

Q.F.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PC
SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No.

05-3510

54. TITULO DERIVADOS DE ACIDO BENZOICO ORTO-SUSTITUIDO PARA EL TRATAMIENTO
DE RESISTENCIA A LA INSULINA

51. CLASIFICACION INTERNACIONAL

71. SOLICITANTE ASTRAZENECA AB

DOMICILIO SODERTALJE, SUECIA

74. APODERADO JUAN PABLO CADENA SARMIENTO

22. SANTAFE DE BOGOTA, D.C.

SS
Oficina de Comunicaciones

27/6/09

PETITORIO

AS: 95.953



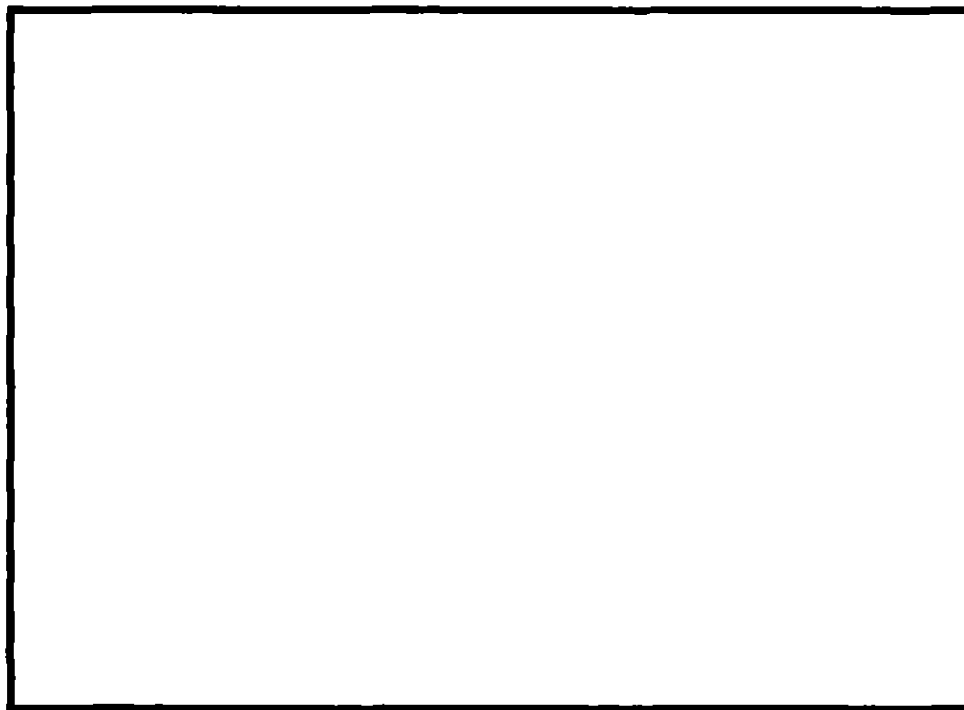
SUPERINDUSTRIA Y COMERCIO
 Radicación : 05003510 00000000 Folios: 152
 Fecha (AMB): 2003-01-10 17:06:41
 Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
 Dependencias: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO 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-1-51 85 Sodertälje, 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 <u>80.410.337 TP 57492</u>
4 INVENTOR (ES) (72)	Nombre: Lanna Li Dirección: AstraZeneca R & D Mölndal, S-431 83 Mölndal, Suecia Nacionalidad o Domicilio: Suecia		
5 PCT (86) Solicitud Internacional No. <u>PCT/GB2003/002584</u> Fecha <u>17-06-2003</u> Publicación Internacional No. <u>WO 2004/000790 A1</u> Fecha <u>31-12-2003</u>			
Título (54): <u>DERIVADOS DE ACIDO BENZOICO ORTO-SUSTITUIDO PARA EL TRATAMIENTO DE RESISTENCIA A LA INSULINA</u>			
7 Clasificación Internacional (51) <u>007C 235/34</u>			
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	SE	20-06-2002	0201935-4
	SE	20-12-2002	0203826-3
9 Comprobante de pago No. <u>04:966354054679</u> Fecha <u>04/04/2005</u>			
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.			

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

11 FIGURA CARACTERÍSTICA:



12 Sobre la concesión de la patente

NOMBRE: JUAN PABLO CADENA SARMENTO

FIRMA:

CÓDIGO: 1033766157492 del CSO

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

3

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 96,635
FECHA : DICIEMBRE 14 DE 2004

SUPERINDUSTRIA Y COMERCIO
Radacion : 85083518 00000000 Folios: 152
Fecha (AMD): 2005-01-18 17:06:41
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	28028763	14/12/2004	16,520,000.00

***** 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. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 890176009-2

CERTIFICACION DE EXCEDENTE : 05 - 679
FECHA : ENERO 4 DE 2005

SUPERINDUSTRIA Y COMERCIO
Radicacon : 05003510 00000000 Folios: 152
Fecha (MS): 2005-01-18 17:06:41
Tramite : 011 PCT-PATENT 379 FASE NACT 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
BRIGARO & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	030-00110-6	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 SERVICIOS 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.

X5

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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
31 December 2003 (31.12.2003)

PCT

(10) International Publication Number
WO 2004/000790 A1

(51) International Patent Classification⁷: C07C 235/34, 323/62, A61K 31/19, A61P 3/06, 3/10

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

(21) International Application Number:
PCT/GB2003/002584

(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, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 17 June 2003 (17.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0201935-4 20 June 2002 (20.06.2002) SE
0203826-3 20 December 2002 (20.12.2002) SE

(84) Designated States (*regional*): ARIPO patent (GH, GM, KR, 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).

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

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

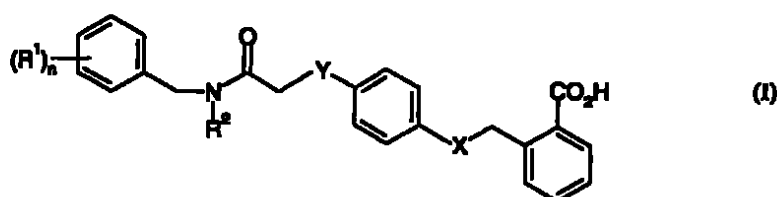
(71) Applicant (*for MG only*): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): LL, Lanna [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

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: ORTHO-SUBSTITUTED BENZOIC ACID DERIVATIVES FOR THE TREATMENT OF INSULIN RESISTANCE



(57) Abstract: The present invention provides a compound of formula (I), wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different; R² represents a C₂₋₆alkyl group which is optionally interrupted by oxygen; Y is absent or represents methylene; and X is O or S; and pharmaceutically acceptable salts and prodrugs thereof, to processes for preparing such compounds, to their utility in treating clinical conditions associated with insulin resistance, to methods for their therapeutic use and to pharmaceutical compositions containing them.

6
X**ORTHO-SUBSTITUTED BENZOIC ACID DERIVATIVES FOR THE TREATMENT OF INSULIN RESISTANCE****Field of the invention**

The present invention relates to certain novel benzoic acid derivatives, to processes for preparing such compounds, to their utility in treating clinical conditions associated with insulin resistance, to methods for their therapeutic use and to pharmaceutical compositions containing them.

Background of the invention

The Insulin Resistance Syndrome (IRS) including type 2 diabetes mellitus, which refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possible type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins), small dense LDL particles and reduced HDL (high density lipoprotein) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is awareness of the need to increase the insulin sensitivity in IRS suffering patients and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally well defined disease.

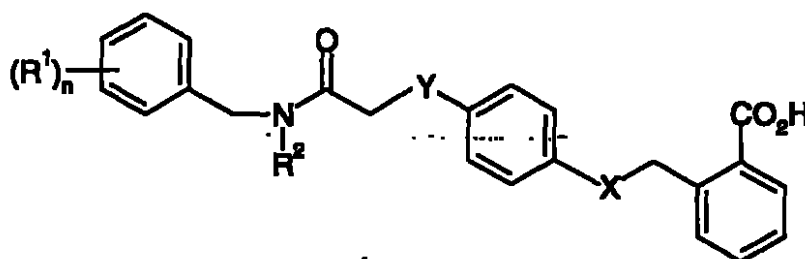
Modulators of peroxisome proliferator-activated receptors (PPAR, for a review of the PPARs see T. M. Willson et al, J Med Chem 2000, Vol 43, 527) are effective in treating conditions associated with insulin resistance.

US 5,750,783 discloses that certain benzyloxy-substituted phenylglycinolamides which have a cycloalkyl substituent are antiatherosclerotic medicaments. This document does not disclose or suggest the compounds of the present invention.

- 5 Surprisingly a series of compounds has now been found which are selective PPAR α modulators.

Description of the invention

- 10 The present invention provides a compound of formula I



- wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different;

- R² represents a C₂₋₄alkyl group which is optionally interrupted by oxygen;

20

Y is absent or represents methylene; and

X is O or S;

- 25 and pharmaceutically acceptable salts and prodrugs thereof.

Further values of R^1 , R^2 , Y and X in compounds of Formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

5 In one aspect X is O.

In a second aspect X is S.

In a third aspect Y is methylene.

In a fourth aspect Y is absent.

In a fifth aspect R^1 is halo, a C_{1-4} alkyl group or a C_{1-4} alkoxy group and n is 0, 1 or 2.

10 Particularly R^1 is fluoro, methoxy, or isopropyl when n is 1 or 2. Particularly n is 0.

In a sixth aspect R^2 represents a C_{5-7} alkyl group.

The term C_{2-8} alkyl denotes a straight-chain or branched saturated aliphatic hydrocarbon having from 2 to 8 carbon atoms. Examples of said alkyl include ethyl, n-propyl, iso-
15 propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl, hexyl, heptyl and octyl.

It will be understood by those skilled in the art that the term interrupted as used above means that the oxygen atom is situated within the alkyl chain and is not the terminal atom.

20 The term "prodrug" as used in this specification includes derivatives of the carboxylic acid group which are converted in a mammal, particularly a human, into the carboxylic acid group or a salt or conjugate thereof. It should be understood that, whilst not being bound by theory, it is believed that most of the activity associated with the prodrugs arises from the activity of the compound of formula I into which the prodrugs are converted. Prodrugs
25 can be prepared by routine methodology well within the capabilities of someone skilled in the art. Various prodrugs of carboxy are known in the art. For examples of such prodrug derivatives, see:

- a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, 42: 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- 30 b) *A Textbook of Drug Design and Development*, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p.113-191 (1991);

- c) H. Bundgaard, *Advanced Drug Delivery Reviews*, 8:1-38 (1992);
d) H. Bundgaard, *et al.*, *Journal of Pharmaceutical Sciences*, 77:285 (1988); and
e) N. Kakeya, *et al.*, *Chem Pharm Bull*, 32:692 (1984).

The above documents a to e are herein incorporated by reference.

5 *In vivo* cleavable esters are just one type of prodrug of the parent molecule.

The compounds of formula I have activity as medicaments, in particular the compounds of formula I are selective agonists of PPAR α , that is, their EC₅₀ for PPAR α is at least three times lower, preferably at least four times lower and more preferably 10 or 50 times lower than their respective EC₅₀ for PPAR γ wherein the EC₅₀s are measured and calculated as described in the assays later in this document. The compounds of formula I are potent and selective.

Specific compounds of the invention are one or more of the following:

- 15 2-[(4-{3-[benzyl(hexyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
2-[[4-(2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl)phenyl]thio]methyl]benzoic acid;
2-[(4-{2-[benzyl(hexyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid;
2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid;
20 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
2-[[4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl]thio]methyl]benzoic acid;
2-[(4-{3-[butyl(2,3-dimethoxybenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
2-[(4-{3-[(2,3-dimethoxybenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic
25 acid;
2-[(4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy)methyl]-benzoic acid ;
2-[(4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
2-[(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid;
30 2-[(4-{3-[ethyl(2-fluorobenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
2-[[4-(2-[ethyl[4-(trifluoromethyl)benzyl]amino]-2-oxoethyl)phenyl]thio]-methyl]benzoic acid;

X/10

2-[[[3-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl]thio]methyl]benzoic acid; and

2-[[[4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethyl}phenyl]thio]methyl]benzoic acid and pharmaceutically acceptable salts thereof.

5

A second group of specific compounds of the invention comprises a compound selected from:

2-[[[4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl]thio]methyl]benzoic acid;

10 2-[[[4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl]thio]methyl]benzoic acid;

2-[[[4-{2-[ethyl[4-(trifluoromethyl)benzyl]amino]-2-oxoethyl}phenyl]thio]methyl]benzoic acid;

15 2-[[[3-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl]thio]methyl]benzoic acid; and

2-[[[4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethyl}phenyl]thio]methyl]benzoic acid and pharmaceutically acceptable salts thereof.

A third group of specific compounds of the invention comprises a compound selected from:

20

2-[[[4-{3-[benzyl(hexyl)amino]-3-oxopropyl}phenoxy]methyl]benzoic acid;

2-[[[4-{2-[benzyl(hexyl)amino]-2-oxoethyl}phenoxy]methyl]benzoic acid;

2-[[[4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy]methyl]benzoic acid;

2-[[[4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy]methyl]benzoic acid;

25 2-[[[4-{3-[butyl(2,3-dimethoxybenzyl)amino]-3-oxopropyl}phenoxy]methyl]benzoic acid;

2-[[[4-{3-[(2,3-dimethoxybenzyl)(heptyl)amino]-3-oxopropyl}phenoxy]methyl]benzoic acid;

2-[[[4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy]methyl]benzoic acid ;

30 2-[[[4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy]methyl]benzoic acid;

2-[[[4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy]methyl]benzoic acid;

2-[[[4-{3-[ethyl(2-fluorobenzyl)amino]-3-oxopropyl}phenoxy]methyl]benzoic acid;

11
Z

and pharmaceutically acceptable salts thereof.

Certain compounds of the present invention may exist as tautomers. It is to be understood that the present invention encompasses all such tautomers.

5

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof. Isomers may be separated using
10 conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting
15 materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

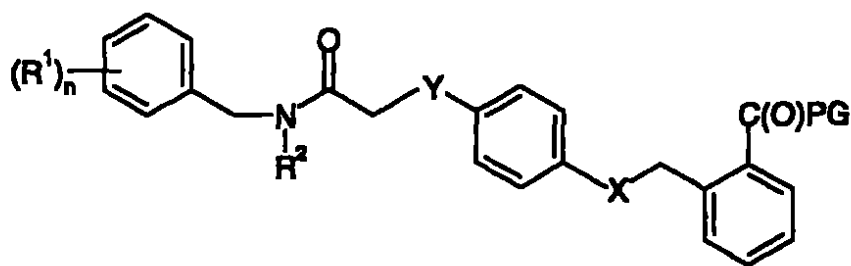
Methods of preparation

20

The compounds of the invention may be prepared as outlined below. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art. The reactions can be carried out according to standard procedures or as described in the experimental section.

25

Compounds of formula I may be prepared by reacting a compound of formula II

312
X

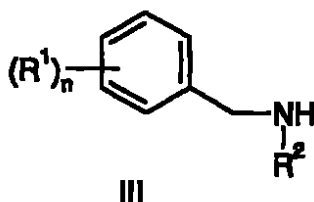
II

in which R^1 , R^2 , X and Y are as previously defined and PG represents a protecting group for a carboxylic hydroxy group as described in the standard text "Protective Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts, with a de-protecting agent.

- 5 The protecting group may also be a resin, such as Wang resin or 2-chlorotrityl chloride resin. Protecting groups may be removed in accordance to techniques which are well known to those skilled in the art. One such protecting group is where PG represents a C_{1-6} alkoxy group or an arylalkoxy group eg benzyl, such that COPG represents an ester. Such esters can be reacted with a hydrolysing agent, for example lithium hydroxide in the presence of a solvent for example a mixture of THF and water or potassium hydroxide in
- 10 a C_{1-3} alcohol for example methanol, at a temperature in the range of 0-200°C or by microwave radiation to give compounds of formula I.

Compounds of formula II may be prepared by reacting a compound of formula III

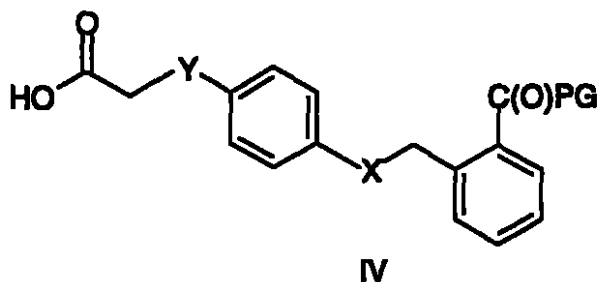
15



III

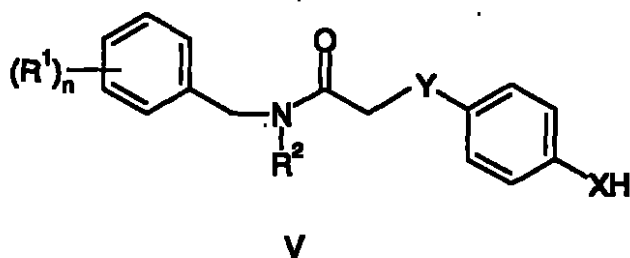
or a salt thereof, for example a hydrochloride salt, in which R^1 , R^2 and n are as previously defined with a compound of formula IV

13

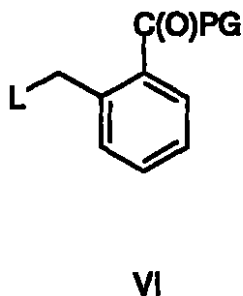


or the acid chloride thereof in which X, Y and PG are as previously defined in an inert solvent, for example dichloromethane, optionally in the presence of a coupling agent, for example 4-dimethylaminopyridine or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, at a temperature in the range of -25°C to 150°C.

Compounds of formula II may also be prepared by reacting a compound of formula V



in which R^1 , n , R^2 , X and Y are as previously defined with a compound of formula VI



in which PG is as previously defined and L represents a leaving group, for example halo, e.g. bromo, optionally in the presence of solvent, for example acetonitrile, and optionally in the presence of a base, for example potassium carbonate, at a temperature in the range of 0 to 150°C.

14
X

Compounds of formula III, IV, V and VI may be prepared by methods described in the Examples or by analogous methods known to those skilled in the art.

5 Compounds of formula II, III, IV and V are useful intermediates in the preparation of compounds of formula I. Certain of these compounds are believed to be novel. Novel compounds of formula II, or formula III, or formula IV or formula V are herein claimed as a further aspect of the present invention.

10 The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process
15 steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

20 In any of the preceding methods of preparation, where necessary, hydroxy, amino or other reactive groups may be protected using a protecting group, R^P as described in the standard text "Protective groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts. The protecting group may also be a resin, such as Wang resin or 2-chlorotrityl chloride resin. The protection and deprotection of functional groups may take place before or after
25 any of the reaction steps described hereinbefore. Protecting groups may be removed in accordance to techniques which are well known to those skilled in the art.

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield
30 of the desired product.

15
X

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid or as a pharmaceutically acceptable salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.001-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including any of the compounds of the invention, or a pharmaceutically acceptable salt thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The present compounds of formula (I) are useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type

16
X

2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

The compounds of the present invention are expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and postprandial dyslipidemia with or without other manifestations of the metabolic syndrome.

Treatment with the present compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of their insulin sensitizing effect the compounds of formula I are also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed. Furthermore the compounds may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease and multiple sclerosis.

