoilmetoxi]fenil}azetidin-2-ona,
3-(R)-4-(R)-1-(fenil)-3-[2-(tien-3-il)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona,
3-(R)-4-(R)-1-(fenil)-3-(4-fluorobenzoilmetilsulfanil)-4-(4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona, y
3-(R)-4-(R)-1-(fenil)-3-[2-(4-fluorofenil)-2-hidroxietilsulfanil]-4-{4-[*N*-((R)-α-{*N*-[(S)-1-(carboxi)-2-(hidroxi)etil]carbamoil}bencil) carbamoilmetoxi]fenil}azetidin-2-ona,
o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profarmaco

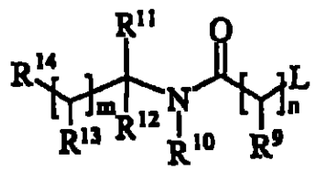
18 Un proceso para preparar un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, proceso que (en donde los grupos variables, a menos que se especifique lo contrario, son como se define en la reivindicacion 1) consta de

Proceso 1) hacer reaccionar un compuesto de fórmula (II)



(II)

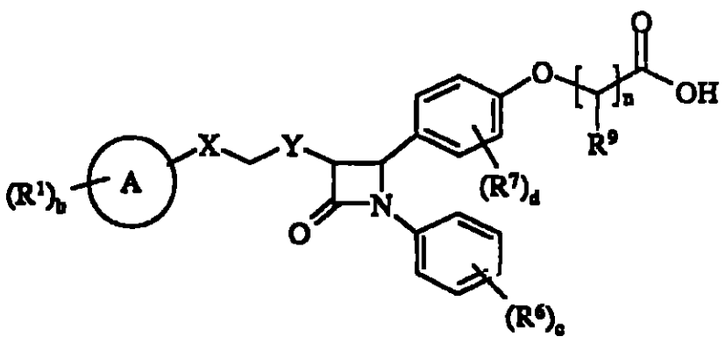
con un compuesto de fórmula (III)



(III)

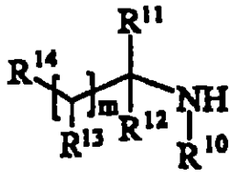
en donde L es un grupo desplazable,

Proceso 2) hacer reaccionar un ácido de fórmula (IV)



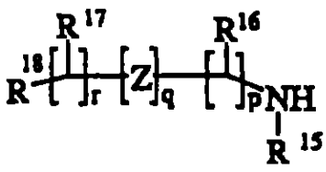
(IV)

o su derivado activado, con una amina de fórmula (V)



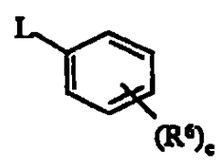
(V)

Proceso 3) para compuestos de fórmula (I) en donde R^{14} es un grupo de fórmula (IA), hacer reaccionar un compuesto de fórmula (VI) en donde R^{14} es carboxi, o su derivado activado, con una amina de formula (VI)



(VI)

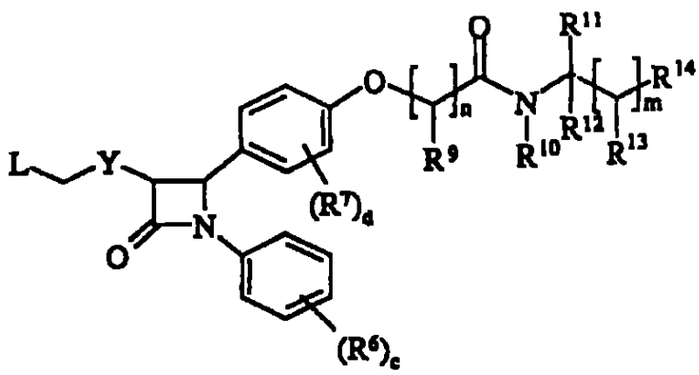
Proceso 4) para compuestos de fórmula (I) en donde R^{14} es un grupo de fórmula (IA), Z es $-N(R^{35})C(O)-$ y q es 1, hacer reaccionar un acido de formula (VII)



(XI)

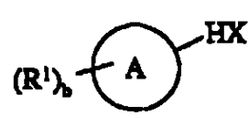
en donde L es un grupo desplazable,

Proceso 7) para compuestos de fórmula (I) en donde X se selecciona de -O-, $-NR^x-$ y $-S(O)_a$ en donde a es 0, hacer reaccionar un compuesto de formula (XII)



