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SUPERINDUSTRIA Y COMERCIO
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

REF: Expediente No. 05 001.807 - Solicitud de Patente FASE NACIONAL

Corresp. a la Solicitud Internacional PCT/GB03/02499

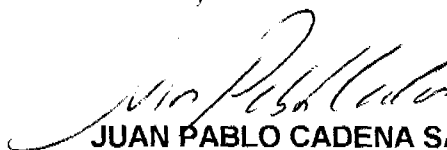
a favor de: **ASTRAZENECA AB**

TITULADA: DERIVADOS DE PÉPTIDOS QUE COMPRENDEN EL GRUPO
TIAZEPINA PARA EL TRATAMIENTO DE AFECCIONES HIPERLIPIDÉMICAS

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad **ASTRAZENECA AB**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 05-40,319 por valor de \$186.000.

De la señora Jefe atentamente,


JUAN PABLO CADENA SARMIENTO

C.C. No. 80.410.337 de Usaquén

T.P. No.57492 del C.S.J.

Cra 7 No. 16-56 Piso 9

Agosto 16, 2005

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ADMINISTRACION DE INDUSTRIAS Y COMERCIO

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Tramite: 011 PCT-PATENT 379 FASE MACI 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FECHA ORIGINAL DE CREACION: 01/01/2005
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***** C O N T E N I D O M A C I O N *****

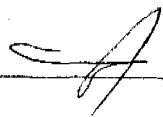
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***** C O N T E N I D O *****

CANT. CONCEPTO	CONCEPTO	TOTAL CONCEPTO
1	INDUSTRIAL DE SOLICITANTES	100.000,00
2	PTO CAP DE EXAMEN DE PATENTABILIDAD	100.000,00
	TOTAL:	200.000,00

NOTA: CANTAS CONCEPTO Y MONTO DEL PAGO

RESPONSABLE:



RECIBO DE PAGO APLICADO AL EXPERIMENTO Nº:

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-001807

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **550** DE

FECHA **31 DE MARZO DE 2005** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **28 DE JUNIO DEL 2005**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

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Pepparedsleden 1, S-431 83 Molndal (SE).

(21) International Application Number: PCT/GB01/00909

(74) Agent: **BRYANT, Tracey**; AstraZeneca, Global Intellectual Property, Alderley Park, Mereside, Macclesfield, P.O. Box 272, Cheshire SK10 4GR (GB).

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(71) Applicant (for MG only): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

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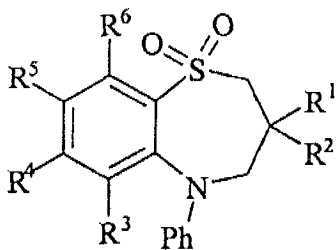
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(72) Inventors; and

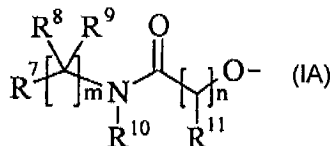
(75) Inventors/Applicants (for US only): **STARKE, Ingemar** [SE/SE]; Pepparedsleden 1, S-431 83 Molndal (SE).
DAHLSTROM, Michael [SE/SE]; Pepparedsleden 1,

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: 1,5-BENZOTHAZEPINES AND THEIR USE AS HYPOLIPIDAEMICS



(I)



(IA)

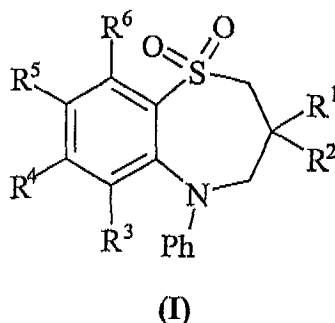
(57) Abstract: The present invention relates to compounds of formula (I) wherein R¹ and R² are independently selected from C₁₋₆alkyl; one of R⁴ and R⁵ is a group of formula (IA); R³, R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ and the other of R⁴ and R⁵ are as defined within, pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof and their use as ileal bile acid transport (IBAT) inhibitors for the treatment of hyperlipidaemia. Processes for their manufacture and pharmaceutical compositions containing them are also described.

WO 01/66533 A1

Substituted benzothiazepines possessing such IBAT inhibitory activity have been described, see for instance hypolipidaemic benzothiazepine 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 and EP 0 864 582.

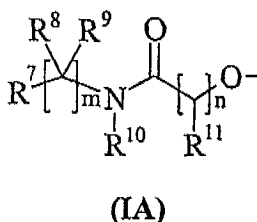
5 The present invention is based on the discovery that certain benzothiazepine compounds surprisingly inhibit IBAT and that they possess characteristics that make them particularly suitable as medicaments. Such properties are expected to be of value in the treatment of disease states associated with hyperlipidaemic conditions.

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



wherein:

R^1 and R^2 are independently selected from C_{1-6} alkyl;
one of R^4 and R^5 is a group of formula (IA):

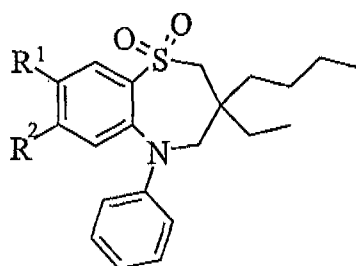


R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl)₂sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{14} ;

R^7 is carboxy, sulphy, 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 , R^b , are independently selected from C_{1-6} alkyl; or R^7 is a group of formula (IB):

Examples 9-11

The following compounds were synthesised by the procedure of Example 8.