The compounds of the present invention are expected to be useful in controlling glucose levels in patients suffering from type 2 diabetes.

The present invention provides a method of treating or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the

17
~~17~~

administration of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating or preventing type 2 diabetes
5 comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of formula I as a medicament.

10

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

15 Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and
20 obesity. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

25 The compounds of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase
30 inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide.

18
X

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 another PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma and /or delta 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 BMS 298585, clofibrate, fenofibrate, bezafibrate, gemfibrozil and ciprofibrate; GW 9578, pioglitazone, rosiglitazone, rivoglitazone, balaglitazone, 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-methanesulphonyloxy-phenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

In addition the combination of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcyamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. Therefore the present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this paragraph. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to

2019

in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, bervastatin, cerivastatin, dalvastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, 5 nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt. 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 particularly preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-
10 fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[N-methyl-N-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-
15 pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now known under its generic name rosuvastatin.

20 In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination
25 with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor).

30 Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO

20

94/24087, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO98/07749,
WO 98/38182, WO 98/40375, WO 98/56757, WO 99/32478, WO 99/35135, WO
99/64409, WO 99/64410, WO 00/01687, WO 00/20392, WO 00/20393, WO 00/20410,
WO 00/20437, WO 01/34570, WO 00/35889, WO 00/47568, WO 00/61568, WO
5 01/68637, WO 01/68096, WO 02/08211, WO 00/38725, WO 00/38726, WO 00/38727,
WO 00/38728, WO 00/38729, DE 19825804, 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, EP 864 582, 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
10 herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are
benzothiepines, and the compounds described in the claims, particularly claim 1, of WO
00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other
15 suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and
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-
20 3-ethyl-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl β -D-
glucopyranosiduronic acid (EP 864 582). Other suitable IBAT inhibitors include one of:
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-(*R*)-1'-phenyl-1'-[*N'*-(carboxymethyl)
carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-(*R*)- α -[*N'*-
25 (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;
30 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;
- 5 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;
- 10 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;
- 15 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;
- 20 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;
- 25 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;
- 30

22
h

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

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

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

10 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- $\{N-[(R)-\alpha-(N'-(2-((methyl)(hydroxy)$
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- $\{N-[(R)-\alpha-[(R)-N'-(2-methylsulphinyl-1-$
15 carboxyethyl)carbamoyl]benzyl]carbamoylmethoxy\}-2,3,4,5-tetrahydro-1,5-
benzothiazepine;

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

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- $\{N-[(R)-\alpha-[N-((R)-1-carboxy-2-$
methylthio-ethyl)carbamoyl]-4-hydroxybenzyl]carbamoylmethoxy\}-2,3,4,5-tetrahydro-
20 1,2,5-benzothiadiazepine;

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

30 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- $\{N-[(R)-\alpha-[N-((S)-1-carboxypropyl)$
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;
- 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}-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*-(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; and
- 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;

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

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

5 compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and
10 described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;

a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;

a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282,
15 751-54, 1998 which are incorporated herein by reference;

a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and niceritrol;

a phytosterol compound for example stanols;
probucol;

20 an omega-3 fatty acid for example Omacor™;

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha
25 adrenergic blocker, a beta adrenergic blocker for example metoprolol, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ;

30 aspirin;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;
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.

5

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such
salts or a prodrugs thereof, including active metabolites, which can be used in combination
with a compound of formula I include but are not limited to, the following compounds:
alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride,
10 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,
idrapiel, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B,
15 mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C,
pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride,
quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril,
spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril,
trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE
20 inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and
enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril
and ramiprilat.

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

30

26
27

Therefore in an additional feature of the invention, there is provided a method for the treatment of type 2 diabetes and its associated complications 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 one the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section 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 one of the other compounds described in this combination section 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 one of the other compounds described in this combination section 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:

27

- 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) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
- 5 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) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- 10 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 one of the other compounds described in this combination section, or

20 a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or

25 a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

30

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

22/5/28

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 one of the other compounds described in this combination section, 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.

Examples

¹H NMR and ¹³C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ¹H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ¹³C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Abbreviations

IRS	insulin resistance syndrome
TLC	thin layer chromatography
HOBt	1-hydroxybenzotriazole-hydrate
DIBAL	diisobutylaluminium hydride
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
DMF	N,N-dimethylformamide
THF	tetrahydrofuran
PEG	polyethylene glycol
HPLC	high performance liquid chromatography
MeCN	acetonitrile
TFA	trifluoroacetic acid
Pd/C	palladium on charcoal

29

HATU O-(7-azabenzotriazolyl-1-yl)-N,N,N',N'-tetramethyluronium
hexafluorophosphate

DCM dichloromethane

TBTU O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoborate

DIPEA *N,N*-diisopropylethylamine

DMAP 4-dimethylaminopyridine

Trisamine Tris(hydroxymethyl)aminomethane

ISOLUTE ® FLASH Si is a silica column suitable for chromatography

Borohydride on polymer support is Borohydride on Amberlite IRA-400 available from

10 Aldrich

EDC 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

NH₄OAc ammonium acetate

t triplet

s singlet

15 d doublet

q quartet

qvint quintet

m multiplet

br broad

20 bs broad singlet

dm doublet of multiplet

bt broad triplet

dd doublet of doublet

25 Example 1

a) *N*-benzyl-*N*-hexyl-3-(4-hydroxyphenyl)propanamide

N-hexylbenzylamine (0.6 g, 3.136 mmol) and 3-(4-hydroxyphenyl)propionic acid (0.52 g, 3.136 mmol) were mixed in DMF (10 ml) and the mixture was cooled. HOBT (0.424 g, 3.136 mmol) and the TBTU (1 g, 3.136 mmol) reagent were added followed by DIPEA (1.216 g, 9.409 mmol). The mixture was stirred at room temperature overnight and then evaporated. The resulting mixture was partitioned between ethyl acetate and sodium

30

30
M

hydrogencarbonate aqueous solution (sat.). The aqueous portion was extracted with ethyl acetate and the combined organic extracts dried with magnesium sulphate and then evaporated. Chromatography of the residue on a column (ISOLUTE® SI, 5g/25 ml) using ethyl acetate/heptane (10:90, then 25:75) as eluant gave 760 mg the desired product, yield 71%.

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.84 (t, 3H), 1.16-1.27 (m, 6H), 1.41-1.51 (m, 2H), 2.55, 2.63 (t, t, 2H), 2.88, 2.94 (t, t, 2H), 3.09, 3.31 (t, t, 2H), 4.40, 4.57 (s, s, 2H), 6.69, 6.73 (d, d, 2H), 6.98 (d, 2H), 7.05, 7.07 (d, d, 2H), 7.14 (d, 1H) and 7.21-7.31 (m, 5H)

b) Methyl 2-[(4-{3-[benzyl(hexyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate

N-benzyl-N-hexyl-3-(4-hydroxyphenyl)propanamide (183mg, 0.54mmol), methyl 2-(bromomethyl)benzoate (136mg, 0.59mmol) and potassium carbonate (112mg, 0.81mmol) were mixed in acetonitrile. The mixture was stirred at 66°C overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The organic phase was washed (water x2, brine x1), dried (Na₂SO₄) and evaporated. Further purification by preparative HPLC (using a gradient of CH₃CN/ 10%CH₃CN-waterphase containing 0.1M NH₄OAc as eluant) gave 91mg (yield 34%) of the desired product.

¹H NMR (rotamers, 400MHz, CDCl₃): δ 0.84-0.88 (m, 3H), 1.19-1.29 (m, 6H), 1.42-1.53 (m, 2H), 2.57, 2.65 (t, t, 2H), 2.92, 2.99 (t, 2H), 3.10, 3.34 (t, t, 2H), 3.89, 3.90 (s, s, 3H), 4.42, 4.60 (s, s, 2H), 5.47, 5.48 (s, s, 2H), 6.86-6.93 (m, 2H), 7.07 (t, 2H), 7.14-7.19 (m, 2H), 7.21-7.38 (m, 4H), 7.52-7.56 (m, 1H), 7.75 (t, 1H), 8.00-8.03 (m, 1H).

c) 2-[(4-{3-[Benzyl(hexyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid

Methyl 2-[(4-{3-[benzyl(hexyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate (61mg, 0.13mmol) and lithium hydroxide (7mg, 0.29mmol) were dissolved in 3ml of a 1:1 mixture of THF and water in a microwave vial. The resulting reaction mixture was irradiated in a microwave oven at 120°C for 40min.

31

Water was added and the THF was evaporated under reduced pressure. The residue was acidified with 1M hydrochloric acid and extracted with ethyl acetate (x3). The organic phases were combined, washed (water, brine), dried (Na_2SO_4) and evaporated. The crude product was further purified by preparative HPLC (using a gradient of CH_3CN /

5 10% CH_3CN -waterphase containing 0.1M NH_4OAc as eluant).

38mg (yield 64%) of pure product was obtained after freeze-drying.

^1H NMR (rotamers, 400MHz, CDCl_3): δ 0.86 (t, 3H), 1.19-1.28 (m, 6H), 1.43-1.55 (m, 2H), 2.60, 2.69 (t, t, 2H), 2.92, 2.99 (t, t, 2H), 3.11, 3.36 (t, t, 2H), 4.43, 4.61 (s, s, 2H), 5.52, 5.53 (s, s, 2H), 6.87-6.93 (m, 2H), 7.05-7.09 (m, 2H), 7.14-7.33 (m, 5H), 7.36-7.40 (m, 1H), 7.55-7.59 (m, 1H), 7.77 (t, 1H) and 8.12-8.15 (m, 1H).

10 ^{13}C NMR (rotamers, 100MHz, CDCl_3): δ 14.17, 14.23, 22.73, 22.79, 26.75, 26.88, 27.68, 27.72, 31.11, 31.26, 31.61, 31.82, 35.39, 35.68, 46.84, 47.48, 48.72, 51.35, 68.42, 115.16, 115.22, 126.39, 127.15, 127.42, 127.49, 127.72, 128.23, 128.70, 129.10, 129.72, 131.81, 133.45, 133.81, 133.84, 137.10, 137.82, 140.88, 157.33, 157.40, 171.20, 173.10, 173.39.

15

Example 2

a) *N*-(2,4-difluorobenzyl)-*N*-heptylamine

Heptylamine (345.6 mg, 3 mmol) was added into 2,4-difluorobenzaldehyde (440.5 mg, 3.1 mmol) in MeOH (3 ml) and trimethyl orthoformate (2 ml), followed by acetic acid (0.05 ml). The mixture was in microwave oven (Smith Synthesizer) at 150 °C for 10 minutes. DCM (3 ml) was then added and followed borohydride on polymer support (1.2g, ~3 mmol). The mixture was shaken overnight and more of borohydride on polymer support (1.2 g) was added. The mixture was shaken over weekend and then filtered and evaporated.

20 The residue was put on a column ((ISOLUTE®PRS, 10g) and eluted with MeCN, MeOH and then MeOH (NH_3 sat.). 536 mg of oil product was obtained, yield 72%.

25

^1H NMR (400 MHz, CDCl_3): δ 0.87 (t, 3H), 1.23-1.32 (m, 8H), 1.45-1.52 (m, 2H), 2.59 (t, 2H), 3.78 (s, 2H), 6.75-6.85 (m, 2H) and 7.27-7.33 (m, 1H)

32
Mb) 4-([2-(Methoxycarbonyl)benzyl]thio)phenyl)acetic acid

4-Mercaptophenylacetic acid (995 mg, 5.915 mmol) in THF (15 ml) was cooled in an ice-bath and sodium hydride (55-65%, 520 mg, ~13 mmol) was added. The mixture was stirred for 30 minutes and then 2-bromomethyl-benzoic acid methyl ester (1.49 g, 6.507 mmol) in THF (5 ml) was added. The resulting mixture was stirred overnight and the temperature was allowed going up to room temperature. Water was dropped in and the mixture was stirred for ca. 20 minutes. It was then evaporated to remove THF. The residue was acidified with 1% hydrochloric acid, pH~3, and then extracted with ethyl acetate. The organic extracts were combined, dried with magnesium sulphate and evaporated. Chromatography of the residue on a column (ISOLUTE® SI, 20g/70ml) using DCM, then MeOH/DCM (1:99) as eluant gave 224 mg desired product, yield 65%.

¹H NMR (500 MHz, CDCl₃): δ 3.62 (s, 2H), 3.90 (s, 3H), 4.52 (s, 2H), 7.17 (d, 2H), 7.23-7.40 (m, 5H) and 7.94 (d, 1H).

c) Methyl 2-([4-(2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl)phenyl]thio)-methyl]benzoate

(4-([2-(Methoxycarbonyl)benzyl]thio)phenyl)acetic acid (581 mg, 1.836 mmol) and *N*-(2,4-difluorobenzyl)-*N*-heptylamine (465.3 mg, 1.968 mmol) were combined in DMF and the mixture was cooled in an ice-bath. HOBT (260.6 mg, 1.928 mmol) and TBTU (619 mg, 1.928 mmol) were added, followed by DIPEA (747.7 mg 5.785mmol). The mixture was stirred at room temperature overnight and then evaporated. The resulting mixture was partitioned between ethyl acetate and sodium hydrogencarbonate aqueous solution (sat.). The aqueous portion was extracted with ethyl acetate and the combined organic extracts was dried with magnesium sulphate and then evaporated. Chromatography of the residue on a column (ISOLUTE® SI, 20g/70ml) using ethyl acetate/heptane (5:95, then 10:90) as eluant gave 767 mg the desired product, yield 77%.

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.88-0.93 (m, 3H), 1.23-1.34 (m, 8H), 1.48-1.57 (m, 2H), 3.19-3.24, 3.30-3.37 (m, m, 2H), 3.67-3.74 (m, 2H), 3.92 (s, 3H), 4.50, 4.63 (s, s, 2H), 4.53 (s, 2H), 6.78-6.89 (m, 2H), 7.00-7.40 (m, 8H) and 7.95 (d, 2H).

33
X
A

d) 2-[[[4-[2-[(2,4-Difluorobenzyl)(heptyl)amino]-2-oxoethyl]phenyl]thio]methyl]benzoic acid

Methyl 2-[[[4-[2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl]phenyl]thio]methyl]-benzoate (31 mg, 0.057 mmol) was dissolved in THF (1 ml) and cooled in an ice-bath.

5 Lithium hydroxide (2 mg, 0.075 mmol) in water (1 ml) was added. After the addition, the cooling bath was removed and the mixture was stirred overnight. LC-MS showed there was very little product. More lithium hydroxide (3 mg) was added and the mixture was stirred for 6 days more and HPLC showed about 30% product. More (3 mg) of lithium hydroxide was added and the mixture was stirred for 13 days more. It was evaporated in
10 vacuum to remove THF. The residue was acidified with 10% hydrochloric acid, pH~3, and extracted with ethyl acetate (x2). The organic phases were combined, dried (magnesium sulphate) and evaporated. Chromatography of the residue on a column (ISOLUTE® SI, 500g/3ml) using DCM, MeOH/DCM (0.5:99.5) as eluant gave 17 mg desired product, yield 56%.

15 ¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.89-0.93 (m, 3H), 1.25-1.34 (m, 8H), 1.52-1.60 (m, 2H), 3.27, 3.37 (t, t, 2H), 3.71, 3.76 (s, s, 2H), 4.55, 4.65 (s, s, 2H), 6.80-6.92 (m, 2H), 7.07-7.17 (m, 2H), 7.28-7.37 (m, 5H), 7.42-7.47 (m, 1H) and 7.95-7.98 (m, 1H).

¹³C NMR (rotamers, 125 MHz, CDCl₃): δ 14.01, 22.51, 26.78, 26.85, 27.28, 28.56, 28.85, 28.93, 31.65, 31.70, 38.22, 39.94, 40.25, 41.57, 41.60, 45.16, 46.48, 47.94, 103.53 (t),
20 104.26(t), 111.50(br), 111.71(br), 119.65(d), 120.37(d), 127.05, 128.95 (br), 129.61, 129.68, 131.15, 131.66(d), 131.76(d), 132.41, 132.80, 132.88, 133.85, 134.03, 140.43, 160.58 (dd), 160.91(dd), 162.21(dd), 162.53(dd), 170.46, 171.44 and 171.54.

Example 3

25 a) (4-[[2-(Methoxycarbonyl)benzyl]oxy]phenyl)acetic acid

4-Hydroxyphenylacetic acid (760 mg, 4.995 mmol) was dissolved in ethanol (99.5%, 20 ml). Potassium hydroxide (560.5 mg, 9.99 mmol) was added. The mixture was stirred at room temperature for 30 minutes. 2-Bromomethylbenzoic acid methyl ester (1144.2 mg,
30 4.995 mmol) was then dropped in. The resulting mixture was heated to reflux for 2 hours and then evaporated in vacuum to dry. Water and ethyl acetate were added into the residue and the phases were separated. The water phase was acidified with 10% hydrochloric acid,

pH~5, and then extracted with ethyl acetate. The organic phase was dried with magnesium sulphate and evaporated in vacuum to dry. Chromatography of the residue on a column (ISOLUTE® SI, 5g/6ml) using DCM, MeOH/DCM (1:99) as eluant gave the desired product (262 mg), yield 17.5%.

¹H NMR (500 MHz, CDCl₃): δ 3.61 (s, 2H), 3.91 (s, 3H), 5.50 (s, 2H), 6.97 (d, 2H), 7.22 (d, 2H), 7.39 (t, 1H), 7.57 (t, 1H), 7.76 (d, 1H) and 8.04 (d, 1H).

b) Methyl 2-[(4-{2-[benzyl(hexyl)amino]-2-oxoethyl}phenoxy)methyl]benzoate

(4-{[2-(Methoxycarbonyl)benzyl]oxy}phenyl)acetic acid (50 mg, 0.166 mmol) was dissolved in DCM (2 ml), N-hexylbenzylamine (38.2 mg, 0.2 mmol) was added, then EDC (38.3 mg, 0.2 mmol) was added and then DMAP (24.4 mg, 0.2 mmol) was added. The mixture was stirred at room temperature overnight. 1% HCl (1 ml) and water (1 ml) were added into the mixture. The two phases were separated by using a Whatman Filter Tube. The obtained organic solution was evaporated in vacuum and the oil product (71 mg) was left. It was then used directly in next step.

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.86-0.91 (m, 3H), 1.22-1.32 (m, 6H), 1.47-1.58 (m, 2H), 3.21, 3.39 (t, t, 2H), 3.65, 3.75 (s, s, 2H), 3.93 (s, 3H), 4.53, 4.64 (s, s, 2H), 5.51, 5.52 (s, s, 2H), 6.96, 6.99 (d, d, 2H), 7.16 (d, 2H), 7.23-7.42 (m, 6H), 7.59 (t, 1H), 7.78 (d, 1H) and 8.06 (d, 1H).

c) 2-[(4-{2-[Benzyl(hexyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid

Methyl 2-[(4-{2-[benzyl(hexyl)amino]-2-oxoethyl}phenoxy)methyl]benzoate (70 mg, 0.148 mmol) in THF (2 ml) was cooled in an ice-bath. Lithium hydroxide (7.08 mg, 0.296 mmol) in water (1 ml) was dropped in. The cooling-bath was then removed and the mixture was stirred overnight. HPLC showed that the reaction was not complete. More lithium hydroxide (0.2M, 0.5 ml) was added. The reaction mixture was stirred for 4 days more. It was then evaporated in vacuum to remove THF. The residue was acidified with 1% hydrochloric acid, pH=3-4, and extracted with ethyl acetate. The organic phase was dried (magnesium sulphate) and evaporated. Chromatography of the residue on a column

35
26

(ISOLUTE® SI, 2g/6 ml) using DCM, MeOH/DCM (1:99, and then 2:98) as eluant gave 24 mg the desired product, yield 35%.