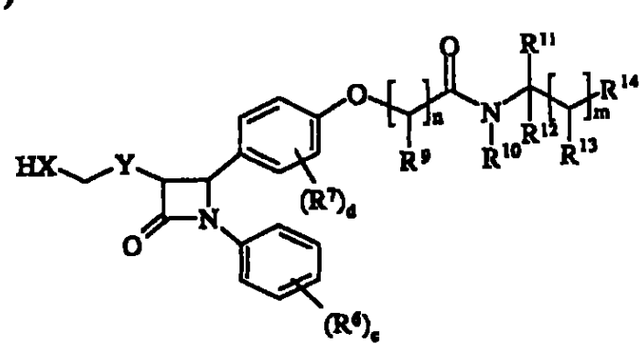
(XII)

en donde L es un grupo desplazable, con un compuesto de formula (XIII)



(XIII)

Proceso 8) para compuestos de fórmula (I) en donde X se selecciona de -O-, $-NR^x-$ y $-S(O)_a$ - en donde a es 0, hacer reaccionar un compuesto de fórmula (XIV)



(XIV)

con un compuesto de formula (XV)

una cualquiera de las reivindicaciones 1-16, para uso como un medicamento

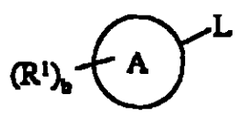
22 El uso de un compuesto de la formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1-16, en la producción de un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre

23 El uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1-16, en el tratamiento de afecciones hiperlipidemicas en un animal de sangre caliente, tal como el hombre

24 El uso de un compuesto de la fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco, como se reivindica en una cualquiera de las reivindicaciones 1-16, en la manufactura de un medicamento para uso en la producción de un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre

25 El uso de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1-16, en la manufactura de un medicamento para uso en el tratamiento de afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre

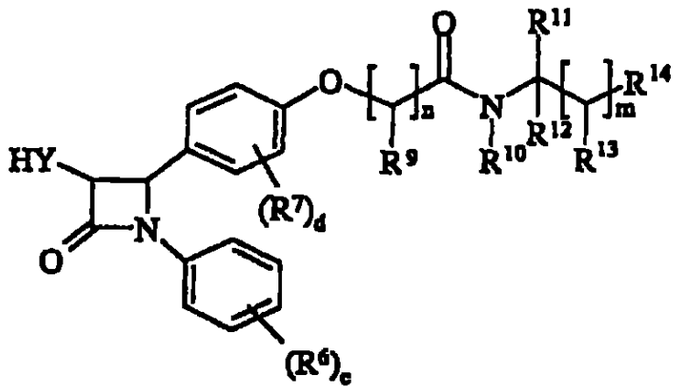
26 Un método para producir un efecto inhibidor de absorcion de colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco, como se reivindica en una cualquiera de las reivindicaciones 1-16



(XV)

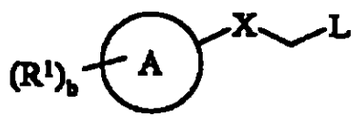
en donde L es un grupo desplazable,

Proceso 9) para compuestos de formula (I) en donde Y se selecciona de -O-, $-NR^z-$ y $-S(O)_a$ en donde a es 0, hacer reaccionar un compuesto de fórmula (XVI)



(XVI)

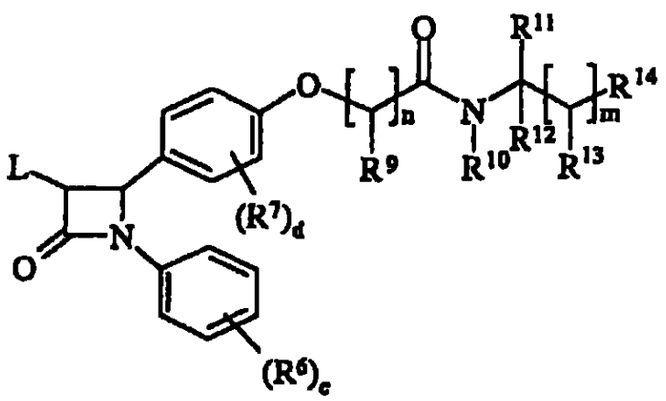
con un compuesto de fórmula (XVII)



(XVII)

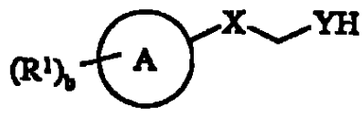
en donde L es un grupo desplazable,

Proceso 10) para compuestos de formula (I) en donde Y se selecciona de -O-, $-NR^z-$ y $-S(O)_a-$ en donde a es 0, hacer reaccionar un compuesto de fórmula (XVIII)



(XVIII)

en donde L es un grupo desplazable, con un compuesto de formula (XIX)



(XIX)