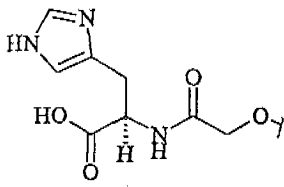
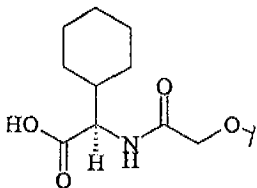
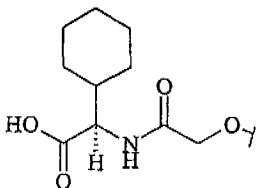
Ex	R ¹	R ²	NMR	SM
9	HOS(O) ₂ (CH ₂) ₃ NH-C(O)CH ₂ O-	Br	500 MHz: 0.6-0.8 (m, 6H), 0.9-1.6 (m, 8H), 2.0 (brs, 2H), 2.9 (brs, 2H), 3.2 (m, 2H), 3.4 (brs, 2H), 3.7 (brs, 2H), 4.6 (s, 2H), 6.9-7.1 (m, 4H), 7.2 (m, 2H), 7.4 (brs, 1H), 7.5 (s, 1H)	Meth 2
10	H	HOS(O) ₂ (CH ₂) ₂ NH-C(O)CH ₂ O-	300 MHz: 0.6-0.8 (m, 6H), 0.9-1.6 (m, 8H), 3.1 (brs, 4H), 3.6 (brs, 4H), 4.4 (s, 2H), 6.8-7.2 (m, 7H), 7.4 (brs, 1H), 7.5 (s, 1H)	Meth 1
11	HOS(O) ₂ (CH ₂) ₂ NH-C(O)CH ₂ NHC(O)-CH ₂ O-	Br	0.6-0.8 (m, 6H), 0.9-1.6 (m, 8H), 3.0-3.2 (m, 4H), 3.6 (brs, 4H), 4.0 (s, 2H), 4.6 (s, 2H), 6.9-7.1 (m, 4H), 7.2 (m, 2H), 7.5 (s, 1H), 7.8 (brs, 2H)	Ex 5

5 Example 12

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-{N-R-[1-carboxy-2-(pyrid-3-yl)ethyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-{N-R-[1-methoxycarbonyl-2-(pyrid-3-yl)ethyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 8; 85 mg, 0.13 mmol) was dissolved in ethanol (2 ml). NaOH (40 mg in 0.1 ml water) was added to the solution and the mixture was stirred at 50°C for 15 min. AcOH (0.1 ml) was added. The

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33 ⁵		Br	Et	(400 MHz, CD ₃ CN) 0.73-0.84 (m, 6H), 0.96-1.63 (m, 8H), 3.14 (dd, 1H), 3.24 (brs, 2H), 3.40 (dd, 1H), 3.56-3.81 (m, 2H), 4.66 (ABq, 2H), 4.87-4.94 (m, 1H), 6.99 (t, 1H), 7.07 (d, 2H), 7.17 (s, 1H), 7.19 (s, 1H), 7.29 (t, 2H), 7.41 (s, 1H), 7.73 (brd, NH), 8.36 (brs, 1H)	Meth 36
34 ⁵		MeS	<i>n</i> -Bu	(400 MHz, CD ₃ OD) 0.75-0.85 (m, 6H), 0.97-1.94 (m, 23H), 2.18 (s, 3H), 3.25 (brs, 2H), 3.6-3.9 (m, 2H), 4.33 (d, 1H), 4.67 (ABq, 2H), 6.71 (s, 1H), 6.98 (t, 1H), 7.12 (brd, 2H), 7.28 (t, 2H), 7.41 (s, 1H)	Meth 37
35 ⁵		MeO	<i>n</i> -Bu	(400 MHz, CD ₃ OD): δ 0.75-0.85 (m, 6H), 0.96-1.91 (m, 23H), 3.22 (brs, 2H), 3.6-3.9 (m, 5H), 4.33 (d, 1H), 4.59 (d, 2H), 6.51 (s, 1H), 6.98 (t, 1H), 7.13 (brd, 2H), 7.28 (t, 2H), 7.52 (s, 1H)	Meth 38

¹ The compound was not purified.

² 1.9 eq LiOH and no purification.

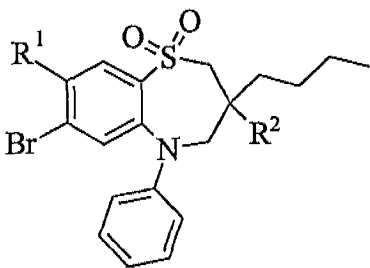
³ 7.6 eq of LiOH, added in portions, total reaction time approximately 6 hours.

5 ⁴ 4 eq LiOH.

⁵ Extracted with DCM, no further purification.

⁶ 8 eq of LiOH, reaction time was 5 days and then extracted with DCM, no further purification.

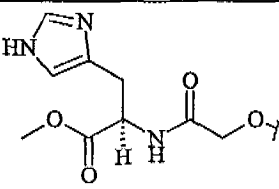
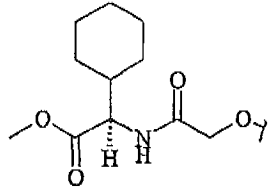
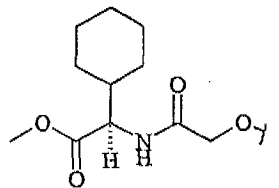
(Method 42) or 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-(1-carboxyethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 40) by the procedure of Method 5.



Method	R ¹	R ²	NMR / M/z
6		Et	500MHz: 0.7-0.8 (m, 6H), 1.0-1.7 (m, 17H), 3.2 (m, 2H), 3.7 (brs, 2H), 4.1 (d, 2H), 4.6 (s, 2H), 7.0-7.1 (m, 3H), 7.15 (s, 1H), 7.3 (m, 2H), 7.5 (s, 1H)
7		Et	300MHz: 0.7-0.8 (m, 6H), 1-1.7 (m, 14H), 2-2.5 (m, 4H), 3.2 (m, 2H), 3.8 (brs, 2H), 4.1 (q, 2H), 4.2 (q, 2H), 4.6 (dd, 2H), 4.8 (m, 1H), 7-7.15 (m, 4H), 7.3 (m, 2H), 7.4 (d, 1H), 7.5 (s, 1H)
8		Et	m/z = 673.3
9		Et	m/z = 610.2
10		Et	m/z = 686.3
11		Et	m/z = 730.1

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29 ⁹		Br	Et	m/z 661.6	Meth 2
30 ⁹		Br	Et	m/z 675.6	Meth 2
31 ⁸		Br	Et	m/z 681.7	Meth 2
32 ⁸		Br	Et	m/z 656.7	Meth 2
33 ²		Br	Et	m/z 637.6	Meth 2
34 ⁸		Br	Et	m/z 677.7	Meth 2
35 ⁸		Br	Et	m/z 623.6	Meth 2

36 ⁹		Br	Et	m/z 661.6	Meth 2
37 ^{8,10}		MeS	<i>n</i> -Bu	m/z 658.9	Meth 44
38 ^{8,10}		MeO	<i>n</i> -Bu	m/z 642.7	Meth 46

¹ Reaction time 40 minutes.