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.86-0.90 (m, 3H), 1.21-1.30 (m, 6H), 1.46-1.58 (m, 2H), 3.21, 3.39 (t, t, 2H), 3.68, 3.77 (s, s, 2H), 4.53, 4.65 (s, s, 2H), 5.53, 5.54 (s, s, 2H), 6.95, 6.98 (d, d, 2H), 7.14-7.17 (m, 2H), 7.22-7.33 (m, 4H), 7.35-7.43 (m, 2H), 7.60 (t, 1H), 7.80 (d, 1H) and 8.16 (d, 1H).

¹³C NMR (rotamers, 125 MHz, CDCl₃): δ 13.94, 13.97, 22.49, 22.53, 26.47, 26.57, 27.29, 28.36, 31.40, 31.50, 39.82, 40.12, 46.50, 47.43, 48.28, 51.31, 68.21, 115.15, 126.25, 126.85, 127.20, 127.24, 127.36, 127.48, 127.54, 127.97, 128.49, 128.87, 129.76, 129.89, 131.52, 133.18, 136.80, 137.57, 140.40, 157.59, 170.60, 171.76 and 172.03.

Example 4

a) Methyl 2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy)methyl]benzoate

N-(2,4-Difluorobenzyl)-*N*-heptylamine (106 mg, 0.44 mmol) was added into 4-[(2-(methoxycarbonyl)benzyl]oxy}phenyl)acetic acid (120 mg, 0.4 mmol) in DCM (10 ml) and followed by EDC (84.3 mg, 0.44 mmol) and then DMAP (54 mg, 0.44 mmol). The mixture was stirred at room temperature overnight, and then washed with 1% hydrochloric acid, water and brine and dried with magnesium sulphate and evaporated. Chromatography of the residue on a column (ISOLUTE®SI, 5g/15 ml) using DCM and MeOH/DCM (0.5:99.5) as eluant gave 155 mg desired product, yield 74%.

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.88-0.92 (m, 3H), 1.23-1.33 (m, 8H), 1.49-1.57 (m, 2H), 3.24, 3.34 (t, t, 2H), 3.66, 3.72 (s, s, 2H), 3.92 (s, 3H), 4.53, 4.62 (s, s, 2H), 5.50, 5.51 (s, s, 2H), 6.77-6.89 (m, 2H), 6.95, 6.98 (d, d, 2H), 6.99-7.04, 7.29-7.33 (m, m, 1H), 7.17, 7.20 (d, d, 2H), 7.39 (t, 1H), 7.57 (t, 1H), 7.75-7.79 (m, 1H) and 8.05 (d, 1H).

b) 2-[(4-{2-[(2,4-Difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid

Lithium hydroxide (13.3 mg, 0.554 mmol) in water (1.5 ml) was added into 70335 methyl 2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy)methyl]benzoate (145 mg, 0.277 mmol) dissolved in THF (3 ml). The mixture was then in microwave oven

A 36

(Smith Synthesizer) at 150 °C for 7 minutes and then evaporated to remove THF. The residue was acidified with 1% hydrochloric acid, pH~4 and then extracted with ethyl acetate (x2). The organic portions were combined, washed with brine, dried with magnesium sulphate and then evaporated. Chromatography of the residue on a column (ISOLUTE® SI, 2g/6ml) using DCM then MeOH/DCM (0.5:99.5, then 1:99) as eluant gave 94 mg desired product, yield 67%.

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.86-0.91 (m, 3H), 1.22-1.32 (m, 8H), 1.48-1.56 (m, 2H), 3.23, 3.34 (t, t, 2H), 3.68, 3.73 (s, s, 2H), 4.52, 4.63 (s, s, 2H), 5.53 (s, br, 2H), 6.77-6.87 (m, 2H), 6.93- 6.97 (m, 2H), 6.99-7.04, 7.27-7.33 (m, m, 1H), 7.16-7.20 (m, 2H), 7.41 (t, 1H), 7.58-7.62 (m, 1H), 7.78 (d, 1H) and 8.15(d, 1H).

¹³C NMR (rotamers, 125 MHz, CDCl₃): δ 14.00, 22.51, 26.75, 26.84, 27.26, 28.54, 28.86, 28.94, 31.64, 31.70, 39.75, 40.08, 41.39, 45.05, 46.30, 47.98, 68.21, 103.67 (t), 104.12 (t), 111.52 (d), 115.17, 119.80 (d), 120.52 (d), 126.97, 127.04, 127.21, 128.81 (br), 129.78, 129.85, 131.52, 133.16, 140.33, 157.65, 160.48 (dd), 160.85 (dd), 162.13 (dd), 162.46 (dd), 171.01, 171.93 and 171.99.

Example 5

a) *N*-(2,4-difluorobenzyl)-*N*-heptyl-3-(4-hydroxyphenyl)propanamide

3-(4-Hydroxyphenyl)propionic acid (108 mg, 0.650 mmol) was dissolved in DMF. *N*-(2,4-difluorobenzyl)-*N*-heptylamine (164.7 mg, 0.682 mmol) was added. The mixture was cooled in an ice-bath. TBTU (219 mg, 0.682 mmol) was added and followed by DIPRA (0.238 ml, 1.365 mmol). The mixture was stirred overnight and the temperature was allowed up to room temperature. Ethyl acetate and sodium hydrogencarbonate aqueous solution (sat.) were added and then the two phases were separated. The water phase was extracted with ethyl acetate. The organic phases were combined and dried with magnesium sulphate and evaporated. Chromatography of the residue on a column (ISOLUTE® SI, 5g/15 ml) using DCM and then MeOH/DCM (1:99) as eluant gave 223 mg desired product, yield 88%.

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.86-0.90 (m, 3H), 1.21-1.31 (m, 8H), 1.47-1.53 (m, 2H), 2.60, 2.67 (t, t, 2H), 2.85-2.96 (m, 2H), 3.15, 3.32 (t, t, 2H), 4.41, 4.60 (s, s, 2H), 6.75-6.85 (m, 4H), 6.90-6.96, 7.12-7.18 (m, m, 1H) and 7.00, 7.04 (d, d, 2H).

2535

b) Methyl 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate

5 *N*-(2,4-difluorobenzyl)-*N*-heptyl-3-(4-hydroxyphenyl)propanamide (195 mg, 0.501 mmol), 2-bromomethylbenzoic acid methyl ester (120.4 mg, 0.526 mmol) and anhydrous potassium carbonate (103 mg, 0.751 mmol) were mixed in acetonitrile (15 ml). The mixture was heated to reflux overnight and then evaporated to dryness. Water and ethyl acetate were added and the two phases were separated. The organic phase was dried
10 (magnesium sulphate) and evaporated. Chromatography of the residue on a column (ISOLUTE® SI, 2g/6ml) using heptane/DCM (50:50), then DCM and then MeOH/DCM (0.5:99.5) as eluant gave 187 mg desired product, yield 69.5%.

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.87-0.91 (m, 3H), 1.21-1.31 (m, 8H), 1.44-1.56 (m, 2H), 2.56-2.69 (m, 2H), 2.91-3.01 (m, 2H), 3.14, 3.32 (t, t, 2H), 3.92 (s, 3H), 4.43,
15 4.59 (s, s, 2H), 5.49 (s, 2H), 6.75-6.97 (m, 4H), 7.08-7.28 (m, 3H), 7.38 (t, 1H), 7.56 (t, 1H), 7.76 (d, 1H) and 8.04 (d, 1H).

c) 2-[(4-{3-[(2,4-Difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid

20

Lithium hydroxide (13.3 mg, 0.554 mmol) in water (1 ml) was added into methyl 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate (149 mg, 0.277 mmol) dissolved in THF (2 ml). The mixture was then placed in microwave oven (Smith Synthesizer) at 150 °C for 7 minutes and then evaporated to remove THF. The
25 residue was acidified with 1% hydrochloric acid, pH~4, and extracted with ethyl acetate (x2). The organic extracts were combined and washed with brine and dried with magnesium sulphate and then evaporated. Chromatography of the residue on a column (ISOLUTE® SI, 2g/6ml) using DCM, then MeOH/DCM (1:99) as eluant gave 121 mg desired product, yield 83%.

30 ¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.89-0.93 (m, 3H), 1.24-1.33 (m, 8H), 1.49-1.58 (m, 2H), 2.64-2.74 (m, 2H), 2.97-3.03 (m, 2H), 3.17, 3.37 (t, t, 2H), 4.46, 4.65 (s, s, 2H), 5.58, 5.59 (s, s, 2H), 6.78-6.87 (m, 2H), 6.94-6.97 (m, 2H), 6.99-7.04, 7.27-7.31 (m, m,

38
2/3

1H), 7.14, 7.17 (d, d, 2H), 7.42-7.45 (m, 1H), 7.61-7.64 (m, 1H), 7.82-7.85 (m, 1H) and 8.19-8.22 (d, 1H),

¹³C NMR (rotamers, 125 MHz, CDCl₃): δ 13.96, 22.46, 22.49, 26.67, 26.85, 27.38, 28.57, 28.80, 28.94, 30.69, 30.84, 31.58, 31.67, 35.01, 35.26, 41.63, 44.76, 44.78, 46.43, 47.78, 68.15, 103.60(t), 104.07(t), 111.41(dd), 111.49 (dd), 114.91, 119.74 (d), 120.45 (d), 126.86, 127.12, 128.53 (br), 129.40, 131.49, 131.58, 133.15, 133.32, 140.54, 157.12, 160.33 (dd), 160.81 (dd), 162.07 (dd), 162.33 (dd), 171.07, 173.04 and 173.11.

Example 6

10

a) 3-(4-Mercaptophenyl)propanoic acid (2.0 g, 10.97 mmol) was dissolved in dry THF (60 ml) and cooled to 0° C. Sodium hydride (0.64 g, 24.1 mmol) was added. The mixture was stirred for 30 minutes, methyl 2-(bromomethyl)benzoate (2.77 g, 12.07 mmol) dissolved in dry THF (10 ml) was added dropwise. The solution was allowed to warm up to room temperature and was stirred overnight. Dropwise addition of water (10 ml) deactivated the remaining sodium hydride. The solvent was removed by evaporation, and the residue was acidified to pH 3 (HCl 1%). The water phase was washed with EtOAc (3 X 10 ml). The organic phases were combined, dried (MgSO₄) and evaporated. The crude was purified by preparative HPLC (started with acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried (MgSO₄). Removing the solvent by evaporation gave 2.26 gram of 3-(4-{[2-(methoxycarbonyl)benzyl]thio}phenyl)propanoic acid (yield 62.3%).

25

¹H NMR (500 MHz, CDCl₃): δ 2.66 (t, 2H), 2.92 (t, 2H), 3.90 (s, 3H), 4.51 (s, 2H), 7.10 (d, 2H), 7.19 (d, 1H), 7.25 (d, 2H), 7.29 (t, 1H), 7.36 (t, 1H) and 7.94 (d, 1H).

39
A

b) Methyl 2-{[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]-methyl}benzoate

N-(2,4-difluorobenzyl)-*N*-heptylamine (0.64 g, 2.65 mmol) was dissolved in DMF (10 ml),
5 3-(4-{[2-(methoxycarbonyl)benzyl]thio}phenyl)propanoic acid (0.80 g, 2.41 mmol) was
added and the mixture was cooled to 0° C. *N*-[(1*H*-1,2,3-benzotriazol-1-yloxy)-
(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate (0.85 g, 2.65
mmol) and diisopropylethylamine (0.65 g, 5.05 mmol) was added. The mixture was
allowed to warm to room temperature and stirred overnight. EtOAc (15 ml) was added and
10 the organic phase was washed with two portions of sodium hydrogencarbonate (aq, 10 ml).
EtOAc was removed by evaporation and the crude was purified by preparative HPLC
(started with acetonitrile/buffer 60/40 and then the acetonitrile concentration was
increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium
acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product
15 containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc
(10 ml) was added and the organic phase was washed with two portions of brine and dried
(MgSO₄). The solvent was removed by evaporation and gave 1.10 gram of methyl 2-[(4-
{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]methyl}benzoate (yield
82.2%).

20

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.89 (t, 3H), 1.22-1.32 (m, 8H), 1.47-1.55 (m,
2H), 2.55, 2.66 (t, t, 2H), 2.95-3.01 (m, 2H), 3.16, 3.33 (t, t, 2H), 3.89, 3.90 (s, s, 3H), 4.44,
4.60 (s, s, 2H), 4.50, 4.51 (s, s, 2H), 6.76-6.85 (m, 2H), 6.92-6.96, 7.20-7.25 (m, m, 4H),
7.07, 7.12 (d, d, 2H), 7.27-7.31 (m, 1H), 7.32-7.34 (m, 1H) and 7.91-7.92 (m, 1H).

25

c) 2-[(4-{3-[(2,4-Difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]-methyl}benzoic acid

Methyl 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]-
30 methyl}benzoate (1.05 g, 1.89 mmol) was dissolved in EtOH (95%, 5 ml), potassium
hydroxide (0.21 g, 3.77 mmol) was added. The reaction was performed in a single mode
microwave oven (7 min, 150° C). Workup was by addition of EtOAc (5 ml) and washing

4140

with HCl (2 X 5 ml, 1M). The organic layer was dried (MgSO₄) and the solvent was removed by evaporation to give 0.96 gram of 2-[[[4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]methyl]benzoic acid (yield 94.3%).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.88-0.92 (m, 3H), 1.24-1.33 (m, 8H), 1.50-1.57 (m, 2H), 2.64, 2.69 (t, t, 2H), 2.95-3.00 (m, 2H), 3.20, 3.34 (t, t, 2H), 4.48, 4.62 (s, s, 2H), 4.55, 4.56 (s, s, 2H), 6.79-6.87 (m, 2H), 6.98-7.03, 7.27-7.30 (m, m, 2H), 7.06-7.10 (m, 2H), 7.22-7.24 (m, 2H), 7.31-7.36 (m, 1H), 7.41-7.46 (m, 1H) and 8.03 (d, 1H).

¹³C NMR (rotamers, 125 MHz, CDCl₃): δ 14.01, 22.51, 22.54, 26.74, 26.90, 27.42, 28.63, 28.86, 28.98, 30.92, 31.18, 31.64, 31.72, 34.65, 38.23, 38.28, 41.58, 44.82, 46.44, 47.77, 103.46 (t), 104.14 (t), 111.52 (dd), 111.58 (dd), 119.74 (dd), 120.51 (dd), 127.09, 128.55, 128.63, 129.03, 131.16, 131.49, 131.55, 131.78 (dd), 132.30, 132.50, 132.96, 140.04, 140.11, 140.59, 140.68, 160.47 (dd), 160.88 (dd), 162.16 (dd), 162.44 (dd), 170.88 (br), 172.56 and 172.59.

Example 7

a) *N*-(2,3-dimethoxybenzyl)butan-1-amine (0.59 g, 2.65 mmol) was dissolved in DMF (10 ml), 3-(4-hydroxyphenyl)propanoic acid (0.4 g, 2.41 mmol), was added and the mixture was cooled to 0° C. *N*-[(1*H*-1,2,3-benzotriazol-1-yloxy)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate (0.85 g, 2.65 mmol) and diisopropylethylamine (0.65 g, 5.05 mmol) was added. The mixture was allowed to warm to room temperature and stirred over night. EtOAc (15 ml) was added and the organic phase was washed with two portions of sodium hydrogencarbonate (aq, 10 ml). EtOAc was removed by evaporation and the crude was purified by preparative HPLC (started with acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions was pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried (MgSO₄). The solvent was

41
2
D

removed by evaporation and gave 1.08 gram of *N*-butyl-*N*-(2,3-dimethoxybenzyl)-3-(4-hydroxyphenyl)propanamide (yield 82.3%).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.85-0.89 (m, 3H), 1.20-1.30 (m, 2H), 1.44-1.53 (m, 2H), 2.60, 2.65 (t, t, 2H), 2.88, 2.94 (t, t, 2H), 3.13, 3.33 (t, t, 2H), 3.78, 3.80 3.83, 3.85 (s, s, s, s, 6H), 4.43, 4.68 (s, s, 2H), 6.57, 6.67 (d, d, 1H), 6.74-6.86 (m, 3H) and 6.95-7.05 (m, 3H).

b) *N*-butyl-*N*-(2,3-dimethoxybenzyl)-3-(4-hydroxyphenyl)propanamide (50 mg, 0.13 mmol) and methyl 2-(bromomethyl)benzoate (0.034 g, 0.15 mmol) was dissolved in acetonitrile (10 ml) and potassium carbonate (37 mg, 0.27 mmol) was added. The mixture was stirred at 60° C for three hours. Polymer supported trisamine (0.3 eqv) was added and stirred overnight. The polymer was filtered off and solvent was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with three portions of water. After drying the crude (MgSO₄), the solvent had been removed by evaporation. The residue was purified by preparative HPLC (started with acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried (MgSO₄). Removing the solvent by evaporation gave 15 mg of methyl 2-[(4-{3-[butyl(2,3-dimethoxybenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate (21.4%).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.89-0.95 (m, 3H), 1.24-1.35 (m, 2H), 1.48-1.57 (m, 2H), 2.62, 2.69 (t, t, 2H), 2.95, 3.01 (t, t, 2H), 3.17, 3.36 (t, t, 2H), 3.83, 3.86, 3.89, 3.90, 3.93, 3.94 (s, s, s, s, s, s, 9H), 4.48, 4.71 (s, s, 2H), 5.50, 5.52 (s, s, 2H), 6.62, 6.75 (d, d, 1H), 6.84-6.97 (m, 3H), 7.00-7.04 (m, 1H), 7.11, 7.19 (d, d, 2H), 7.38-7.42 (m, 1H), 7.56-7.60 (m, 1H), 7.78 (t, 1H) and 8.04-8.07 (m, 1H).

c) Methyl 2-[(4-{3-[butyl(2,3-dimethoxybenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate (15 mg, 0.029 mmol) was dissolved in THF/water (2/1, 2 ml) and LiOH (1.4 mg,

42
2
A

0.058 mmol) was added. The reaction was performed in a single mode microwave oven (150° C, 7 min). Workup was done by adding EtOAc (10 ml) and washing the organic phase with two portions of HCl (2 X 5 ml, 1 M). The organic phase was dried (MgSO₄) and the solvent was removed by evaporation to give 13 mg of 2-[(4-{3-[butyl(2,3-dimethoxybenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid (yield 89%).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.89-0.95 (m, 3H), 1.24-1.35 (m, 2H), 1.48-1.57 (m, 2H), 2.62, 2.69 (t, t, 2H), 2.95, 3.01 (t, t, 2H), 3.17, 3.36 (t, t, 2H), 3.83, 3.85, 3.88, 3.89 (s, s, s, s, 6H), 4.48, 4.71 (s, s, 2H), 5.50, 5.52 (s, s, 2H), 6.62, 6.75 (d, d, 1H), 6.84-6.97 (m, 3H), 7.00-7.04 (m, 1H), 7.11, 7.19 (d, d, 2H), 7.38-7.42 (m, 1H), 7.56-7.60 (m, 1H), 7.78 (t, 1H) and 8.04-8.07 (m, 1H).