Proceso 11) para compuestos de fórmula (I) en donde X ó Y es $-S(O)_a-$ y a es 1 o 2, oxidar un compuesto de formula (I) en donde X ó Y es $-S(O)_a-$ y a es 0 (para compuestos de fórmula (I) en donde a es 1 ó 2) o a es 1 (para compuestos de fórmula (I) en donde y a es 2),

y posteriormente, si es necesario o deseable,

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

ii) retirar cualesquiera grupos protectores,

iii) formar una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco, o

iv) separar dos o más enantiomeros

19 Una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1-16, en asociacion con un diluyente o vehículo farmacéuticamente aceptables

20 Un compuesto de la fórmula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1-16, para uso en un metodo de tratamiento terapéutico o profiláctico de un animal de sangre caliente, tal como el hombre

21 Un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se reivindica en

27 Un método de tratar afecciones hiperlipidemicas en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de formula (I), o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1-16

28 Una combinación de un compuesto de formula (I), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, como se reivindica en una cualquiera de las reivindicaciones 1-16, y un inhibidor de HMG Co-A reductasa, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco

29 Una combinacion de acuerdo con la reivindicacion 28 en donde los inhibidores de HMG Co-A reductasa se seleccionan de fluvastatina, lovastatina, pravastatina, simvastatina, atorvastatina, cerivastatina, bervastatina, dalvastatina, pitvastatina, mevastatina y rosuvastatina, o su sal farmaceuticamente aceptable, solvato, solvato de tal sal o profarmaco

30 Una composición farmacéutica que comprende una combinación de acuerdo con una cualquiera de las reivindicaciones 28 ó 29, en asociación con un diluyente o vehiculo farmacéuticamente aceptables

31 El uso de una combinación de acuerdo con una cualquiera de las reivindicaciones 28 ó 29, en la produccion de un efecto reductor del colesterol en un animal de sangre caliente, tal como el hombre

32 El uso de una combinación de acuerdo con una cualquiera de las reivindicaciones 28 ó 29, en el tratamiento de afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre

230

33 El uso de una combinación de acuerdo con una cualquiera de las reivindicaciones 28 o 29, en la manufactura de un medicamento para uso en la producción de un efecto reductor del colesterol

34 El uso de una combinación de acuerdo con una cualquiera de las reivindicaciones 28 ó 29, en la manufactura de un medicamento para uso en el tratamiento de afecciones hiperlipidémicas

35 Un método para producir un efecto inhibidor de absorción de colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad eficaz de una combinacion de acuerdo con una cualquiera de las reivindicaciones 28 ó 29

36 Un método de tratar afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de una combinación de acuerdo con una cualquiera de las reivindicaciones 28 o 29

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
100758-1 WO		
International application No.	**International filing date** *(day/month/year)*	**Priority date** *(day/month/year)*
PCT/GB03/02811	01/07/2003	05/07/2002
International Patent Classification (IPC) or national classification and IPC		
C07D205/08		
Applicant		
ASTRAZENECA AB et al		

CODE		NTD

ANKOM 13 MAY 2004 GIPS

ENTERED
FINAL CHECK

1 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36

2 This REPORT consists of a total of 2 sheets including this cover sheet.

☐ This report is also accompanied by ANNEXES i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3 This report contains indications relating to the following items:

I ☒ Basis of the report

II ☐ Priority

III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/01/2004	05/05/2004
Name and mailing address of the IPEA/	**Authorized officer**
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax. (+49-89) 2399-4465	VERHULST W Tel. (+49-89) 2399 2828

Europäisches Patentamt
European Patent Office
Office européen des brevets

232

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No PCT/GB03/02811

I Basis of the report

The basis of this international preliminary examination is the application as originally filed

III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66 1(e) PCT), see also international search report)

V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out

In light of the documents cited in the International search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT i e does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references)

TRATADO S BRE C PERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 PCT)

(Informe sustentado de acuerdo con la nota del presidente del editor de la Organización Europea de Patentes (EPO) en el OJ11/2001)

No de Expediente del Solicitante o Apoderado	PROCEDIMIENTO POSTERIOR	véase comunicación sobre el envío del Informe de examen preliminar internacional (Formulario PCT/IPEA/416)
100758-1 WO		

No de Expediente Internacional	Fecha Internacional de Presentación *(día/mes/año)*	Fecha de Prioridad *(día/mes/año)*
PCT/GB03/02811	01/07/2003	05/07/2002

Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC

C07D205 / 08

Solicitante

ASTRAZENECA AB et al

1 Este informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 36

2 Este INFORME comprende un total de 2 hojas inclusive esta portada

☐ Además se adjuntan ANEXOS al informe: en este caso se trata de hojas con descripciones, reivindicaciones y/o dibujos que se modificaron y que sirven de base a este informe y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70 16 y Sección 607 de las Instrucciones administrativas al PCT)