² Reaction time 1.5 hours.

³ Reaction time 2 hours and chromatographed twice.

5 ⁴ 1.3 eqv amino acid, TBTU 1.3 eqv and eluted first with DCM then DCM:EtOAc 9:1 to 8:2.

⁵ Reaction time 45 minutes and eluted first with DCM then DCM:EtOAc 9:1 to 8:2.

⁶ Reaction time 1 hour and eluted first with DCM then DCM:EtOAc 9:1 to 8:2.

⁷ Reaction time 40 minutes and eluted first with DCM then DCM:EtOAc 9:1 to 8:2.

⁸ Reaction time overnight.

10 ⁹ Reaction time overnight and the product was eluted with EtAc:MeOH (saturated with NH₃) 9:1

¹⁰ Amine: Justus Liebigs Ann. Chem.; 523; 1936; 199

Method 39

15 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-(1-ethoxycarbonylethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

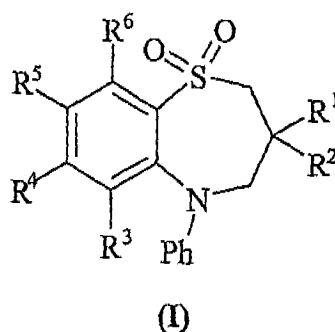
Sodium carbonate (0.30 g, 2.83 mmol), 2-bromopropanoic acid ethyl ester (0.145 g, 0.796 mmol) and tetrabutylammonium bromide (0.022g, 0.07 mmol) was added to a solution of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-

20 benzothiazepine (WO 96/16051; 0.300 g, 0.663 mmol) in MeCN (10 ml). The suspension was heated under reflux over night. The solvent was evaporated and the crude mixture was

Claims

What we claim is:

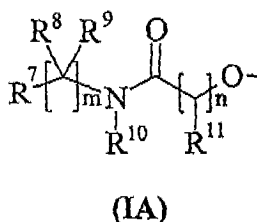
1. A compound of formula (I):



wherein:

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

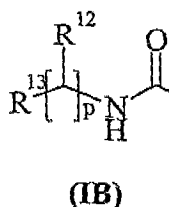
one of R^4 and R^5 is a group of formula (IA):



10

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl)₂sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{14} ;

R^7 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; or R^7 is a group of formula (IB):



20

R^8 and R^9 are independently hydrogen, C_{1-4} alkyl or a saturated cyclic group, or R^8 and R^9 together form C_{2-6} alkylene; wherein R^8 and R^9 or R^8 and R^9 together may be independently optionally substituted on carbon by one or more substituents selected from R^{15} ; and wherein if said saturated cyclic group contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{20} ;

R^{10} is hydrogen or C_{1-4} alkyl; wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{24} ;

R^{11} is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl; wherein R^{11} is optionally substituted on carbon by one or more substituents selected from R^{16} ; and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{21} ;

R^{12} is hydrogen or C_{1-4} alkyl, carbocyclyl or heterocyclyl; wherein R^{12} is optionally substituted on carbon by one or more substituents selected from R^{17} ; and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{22} ;

R^{13} is carboxy, sulphy, sulphino, phosphono, $-P(O)(OR^c)(OR^d)$, $-P(O)(OH)(OR^c)$, $-P(O)(OH)(R^c)$ or $-P(O)(OR^c)(R^d)$ wherein R^c and R^d are independently selected from C_{1-6} alkyl;

m is 1-3; wherein the values of R^8 and R^9 may be the same or different;

n is 1-3; wherein the values of R^{11} may be the same or different;

p is 1-3; wherein the values of R^{12} may be the same or different;

R^{14} and R^{16} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, $N-(C_{1-4}alkyl)amino$, $N,N-(C_{1-4}alkyl)_2amino$, $C_{1-4}alkanoylamino$, $N-(C_{1-4}alkyl)carbamoyl$, $N,N-(C_{1-4}alkyl)_2carbamoyl$, $C_{1-4}alkylS(O)_a$ wherein a is 0 to 2, $C_{1-4}alkoxycarbonyl$, $N-(C_{1-4}alkyl)sulphamoyl$ and $N,N-(C_{1-4}alkyl)_2sulphamoyl$; wherein R^{14} and R^{16} may be independently optionally substituted on carbon by one or more R^{18} ;

R^{15} and R^{17} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, $N-(C_{1-4}alkyl)amino$, $N,N-(C_{1-4}alkyl)_2amino$, $C_{1-4}alkanoylamino$, $N-(C_{1-4}alkyl)carbamoyl$, $N,N-(C_{1-4}alkyl)_2carbamoyl$, $C_{1-4}alkylS(O)_a$ wherein a is 0 to 2, $C_{1-4}alkoxycarbonyl$, $N-(C_{1-4}alkyl)sulphamoyl$ and $N,N-(C_{1-4}alkyl)_2sulphamoyl$, carbocyclyl,

heterocyclyl, sulpho, sulphino, amidino, 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; wherein R^{15} and R^{17} may be independently optionally substituted on carbon by one or more R^{19} ; and wherein if said heterocyclyl contains an $-NH-$ moiety, that nitrogen may be

5 optionally substituted by one or more R^{23} ;

R^{18} , R^{19} and R^{25} are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, methylamino, dimethylamino,

10 N -methylcarbamoyl, N,N -dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, N -methylsulphamoyl and N,N -dimethylsulphamoyl;