¹³C NMR (rotamers, 125 MHz, CDCl₃): δ 13.76, 13.85, 20.02, 20.21, 29.55, 30.30, 30.69, 30.84, 30.96, 35.13, 35.34, 42.60, 46.17, 46.37, 47.20, 55.69, 55.75, 60.35, 61.74, 68.20, 111.23, 111.79, 114.88, 114.96, 118.79, 120.88, 124.15, 124.21, 126.81, 127.18, 127.26, 129.46, 130.51, 131.25, 131.52, 133.23, 133.65, 140.59, 146.50, 147.17, 152.48, 152.61, 157.02, 157.10, 170.79, 172.93 and 173.25.

Example 8

a) *N*-(2,3-Dimethoxybenzyl)-*N*-heptylamine (0.70 g, 2.65 mmol) was dissolved in DMF (10 ml), 3-(4-hydroxyphenyl)propanoic acid (0.4 g, 2.41 mmol), was added and the mixture was cooled to 0° C. *N*-[(1*H*-1,2,3-benzotriazol-1-yl)oxy](dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate (0.85 g, 2.65 mmol) and diisopropylethylamine (0.65 g, 5.05 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. EtOAc (15 ml) was added and the organic phase was washed with two portions of sodium hydrogencarbonate (aq, 10 ml). EtOAc was removed by evaporation and the crude was purified by preparative HPLC (started with acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried

43

(MgSO₄). The solvent was removed by evaporation and gave 0.98 gram *N*-(2,3-dimethoxybenzyl)-*N*-heptyl-3-(4-hydroxyphenyl)propanamide (yield 70%).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.85-0.89 (m, 3H), 1.20-1.30 (m, 8H), 1.47-1.56 (m, 2H), 2.62, 2.67 (t, t, 2H), 2.89, 2.95 (t, t, 2H), 3.14, 3.33 (t, t, 2H), 3.79, 3.80, 3.84, 3.85 (s, s, s, s, 6H), 4.45, 4.69 (s, s, 2H), 6.58, 6.68 (d, d, 1H), 6.74-6.88 (m, 3H) and 6.96-7.05 (m, 3H).

b) *N*-(2,3-dimethoxybenzyl)-*N*-heptyl-3-(4-hydroxyphenyl)propanamide 0.196 g, 0.47 mmol) and methyl 2-(bromomethyl)benzoate (0.12 g, 0.52 mmol) was dissolved in acetonitrile (10 ml) and potassium carbonate (131 mg, 0.95 mmol) was added. The mixture was stirred at 60° C for three hours. Polymersupproted trisamine (0.3 eqv) was added and stirred over night. The polymer was filtered of, solvent was removed by evaporation, addition of EtOAc (10 ml) and the organic phase was washed with three potions of water. After drying the crude (MgSO₄) and the solvent had been removed by evaporation, the crude was purified by preparative HPLC (started with acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions was pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two potions of brine and dried (MgSO₄). Removing the solvent by evaporation gave 39 mg of methyl 2-[(4-{3-[(2,3-dimethoxybenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate (yield 14.6%).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.86-0.89 (m, 3H), 1.19-1.30 (m, 8H); 1.46-1.55 (m, 2H), 2.60, 2.66 (t, t, 2H), 2.93, 2.98 (t, t, 2H), 3.14, 3.33 (t, t, 2H), 3.80, 3.83, 3.86, 3.87, 3.90, 3.91 (s, s, s, s, s, 9H), 4.45, 4.68 (s, s, 2H), 5.48, 5.49 (s, s, 2H), 6.59, 6.73 (d, d, 1H), 6.81-7.01 (m, 4H) 7.08, 7.16 (d, d, 2H) 7.35-7.39 (m, 1H), 7.53-7.57 (m, 1H), 7.76 (t, 1H) and 8.01-8.04 (m, 1H).

c) Methyl 2-[(4-{3-[(2,3-dimethoxybenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate (39 mg, 0.069 mmol) was dissolved in THF/water (2/1, 2 ml) and LiOH (3.3 mg,

44

0.14 mmol) was added. The reaction was performed in a single mode microwave oven (150°C, 7 min). Workup was done by adding EtOAc (10 ml) and washing the organic phase with two portions of HCl (2 X 5 ml, 1 M). The organic phase was dried (MgSO₄) and the solvent was removed by evaporation to give 30 mg of 2-[(4-{3-[(2,3-dimethoxybenzyl)(heptyl)-amino]-3-oxopropyl}phenoxy)methyl]benzoic acid (yield 78.9).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.84-0.87 (m, 3H), 1.20-1.28 (m, 8H), 1.45-1.55 (m, 2H), 2.63, 2.69 (t, t, 2H), 2.93, 2.99 (t, t, 2H), 3.13, 3.33 (t, t, 2H), 3.79, 3.81, 3.84, 3.85 (s, s, s, s, 6H), 4.45, 4.69 (s, s, 2H), 5.52, 5.53 (s, s, 2H), 6.60, 6.72 (d, d, 1H), 6.79-7.01 (m, 4H) 7.08, 7.16 (d, d, 2H) 7.36-7.41 (m, 1H), 7.55-7.60 (m, 1H), 7.79 (t, 1H) and 8.13-8.16 (m, 1H).

¹³C NMR (rotamers, 125 MHz, CDCl₃): δ 14.04, 22.52, 22.56, 26.77, 26.96, 27.45, 28.60, 28.92, 29.03, 30.83, 30.97, 31.66, 31.75, 35.16, 35.36, 42.61, 46.42, 46.46, 47.45, 55.69, 55.75, 60.35, 60.73, 68.19, 111.26, 111.83, 114.88, 114.95, 118.84, 120.91, 124.14, 124.20, 126.85, 127.15, 127.22, 129.46, 130.52, 131.26, 131.51, 133.19, 133.66, 140.61, 146.59, 147.19, 152.48, 152.60, 157.02, 157.11, 170.77, 172.92 and 173.23.

Example 9

a) N-(3-ethoxypropyl)-N-(4-isopropylbenzyl)amine

20

p-iso-Propylbenzaldehyde (1.007 g, 6.798 mmol) was dissolved in methanol (5 ml). Trimethyl orthoformate (5 ml) was added. 3-Ethoxypropylamine (681 mg, 6.6 mmol) was then added and followed by acetic acid (0.2 ml). After standing at room temperature overnight, DCM (5 ml) was added and followed by borohydride on polymer support (5.28 g, 13.2 mmol). The mixture was shaken at room temperature for 4 days and then filtered. The filtrate was evaporated. The residue was dissolved in acetonitrile, then divided into two portions and loaded on 2 columns (ISOLUTE® PRS, 10g/70 ml, wetted with acetonitrile). It was eluted with acetonitrile, then methanol and then methanol (NH₃ sat.). The product fractions were combined and evaporated. Oil product 1.283 g was obtained, yield 83%.

30

¹H NMR (300 MHz, CDCl₃): δ 1.19 (t, 3H), 1.25 (d, 6H), 1.75-1.84 (m, 2H), 2.73 (t, 2H), 2.85-2.94 (m, 1H), 3.43-3.52 (m, 4H), 3.75 (s, 2H), 7.18 (d, 2H) and 7.24 (d, 2H).

X-45

b) *N*-(3-ethoxypropyl)-*N*-(4-isopropylbenzyl)amine (0.62 g, 2.65 mmol) was dissolved in DMF (10 ml), 3-(4-hydroxyphenyl)propanoic acid (0.4 g, 2.41 mmol), was added and the mixture was cooled to 0° C. *N*-[(1*H*-1,2,3-benzotriazol-1-yloxy)(dimethylamino)-methylene]-*N*-methylmethanaminium tetrafluoroborate (0.85 g, 2.65 mmol) and diisopropylethylamine (0.65 g, 5.05 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. EtOAc (15 ml) was added and the organic phase was washed with two portions of sodium hydrogencarbonate (aq, 10 ml). EtOAc was removed by evaporation and the crude was purified by preparative HPLC (started with acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried (MgSO₄). The solvent was removed by evaporation and gave 1.0 gram of *N*-(3-ethoxypropyl)-3-(4-hydroxyphenyl)-*N*-(4-isopropylbenzyl)propanamide (yield 75.8%).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 1.16-1.21 (m, 3H), 1.26, 1.27 (d, d, 6H), 1.75-1.80, 1.84-1.90 (m, m, 2H), 2.64, 2.74 (t, t, 2H), 2.86-3.00 (m, 3H), 3.33, 3.37 (t, t, 2H), 3.41-3.50 (m, 4H), 4.43, 4.62 (s, s, 2H), 6.80-6.84 (m, 2H) and 6.97-7.22 (m, 6H).

c) *N*-(3-ethoxypropyl)-3-(4-hydroxyphenyl)-*N*-(4-isopropylbenzyl)propanamide (0.18 g, 0.47 mmol) and methyl 2-(bromomethyl)benzoate (0.12 g, 0.52 mmol) was dissolved in acetonitrile (10 ml) and potassium carbonate (131 mg, 0.95 mmol) was added. The mixture was stirred at 60° C for three hours. Polymer-supported trisamine (0.3 eqv) was added and stirred overnight. The polymer was filtered off, solvent was removed by evaporation, addition of EtOAc (10 ml) and the organic phase was washed with three portions of water. After drying the crude (MgSO₄) and the solvent had been removed by evaporation, the crude was purified by preparative HPLC (started with acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase

46
~~2~~

was washed with two portions of brine and dried (MgSO₄). Removing the solvent by evaporation gave 0.16 gram of methyl 2-[(4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate (yield 63.5%).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 1.17, 1.21 (t, t, 3H), 1.27, 1.28 (d, d, 6H), 1.75-1.80, 1.84-1.89 (m, m, 2H), 2.63, 2.73 (t, t, 2H), 2.89-3.04 (m, 3H), 3.32, 3.37 (t, t, 2H), 3.41-3.50 (m, 4H), 3.93, 3.94 (s, s, 3H), 4.46, 4.61 (s, s, 2H), 5.51, 5.53 (s, s, 2H), 6.92, 6.95 (d, d, 2H), 7.04-7.22 (m, 6H), 7.40 (t, 1H), 7.58 (t, 1H), 7.78-7.80 (m, 1H) and 8.05-8.07 (m, 1H).

d) Methyl 2-[(4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate (0.16 g, 0.30 mmol) was dissolved in THF/water (2/1, 2 ml) and LiOH (14.4 mg, 0.60 mmol) was added. The reaction was performed in a single mode microwave oven (150° C, 7 min). Workup was done by adding EtOAc (10 ml) and washing the organic phase with two portions of HCl (2 X 5 ml, 1 M). The organic phase was dried (MgSO₄) and the solvent was removed by evaporation to give 0.108 gram of 2-[(4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid (yield 69.3%).

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 1.15, 1.19 (t, t, 3H), 1.23-1.25 (m, 6H), 1.74-1.79, 1.84-1.89 (m, m, 2H), 2.66, 2.76 (t, t, 2H), 2.86-3.03 (m, 3H), 3.30, 3.36 (t, t, 2H), 3.40-3.50 (m, 4H), 4.44, 4.61 (s, s, 2H), 5.55, 5.56 (s, s, 2H), 6.90-6.94 (m, 2H), 7.02-7.20 (m, 6H), 7.40 (t, 1H), 7.57-7.60 (m, 1H), 7.79-7.82 (m, 1H) and 8.15-8.18 (m, 1H).

¹³C NMR (rotamers, 125 MHz, CDCl₃): δ 15.15, 23.98, 27.78, 28.61, 30.93, 31.01, 33.73, 35.07, 35.38, 43.86, 44.13, 47.96, 51.26, 66.06, 66.22, 66.82, 67.98, 68.13, 114.77, 126.03, 126.38, 126.72, 126.97, 127.90, 129.31, 131.31, 132.88, 133.23, 133.39, 133.84, 134.56, 140.30, 140.38, 147.71, 148.05, 156.90, 170.48, 173.02 and 173.26.

Example 10

a) N-(2,4-difluorobenzyl)-N-propylamine

2,4-Difluorobenzaldehyde (1.003 g, 7.055 mmol) was dissolved in methanol (5 ml). Trimethyl orthoformate (5 ml) was added. Propylamine (401 mg, 6.784 mmol) was then added and followed by acetic acid (0.2 ml). After 1 hour, DCM (5 ml) was added and

47
28

followed by borohydride polymer-supported (2.5mmol/g, 5.42 g, 13.55 mmol). The mixture was shaken at room temperature for 4 days and then filtered. The filtrate was evaporated. The residue was dissolved in acetonitrile, then divided into two portions and loaded on two columns (ISOLUTE®PRS, 10g/70 ml, wetted with acetonitrile). It was eluted with acetonitrile, then methanol and then methanol (NH₃ sat.). The product fractions were combined and evaporated. Oil product (892 mg) was obtained, yield 71%.
¹H NMR (400 MHz, CDCl₃): δ 0.91 (t, 3H), 1.47-1.56 (m, 2H), 2.57 (t, 2H), 3.79 (s, 2H), 6.75-6.85 (m, 2H) and 7.27-7.33 (m, 1H).

10 b) N-(2,4-difluorobenzyl)-3-(4-hydroxyphenyl)-N-propylpropanamide

3-(4-Hydroxyphenyl)propionic acid (245 mg, 1.474 mmol) in DMF (5 ml) was cooled in an ice-bath. N-(2,4-Difluorobenzyl)-N-propylamine (300.4 mg, 1.622 mmol) was added and then TBTU (521 mg, 1.622 mmol) followed by DIPEA (400 mg, 3.096 mmol). The mixture was stirred at room temperature overnight. Sodium hydrogencarbonate aqueous solution (sat.) was added. The mixture was extracted with ethyl acetate (x2). The extracts were combined and dried (magnesium sulphate) and evaporated. Chromatography of the residue on a column (ISOLUTE® SI, 5g/25 ml) using DCM/heptane (50:50), DCM and then MeOH/DCM (1:99, then 2:98) as eluant gave 336 mg the desired product, yield 68%.
¹H NMR (rotamers, 300 MHz, CDCl₃): δ 0.82-0.88 (m, 3H), 1.45-1.58 (m, 2H), 2.59, 2.65 (t, t, 2H), 2.88-2.98 (m, 2H), 3.11, 3.27 (t, t, 2H), 4.40, 4.59 (s, s, 2H), 6.71-7.03 (m, 6H), 7.07-7.16 (m, 1H) and 7.79 (s, br, 1H).

25 c) Methyl 2-[(4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)methyl]benzoate

N-(2,4-Difluorobenzyl)-3-(4-hydroxyphenyl)-N-propylpropanamide (290 mg, 0.87 mmol) was dissolved in acetonitrile (10 ml). 2-Bromomethyl-benzoic acid methyl ester (209 mg, 0.913 mmol) was added followed by potassium carbonate, anhydrous (180 mg, 1.305 mmol). The mixture was heated to reflux overnight and then evaporated to dry. Water and ethyl acetate were added and two phases were separated. The organic phase was dried (magnesium sulphate) and evaporated. Chromatography of the residue on a column

48
49

(ISOLUTE®SI, 20g/70ml) using DCM and then MeOH/DCM (1:99) as eluant gave 184 mg the desired product, yield 44%.

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 0.85-0.92 (m, 3H), 1.52-1.60 (m, 2H), 2.61, 2.68 (t, t, 2H), 2.95-3.01 (m, 2H), 3.15, 3.32 (t, t, 2H), 3.92, 3.93 (s, s, 3H), 4.45, 4.62 (s, s, 2H),
5 5.51, 5.52 (s, s, 2H), 6.77-6.86 (m, 2H), 6.92-6.99, 7.23-7.27 (m, m, 3H), 7.12, 7.16 (d, d, 2H), 7.38-7.42 (m, 1H), 7.57 (t, 1H) 7.78 (d, 1H) and 8.04-8.07 (m, 1H).

d) 2-[(4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid

10 A mixture of methyl 2-[(4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)-methyl]benzoate (0.184 g, 0.382 mmol) and lithium hydroxide (0.018 g, 0.76 mmol) in THF (2 ml) and water (2 ml) was heated at 150 degrees for 7 minutes. The mixture was diluted with water, acidified with hydrochloric acid and extracted with methylene chloride. The combined extracts were dried with magnesium sulfate and evaporated to give 2-[(4-
15 {3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid.
¹H NMR (400 MHz, CDCl₃): δ 0.85 (t, 3), 1.4-1.6 (m, 2), 2.6-2.7 (m, 2), 2.9-3.0 (m, 2), 3.05-3.15 and 3.25-3.35 (multiplets, rotamers, 2), 4.4 and 4.6 (singlets, rotamers, 2), 5.5 (m, 2), 6.7-6.8 (m, 2), 6.9-7.0 (m, 2), 7.05-7.2 (m, 2), 7.4 (t, 1), 7.6 (t, 1), 7.8 (d, 1), 8.15 (d, 1).

20

Example 11

a) Methyl 2-[(4-{2-[ethyl[4-(trifluoromethyl)benzyl]amino]-2-oxoethyl}phenyl]thio)methyl]benzoate

25 Ethyl[4-(trifluoromethyl)benzyl]amine (284 mg, 1.40 mmol) and (4-{[2-(methoxycarbonyl)benzyl]thio}phenyl)acetic acid (443 mg, 1.40 mmol, See Example 2 b) were mixed in DMF (15 ml). TBTU (472 mg, 1.47 mmol) was added and then DIPEA (190 mg, 1.47 mmol) was added. The mixture was stirred at room temperature for 1 hour. EtOAc (20 ml) was added. The mixture was then washed with sodium hydrogencarbonate aqueous solution (sat.), 1% HCl, water (x2) and brine, dried with magnesium sulphate and
30 evaporated. The title compound (663 mg) was left, yield 94%.

249

¹H NMR (rotamers, 500 MHz, CDCl₃): δ 1.08-1.15 (m, 3H), 3.31, 3.45 (q, q, 2H), 3.63, 3.76 (s, s, 2H), 3.92 (s, 3H), 4.52-4.66 (m, 4H), 7.09-7.40 (m, 8H), 7.56, 7.62 (d, d, 2H) and 7.94 (d, 2H).

5 **b) 2-([4-(2-[ethyl[4-(trifluoromethyl)benzyl]amino]-2-oxoethyl)phenyl]thio)methyl]benzoic acid**

Methyl 2-([4-(2-[ethyl[4-(trifluoromethyl)benzyl]amino]-2-oxoethyl)phenyl]thio)methyl]benzoate (640 mg, 1.276 mmol) was dissolved in THF (20
10 ml). Lithium hydroxide (61 mg, 2.552 mmol) in water (10 ml) was added. The mixture was stirred at room temperature and the reaction was followed by LC-MS. After 24 hours, more lithium hydroxide (30 mg) and water (10 ml) were added. After in total 70 hour, LC-MS showed the reaction was complete. The mixture was evaporated to remove THF. The residue was washed with diethyl ether, then acidified with 10% HCl, pH=2, and extracted
15 with EtOAc (x2). The extracts were combined and washed with brine, dried with magnesium sulphate and evaporated. Chromatography of the residue on a column (ISOLUTE SI, 5g/25 ml), using DCM and then MeOH/DCM (0.5:99.5, then 1:99) as eluant, gave the title compound (510 mg), yield 82%.