Estos anexos comprenden en total de _____ hojas

3 Este informe contiene datos con respecto a los siguientes puntos

I	☒	Base del Informe
II	☐	Prioridad
III	☒	Sin elaboración de un dictamen sobre novedad actividad inventiva y posibilidad de aplicación industrial
IV	☐	Uniformidad deficiente de la invención
V	☒	Declaración justificada según Artículo 35(2) con respecto a la novedad la actividad inventiva y la posibilidad de aplicación industrial documentos y explicaciones que sustentan esta declaración
VI	☐	Ciertos documentos enumerados
VII	☐	Ciertas deficiencias del registro internacional
VIII	☐	Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición	Fecha de la conclusión de este informe
20/01/2004	05/05/2004

Nombre y dirección postal de la Oficina Encargada del Examen Preliminar Internacional (IPEA)	Empleado Autorizado
Oficina Europea de Patentes D-80298 Munich Tel (+49 89) 2399 – 0 Tx. 523656 epmu d Fax (+49 89) 2399 – 4465	VERHULST W Tel (+ 49-89) 2399 2828

Formulario PCT/IPEA/409 (portada) P20476 (octubre 2002)

234

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL No de Solicitud Internacional PCT/GB03/02811

I Base del Informe

La base de este informe de examen preliminar la constituye la solicitud tal como se radicó originalmente

III Ausencia de formulación de opinión en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial

La cuestión de si la invención reivindicada parece ser novedosa, implicar una actividad inventiva o ser aplicable industrialmente no ha sido objeto del examen preliminar internacional con respecto a las reivindicaciones que no se han investigado (Artículo 17(2) (a) ó (3) y Regla 66 1 (e) PCT), véase también el informe de busqueda internacional)

V Declaración motivada bajo Regla 66 2(a)(ii) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial

En la medida en que se ha llevado a cabo el examen preliminar internacional (véase ítem III más amba en el texto), se señala lo siguiente

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención como se define en por lo menos algunas de las reivindicaciones, que han sido objeto de un informe de busqueda internacional, no parece satisfacer los criterios mencionados en Artículo 33(1) PCT, es decir, no parece ser novedosa y/o implicar una actividad inventiva (véase informe de busqueda internacional, en particular los documentos citados X y/o Y y referencias de reivindicaciones correspondientes)

A595983

PCT REQUEST

100758-1 WO

Original (for SUBMISSION) printed on 30 06 2003 11 58:26 AM

0	For receiving Office use only	
0 1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2 92 (updated 01 04 2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0 7	Applicant's or agent's file reference	100758-1 WO
I	Title of invention	CHEMICAL COMPOUNDS
II	Applicant	
II 1	This person is	applicant only
II-2	Applicant for	AP (GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW), EA (AM AZ BY KG KZ MD RU TJ TM), EP (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR), OA (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG), AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address	Sodertalje S-151 85 Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No	+44 1625 230148
II-9	Facsimile No	+44 1625 510752

236

III 1	Applicant and/or Inventor	
III 1 1	This person is	applicant only
III-1-2	Applicant for	MG
III-1-4	Name	ASTRAZENECA UK LIMITED
III 1-5	Address	15 Stanhope Gate London, Greater London W1K 1LN United Kingdom
III-1-6	State of nationality	GB
III 1 7	State of residence	GB
III-2	Applicant and/or Inventor	
III-2-1	This person is	applicant and inventor
III-2 2	Applicant for	US only
III-2-4	Name (LAST First)	STARKE, Ingemar
III-2-5	Address	AstraZeneca R&D Molndal S-431 83 Molndal Sweden
III-2-6	State of nationality	SE
III-2 7	State of residence	SE
III-3	Applicant and/or Inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III 3-4	Name (LAST First)	DAHLSTROM, Mikael, Ulf, Johan
III-3-5	Address	AstraZeneca R&D Molndal S-431 83 Molndal Sweden
III-3-6	State of nationality	FI
III-3-7	State of residence	SE
III-4	Applicant and/or Inventor	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST First)	LINDQVIST, Ann-Margret
III-4-5	Address	AstraZeneca R&D Molndal S-431 83 Molndal Sweden
III-4-6	State of nationality	SE
III-4-7	State of residence	SE
III-5	Applicant and/or Inventor	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST First)	NORDBERG, Mats, Peter
III-5-5	Address	AstraZeneca R&D Molndal S-431 83 Molndal Sweden
III-5-6	State of nationality	SE
III-5-7	State of residence	SE