R^{20} , R^{21} , R^{22} , R^{23} and R^{26} are independently C_{1-4} alkyl, C_{1-4} alkanoyl, C_{1-4} alkylsulphonyl, sulphamoyl, N -(C_{1-4} alkyl)sulphamoyl, N,N -(C_{1-4} alkyl)₂sulphamoyl, C_{1-4} alkoxycarbonyl, carbamoyl, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, benzyl, phenethyl, benzoyl,

15 phenylsulphonyl and phenyl;

R^{24} 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)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a wherein a is 0 to 2,

20 C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl)₂sulphamoyl, carbocyclyl, heterocyclyl; wherein R^{24} may be independently optionally substituted on carbon by one or more R^{25} ; and wherein if said heterocyclyl contains an $-NH-$ moiety, that nitrogen may be optionally substituted by one or more R^{26} ;

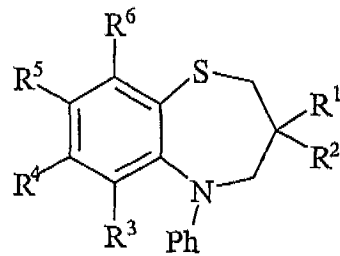
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

25

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

30 3. A compound of formula (I) according to either of claims 1 or 2 wherein R^3 is hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

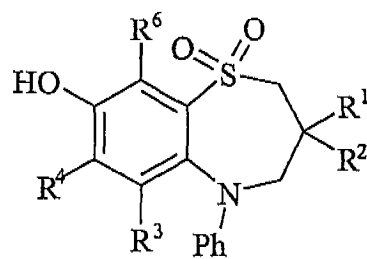
4. A compound of formula (I) according to any one of claims 1 to 3 wherein R⁵ is a group of formula (IA) and R⁴ is bromo, methoxy or methylthio or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
5. A compound of formula (I) according to any one of claims 1 to 4 wherein R⁵ is *N*-(carboxymethyl)carbamoylmethoxy, *N*-(2-sulphoethyl)carbamoylmethoxy, *N*-(1,3-dicarboxypropyl)carbamoylmethoxy, *N*-(3-sulphopropyl)carbamoylmethoxy, *N*-[*N*-(2-sulphoethyl)carbamoylmethyl]carbamoylmethoxy, *N*-[1-carboxy-2-(4-hydroxyphenyl)ethyl]carbamoylmethoxy, *N*-(1-carboxy-2-phenylethyl)carbamoylmethoxy, *N*-(1-carboxy-3-methylbutyl)carbamoylmethoxy, *N*-(1-carboxy-2-indol-3-ylethyl)carbamoylmethoxy, *N*-(1-carboxy-2-pyrid-3-ylethyl)carbamoylmethoxy, *N*-(carboxymethyl)-*N*-(benzyl)carbamoylmethoxy, *N*-(1-carboxyethyl)carbamoylmethoxy, 1-[*N*-(carboxymethyl)carbamoyl]ethoxy, *N*-(1-carboxy-2-hydroxyethyl)carbamoylmethoxy, *N*-(1-carboxycycloprop-1-yl)carbamoylmethoxy, *N*-(1-carboxy-1-methylethyl)carbamoylmethoxy, *N*-(1-carboxy-2-cyclohexylethyl)carbamoylmethoxy, *N*-(1-carboxy-2-methylpropyl)carbamoylmethoxy, *N*-(1-carboxy-2-imidazol-4-ylethyl)carbamoylmethoxy, *N*-[1-carboxy-2-(1-methylimidazol-4-yl)ethyl]carbamoylmethoxy, *N*-(1-carboxy-2-*t*-butoxypropyl)carbamoylmethoxy, *N*-(1-carboxy-3-methylthiopropyl)carbamoylmethoxy, *N*-(1-carboxy-2-methylbutyl)carbamoylmethoxy, *N*-(1-carboxy-2-imethylpropyl)carbamoylmethoxy, *N*-(1-carboxy-1-methyl-2-indol-3-ylethyl)carbamoylmethoxy, *N*-(1-carboxy-2-hydroxypropyl)carbamoylmethoxy and *N*-(1-carboxy-1-cyclohexylmethyl)carbamoylmethoxy and R⁴ is bromo, methoxy or methylthio 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 R⁶ is hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
7. A process for preparing a compound of the formula (I) which comprises of:-
- 30 Process 1):
oxidising a benzothiazepine of formula (II):



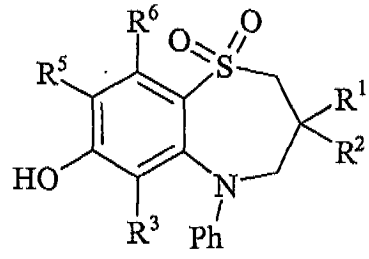
(II);

Process 2):

reacting an alcohol of formula (IIIa) or (IIIb):

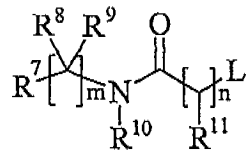


(IIIa)



(IIIb)

with a compound of formula (IV):

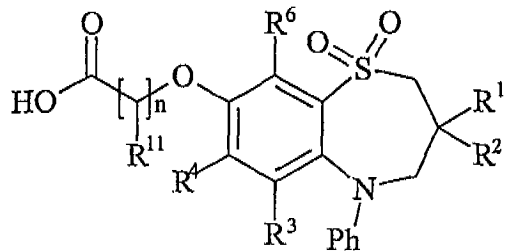


(IV)

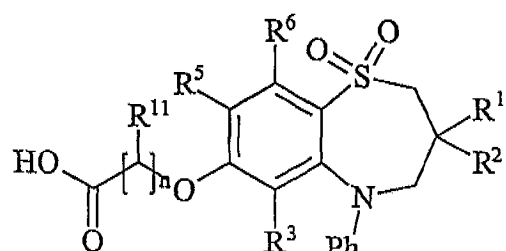
10 wherein L is a displaceable group;

Process 3):

reacting an acid of formula (Va) or (Vb):



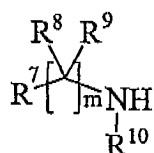
(Va)



(Vb)