¹H NMR (rotamers, 300 MHz, CDCl₃): δ 1.07-1.15 (m, 3H), 3.31, 3.45 (q, q, 2H), 3.64, 3.77 (s, s, 2H), 4.54 (s, 2H), 4.55, 4.66 (s, s, 2H), 7.05-7.40 (m, 8H), 7.55, 7.60 (d, d, 2H)
20 and 7.97 (d, 2H).

¹³C NMR (rotamers, 75 MHz, CDCl₃): δ 12.60, 13.80, 38.17, 38.25, 40.00, 40.44, 41.63, 42.40, 47.94, 50.61, 118-134 (complex multiplet), 140.32, 140.70, 141.50, 170.48 and 171.20.

25

Example 12

2-([4-(2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl)phenoxy)methyl]benzoic acid.

a) *N*-(2-Fluorobenzyl)ethanamine (0.554 g, 3.615 mmol) was dissolved in DMF (10 ml). (4-Hydroxyphenyl)acetic acid (0.500 g, 3.286) was added and the mixture was cooled to 0°
30 C. *N*-[(1*H*-1,2,3-Benzotriazol-1-yloxy)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate (1.161 g, 3.615 mmol) and *N*-ethyl-*N,N*-diisopropylamine (0.892 g, 6.901 mmol) were added. The solution was stirred overnight at

750
H

room temperature. EtOAc (20 ml) was added and the organic phase was washed with two portions of Na₂CO₃ (2 X 20 ml, aq). The organic layer was dried (MgSO₄) and the solvent was removed by evaporation. The crude was purified by preparative HPLC (started with isocratic acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product-containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried (MgSO₄) and the solvent was removed by evaporation to give 0.69 g of *N*-ethyl-*N*-(2-fluorobenzyl)-2-(4-hydroxyphenyl)acetamide (yield 73.1%).

¹HNMR (Rotamers, 500 MHz, CDCl₃): δ 1.12 (m, 3H), 3.35-3.5 (m, 2H), 3.62-3.72 (m, 2H), 4.57-4.78 (m, 2H), 6.7 (t, 2H), 6.98-7.38 (m, 6H).

b) *N*-Ethyl-*N*-(2-fluorobenzyl)-2-(4-hydroxyphenyl)acetamide (0.381 g, 1.327 mmol) and methyl 2-(bromomethyl)benzoate (0.334 g, 1.460 mmol) were dissolved in acetonitrile (10 ml) and potassium carbonate (0.367 g, 2.654 mmol) was added. The mixture was stirred at 65° C for three hours. When *N*-ethyl-*N*-(2-fluorobenzyl)-2-(4-hydroxyphenyl)acetamide was consumed, PS-trisamine (0.3 eqv) was added and the solution was stirred overnight at room temperature. The polymer was filtered off and acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of water, dried (MgSO₄) and the solvent was removed by evaporation to give 0.545 g of methyl 2-[(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy)methyl]benzoate (yield 94.3%):

¹HNMR (Rotamers, 300 MHz, CDCl₃): δ 1.12 (m, 3H), 3.23-3.35 (m, 2H), 3.6-3.75 (m, 2H), 3.88 (s, 3H), 4.45-4.70 (m, 2H), 5.45 (s, 2H), 6.84-7.35 (m, 9H), 7.5 (t, 1H), 7.72 (d, 1H), 8.0 (d, 1H).

c) Methyl 2-[(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy)methyl]-benzoate (0.545 g, 1.251 mmol) was dissolved in EtOH (5 ml) and potassium hydroxide (0.105 g, 1.877 mmol) was added. The reaction was performed in a single mode microwave oven (7 min, 150° C). Workup was by removing the solvent by evaporation, addition of HCl (20 ml, 1 M) and the water phase was washed with two portions of EtOAc (20 ml). The

451
H

organic phases were pooled and the solvent was removed by evaporation. The crude was purified by preparative HPLC (starting with isocratic acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product-containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried (MgSO₄). The solvent was removed by evaporation to give 0.124 g of 2-[(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid (23.5%).

¹HNMR (Rotamers, 500 MHz, CDCl₃): δ 1.12 (m, 3H), 3.25-3.5 (m, 2H), 3.65-3.8 (m, 2H), 4.5-4.75 (m, 2H), 5.52 (m, 2H), 6.84-7.45 (m, 9H), 7.55 (t, 1H), 7.78 (d, 1H), 8.13 (d, 1H).

Example 13

2-[(4-{3-[Ethyl(2-fluorobenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid.

a) *N*-(2-Fluorobenzyl)ethanamine (0.554 g, 3.615 mmol) was dissolved in DMF (10 ml). 3-(4-hydroxyphenyl)propanoic acid (0.546 g, 3.286 mmol) was added and the mixture was cooled to 0° C. *N*-[(1*H*-1,2,3-benzotriazol-1-yloxy)(dimethylamino)-methylene]-*N*-methylmethanaminium tetrafluoroborate (1.161 g, 3.615 mmol) and *N*-ethyl-*N,N*-diisopropylamine (0.892 g, 6.901 mmol) was added. The solution was stirred overnight at room temperature. EtOAc (20 ml) was added and the organic phase was washed with two portions of Na₂CO₃ (2 X 20 ml, aq). The organic layer was dried (MgSO₄) and the solvent was removed by evaporation. The crude was purified by preparative HPLC (starting with isocratic acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product-containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried (MgSO₄) and then solvent was removed by evaporation to give 0.803 g of *N*-ethyl-*N*-(2-fluorobenzyl)-3-(4-hydroxyphenyl)propanamide (yield 81.1%).

¹HNMR (Rotamers, 500 MHz, CDCl₃): δ 1.1 (m, 3H), 2.58-2.72 (m, 2H), 2.83-3.0 (m, 2H), 3.2-3.5 (m, 2H), 4.45-4.7 (m, 2H), 6.78 (t, 2H), 6.95-7.35 (m, 6H).



- b) *N*-Ethyl-*N*-(2-fluorobenzyl)-3-(4-hydroxyphenyl)propanamide (0.400 g, 1.327 mmol) and methyl 2-(bromomethyl)benzoate (0.334 g, 1.460 mmol) were dissolved in acetonitrile (10 ml) and potassium carbonate (0.367 g, 2.654 mmol) was added. The mixture was stirred at 65° C for three hours. When *N*-ethyl-*N*-(2-fluorobenzyl)-2-(4-hydroxyphenyl)acetamide was consumed, PS-trisamine (0.3 eqv) was added and the solution was stirred overnight at room temperature. The polymer was filtered off and acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of water, dried (MgSO₄) and the solvent was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions on water, dried (MgSO₄) and the solvent was removed by evaporation. The crude was purified by preparative HPLC (starting with isocratic acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product -containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried (MgSO₄). The solvent was removed by evaporation to give 0.454 g of methyl 2-[(4-{3-[ethyl(2-fluorobenzyl)amino]-3-oxopropyl}phenoxy)methyl]-benzoate (yield 76.1%).
- ¹HNMR (Rotamers, 400 MHz, CDCl₃): δ 1.08 (m, 3H), 2.52-2.68 (m, 2H), 2.9-3.03 (m, 2H), 3.18-3.45 (m, 2H), 3.88 (s, 3H), 4.45-4.7 (m, 2H), 5.45 (s, 2H), 6.82-7.28 (m, 8H), 7.36 (t, 1H), 7.53 (t, 1H), 7.73 (d, 1H), 8.0 (d, 1H).
- c) Methyl 2-[(4-{3-[ethyl(2-fluorobenzyl)amino]-3-oxopropyl}phenoxy)methyl]-benzoate (0.454 g, 1.001 mmol) was dissolved in EtOH (5 ml) and potassium hydroxide (0.085 g, 1.514 mmol) was added. The reaction was performed in a single mode microwave oven (7 min, 150° C). Workup was by removing the solvent by evaporation, addition of HCl (20 ml, 1 M) and the water phase was washed with two portions of EtOAc (20 ml). The organic phases were pooled and the solvent was removed by evaporation. The crude was purified by preparative HPLC (starting with isocratic acetonitrile/buffer 60/40 and then the acetonitrile concentration was increased to 100%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8,

LS3

50 mm X 250 mm, flow 40 ml/min). The product-containing fractions were pooled and the acetonitrile was removed by evaporation. EtOAc (10 ml) was added and the organic phase was washed with two portions of brine and dried (MgSO₄). The solvent was removed by evaporation to give 0.079 g of 2-[(4-{3-[ethyl(2-fluorobenzyl)amino]-3-oxopropyl}-phenoxy)methyl]benzoic acid (18.0%).

¹HNMR (Rotamara, 500 MHz, CDCl₃): δ 1.12 (m, 3H), 2.60-2.75 (m, 2H), 3.03 (m, 2H), 3.23-3.50 (m, 2H), 4.45-4.73 (m, 2H), 5.57 (s, 2H), 6.88-7.35 (m, 8H), 7.41 (t, 1H), 7.60 (t, 1H), 7.80 (d, 1H), 8.18 (d, 1H).

10 The following Examples were prepared in a similar manner.

Example 14

2-[[[(3-{2-[(2,4-Difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl)thio]methyl]benzoic acid.

15 Example 15

2-[[[(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethyl}phenyl)thio]methyl]benzoic acid.

Biological activity

Formulations

Compounds were dissolved in DMSO to obtain 16 mM stock solutions. Before assays,
20 stock solutions were further diluted in DMSO and culture media.

GENERAL CHEMICALS AND REAGENTS

Luciferase assay reagent was purchased from Packard, USA. Restriction Enzymes were from Boehringer and Vent polymerase from New England Biolabs.

25

CELL LINES AND CELL CULTURE CONDITIONS

U2-OS, (Osteogenic sarcoma, Human) was purchased from ATCC, USA. Cells were expanded and refrozen in batches from passage number six. Cells were cultured in Dulbecco's modified Eagle medium (DMEM) with 25 mM glucose, 2 mM glutamine or 4
30 mM L-alanyl-L-glutamine, 10% fetal calf serum, at 5% CO₂. Phosphate buffered saline

1534

(PBS) without addition of calcium or magnesium was used. All cell culture reagents were from Gibco (USA) and 96-well cell culture plates were purchased from Wallach.

PLASMID CONSTRUCTS FOR HETEROLOGOUS EXPRESSION

- 5 Standard recombinant DNA techniques were carried out as described by Ausubel (7). The Luciferase reporter vector, pGL3UAS (clone consists of five copies of the GAL4 DNA binding sequence, 5'-CGACGGAGTACTGTCCTCCGAGCT-3', cloned into the SacI/XhoI sites of pGL3-Promoter (Promega). The SacI/XhoI fragment carrying the UAS sites was constructed using annealed overlapping oligonucleotides.

10

Expression vectors used are based upon pSG5 (Stratagene). All vectors contain an EcoRI/NheI fragment encoding the DNA binding domain of GAL4 (encoding amino acid positions 1-145 of database accession number P04386) followed by an in-frame fusion to a fragment encoding the nuclear localisation sequence from T antigen of Polyoma Virus.

- 15 The nuclear localisation sequence was constructed using annealed overlapping oligonucleotides creating NheI/KpnI sticky ends

(5'-CTAGCGCTCCTAGAAGAAACGCAAGGTTGGTAC-3'). The ligand binding domains from human and mouse PPAR α and human and mouse PPAR γ were PCR amplified as KpnI/BamHI fragments and cloned in frame to the GAL4 DNA binding

- 20 domain and the nuclear localisation sequence. The sequence of all plasmid constructs used were confirmed by sequencing.

The following expression vectors were used for transient transfections:

vector	encoded PPAR subtype	sequence reference ¹
pSGGALhPP α	human PPAR α	S74349, nt 625-1530
pSGGALmPP α	murine PPAR α	X57638, nt 668-1573
pSGGALhPP γ	human PPAR γ	U63415, nt 613-1518

pSGGALmPPg	murine PPAR γ	U09138, nt 652-1577
------------	----------------------	---------------------

¹ refers to nucleotide positions of data base entry used to express the ligand binding domain.

5 TRANSIENT TRANSFECTIONS

Frozen stocks of cells from passage number six were thawed and expanded to passage number eight before transfections. Confluent cells were trypsinised, washed and pelleted by centrifugation at 270xg for 2 minutes. The cell pellet was resuspended in cold PBS to a cell concentration of about 18×10^6 cells/ml. After addition of DNA, the cell suspension
10 was incubated on ice for approximately 5 minutes before electroporation at 230 V, 960 μ F in Biorad's Gene PulserTM in 0.5 ml batches. A total of 50 μ g DNA was added to each batch of 0.5 ml cells, including 2.5 μ g expression vector, 25 μ g reporter vector and 22.5 μ g unspecific DNA (pBluescript, Stratagene).

15 After electroporation, cells were diluted to a concentration of 320'000 cells/ml in DMEM without phenol red, and approximately 25'000 cells/well were seeded in 96-well plates. In order to allow cells to recover, seeded plates were incubated at 37°C for 3-4 hours before addition of test compounds. In assays for PPAR α , the cell medium was supplemented with resin-charcoal stripped fetal calf serum (FCS) in order to avoid background activation by
20 fatty acid components of the FCS. The resin-charcoal stripped FCS was produced as follows; for 500 ml of heat-inactivated FCS, 10 g charcoal and 25 g Bio-Rad Analytical Grade Anion Exchange Resin 200-400 mesh were added, and the solution was kept on a magnetic stirrer at room temperature over night. The following day, the FCS was centrifuged and the stripping procedure was repeated for 4-6 hours. After the second
25 treatment, the FCS was centrifuged and filter sterilised in order to remove remnants of charcoal and resin.

56


ASSAY PROCEDURE

Stock solutions of compounds in DMSO were diluted in appropriate concentration ranges in master plates. From master plates, compounds were diluted in culture media to obtain test compound solutions for final doses.

5

After adjustment of the amount of cell medium to 75 μ l in each well, 50 μ l test compound solution was added. Transiently transfected cells were exposed to compounds for about 24 hours before the luciferase detection assay was performed. For luciferase assays, 100 μ l of assay reagent was added manually to each well and plates were left for approximately 20
10 minutes in order to allow lysis of the cells. After lysis, luciferase activity was measured in a 1420 Multiwell counter, Victor, from Wallach.

Reference compounds

The TZD pioglitazone was used as reference substance for activation of both human and
15 murine PPAR γ . 5,8,11,14-Eicosatetrayonic acid (ETYA) was used as reference substance for human PPAR α .

Calculations and analysis

For calculation of EC₅₀ values, a concentration-effect curve was established. Values used
20 were derived from the average of two or three independent measurements (after subtraction of the background average value) and were expressed as the percentage of the maximal activation obtained by the reference compound. Values were plotted against the logarithm of the test compound concentration. EC₅₀ values were estimated by linear intercalation between the data points and calculating the concentration required to achieve 50% of the
25 maximal activation obtained by the reference compound.

The compounds of formula I have an EC₅₀ of less than 50 μ mol/l for PPAR α and preferred compounds have an EC₅₀ of less than 5 μ mol/l. For example the EC₅₀s of some of the Examples for human PPAR alpha are:

57



Example 5 0.163 $\mu\text{mol/l}$;

Example 10 0.168 $\mu\text{mol/l}$;

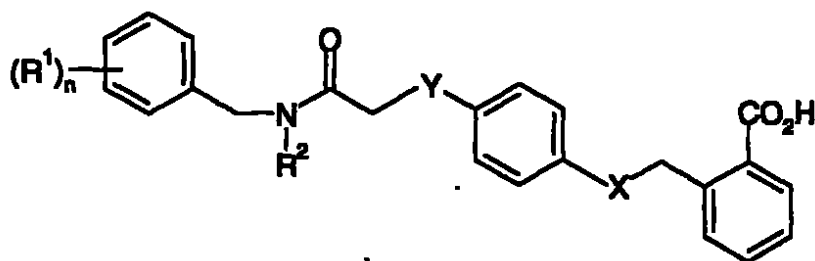
Example 11 0.026 $\mu\text{mol/l}$; and

Example 15 0.027 $\mu\text{mol/l}$.

58
~~27~~
 1

Claims

1. A compound of formula I



wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different;

R² represents a C₂₋₄alkyl group which is optionally interrupted by oxygen;

Y is absent or represents methylene; and

X is O or S;

and pharmaceutically acceptable salts and prodrugs thereof.

2. A compound according to claim 1 in which X is O.

3. A compound according to claim 1 in which X is S.

4. A compound according to any preceding claim in which Y is methylene.

5. A compound according to any one of claims 1, 2 or 3 in which Y is absent.

6. A compound according to any preceding claim in which R¹ is halo, a C₁₋₄alkyl group or a C₁₋₄alkoxy group and n is 0, 1 or 2.

59
X

7. A compound according to any preceding claim in which R¹ is fluoro, methoxy, or isopropyl when n is 1 or 2.

8. A compound according to any preceding claim in which n is 0.

9. A compound according to any preceding claim in which R² represents a C₃₋₇alkyl group.

10. A compound selected from:

2-[(4-{3-[benzyl(hexyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;

10 2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl)thio]methyl]benzoic acid;

2-[(4-{2-[benzyl(hexyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid;

2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid;

2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;

15 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]methyl]benzoic acid;

2-[(4-{3-[butyl(2,3-dimethoxybenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;

2-[(4-{3-[(2,3-dimethoxybenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;

20 2-[(4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;

2-[(4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;

2-[(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid;

2-[(4-{3-[ethyl(2-fluorobenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;

25 2-[(4-{2-[ethyl[4-(trifluoromethyl)benzyl]amino]-2-oxoethyl}phenyl)thio]methyl]benzoic acid;

2-[(3-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl)thio]methyl]benzoic acid; and

2-[(4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethyl}phenyl)thio]methyl]benzoic acid

30 and pharmaceutically acceptable salts thereof.

60
/

11. A compound according to claim 2 selected from:

2-[(4-{3-[benzyl(hexyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
 2-[(4-{2-[benzyl(hexyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid;
 2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid;
 5 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
 2-[(4-{3-[butyl(2,3-dimethoxybenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
 2-[(4-{3-[(2,3-dimethoxybenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic
 acid;
 2-[(4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy)methyl]-
 10 benzoic acid ;
 2-[(4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
 2-[(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid;
 2-[(4-{3-[ethyl(2-fluorobenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid;
 and pharmaceutically acceptable salts thereof.

15

12. A compound according to claim 3 selected from:

2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl)thio]methyl]benzoic
 acid;
 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]methyl]benzoic
 20 acid;
 2-[(4-{2-[ethyl[4-(trifluoromethyl)benzyl]amino]-2-oxoethyl}phenyl)thio]-
 methyl]benzoic acid;
 2-[(3-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl)thio]methyl]benzoic
 acid; and
 25 2-[(4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethyl}phenyl)thio]methyl]benzoic acid
 and pharmaceutically acceptable salts thereof.

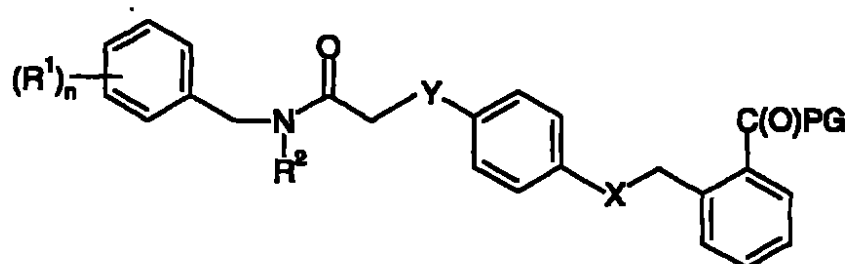
13. A pharmaceutical formulation comprising a compound according to any preceding
 claim in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

30 14. A method of treating or preventing insulin resistance comprising the administration of
 a compound according to any one of claims 1 to 12 to a mammal in need thereof.