PCT REQUEST

100758-1 WO

Original (for SUBMISSION) printed on 30 06.2003 11 56:26 AM

III-6	Applicant and/or Inventor	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST First)	SKJARET, Tore
III-6-5	Address	AstraZeneca R&D Molndal S-431 83 Molndal Sweden
III-6-6	State of nationality	NO
III-6-7	State of residence	SE
III 7	Applicant and/or Inventor	
III 7 1	This person is	applicant and inventor
III 7-2	Applicant for	US only
III-7-4	Name (LAST First)	LEMURELL, Malin, Anita
III-7-5	Address	AstraZeneca R&D Molndal S-431 83 Molndal Sweden
III 7-6	State of nationality	SE
III-7 7	State of residence	SE
IV 1	Agent or common representative or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as	agent
IV 1 1	Name	ASTRAZENECA
IV 1-2	Address	Global Intellectual Property Mereside Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
IV 1-3	Telephone No	+44 1625 230148
IV 1-4	Facsimile No.	+44 1625 510752

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any are specified between parentheses after the designation(s) concerned)	AP GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment if any are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V 1 V-2 and V-3 the applicant also makes under Rule 4 9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI 1 1	Filing date	05 July 2002 (05 07 2002)
VI 1-2	Number	0215579 4
VI-1-3	Country	GB
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

PCT REQUEST 100758-1 WO

Original (for SUBMISSION) printed on 30 06 2003 11 56 26 AM

VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement as at the international filing date to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	-
IX-2	Description	112	-
IX-3	Claims	17	-
IX-4	Abstract	1	EZABST00 TXT
IX-5	Drawings	0	-
IX-7	TOTAL	136	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX 19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X 1	Signature of applicant, agent or common representative		
X-1 1	Name	ASTRAZENECA	
X-1-2	Name of signatory	Lucy C Padget	
X-1 3	Capacity	Agent	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings	
10-2 1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP

PCT REQUEST

100758-1 WO

Original (for SUBMISSION) printed on 30 06.2003 11 58 28 AM

10-5	Transmittal of search copy delayed until search fee is paid	

240

FOR INTERNATIONAL BUREAU USE ONLY

11 1	Date of receipt of the record copy by the International Bureau	

241

242

The demand must be filed directly with the competent International Preliminary Examining Authority or if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 100758-1 WO
International application No PCT/GB2003/002811	International filing date *(day/month/year)* 01 July 2003 (01/07/2003)	(Earliest) Priority date *(day/month/year)* 05 July 2002 (05/07/2002)

Title of invention
DIPHENYLAZETIDINONE DERIVATIVES FOR TREATING DISORDERS OF THE LIPID METABOLISM

Box No. II APPLICANT(S)

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country)*	Telephone No. +44 1625230148
ASTRAZENECA AB SE-151 95 Sodertalje Sweden	Facsimile No. +46 8 553 28820
	Teleprinter No.
	Applicant's registration No. with the Office

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

Name and address *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country)*
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London
W1K 1LN
United Kingdom

State *(that is country)* of nationality GB	State *(that is country)* of residence GB

Name and address *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country)*
STARKE, Ingemar
AstraZeneca R&D Molndal
SE-431 83 Molndal
Sweden

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

[X] Further applicants are indicated on a continuation sheet.

242

Sheet No 2.

International application No.
100758-1 WO

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*
DAHLSTROM, Mikael Ulf Johan
AstraZeneca R&D Molndal
SE-431 83 Molndal
Sweden

State *(that is, country)* of nationality	State *(that is country)* of residence
FI	SE

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*
LINDDQVIST, Ann-Margret
AstraZeneca R&D Molndal
SE-431 83 Molndal
Sweden

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

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*
NORDBERG, Mats Peter
AstraZeneca R&D Molndal
SE-431 83 Molndal
Sweden

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

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*
SKJARET, Tore
AstraZeneca R&D Molndal
SE-431 83 Molndal
Sweden

State *(that is, country)* of nationality	State *(that is country)* of residence
NO	SE

☒ Further applicants are indicated on another continuation sheet

243

Sheet No

International application No
PCT/GB2003/002811

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address. *(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country.)*

LEMURELL, Malin Anita
AstraZeneca R&D Molndal
SE-431 83 Molndal
Sweden

State *(that is, country)* of nationality	State *(that is country)* of residence.
SE	SE

Name and address: *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is country)* of nationality	State *(that is country)* of residence

Name and address. *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is country)* of nationality	State *(that is country)* of residence

Name and address. *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality	State *(that is country)* of residence

☐ Further applicants are indicated on another continuation sheet

244

Sheet No 4

International application No
PCT/GB2003/002811

Box No. III AGENT OR COMMON REPRESENTATIVE, OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority in addition to the agent(s)/common representative appointed earlier

Name and address *(Family name followed by given name for a legal entity, full official designation The address must include postal code and name of country.)*

Lucy Clare PADGET
ASTRAZENECA
Global Intellectual Property
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

Telephone No.
+44 1625 517845

Facsimile No
+46 8 553 28820

Teleprinter No

Agent s registration No with the Office

☐ **Address for correspondence** Mark this check box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments *

1 The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2 ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3 ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69 1(d)

4 ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54*bis* 1(a)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT

245

Sheet No 5

International application No
PCT/GB2003/002811

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No IV for the purposes of international preliminary examination.