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

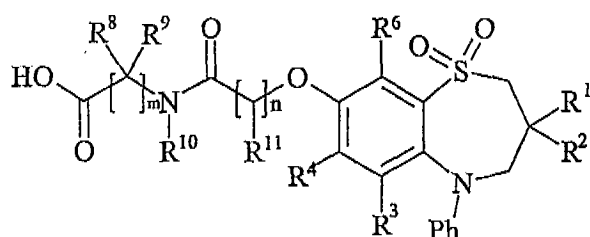
- 66 -



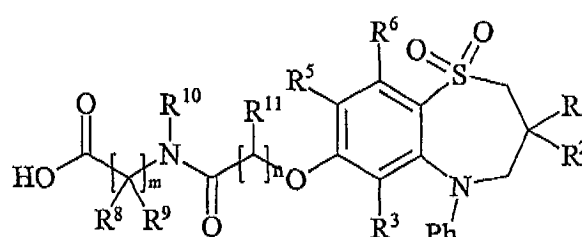
(VI);

Process 4):

for compounds of formula (I) wherein R⁷ is a group of formula (IB); reacting an acid of
5 formula (VIIa) or (VIIb):

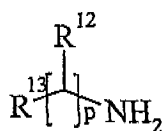


(VIIa)



(VIIb)

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



(VI);

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.

8. A compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 6 for use as a medicament.

20 9. A compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 6 for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

10. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 6 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

5

11. A method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 6.

10

12. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 6, in association with a pharmaceutically-acceptable diluent or carrier.

15

13. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 6, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in

20 association with a pharmaceutically acceptable diluent or carrier.

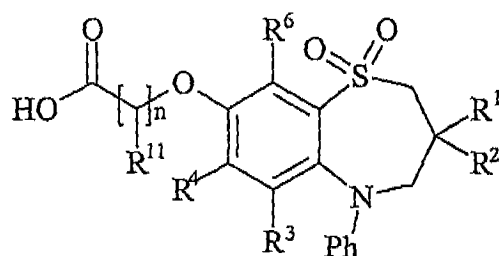
14. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 6, and a bile acid binder, in association with a

25 pharmaceutically acceptable diluent or carrier.

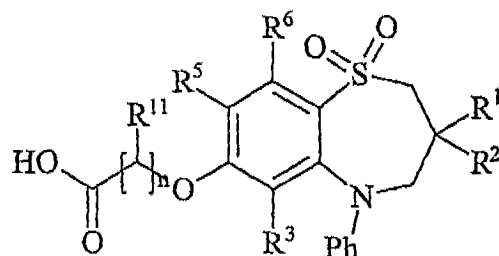
15. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 6, and an HMG Co-A reductase inhibitor, or a

30 pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder in association with a pharmaceutically acceptable diluent or carrier.

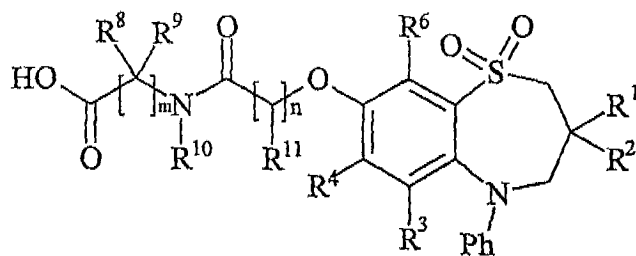
16. A compound of formula (Va), (Vb), (VIIa) or (VIIb) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof:



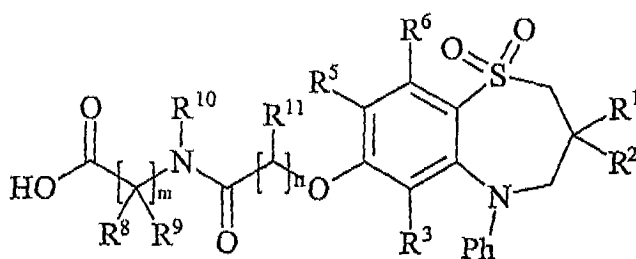
(Va)



(Vb)



(VIIa)



(VIIb)

17. A compound of the formula (Va), (Vb), (VIIa) or (VIIb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in claim 19 for use as a medicament.

18. A compound of formula (Va), (Vb), (VIIa) or (VIIb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in claim 19 for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

5

19. The use of a compound of the formula (Va), (Vb), (VIIa) or (VIIb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in claim 19 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

10

20. A method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (Va), (Vb), (VIIa) or (VIIb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in claim 19.

15

21. A pharmaceutical composition which comprises a compound of formula (Va), (Vb), (VIIa) or (VIIb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in claim 19 in association with a pharmaceutically-acceptable diluent or carrier.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
JUAN PABLO CADENA SARMIENTO
Apoderado

ASUNTO	Radicación	05001807
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	- 11878
	Folios	139

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐	Cap. I	☐
Vía PCT (fase nacional)	☒	Cap. II	☒
No. Sol. Internacional		PCT/FB03/02499	
Fecha de Presentación Internal.		10/06/2003	

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 33 a 77

1.2. Reivindicaciones: Folios 78 a 88

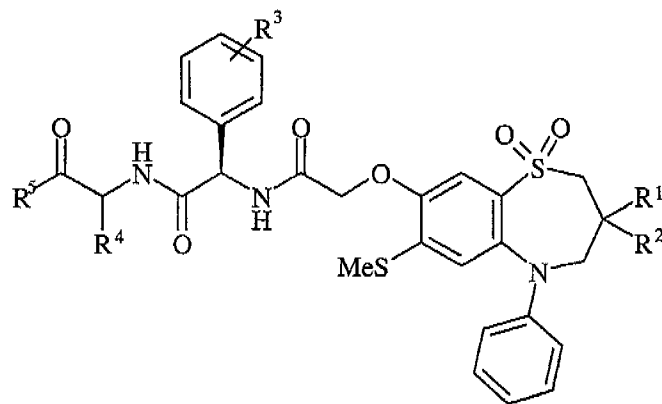
1.3. Prioridad: Fecha: 14/06/2002, país: GB, número: 0213669.5