61
62

15. The use of a compound according to any one of claims 1 to 12 in the manufacture of a medicament for the treatment of insulin resistance.

16. A process to prepare a compound of formula I comprising reacting a compound of
5 formula II



in which R¹, R², X and Y are as previously defined and PG represents a protecting group for a carboxylic hydroxy group with a de-protecting agent.

10

17. A compound of formula II as described in claim 16.

18. A combination treatment comprising a compound according to any one of claims 1 to 12 in combination with another therapeutic agent that is useful in the treatment of disorders
15 associated with the development and progress of atherosclerosis, hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity.

INTERNATIONAL SEARCH REPORT

Internat. Application No. ...

PCT/GB 03/02584

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C235/34 C07C323/62 A61K31/19 A61P3/06 A61P3/10

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 C07C

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, BEILSTEIN Data, WPI Data, CHEM ABS Data, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 802 186 A (BAYER AG) 22 October 1997 (1997-10-22) abstract page 15; example 31; table 1	1-18
A	EP 1 184 366 A (KYORIN SEIYAKU KK) 6 March 2002 (2002-03-06) abstract; claims; examples; tables	1-18

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

* Special categories of cited documents:

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

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

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

O document relating 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

A document member of the same patent family

Date of the actual completion of the international search

16 October 2003

Date of mailing of the international search report

22/10/2003

Name and mailing address of the ISA

European Patent Office, P.O. Box 5816 Patentplan 2
NL - 2200 HV Rijswijk
Tel. (+31-70) 340-8340, Tx. 31 651 epo nl,
Fax (+31-70) 340-8018

Authorized officer

Kiernan, A

INTERNATIONAL SEARCH REPORT

in national application No.
PCT/GB 03/02584

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

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 14 and 18 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 dependant claims and are not drafted in accordance with the second and third sentences of Rule 8.4(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

ation on patent family members

Internat. application No.

PCT/GB 03/02584

64
6

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0802186 A	22-10-1997	DE 19615263 A1	23-10-1997
		AT 197794 T	15-12-2000
		CA 2202704 A1	18-10-1997
		DE 59702677 D1	04-01-2001
		DK 802186 T3	27-12-2000
		EP 0802186 A1	22-10-1997
		ES 2153141 T3	16-02-2001
		GR 3035371 T3	31-05-2001
		JP 10059915 A	03-03-1998
		PT 802186 T	30-04-2001
		US 5750783 A	12-05-1998
EP 1184366 A	06-03-2002	JP 2001055367 A	27-02-2001
		AU 5106700 A	28-12-2000
		BR 0011734 A	05-03-2002
		CA 2376094 A1	04-12-2000
		EP 1184366 A1	06-03-2002
		NO 20016001 A	11-02-2002
		NZ 515705 A	28-02-2003
		US 6506797 B1	14-01-2003
		CN 1354742 T	19-06-2002
		HU 0201654 A2	28-09-2002
		WO 0075103 A1	14-12-2000
		ZA 200109512 A	19-06-2002

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJ EL TRATADO DE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional



(43) Fecha de Publicación Internacional
31 de diciembre de 2003 (31.12.2003)

(10) Número de Publicación Internacional
WO 2004/000790 A1

(51) Clasificación Internacional de Patentes⁷: C07C 235/34, 323/62, A61K 31/19, A61P 3/08, 3/10

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

(21) No. Solicitud Internacional: PCT/GB2003/002584

(22) Fecha de Presentación Internacional:
17 de junio de 2003 (17.06.2003)

(25) Idioma de Presentación: Inglés

(26) Idioma de Publicación: Inglés

(81) Países designados (nacionales): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, 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, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(30) Datos relativos a la Prioridad:
0201935-4 20 de junio de 2002 (20.06.2002) SE
0203826-3 20 de diciembre de 2002 (20.12.2002) SE

(84) Países designados (regionales): Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, 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).

(71) Solicitante (para todos los países destinatarios con excepción de MG, US): ASTRAZENECA AB [SE/SE]; S-151 85 Sodertälje (SE).

(71) Solicitante (para MG únicamente): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

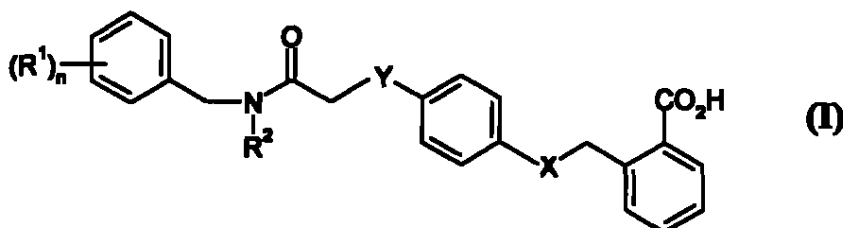
Publicado:

- con informe internacional de búsqueda
- antes del vencimiento del tiempo límite para modificar las reivindicaciones y para volver a publicar en el caso de recibo de modificaciones

(72) Inventores, o
(76) Inventores/Solicitantes (para US únicamente): Li, Lanna [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE)

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 ÁCIDO BENZOICO ORTO-SUSTITUIDO PARA EL TRATAMIENTO DE RESISTENCIA A LA INSULINA



(57) Extracto: La presente invención proporciona un compuesto de fórmula (I), en donde n es 0, 1 ó 2 y R¹ representa halo, un grupo C₁₋₄alquilo que se sustituye de manera opcional por uno o más de fluoro, un grupo C₁₋₄alcoxi que se sustituye de manera opcional por uno o más fluoro y en donde cuando n es 2 los sustituyentes R¹ pueden ser los mismos o diferentes; R² representa un grupo C₂₋₄alquilo, el cual se interrumpe de manera opcional por oxígeno; Y está ausente o representa metileno; y X es O ó S; y sus sales farmacéuticamente aceptables y profármacos; se refiere a procesos para preparar tales compuestos, a su utilidad en tratar afecciones clínicas asociadas con resistencia a la insulina, a métodos para su uso terapéutico y a composiciones farmacéuticas que los contienen.

WO 2004/000790 A1

6766

DERIVADOS DE ÁCIDO BENZOICO ORTO-SUSTITUIDO PARA EL TRATAMIENTO DE RESISTENCIA A LA INSULINA

Campo de la Invención

La presente invención se refiere a ciertos derivados novedosos de ácido benzoico, a procesos para preparar tales compuestos, a su utilidad en tratar afecciones clínicas asociadas con resistencia a la insulina, a métodos para su uso terapéutico y a composiciones farmacéuticas que los contienen.

Antecedentes de la Invención

El síndrome de resistencia a la insulina (IRS) incluida la diabetes sacarina tipo 2, que se refiere a una agrupación de manifestaciones incluida la resistencia a la insulina hiperinsulinemia concomitante, posible diabetes sacarina tipo 2, hipertensión arterial, obesidad central (visceral), dislipidemia observada como niveles desordenados de lipoproteína caracterizados típicamente por VLDL elevadas (lipoproteínas de muy baja densidad), partículas pequeñas de LDL densa y concentraciones reducidas de HDL (lipoproteína de baja densidad) y fibrinólisis reducida.

La reciente investigación epidemiológica ha documentado que los individuos con resistencia a la insulina corren un riesgo grandemente incrementado de morbilidad cardiovascular, que sufren notablemente de infarto del miocardio y apoplejía. En la diabetes sacarina tipo 2, las afecciones relacionadas con la aterosclerosis causan hasta el 80% de todas las muertes.

En la medicina clínica existe una conciencia de la necesidad de incrementar la sensibilidad a la insulina en pacientes que padecen de IRS y, por consiguiente, de corregir la dislipidemia, que se considera que causa la evolución acelerada de aterosclerosis. Sin embargo, en la actualidad ésta no es una enfermedad universalmente bien definida.

67

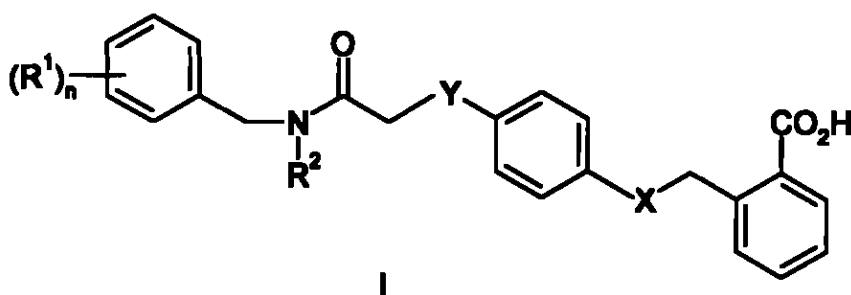
Moduladores de receptores activadores de proliferador de peroxisomas (PPAR, para una recapitulación de los PPARs véase T. M. Willson y colaboradores, J Med Chem 2000, Vol 43, 527) son efectivos en tratar afecciones asociadas con resistencia a la insulina.

US 5,750,783 divulga que ciertas fenilglicinolamidas benciloxi sustituidas, que poseen un sustituyente cicloalquilo son medicamentos antiateroescleróticos. Este documento no divulga o sugiere los compuestos de la presente invención.

Sorprendentemente se ha descubierto ahora una serie de compuestos que son moduladores selectivos de PPAR α .

Descripción de la Invención

La presente invención provee un compuesto de fórmula I



en donde n es 0, 1 ó 2 y R¹ representa halo, un grupo C₁₋₄alquilo, el cual se sustituye de manera opcional por uno o más fluoro, un grupo C₁₋₄alcoxi, el cual se sustituye de manera opcional por uno o más fluoro y en donde cuando n es 2 los sustituyentes R¹ pueden ser los mismos o diferentes;

R² representa un grupo C₂₋₈alquilo que se interrumpe de manera opcional por oxígeno

69/69

Y está ausente o representa metileno; y

X es O ó S;

y sus sales farmacéuticamente aceptables y profármacos.

Otros valores de R¹, R², Y y X en compuestos de Fórmula I siguen a continuación. Se entenderá que tales valores pueden usarse donde sea apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas más arriba o más adelante.

En un aspecto X es O.

En un segundo aspecto X es S.

En un tercer aspecto Y es metileno.

En un cuarto aspecto Y está ausente.

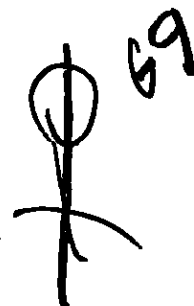
En un quinto aspecto R¹ es halo, un grupo C₁₋₄alquilo o un grupo C₁₋₄alcoxi y n es 0, 1 ó 2. Particularmente R¹ es fluoro, metoxi, o isopropilo cuando n es 1 ó 2. Particularmente n es 0.

En un sexto aspecto R² representa un grupo C₃₋₇alquilo.

El término C₂₋₈alquilo denota un hidrocarburo alifático saturado de cadena recta o ramificada que tiene de 2 a 8 átomos de carbono. Ejemplos de dicho alquilo incluyen etilo, n-propilo, iso-propilo, n-butilo, iso-butilo, sec-butilo, t-butilo y pentilo de cadena recta o ramificada, hexilo, heptilo y octilo.

Se entenderá por aquellas personas expertas en el arte que el término interrumpido, como se usa más arriba, significa que el átomo de oxígeno está situado en la cadena alquilo y no es un átomo terminal.

El término "profármaco" como se utiliza en esta especificación incluye derivados del grupo de ácido carboxílico, los cuales se convierten en un mamífero, particularmente un humano, en el grupo de ácido carboxílico o su sal o conjugado. Debe entenderse que, aunque sin limitarse por la teoría,



se cree que la mayor parte de la actividad asociada con los profármacos surge de la actividad del compuesto de fórmula I, en el cual se convierten los profármacos. Los profármacos pueden prepararse por metodología de rutina, bien como parte de las capacidades de alguien con experiencia en el arte. Varios profármacos de carboxi son conocidos en el arte. Para ejemplos de tales derivados de profármacos, véase:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) y Methods in Enzymology. 42: 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p.113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8:1-38 (1992);
- d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77:285 (1988); y
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32:692 (1984).

Loa anteriores documentos a – e se incorporan aquí por referencia.

Ésteres escindibles *in vivo* son precisamente un tipo de profármaco de la molécula principal.

Los compuestos de Fórmula I poseen actividad como medicamentos, en particular los compuestos de Fórmula I son agonistas selectivos de PPAR α , es decir, su EC₅₀ para PPAR α es por lo menos tres veces menor, preferiblemente por lo menos cuatro veces inferior y, más preferiblemente, 10 ó 50 times inferior que su respectiva EC₅₀ para PPAR γ , en donde las EC₅₀s se miden y calculan como se describe en los análisis incluidos posteriormente en este documento. Los compuestos de Fórmula I son potentes y selectivos.

Compuestos específicos de la invención son uno o más de los siguientes:

ácido 2-[(4-{3-[bencil(hexil)amino]-3-oxopropil} fenoxi)metil]benzoico;
ácido 2-[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenil)tio]metil]benzoico;
ácido 2-[(4-{2-[bencil(hexil)amino]-2-oxoetil} fenoxi)metil]benzoico;
ácido 2-[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenoxi)metil]benzoico;
ácido 2-[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil} fenoxi)metil]benzoico;
ácido 2-[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil} fenil)tio]metil]benzoico;
ácido 2-[(4-{3-[butil(2,3-dimetoxibencil)amino]-3-oxopropil} fenoxi)metil]benzoico;
ácido 2-[(4-{3-[(2,3-dimetoxibencil)(heptil)amino]-3-oxopropil} fenoxi)metil]benzoico;
ácido 2-[(4-{3-[(3-etoxipropil)(4-isopropilbencil)amino]-3-oxopropil} fenoxi)metil]benzoico;
ácido 2-[(4-{3-[(2,4-difluorobencil)(propil)amino]-3-oxopropil} fenoxi)metil]benzoico;
ácido 2-[(4-{2-[etil(2-fluorobencil)amino]-2-oxoetil} fenoxi)metil]benzoico;
ácido 2-[(4-{3-[etil(2-fluorobencil)amino]-3-oxopropil} fenoxi)metil]benzoico;
ácido 2-[(4-{2-[etil[4-(trifluorometil)bencil]amino]-2-oxoetil} fenil)tio]metil]benzoico;
ácido 2-[(3-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenil)tio]metil]benzoico; y
ácido 2-[(4-{2-[(4-clorobencil)(etil)amino]-2-oxoetil} fenil)tio]metil]benzoico y sus sales farmacéuticamente aceptables.

Un segundo grupo de compuestos específicos de la invención comprende un compuesto seleccionado de:



ácido 2-{[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenil)tio]metil}benzoico;

ácido 2-{[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil} fenil)tio]metil}benzoico;

ácido 2-{[(4-{2-{etil[4-(trifluorometil)bencil]amino}-2-oxoetil} fenil)tio]-metil}benzoico;

ácido 2-{[(3-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenil)tio]metil}benzoico; y

ácido 2-{[(4-{2-[(4-clorobencil)(etil)amino]-2-oxoetil} fenil)tio]metil}benzoico

y sus sales farmacéuticamente aceptables.

Un tercer grupo de compuestos específicos de la invención comprende un compuesto seleccionado de:

ácido 2-[(4-{3-[bencil(hexil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{2-[bencil(hexil)amino]-2-oxoetil} fenoxi)metil]benzoico;

ácido 2-[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[butil(2,3-dimetoxibencil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[(2,3-dimetoxibencil)(heptil)-amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[(3-etoxipropil)(4-isopropilbencil)amino]-3-oxopropil} fenoxi)metil]-benzoico;

ácido 2-[(4-{3-[(2,4-difluorobencil)(propil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{2-[etil(2-fluorobencil)amino]-2-oxoetil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[etil(2-fluorobencil)amino]-3-oxopropil} fenoxi)metil]benzoico;

y sus sales farmacéuticamente aceptables.

Ciertos compuestos de la presente invención pueden existir como tautómeros. Hay que entender que la presente invención abarca la totalidad de tales tautómeros.

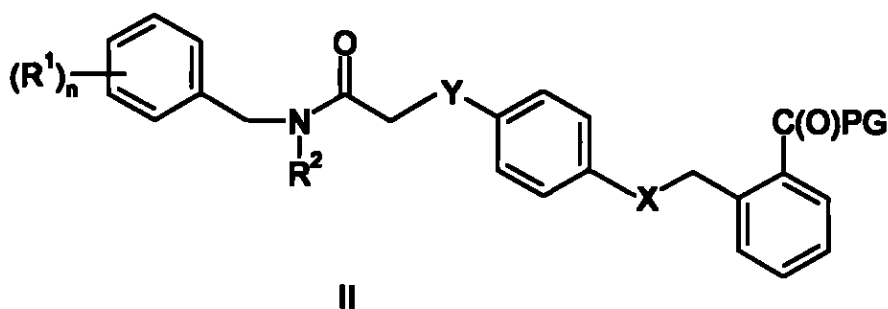
A todo lo largo de la especificación y las reivindicaciones anexas, una fórmula química dada o nombre abarcarán todos sus estereoisómeros e isómeros ópticos y racematos, así como mezclas en diferentes proporciones de los enantiómeros separados, en donde existen tales isómeros y enantiómeros, así como sus sales farmacéuticamente aceptables. Los isómeros pueden separarse usando técnicas convencionales, verbigracia, cromatografía o cristalización fraccionaria. Los enantiómeros pueden aislarse mediante separación de racemato, por ejemplo mediante cristalización fraccionaria, resolución o HPLC. Los diastereómeros pueden aislarse mediante separación de mezclas de isómero, por ejemplo mediante cristalización fraccionaria, HPLC o cromatografía de destello. Alternativamente los estereoisómeros pueden elaborarse mediante síntesis quiral de materiales de partida quirales bajo condiciones que no causen racemización o epimerización, o por derivación, con un reactivo quiral. Todos los estereoisómeros se incluyen en el ámbito de la invención.

Métodos de Preparación

Los compuestos de la invención pueden prepararse como se describe a continuación. No obstante, la invención no se limita a estos métodos; asimismo los compuestos pueden prepararse como se describe para compuestos estructuralmente relacionados en el arte previo. Las reacciones pueden llevarse a cabo de acuerdo con procedimientos estándar o como se describe en la sección experimental.