			For International Preliminary Examining Authority use only: received	not received
1	translation of international application	sheets	☐	☐
2	amendments under Article 34	sheets	☐	☐
3	copy (or where required, translation) of amendments under Article 19	sheets	☐	☐
4	copy (or where required, translation) of statement under Article 19	sheets	☐	☐
5	letter	sheets	☐	☐
6	other *(specify)*	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1 ☒ fee calculation sheet
2 ☐ original separate power of attorney
3 ☐ original general power of attorney
4 ☐ copy of general power of attorney, reference number if any
5 ☐ statement explaining lack of signature
6 ☐ sequence listing in computer readable form
7 ☐ tables in computer readable form related to a sequence listing
8 ☐ other *(specify)*

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Lucy Clare PADGET et al
Global Intellectual Property, Patents, AstraZeneca AB

For International Preliminary Examining Authority use only

1 Date of actual receipt of DEMAND:

2 Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b)

3 ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5 below, does not apply
☐ The applicant has been informed accordingly

4 ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5

5 ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82

6 ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis* 1(a) and item 7 or 8 below, does not apply

7 ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis* 1(a) as extended by virtue of Rule 80.5

8 ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis* 1(a) the delay in arrival is EXCUSED pursuant to Rule 82

For International Bureau use only

Demand received from IPEA on

See Notes to the demand form

AS 95 933

246

APOSTILLA

(Convention de La Haye du 5 octobre 1961)

1 **País** Suecia

El presente documento oficial

2 **ha sido firmado por** Sra Anne-Marie Bonde

3 **en su calidad de** Notario Publico

4 **y lleva el timbre/sello de** Notario Publico en Estocolmo

Atestado

5 **en** Estocolmo 6 **el** 1 de Diciembre de 2004

7 **de** Ministerio de Asuntos Exteriores

8 **Nº** 8566

9 **Timbre/Sello** 10 **Firma**

Madelaine Beronius

100758-IP CO

247

ASSIGNMENT **TRASPASO**

The undersigned, el abajo firmado

Ingemar STARKE
Mikael Ulf Johan DAHLSTROM
Ann-Margret LINDQVIST
Mats Peter NORDBERG
Tore SKJARET
Malin Anita LEMURELL

domiciled in domiciliado en

AstraZeneca R&D Mölndal, SE-431 83 Mölndal,
Sweden
(same address for all inventors)

hereby state under oath to be the sole and true inventor of

declara bajo juramento ser único y verdadero inventor de

DIPHENYLAZETIDINONE DERIVATIVES FOR TREATING DISORDERS OF THE LIPID METABOLISM

We state as well that we assign, without reservations or limitation, in favor of

Declaramos asimismo que cedemos y transferimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

a corporation organized and existing under the laws of

organizada y existente de conformidad con la leyes de

Sweden

domiciled in

domiciliada en

SE-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Ingemar STARKE

Mikael Ulf Johan DAHLSTROM

Ann-Margret LINDQVIST

Mats Peter NORDBERG

Tore SKJARET

Malin Anita LEMURELL

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

La infrascrita Anne-Marie Bonde, Notario Público de Estocolmo, Suecia, acredita que

INGEMAR S T A R K E,
ANN-MARGRET L I N D Q V I S T,
TORE S K J A R E T,
MIKAEL ULF JOHAN D A H L S T R Ö M, y
MALIN ANITA L E M U R E L L

han otorgado y firmado el documento que antecede.