2. Objeto de la invención

- Título de la solicitud: DERIVADOS DE PÉPTIDOS QUE COMPRENDE EL GRUPO TIAZEPINA PARA EL TRATAMIENTO DE AFECCIONES HIPERLIPIDÉMICAS. Número de folio: 1

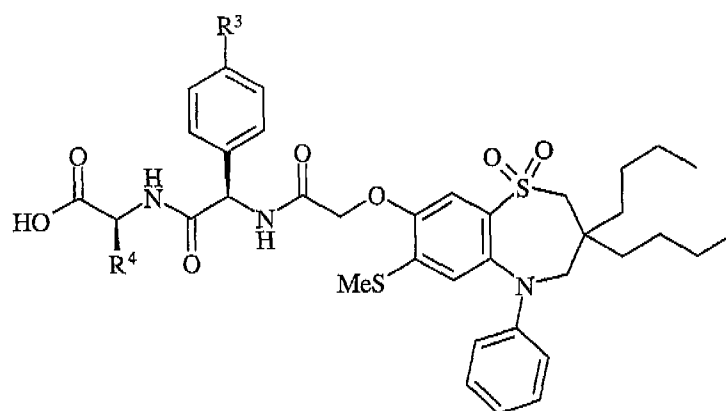
El objeto de la presente solicitud de patente de invención consiste en derivados de benzotiazepina que poseen actividad inhibidora de transporte de ácido biliar en el ileon (IBAT) por lo tanto utiles en el tratamiento de estados patológicos asociados con afecciones hiperlipidémicas, también consiste en procesos para la manufactura de dichos derivados, composiciones farmacéuticas y su uso en la manufactura de medicamentos para inhibir IBAT.

Reivindicaciones 1 – 6, 8: Un compuesto de fórmula (I)



(I)

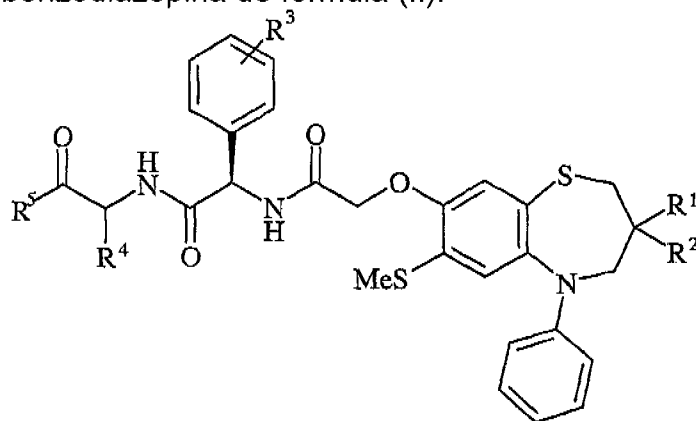
Reivindicación 7: Un compuesto de fórmula (I')



(I')

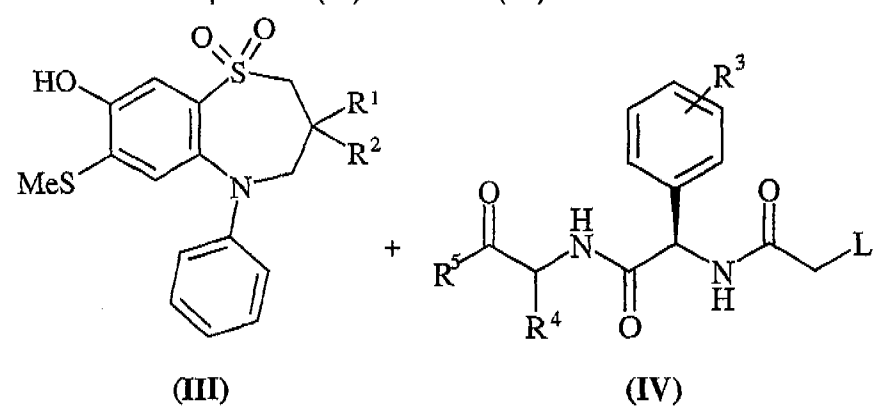
Reivindicación 9: Un proceso para preparar un compuesto de fórmula (I)

1. Oxidar una benzodiazepina de fórmula (II).

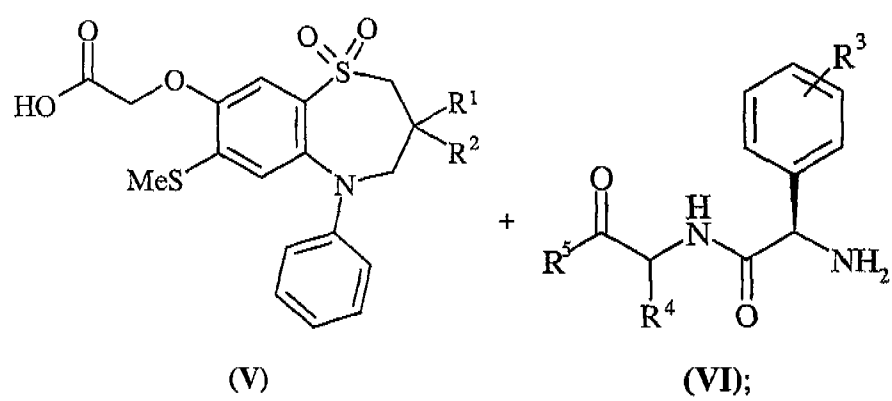


(II);