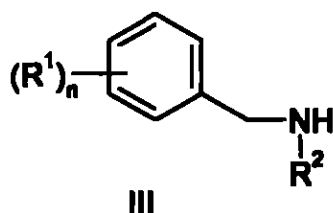
Compuestos de Fórmula I pueden prepararse haciendo reaccionar un compuesto de fórmula II

73

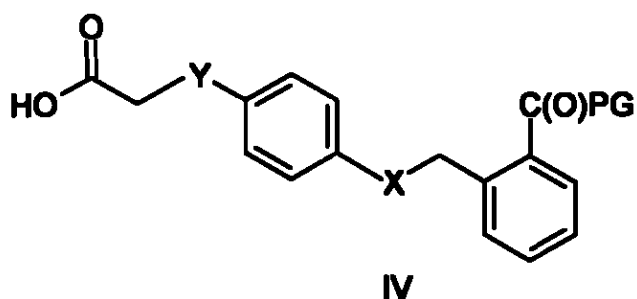


en la cual R^1 , R^2 , X y Y son como se definen previamente y PG representa un grupo protector para un grupo hidroxí carboxílico como se describe en el texto estándar "Protective Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts, con un agente desprotector. El grupo protector puede ser también una resina, tal como una resina de Wang o una resina de cloruro de 2-clorotritilo. Grupos protectores pueden removerse de acuerdo con técnicas que son bien conocidas por aquellas personas expertas en el arte. Un grupo protector tal es donde PG representa un grupo C_{1-6} alcoxi o un grupo arilalcoxi, verbigracia, bencilo, tal que COPG representa un éster. Tales ésteres pueden hacerse reaccionar con un agente hidrolizante, por ejemplo hidróxido de litio en la presencia de un disolvente, por ejemplo una mezcla de THF y agua o hidróxido de potasio en un C_{1-3} alcohol, por ejemplo metanol, a una temperatura en el rango de 0-200°C o mediante radiación de microondas para producir compuestos de Fórmula I.

Compuestos de Fórmula II pueden prepararse haciendo reaccionar un compuesto de fórmula III

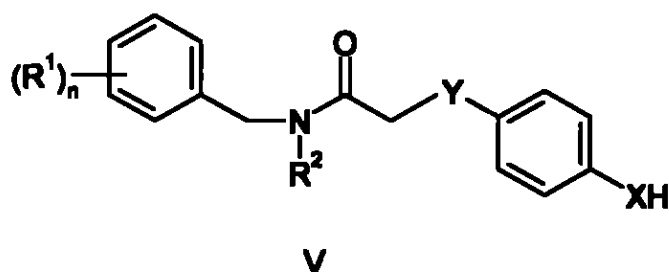


o su sal, por ejemplo una sal clorhidrato, en la cual R^1 , R^2 y n son como se definen previamente con un compuesto de fórmula IV

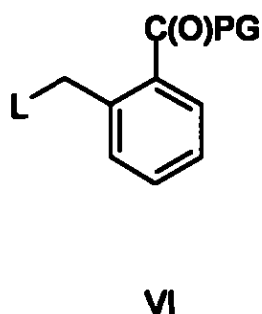


o su cloruro de ácido en la cual X, Y y PG son como se definen previamente en un disolvente inerte, por ejemplo diclorometano, de manera opcional en la presencia de un agente de acoplamiento, por ejemplo 4-dimetilaminopiridina ó clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida, a una temperatura en el rango de -25°C a 150°C.

Compuestos de Fórmula II pueden prepararse igualmente haciendo reaccionar un compuesto de fórmula V



en la cual R^1 , n , R^2 , X y Y son como se definen previamente con un compuesto de fórmula VI



en la cual PG es como se define as previamente y L representa un grupo saliente, por ejemplo halo, verbigracia bromo, de manera opcional en la presencia de disolvente, por ejemplo acetonitrilo, y de manera opcional en

la presencia de una base, por ejemplo carbonato de potasio, a una temperatura en el rango de 0 a 150°C.

Compuestos de Fórmula III, IV, V y VI pueden prepararse por métodos descritos en los Ejemplos o por métodos análogos conocidos por las personas expertas en el arte.

Compuestos de Fórmula II, III, IV y V son intermedios útiles en la preparación de compuestos de Fórmula I. Se cree que algunos de estos compuestos son novedosos. Compuestos novedosos de Fórmula II, o fórmula III, o fórmula IV o fórmula V se reivindican aquí como un aspecto más de la presente invención.

Los compuestos de la invención pueden aislarse de sus mezclas de reacción usando técnicas convencionales.

Personas expertas en el arte observarán que, con el fin de obtener compuestos de la invención en una forma alternativa y, en algunas ocasiones, más conveniente, los pasos de los procesos individuales mencionados más arriba en el texto pueden realizarse en diferente orden, y/o las reacciones individuales puede efectuarse en una etapa diferente en la ruta general (es decir, transformaciones químicas pueden llevarse a cabo con intermedios diferentes a los asociados más arriba en el texto con una reacción particular).

En cualquiera de los métodos precedentes de preparación, donde sea necesario, grupos reactivos hidroxilo, amino u otros grupos reactivos pueden protegerse usando un grupo protector, R^P como se describe en el texto estándar "Protective Groups in Organic Synthesis", 2^a Edición (1991) por Greene y Wuts. El grupo protector puede ser también una resina, tal como una resina de Wang o una resina de cloruro de 2-clorotritilo. La protección

y desprotección de grupos funcionales puede tener lugar antes o después de los pasos de reacción descritos más arriba en el texto. Los grupos protectores pueden removerse de acuerdo con técnicas que son bien conocidas por las personas expertas en el arte.

La expresión "disolvente inerte" se refiere a un disolvente que no reacciona con los materiales de partida, reactivos, intermedios o productos en una manera que afecta adversamente el rendimiento del producto deseado.

Preparaciones Farmacéuticas

Los compuestos de la invención se administrarán normalmente por vía oral, parenteral, intravenosa, intramuscular, subcutánea o inyectable, sublingual, rectal, vaginal, transcutánea y/o nasal y/o mediante inhalación, en la forma de preparaciones farmacéuticas que comprenden el ingrediente activo, ya sea como un ácido libre o como una sal farmacéuticamente aceptable, en una formulación farmacéuticamente aceptable. Dependiendo del trastorno y el paciente por tratar y la vía de administración, las composiciones pueden administrarse en dosis variables.

Dosis diarias apropiadas de los compuestos de la invención en tratamiento terapéutico de humanos son alrededor de 0.0001-100 mg/kg de peso corporal, preferiblemente 0.001-10 mg/kg de peso corporal.

Formulaciones orales, particularmente tabletas o cápsulas, que pueden formularse por métodos conocidos por las personas expertas en el arte, proporcionan dosis del compuesto activo en el rango de 0.5mg a 500mg, por ejemplo 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg y 250mg.

Por lo tanto, de acuerdo con un aspecto adicional de la invención, se provee una formulación farmacéutica que incluye cualquiera de los compuestos de

la invención, o su una sal farmacéuticamente aceptable, en mezcla con coadyuvantes, diluyentes y/o vehículos farmacéuticamente aceptables.

Propiedades Farmacológicas

Los presentes compuestos de Fórmula (I) son útiles para la profilaxis y/o tratamiento de afecciones clínicas asociadas con sensibilidad reducida, inherente o inducida, a la insulina (resistencia a la insulina) y trastornos metabólicos asociados (también conocidos como síndrome metabólico). Estas afecciones clínicas incluirán, pero no se limitarán a, obesidad general, obesidad abdominal, hipertensión arterial, hiperinsulinemia, hiperglucemia, diabetes tipo 2 y la dislipidemia, que aparece de manera característica con la resistencia a la insulina. Esta dislipidemia, conocida también como perfil de lipoproteína aterogénica, se caracteriza por ácidos grasos no esterificados, moderadamente elevados, partículas ricas en triglicéridos de lipoproteína elevada de muy baja densidad (VLDL), altos niveles Apo B, niveles bajos de lipoproteína de alta densidad (HDL), asociados con niveles de partícula bajos de apoAI y niveles elevados de Apo B en la presencia de partículas de lipoproteínas de baja densidad (LDL) pequeñas y densas, fenotipo B.

Se espera que los compuestos de la presente invención sean útiles en tratar pacientes hiperlipidemias combinadas o mixtas o varios grados de hipertrigliceridemias y dislipidemia posprandial, con o sin otras manifestaciones del síndrome metabólico.

Se espera que el tratamiento con los presentes compuestos reduzca la morbimortalidad cardiovascular asociada con la aterosclerosis, debido a sus propiedades antidislipidémicas, así como antiinflamatorias. Los procesos patológicos cardiovasculares incluyen macro-angiopatías de diferentes órganos internos que causan infarto del miocardio, insuficiencia cardíaca congestiva, enfermedad cerebrovascular e insuficiencia arterial

periférica de las extremidades inferiores. Debido a su efecto sensibilizante a la insulina, se espera asimismo que los compuestos de Fórmula I prevengan o retrasen la evolución de la diabetes tipo 2 del síndrome metabólico y la diabetes del embarazo. Por lo tanto, se espera que se retrase la evolución de complicaciones a largo plazo asociadas con hiperglicemia crónica en diabetes sacarina, tales como las micro-angiopatías que causan enfermedad renal, daño de la retina e insuficiencia venosa periférica de los miembros inferiores. Más aún, los compuestos pueden ser útiles en el tratamiento de varias afecciones fuera del sistema cardiovascular, asociadas o no con la resistencia a la insulina, como síndrome de ovario poliquístico, obesidad, cáncer y estados de enfermedad inflamatoria, incluidos trastornos neurodegenerativos tales como trastorno cognitivo leve, enfermedad de Alzheimer, mal de Parkinson y esclerosis múltiple.

Se espera que los compuestos de la presente invención sean útiles en controlar los niveles de glucosa en pacientes que padecen de diabetes tipo 2.

La presente invención provee un método de tratar o prevenir dislipidemias, el síndrome de resistencia a la insulina y/o trastornos metabólicos (como se definen más arriba), que comprende la administración de un compuesto de fórmula I a un mamífero (particularmente un humano), necesitado del mismo.

La presente invención provee un método de tratar o prevenir diabetes tipo 2, que comprende la administración de una cantidad efectiva de un compuesto de fórmula I a un mamífero (particularmente un humano) necesitado del mismo.

En un aspecto adicional la presente invención provee el uso de un compuesto de fórmula I como un medicamento.

En un aspecto adicional la presente invención provee el uso de un compuesto de fórmula I en la manufactura de un medicamento para el tratamiento de resistencia a la insulina y/o trastornos metabólicos.

Terapia de Combinación

Los compuestos de la invención pueden combinarse con otro agente terapéutico, que es útil en el tratamiento de trastornos asociados con el desarrollo y evolución de aterosclerosis tales como hipertensión, hiperlipidemias, dislipidemias, diabetes y obesidad. Los compuestos de la invención pueden combinarse con otro agente terapéutico que disminuya la relación de LDL: HDL o un agente que cause una disminución en los niveles de circulación de colesterol LDL. En pacientes con diabetes sacarina los compuestos de la invención pueden combinarse asimismo con agentes terapéuticos usados para tratar complicaciones relacionadas con micro-angiopatías.

Los compuestos de la invención pueden usarse junto con otras terapias para el tratamiento de síndrome metabólico o diabetes tipo 2 y sus complicaciones asociadas; éstas incluyen medicamentos de biguanida, por ejemplo metformina, fenformina y buformina, insulina (análogos sintéticos de insulina, amilina) y antihiper glucémicos orales (éstos se dividen en reguladores de glucosa prandial e inhibidores de alfa-glucosidasa). Un Ejemplo de un inhibidor de alfa-glucosidasa es acarbosa o voglibosa o miglitol. Un Ejemplo de un regulador de glucosa prandial es repaglinida o nateglinida.

En otro aspecto de la invención, el compuesto de fórmula I, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, puede administrarse en asociación con otro agente modulador de PPAR. Agentes moduladores de PPAR incluyen, pero no se limitan a, un agonista PPAR alfa y/o gamma y/o delta, o sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o sus profármacos. Agonistas apropiados

PPAR alfa y/o gamma, sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o sus profármacos son bien conocidos en el arte. Éstos incluyen los compuestos descritos en WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Opinión Experta sobre Patentes Terapéuticas, 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, todas las cuales se incorporan aquí por referencia. Particularmente un agonista PPAR alfa y/o gamma se refiere a BMS 298585, clofibrato, fenofibrato, bezafibrato, gemfibrozil y ciprofibrato; GW 9578, pioglitazona, rosiglitazona, rivoglitazona, balaglitazona, 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-metansulfonilo-oxi-fenil}etoxi)fenil]propanoico y sus sales farmacéuticamente aceptables.

Adicionalmente, la combinación de la invención puede usarse en conjunción con una sulfonilurea por ejemplo: glimepirida, glibenclamida (gliburida), gliclazida, glipizida, gliquidona, cloropropamida, tolbutamida, acetohexamida, glicopiramida, carbutamida, glibonurida, glisoxepid, glibutiazol, glibuzol, glihexamida, glimidina, glipinamida, fenbutamida, tolcilamida y tolazamida. Preferiblemente la sulfonilurea es glimepirida o glibenclamida (gliburida). Más preferiblemente la sulfonilurea es glimepirida. Por consiguiente, la presente invención incluye la administración de un compuesto de la presente invención en conjunción con una, dos o más terapias existentes descritas en este párrafo. Las dosis de las otras terapias existentes para el tratamiento de diabetes tipo 2 y sus complicaciones asociadas serán las conocidas en el arte y aprobadas para uso por los organismos regulatorios, por ejemplo la FDA y pueden encontrarse en el Orange Book publicado por la FDA. Alternativamente, pueden usarse dosis más pequeñas como resultado de los beneficios derivados de la combinación. La presente invención incluye asimismo un

compuesto de la presente invención en combinación con un agente reductor de colesterol. Los agentes reductores de colesterol referidos en esta solicitud incluyen, pero no se limitan a, inhibidores de HMG-CoA reductasa (3-hidroxi-3-metilglutaril coenzima A reductasa). Inhibidores apropiados de HMG-CoA reductasa es una estatina seleccionada del grupo conformado por atorvastatina, bervastatina, cerivastatina, dalvastatina, fluvastatina, itavastatina, lovastatina, mevastatina, nicostatina, nivastatina, pravastatina y simvastatina, o una sal farmacéuticamente aceptable, especialmente sodio o calcio, o su solvato, o un solvato de tal sal. Una estatina particular es atorvastatina, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco. Una estatina más particular es sal de calcio de atorvastatina. Una estatina particularmente preferida es, sin embargo, un compuesto con el nombre químico de ácido (E)-7-[4-(4-fluorofenil)-6-isopropil-2-[metil(metilsulfonil)-amino]-pirimidin-5-il](3R,5S)-3,5-dihidroxihept-6-enoico, [también conocido como ácido (E)-7-[4-(4-fluorofenil)-6-isopropil-2-[N-metil-N-(metilsulfonil)-amino]pirimidin-5-il](3R,5S)-3,5-dihidroxihept-6-enoico] o una sal farmacéuticamente aceptable o su solvato, o un solvato de tal sal. El compuesto ácido (E)-7-[4-(4-fluorofenil)-6-isopropil-2-[metil-(metilsulfonil)-amino]-pirimidin-5-il](3R,5S)-3,5-dihidroxihept-6-enoico, y sus sales de calcio y sodio se divulgan en la Solicitud de Patente Europea, Publicación No. EP-A-0521471, y en Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. Ésta última estatina se conoce ahora bajo su nombre genérico rosuvastatina.

En la presente solicitud, el término "agente reductor del colesterol" incluye asimismo modificaciones químicas de los inhibidores de HMG-CoA reductasa, tales como ésteres, profármacos y metabolitos, activos o inactivos.

g2
M

Igualmente la presente invención incluye un compuesto de la presente invención en combinación con un agente secuestrante de ácido biliar, por ejemplo colestipol o colestiramina o colestagel.

Del mismo modo, la presente invención incluye un compuesto de la presente invención en combinación con un inhibidor del sistema de transporte de ácido biliar en el íleon (inhibidor IBAT).

Se han descrito compuestos apropiados que poseen actividad inhibidora IBAT, véase por ejemplo los compuestos descritos en WO 93/16055, WO 94/18183, WO 94/18184, WO 94/24087, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO98/07749, WO 98/38182, WO 98/40375, WO 98/56757, WO 99/32478, WO 99/35135, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 00/47568, WO 00/61568, WO 01/68637, WO 01/68096, WO 02/08211, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, DE 19825804, 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, EP 864 582, y EP 1 070 703, y los contenidos de estas solicitudes de patente, particularmente los compuestos descritos en la reivindicación 1 y los Ejemplos nombrados, se incorporan aquí por referencia.

Clases particulares de inhibidores IBAT apropiados para uso en la presente invención son benzotiepinas, y los compuestos descritos en las reivindicaciones, particularmente la reivindicación 1, de WO 00/01687, WO 96/08484 de WO 97/33882 se incorporan aquí por referencia. Otras clases apropiadas de inhibidores IBAT son las 1,2-benzotiazepinas, 1,4-benzotiazepinas y 1,5-benzotiazepinas. Una clase adicional apropiada de inhibidores IBAT son las 1,2,5-benzotiadiazepinas.

Un compuesto apropiado particular que posee actividad inhibidora IBAT es ácido (3*R*,5*R*)-3-butil-3-etil-1,1-dióxido-5-fenil-2,3,4,5-tetrahidro-1,4-benzotiazepin-8-il $\square$ -D-glucopiranosidurónico (EP 864 582). Otros

inhibidores apropiados IBAT incluyen uno de:

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*'-(carboximetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*'-(carboximetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*'-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)-1'-fenil-1'-[*N*'-(2-sulfoetil)carbamoil]metil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*'-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*'-(2-sulfoetil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*'-(2-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*'-(2-carboxietil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*'-(5-carboxipentil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;



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-hidroxi-1-carboxietil)carbamoil]bencil}carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(N-{ α -[N'-(carboximetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-(N-{ α -[N'-(etoxi)(metil)fosforil-metil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3-butil-3-etil-5-fenil-7-metiltio-8-{N-[(R)- α -(N'-(2-[(hidroxi)(metil)fosforil]etil)carbamoil)bencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N'-(2-metiltio-1-carboxietil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-{N-[(R)- α -(N'-(2-[(metil)(etil)fosforil]etil)carbamoil)-4-hidroxibencil]carbamoilmetoxi}-2,3,4,5-tetrahidro-1,5-benzotiazepina;

85

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8- $\{N-[(R)-\alpha-(N'-\{2-[(\text{metil})(\text{hidroxi})\text{fosforil}]\text{etil}\})\text{carbamoil}\}-4\text{-hidroxibencil}\}\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,5-benzotiazepina};$

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8- $\{N-[(R)-\alpha-[(R)-N'(2\text{-metilsulfinil-1-carboxietil})\text{carbamoil}]\text{bencil}\})\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,5-benzotiazepina};$

1,1-dioxo-3,3-dibutil-5-fenil-7-metoxi-8- $\{N-[(R)-\alpha-[N'(2\text{-sulfoetil})\text{carbamoil}]\}-4\text{-hidroxibencil}\}\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,5-benzotiazepina};$

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8- $\{N-[(R)-\alpha-[N-((R)-1\text{-carboxi-2-metiltio-etil})\text{carbamoil}]\}-4\text{-hidroxibencil}\})\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,2,5-benzotiadiazepina};$

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8- $\{N-[(R)-\alpha-[N-((S)-1\text{-carboxi-2-(R)-hidroxipropil})\text{carbamoil}]\}-4\text{-hidroxibencil}\})\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,2,5-benzotiadiazepina};$

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8- $\{N-[(R)-\alpha-[N-((S)-1\text{-carboxi-2-metilpropil})\text{carbamoil}]\}-4\text{-hidroxibencil}\})\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,2,5-benzotiadiazepina};$

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8- $\{N-[(R)-\alpha-[N-((S)-1\text{-carboxibutil})\text{carbamoil}]\}-4\text{-hidroxibencil}\})\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,2,5-benzotiadiazepina};$

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8- $\{N-[(R)-\alpha-[N-((S)-1\text{-carboxipropil})\text{carbamoil}]\text{bencil}\})\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,2,5-benzotiadiazepina};$

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8- $\{N-[(R)-\alpha-[N-((S)-1\text{-carboxietil})\text{carbamoil}]\text{bencil}\})\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,2,5-benzotiadiazepina};$

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8- $\{N-[(R)-\alpha-[N-((S)-1\text{-carboxi-2-(R)-hidroxipropil})\text{carbamoil}]\text{bencil}\})\text{carbamoilmetoxi}\}-2,3,4,5\text{-tetrahidro-1,2,5-benzotiadiazepina};$

H86

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;

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}-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-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahidroxihexil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

y

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-(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;

o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco.