Derechos 400 - Estocolmo, 2004-11-30

Coronas De oficio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

TRADUCCION DE LOS SELLOS QUE SE ENCUENTRAN EN EL DOCUMENTO DE CESIÓN DE DERECHOS SOBRE LA INVENCIÓN, OTORGADO POR LOS INVENTORES INGEMAR STARKE, MIKAEL ULF JOHAN DAHLSTROM, ANN-MARGRET LINDQVIST, MATS PETER NORDBERG, TORE SKJARET, MALIN ANITA LEMURELL, A LA SOCIEDAD **ASTRAZENECA AB**, DOMICILIADA EN S-151 85 SÖDERTÄLJE, SUECIA, DEL SUECO AL CASTELLANO

ANNE-MARIE BONDE
NOTARIO PÚBLICO DE ESTOCOLMO

249

Brigard & Castro

BOGOTA - COLOMBIA

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S**
de Bogotá, Colombia apoderados verdaderos y legales con poder especial amplio y suficiente para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso la obtención de patentes de invención, registros de marcas, diseños industriales modelos de utilidad, depósitos de nombres comerciales y enseñas registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales así como sus prórrogas renovaciones anotaciones de traspaso cambios de nombre y/o domicilio, elaborar tramitar y registrar contratos de licencia y licencias de cualesquiera clases intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez corporación funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como oposiciones al registro de marcas acciones de caducidad cancelación y nulidad, acciones reivindicatorias acciones derivadas de la obtención o explotación de licencias acciones de competencia desleal demandas penales acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad en el ejercicio de medidas cautelares y en otras acciones o medidas similares

A este efecto, lo(a) faculto(amos) para elevar solicitudes, formular descripciones enmiendas, protestas declaraciones oposiciones cancelaciones nulidades apelaciones y reclamos pagar impuestos cuotas y gravámenes prescritos por la ley, renunciar o desistir a derechos concedidos o en curso de concesión recibir toda clase de documentos y valores, dando el descargo respectivo y en general para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que crean conducentes al resguardo de mis (nuestros) intereses) con todas las demás facultades legales necesarias

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado en el como la facultad de desistir, transigir comprometer de sustituirlo en todo o en parte y revocar sustituciones Asimismo nombro(amos) a **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S**
domiciliado(s) en la Carrera 7 No 16-56 Piso 9 mis (nuestros) apoderados en Colombia con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We) ASTRAZENECA AB

domiciled in SE-151-Sodertalje, Sweden

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S**
of Bogotá Colombia, my (our) true and lawful attorneys with special ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities in any instance privileges of patents of invention registration of trademarks industrial designs and utility models registration of commercial names and emblems registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions renewals and recordal of assignments and changes of name and domicile related to the above to prepare prosecute and register licenses of any kind to act as plaintiff or defendant in any instance or recourse and before any judge, corporation public official or authority in judicial administrative and police actions such as oppositions to the registration of trademarks caducity cancellation and nullity actions claim actions derived from the obtaining or exploitation of licenses, action of unfair competition penal demands actions of indemnities for damages claims or observations on patent applications models industrial designs and utility models in the exercise of preventive measures and in other actions or similar proceedings

To that effect they are hereby empowered to file applications formulate descriptions amendments protests declarations oppositions cancellations nullities appeals and claims to pay taxes quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting to receive all kind of documents and valuables giving the respective release of receipt and in general to take before said authorities the necessary steps to such effect, and any measures that they may deem [illegible] the safeguard of my (our) interest(s) [illegible] other necessary legal powers

20 DIC. 2002
NOTARIO CUARENTA
Notary Fernando Mora
Bogotá, D.C. Colombia

This power includes the faculty to ratify or confirm [illegible] and compromise on my (our) behalf and [illegible] this power in whole or in part and to [illegible] substitutions At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S**
domiciled in Carrera 7 No 16 56 Piso 9 my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys

Granted and signed in Macclesfield, Cheshire, England
this 18th day of July 2003

Signature

Name KEVIN BILL
Title Director, IP Services

120816

250

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado que el declarante está autorizado por dicha compañía para conferir este poder que el sello estampado por él al pie de tal poder en nombre y representación de la expresada compañía es el sello oficial de ella y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad

Estado de
con fecha

y que quien confiere el presente poder es su representante

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003
personally appeared before me
KEVIN BILL
to me known and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
ATTORNEY
of
ASTRAZENECA AB

Which is legally constituted for a term not yet expired that deponent is authorized by said Company to confer this Power of Attorney that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof and that purpose for which this instrument is granted included within the corporate purpose of company

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company

State of Sweden
under date of 1st January 2003

and that he (she) who grants the present power of attorney is its Representative

Notary Public (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan

Notario Público (sello)

NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed

Notary Public (Seal)

LEGALIZACION POR APOSTILLA ES REQUERIDA

LEGALIZATION BY APOSTILLE IS REQUIRED

251

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

This public document / Le présent acte public

2. Has been signed by J B Hodgson
a été signé par

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

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

Certified/Attesté
5 at London/à Londres 6. the/le 17 February 2004

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

8. Number/sous No G348987

9 Stamp
timbre

10. Signature: J Ireland

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

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

En la Notaría Cuarenta de esta Ciudad se
extendió la presente fotocopia que reproduce
el original que se ha tenido a la vista.
20 DIC. 2004
NOTARIO CUARENTA (40)
Nerby Fernando Mora Sánchez
Bogotá, D.C., Colombia

TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el **Poder** concedido por **ASTRAZENECA AB**, domiciliada en SE - 151 Sodertalje, Suecia a **Ramiro Castro Duque** y/o **Juan Pablo Cadena Sarmiento** y/o **Beatriz Jaramillo S**, domiciliados en la Carrera 7 #16-56, P 9, Bogotá D C , Colombia

252

AUTENTICACIÓN

(Convención de La Haya del 5 de Octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1 País Reino Unido de Gran Bretaña e Irlanda del Norte

2 Este documento publico

ha sido firmado por **J B Hodgson**

3 actuando en capacidad de **Notario Publico**

4 lleva el sello de **Dicho Notario Publico**

CERTIFICADO

5 en Londres 6 el **17 de Febrero de 2004**

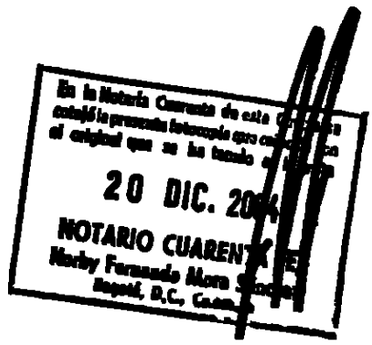
7 por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad

8 No **G348987**

9 Sello 10 Firma

J Ireland (Firma)

Si este documento va a ser utilizado en un país que no es parte de la Convención de La Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión que representa a ese país



GAVIRIA

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

253

Datos de la oficina de registro

Clase de oficina: Registraduría		Notaría	X	Consulado		Corregimiento		Insp. de Policía		Código	9999

País Departamento Municipio Corregimiento o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C NOTARIA 32.

Datos del inscrito

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción

Lugar de la Defunción País Departamento Municipio Corregimiento o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción	Hora	Número de certificado de defunción
Año 2004 Mes 10 Día 30	04:10 PM	A- 2094375.

Juzgado que profirió la sentencia — Presunción de muerte — Fecha de la sentencia: Año Mes Día

Documento presentado		Nombre y cargo del funcionario
Autenticación judicial	Certificación Médica: X	ANDRES DIAZ CAMPOS. R.M. No. 79982662

Datos del denunciante

Apellidos y nombres completos

EDGAR DAVID REGINO II.

Documentos de Identificación (Clase y número)	Firma
C.C.No. 15.030.154 DE LORICA CORDOBA	

Primer testigo

Apellidos y nombres completos

Documentos de Identificación (Clase y número)	Firma

Segundo testigo

Apellidos y nombres completos

Documentos de Identificación (Clase y número)	Firma

Fecha de inscripción	Nombre y firma del funcionario que autoriza
Año 2004 Mes 11 Día 02	BLANCA CECILIA VALENCIA RESTREPO NOTARIA 32

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE ORIGEN

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

CERTIFICO : QUE

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número 5T622491 que expido en la ciudad de Bogotá D C , hoy 11 NOV 2004

NELSON GALVEZ O
SECRETARIO DELEGADO

254

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicacion : 03000595 00000000
Fecha (AMD): 2005-01-05 16:42:47 Folios 254
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ **MODELO DE UTILIDAD**	( )	(✓)
Indicación de que se solicita la concesión de una patente	( )	(✓)
Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	(✓)
- Descripción de la invención	( )	(✓)
Dibujos de ser estos pertinentes. ✓	( )	(✓)
Comprobante de Pago de las tasas establecidas		
COMPLETA ( ) **INCOMPLETA**	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud		
- *Representación gráfica o fotografica del Diseño Industrial o muestra del* Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )

Firma Responsable Claudia M Neva

Fecha

Industria y Comercio
SUPERINTENDENCIA

255

2020
Bogotá D C

Doctor(a)
JUAN PABLO CADENA SARMIENTO
Apoderado(a)
ASTRAZENECA AB

REFERENCIA	Radicación N°	**05-595**
	Solicitud internacional	**PCT/GB2003/002811**
	Fecha limite inicio fase nacional	**2005-02-05**
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	**1895**
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reune los requisitos de forma establecidos en los articulos 26 y 27 de la Decision 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envia el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el articulo 40 de la Decisión 486

Cumplase
Dado en Bogotá D C, 31 ENE 2005

ALIX CARMENZA CESPEDES DE VERGEL
Jefe División de Nuevas Creaciones (