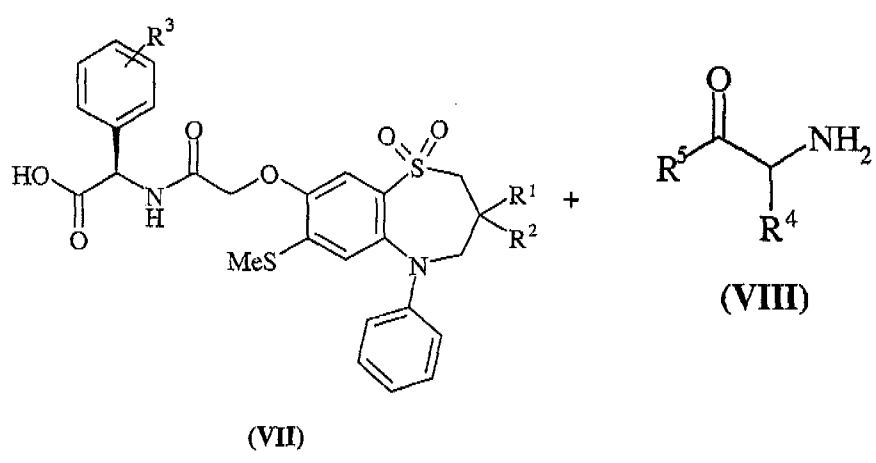
II. Reaccionar un compuesto (III) con uno (IV)



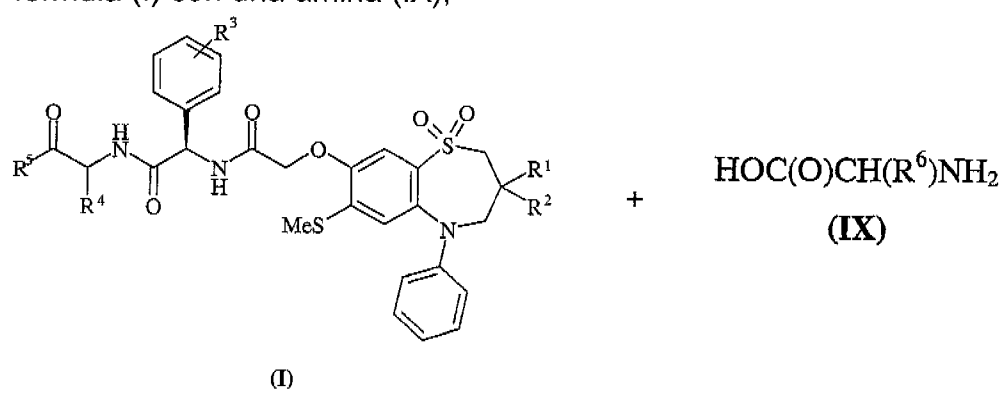
III. Reaccionar un ácido (V) con una amina (VI)



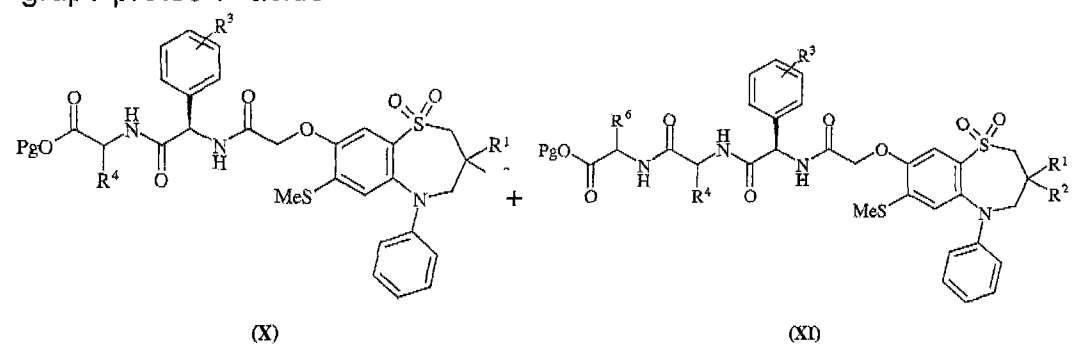
IV. Reaccionar un ácido (VII) con una amina (VIII)



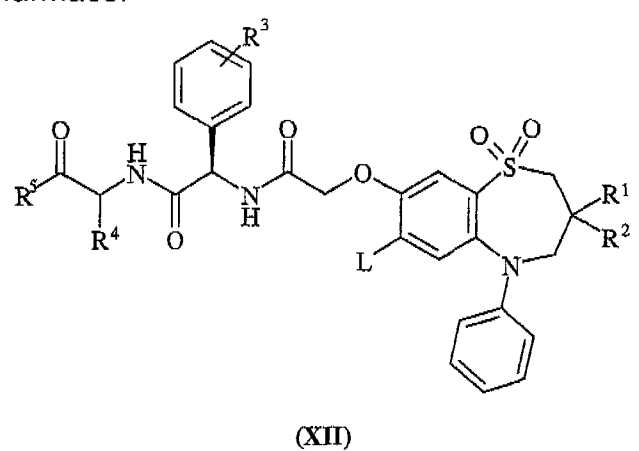
V. Para compuestos de fórmula (I) hacer reaccionar un compuesto de fórmula (I) con una amina (IX),



VI. Desproteger un compuesto (X) o un compuesto (XI) en donde pg es un grupo protector ácido



VII. Reaccionar un compuesto (XII) y después si es necesario convertir un compuesto (I) en otro (I), retirar grupos protectores, formar una sal, solvato o profármaco.



Reivindicaciones 10-11: Un compuesto de fórmula (I) para uso como medicamento o para uso en un método de tratamiento.

Reivindicación 12: Uso de un compuesto (I) en la manufactura de un medicamento.

Reivindicación 13: Método de tratamiento.

Reivindicaciones 14 - 21: Una composición que comprende un compuesto (I) que puede ir en asociación con un inhibidor de HMG Co A reductasa (atorvastatina o rosuvastatina) y/o un secuestrante ácido biliar o un agonista PPAR alfa y/o gamma (ácido (S)- 2-etoxi-3-[4-(2-{4-metano sulfonil oxifenil} etoxi) fenil] propanoico más un diluyente o vehículo.

El problema planteado en esta solicitud es la necesidad de compuestos útiles para el tratamiento de estados patológicos asociados con afecciones hiperlipidémicas.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos derivados de benzotiazepinas que inhiben sorprendentemente IBAT.

Clasificación Internacional de Patentes (IPC.): A61K 38/05, A61P 3/06, A61P 9/10

3. De la solicitud de Patente

3.1. Descripción (artículo 28 D. 486)

- La descripción no explica claramente porqué la solicitud tiene efectos “sorprendentes” con respecto al estado de la técnica.
- No se presentan tablas de resultados que evidencien las ventajas o el salto tecnológico de la solicitud con respecto al estado de la técnica.

3.2. Reivindicaciones (artículo 30 D 486)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

- El solicitante no es claro cuando incluye en sus reivindicaciones los compuestos: “**profármaco**” o “**sal**” o “**solvato**”. Al realizar la lectura del capítulo reivindicatorio, se encuentra que las frases resultan imprecisas, dado que estos términos no especifican con exactitud el(los) compuesto(s) a los cuales se refiere con dichos términos por lo tanto no se aceptan tal como aparecen.
- Reivindicación 8: Se requiere al solicitante presentar las estructuras para los diferentes compuestos en las posibilidades que se desean proteger.
- Reivindicaciones 10 - 11: Se reivindican de fórmula (I) por su posterior uso por lo cual no pueden aceptarse ya que un compuesto se caracteriza únicamente por su fórmula estructural o por su nomenclatura química IUPAC.
- Reivindicaciones 14 - 21: composición que puede ser aceptable en la medida en que las moléculas sean nuevas.

El objeto de la solicitud no es claro e incumple así mismo con el requisito de concisión, dadas las observaciones esbozadas en los numerales precedentes. En este sentido se requiere al interesado para que realice las modificaciones correspondientes a fin de subsanar las no conformidades encontradas por este Despacho.

4. Excepción a la patentabilidad (artículo 20 D486 literal a)-d)

Reivindicación 13: Se refiere a un método de tratamiento por lo tanto no se acepta según la legislación vigente.

5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Reivindicación 12: Se refiere a usos de compuestos para la manufactura de medicamentos por lo tanto no se aceptan según la legislación vigente.

6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 14/06/2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	WO 01/66533	1,5-BENZOTHAZEPINES AND THEIR USE AS HYPOLIPIDAEMICS	13/09/2001

7. Análisis de patentabilidad (artículo 14 D486)

7.1. Novedad (artículo 16 D486)

Reivindicaciones 1 – 8: Un compuesto de fórmula (I) y (I')

Reivindicación 9: Un proceso para preparar un compuesto de fórmula (I)

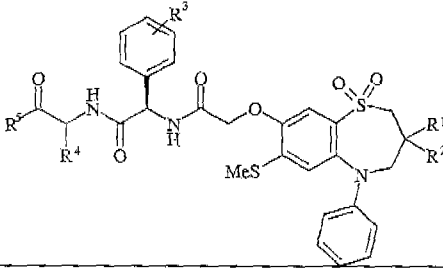
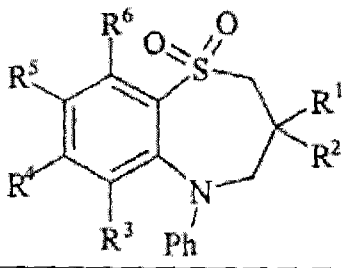
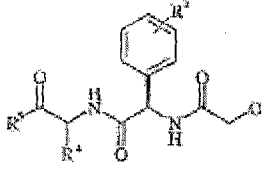
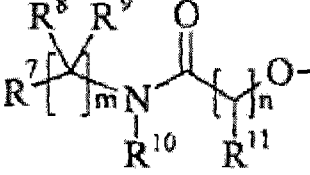
Reivindicaciones 10-11: Un compuesto de fórmula (I).

Reivindicaciones 14 - 21: composiciones que comprenden varias posibilidades de combinar el compuesto.

D₁ enseña (ver folios 117 - 118) compuestos de fórmula (I) y su uso como inhibidores del transporte de ácido biliar ileal (IBAT) para el tratamiento de hiperlipidemia las cuales poseen características que sorprendentemente inhiben IBAT y las hacen particularmente útiles como medicamentos. Procesos para su manufactura y las composiciones farmacéuticas que los contienen.

Así las cosas la formula I y el proceso reivindicados se superponen con la formula I y el proceso reivindicado en el documento D₁, por lo tanto no son novedosos, pues ya se conocían en el estado de la técnica.

- ♦ Los elementos característicos de las fórmulas (I) y (I') y del proceso reivindicado, habían sido divulgados previamente en el Estado de la Técnica (ver D₁ folios 124-132), según la tabla siguiente:

SOLICITUD		ANTERIORIDAD (D ₁)		comparación
(I) (I')		(I)		
R ₁	alquilo		alquilo	Equivalente
R ₂	alquilo		alquilo	Equivalente
R ₃	H		H	Equivalente
R ₄	MetilS (O) _a donde a=0-2		R ₄ = mercapto, sulfamoil, alquilS(O) _a donde a=0-2, N-alquil sulfamoil	Equivalente
		R ₅		Equivalente
	H	R ₆	H	Equivalente

CARACTERÍSTICAS REIVINDICADAS	D ₁
Oxidar una benzodiazepina de fórmula (II)	Si Folio 127
Reaccionar un alcohol (III) con un compuesto (IV)	Si Folio 128
Reaccionar un ácido (V) con una amina (VI)	Si Folio 128
Reaccionar un ácido (VII) con una amina (VIII)	Si Folio 128
Para compuestos de fórmula (I) hacer reaccionar un compuesto de fórmula (I) con una amina (IX)	Si Folio 129
Desproteger un compuesto (X) o un compuesto (XI)	Si Folio 129
Reaccionar un compuesto (XII) y después si es necesario convertir un compuesto (I) en otro (I), retirar grupos protectores, formar una sal, solvato o profármaco	Si Folio 129

De manera que el objeto de esta solicitud, tal como aparece en las reivindicaciones 1 - 11 no son nuevas por lo tanto las composiciones derivadas de tal compuesto 14-21 tampoco son nuevas.

8 Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D ₁	WO 01/66533	1-11, 14-21	NOVEDAD

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.
Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____ 2001

CONCEPTO TÉCNICO No. 1688	EXAMINADOR TÉCNICO Código No. 202087
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