Además, de acuerdo con un aspecto adicional de la presente invención, se provee un tratamiento de combinación que comprende la administración de una cantidad efectiva de un compuesto de la fórmula I, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptable, con la administración simultánea, consecutiva o separada de uno o más de los siguientes agentes seleccionados de:

Un inhibidor de CETP (proteína transportadora de ésteres de colesterol), por ejemplo los referenciados y descritos en WO 00/38725 página 7 renglón 22 - página 10, renglón 17 que se incorporan aquí por referencia;

un antagonista de absorción de colesterol, por ejemplo azetidinonas tales como SCH 58235 y las descritas en US 5,767,115 que se incorporan aquí por referencia;

un inhibidor de MTP (proteína transportadora microsómica) por ejemplo las descritas en Science, 282, 751-54, 1998 que se incorporan aquí por referencia;

un derivado de ácido nicotínico, incluidos productos de combinación y liberación lenta, por ejemplo, ácido nicotínico (niacina), acipimox y niceritrol;

un compuesto de fitosterol por ejemplo estanoles; probucol;

un ácido graso omega-3 por ejemplo OmacorTM;

un compuesto anti-obesidad por ejemplo orlistat (EP 129,748) y sibutramina (GB 2,184,122 y US 4,929,629);

un compuesto antihipertensor por ejemplo un inhibidor de la enzima convertidora de angiotensina (ACE), un antagonista de receptor de angiotensina II, un bloqueador adrenérgico, un bloqueador alfa adrenérgico, un bloqueador beta adrenérgico por ejemplo metoprolol, un bloqueador alfa/beta adrenérgico mixto, un estimulante adrenérgico, bloqueador de canales de calcio, un bloqueador AT-1, un salurético, un diurético o un vasodilatador;

un antagonista CB1 o agonista inverso por ejemplo como se describe en WO01/70700 y EP 65635;

aspirina;

un antagonista de hormona concentradora de melanina (MCH);

un inhibidor de PDK; o

moduladores de receptores nucleares por ejemplo LXR, FXR, RXR, y RORalfa;

o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, de manera opcional conjuntamente, con un diluyente o vehículo farmacéuticamente aceptable a un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento terapéutico.

Inhibidores particulares de ACE o sales farmacéuticamente aceptables, solvatos, solvato de tales sales o su profármaco, incluidos metabolitos activos, que pueden usarse en combinación con un compuesto de fórmula I incluyen, pero no se limitan a, los siguientes compuestos: alacepril, alatriopril, altiopril calcio, ancovenin, benazepril, benazepril clorhidrato, benazeprilat, benzoilcaptopril, captopril, captopril-cisteína, captopril-glutación, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroximitina, fosfenopril, fosenopril, fosenopril sódico, fosinopril, fosinopril sódico, fosinoprilat, ácido fosinoprilico, glicopril, hemorfin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, liciumina A, liciumina B, mixanpril, moexipril, moexiprilat, moveltipril, muraceína A, muraceína B, muraceína C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril clorhidrato, quinaprilat, ramipril, ramiprilat, spirapril, spirapril clorhidrato, spiraprilat, spiropril, spiropril clorhidrato, temocapril, temocapril clorhidrato, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril y zofenoprilat. Activadores ACE preferidos para uso en la presente invención son ramipril, ramiprilat, lisinopril, enalapril y enalaprilat. Inhibidores ACE más preferidos para usos en la presente invención son ramipril y ramiprilat.

5/089

Antagonistas preferidos de angiotensina II, sales farmacéuticamente aceptables, solvatos, solvato de tales sales o su profármaco para uso en combinación con un compuesto de fórmula I incluyen, pero no se limitan a, compuestos: candesartán, candesartán cilexetil, losartán, valsartán, irbesartán, tasosartán, telmisartán y eprosartán. Antagonistas de angiotensina II particularmente preferidos o sus derivados farmacéuticamente aceptables para uso en la presente invención son candesartán y candesartán cilexetil.

Por lo tanto, en una característica adicional de la invención, se provee un método para el tratamiento de diabetes tipo 2 y sus complicaciones asociadas en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula I, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinaciones, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco.

Por consiguiente, en una característica adicional de la invención, se provee un método de tratar afecciones hiperlipidémicas en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula I, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinaciones o su sal farmacéuticamente aceptable, solvato, o 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 fórmula I, o su

9/90

sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, y uno de los demás compuestos descritos en esta sección de combinaciones o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, en asociación con un diluyente o vehículo farmacéuticamente aceptable.

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, o solvato de tal sal o profármaco, y uno de los demás compuestos descritos en esta sección de combinaciones o su sal farmacéuticamente aceptable, solvato, o 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 farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, en una primera formulación farmacéutica unitaria;
- b) uno de los demás compuestos descritos en esta sección de combinaciones o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco; en una segunda formulación farmacéutica unitaria; y
- c) medios de envase para contener dichas formulaciones 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, o solvato de tal sal o profármaco, junto con un diluyente o vehículo farmacéuticamente aceptable, en una primera formulación farmacéutica unitaria;

- b) uno de los demás compuestos descritos en esta sección de combinaciones o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, en una segunda formulación farmacéutica unitaria; y
- c) medios de envase para contener dichas formulaciones farmacéuticas primera y segunda.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula I, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, y uno de los demás compuestos descritos en esta sección de combinaciones, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, en la manufactura de un medicamento para uso en el tratamiento de síndrome metabólico o diabetes tipo 2 y sus complicaciones asociadas en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula I, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, y uno de los demás compuestos descritos en esta sección de combinaciones, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, 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 un aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad efectiva de un compuesto de la fórmula I, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, de manera opcional conjuntamente con un diluyente o vehículo farmacéuticamente aceptable, con la administración simultánea, consecutiva o separada de una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinaciones, o su sal farmacéuticamente aceptable, solvato, o solvato de tal sal o profármaco, de manera opcional

juntos con un diluyente o vehículo farmacéuticamente aceptable a un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento terapéutico.

Ejemplos

Las mediciones ^1H NMR y ^{13}C NMR se llevaron a cabo en un espectrómetro Varian Mercury 300 ó Varian UNITY plus 400, 500 ó 600, que operaban a frecuencias ^1H de 300, 400, 500 y 600 MHz, respectivamente, y a frecuencias ^{13}C de 75, 100, 125 y 150 MHz, respectivamente. Las mediciones se hicieron en la escala (δ).

A menos que se indique lo contrario, los cambios químicos se dan en ppm con el disolvente como estándar interno.

Abreviaturas

IRS	síndrome de resistencia a la insulina
TLC	cromatografía de capa delgada
HOBT	1-hidroxibenzotriazol-hidrato
DIBAH	hidruro de diisobutilaluminio
DMSO	sulfóxido de dimetilo
EtOAc	acetato de etilo
DMF	<i>N,N</i> -dimetilformamida
THF	tetrahidrofurano
PEG	polietilen glicol
HPLC	cromatografía de líquidos de alta eficacia
MeCN	acetonitrilo
TFA	ácido trifluoroacético
Pd/C	paladio sobre carbón
HATU	hexafluorofosfato de O-(7-azabenzotriazolyl-1- il)- <i>N,N,N',N'</i> -tetrametiluronio
DCM	diclorometano

TBTU tetrafluoborato de O-(benzotriazol-1-yl)-N,N,N',N'-tetrametiluronio

DIPEA *N,N*-diisopropiletilamina

DMAP 4-dimetilaminopiridina

Trisamina tris(hidroximetil)aminometano

ISOLUTE ® FLASH Si es una columna de sílice para cromatografía

Borohidruro en soporte de polímero en Amberlita IRA-400 disponible de Aldrich

EDC clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida

NH₄OAc acetato de amonio

t triplete

s singlete

d doblete

q cuartete

qvint quintete

m multiplete

br amplio

bs singlete amplio

dm doblete de multiplete

bt triplete amplio

dd doblete de doblete

Ejemplo 1

a) *N*-bencil-*N*-hexil-3-(4-hidroxifenil)propanamida

N-hexilbencilamina (0.6 g, 3.136 mmol) y ácido 3-(4-hidroxifenil)propiónico (0.52 g 3.136 mmol) se mezclaron en DMF (10 ml) y la mezcla se enfrió. Se agregaron HOBt (0.424 g, 3.136 mmol) y el reactivo TBTU (1 g, 3.136 mmol) seguidos por DIPEA (1.216 g, 9.409 mmol). La mezcla se agitó a temperatura de la sala de un día para otro y luego se evaporó. La mezcla resultante se repartió en porciones entre acetato de etilo y solución acuosa de carbonato hidrogenado de sodio (sat.).

La porción acuosa se extrajo con acetato de etilo y los extractos orgánicos combinados se secaron con sulfato de magnesio y luego se evaporaron. Cromatografía del residuo en una columna (ISOLUTE® SI, 5g/25 ml) usando acetato de etilo/heptano (10:90, luego 25:75) como eluente produjo 760 mg el producto deseado, rendimiento 71%.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.84 (t, 3H), 1.16-1.27 (m, 6H), 1.41-1.51 (m, 2H), 2.55, 2.63 (t, t, 2H), 2.88, 2.94 (t, t, 2H), 3.09, 3.31 (t, t, 2H), 4.40, 4.57 (s, s, 2H), 6.69, 6.73 (d, d, 2H), 6.98 (d, 2H), 7.05, 7.07 (d, d, 2H), 7.14 (d, 1H) y 7.21-7.31 (m, 5H)

b) Metil 2-[(4-{3-[bencil(hexil)amino]-3-oxopropil}fenoxi)metil]benzoato

N-bencil-N-hexil-3-(4-hidroxifenil)propanamida (183mg, 0.54mmol), metil 2-(bromometil)benzoato (136mg, 0.59mmol) carbonato de potasio (112mg, 0.81mmol) se mezclaron en acetonitrilo. La mezcla se agitó a 66°C de un día para otro. El disolvente se evaporó bajo presión reducida y el residuo se disolvió en acetato de etilo. La fase orgánica se lavó (agua x2, salmuera x1), se secó (Na₂SO₄) y se evaporó. Purificación adicional mediante HPLC preparativa (usando una gradiente de CH₃CN/ 10%CH₃CN-fase de agua que contenía 0.1M NH₄OAc como eluente) produjo 91mg (rendimiento 34%) del producto deseado.

¹H NMR (rotámetros, 400MHz, CDCl₃): δ 0.84-0.88 (m, 3H), 1.19-1.29 (m, 6H), 1.42-1.53 (m, 2H), 2.57, 2.65 (t, t, 2H), 2.92, 2.99 (t, 2H), 3.10, 3.34 (t, t, 2H), 3.89, 3.90 (s, s, 3H), 4.42, 4.60 (s, s, 2H), 5.47, 5.48 (s, s, 2H), 6.86-6.93 (m, 2H), 7.07 (t, 2H), 7.14-7.19 (m, 2H), 7.21-7.38 (m, 4H), 7.52-7.56 (m, 1H), 7.75 (t, 1H), 8.00-8.03 (m, 1H).

c) Ácido 2-[(4-{3-[bencil(hexil)amino]-3-oxopropil}fenoxi)metil]benzoico

Metil 2-[(4-{3-[bencil(hexil)amino]-3-oxopropil}fenoxi)metil]benzoato (61mg, 0.13mmol) e hidróxido de litio (7mg, 0.29mmol) se disolvieron en 3ml de una mezcla 1:1 de THF y agua en un frasco para microondas. La mezcla de reacción resultante se irradió en un horno microondas a 120°C durante 40 min.

Se agregó agua y el THF se evaporó bajo presión reducida. El residuo se acidificó con 1M ácido clorhídrico y se extrajo con acetato de etilo (x3). Las fases orgánicas se combinaron, se lavaron (agua, salmuera), se secaron (Na_2SO_4) y se evaporaron. El producto crudo se purificó aún más por HPLC preparativa (usando una gradiente de CH_3CN / 10% CH_3CN -fase de agua que contenía 0.1M NH_4OAc como eluyente).

Se obtuvieron 38mg (rendimiento 64%) de producto puro luego del secamiento por congelamiento.

^1H NMR (rotámetros, 400MHz, CDCl_3): δ 0.86 (t, 3H), 1.19-1.28 (m, 6H), 1.43-1.55 (m, 2H), 2.60, 2.69 (t, t, 2H), 2.92, 2.99 (t, t, 2H), 3.11, 3.36 (t, t, 2H), 4.43, 4.61 (s, s, 2H), 5.52, 5.53 (s, s, 2H), 6.87-6.93 (m, 2H), 7.05-7.09 (m, 2H), 7.14-7.33 (m, 5H), 7.36-7.40 (m, 1H), 7.55-7.59 (m, 1H), 7.77 (t, 1H) y 8.12-8.15 (m, 1H).

^{13}C NMR (rotámetros, 100MHz, CDCl_3): δ 14.17, 14.23, 22.73, 22.79, 26.75, 26.88, 27.68, 27.72, 31.11, 31.26, 31.61, 31.82, 35.39, 35.68, 46.84, 47.48, 48.72, 51.35, 68.42, 115.16, 115.22, 126.39, 127.15, 127.42, 127.49, 127.72, 128.23, 128.70, 129.10, 129.72, 131.81, 133.45, 133.81, 133.84, 137.10, 137.82, 140.88, 157.33, 157.40, 171.20, 173.10, 173.39.

Ejemplo 2

a) N-(2,4-difluorobencil)-N-heptilamina

Heptilamina (345.6 mg, 3 mmol) se agregó en 2,4-difluorobenzaldehído (440.5 mg, 3.1 mmol) en MeOH (3 ml) y ortoformato de trimetilo (2 ml), seguido por ácido acético (0.05 ml). La mezcla estuvo en un horno microondas (Smith Synthesizer) a 150°C durante 10 minutos.

Seguidamente se agregó DCM (3 ml) y borohidruro en soporte polimérico (1.2g, ~3 mmol). La muestra se agitó de un día para otro y se agregó más borohidruro en soporte polimérico (1.2 g). La muestra se agitó durante el fin de semana y luego se filtró y se evaporó. El residuo se puso en una columna ((ISOLUTE®PRS, 10g) y se eluyó con MeCN, MeOH y luego MeOH (NH₃ sat.). Se obtuvieron 536 mg de producto oleoso, rendimiento 72%.

¹H NMR (400 MHz, CDCl₃): δ 0.87 (t, 3H), 1.23-1.32 (m, 8H), 1.45-1.52 (m, 2H), 2.59 (t, 2H), 3.78 (s, 2H), 6.75-6.85 (m, 2H) y 7.27-7.33 (m, 1H)

b) Ácido 4-([2-(metoxycarbonil)bencil]tio)fenil)acético

Ácido 4-mercaptofenilacético (995 mg, 5.915 mmol) en THF (15 ml) se enfrió en un baño helado y (55-65%, 520 mg, ~13 mmol) se agregó hidruro de sodio. La muestra se agitó durante 30 minutos y luego se agregó éster metílico de ácido 2-bromometil-benzoico (1.49 g, 6.507 mmol) en THF (5 ml). La muestra resultante se agitó de un día para otro y se dejó que la temperatura subiera hasta la temperatura de la sala. Se añadió agua por goteo y la muestra se agitó durante aprox. 20 minutos. Luego se evaporó para retirar el THF. El residuo se acidificó con 1% ácido clorhídrico, pH~3, y luego se extrajo con acetato de etilo. Los extractos orgánicos se combinaron, se secaron con sulfato de magnesio y se evaporaron. Cromatografía del residuo en una columna (ISOLUTE® SI, 20g/70ml) usando DCM, luego MeOH/DCM (1:99) como eluyente produjo 224 mg producto deseado, rendimiento 65%.

¹H NMR (500 MHz, CDCl₃): δ 3.62 (s, 2H), 3.90 (s, 3H), 4.52 (s, 2H), 7.17 (d, 2H), 7.23-7.40 (m, 5H) y 7.94 (d, 1H).

c) Metil 2-([(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil}fenil)tio]-metil]benzoato

Ácido (4-{{[2-(metoxycarbonil)bencil]tio}fenil}acético (581 mg, 1.836 mmol) y *N*-(2,4-difluorobencil)-*N*-heptilamina (465.3 mg, 1.968 mmol) se combinaron en DMF y la mezcla se enfrió en un baño helado. Se agregaron HOBt (260.6 mg, 1.928 mmol) y TBTU (619 mg, 1.928 mmol), seguidos por DIPEA (747.7 mg 5.785mmol). La mezcla se agitó a temperatura de la sala de un día para otro y luego se evaporó. La mezcla resultante se repartió en porciones entre acetato de etilo y solución acuosa de carbonato hidrogenado de sodio (sat.). La porción acuosa se extrajo con acetato de etilo y los extractos orgánicos combinados se secaron con sulfato de magnesio y luego se evaporaron. Cromatografía del residuo en una columna (ISOLUTE® SI, 20g/70ml) usando acetato de etilo/heptano (5:95, luego 10:90) como eluente produjo 767 mg el producto deseado, rendimiento 77%.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.88-0.93 (m, 3H), 1.23-1.34 (m, 8H), 1.48-1.57 (m, 2H), 3.19-3.24, 3.30-3.37 (m, m, 2H), 3.67-3.74 (m, 2H), 3.92 (s, 3H), 4.50, 4.63 (s, s, 2H), 4.53 (s, 2H), 6.78-6.89 (m, 2H), 7.00-7.40 (m, 8H) y 7.95 (d, 2H).

d) Ácido 2-{{[4-{{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil}fenil}tio]metil}benzoico

Metil 2-{{[4-{{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil}fenil}tio]metil}-benzoato (31 mg, 0.057 mmol) se disolvió en THF (1 ml) y se enfrió en un baño helado. Se agregó hidróxido de litio (2 mg, 0.075 mmol) en agua (1 ml). Después de la adición, el baño de enfriamiento se retiró y la mezcla se agitó de un día para otro. LC-MS mostró que había muy poco producto. Se agregó más hidróxido de litio (3 mg) y la muestra se agitó durante 6 días más, y HPLC mostró alrededor de 30% de producto. Se agregó más hidróxido de litio (3 mg) y la muestra se agitó durante 13 días más. Se evaporó en vacío para retirar THF. El residuo se acidificó con 10% ácido clorhídrico, pH~3, y se extrajo con acetato de etilo (x2). Las fases orgánicas se combinaron, se secaron (sulfato de magnesio) y se evaporaron. Cromatografía del residuo en una columna (ISOLUTE® SI,

500g/3ml) usando DCM, MeOH/DCM (0.5:99.5) como eluente produjo 17 mg del producto deseado, rendimiento 56%.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.89-0.93 (m, 3H), 1.25-1.34 (m, 8H), 1.52-1.60 (m, 2H), 3.27, 3.37 (t, t, 2H), 3.71, 3.76 (s, s, 2H), 4.55, 4.65 (s, s, 2H), 6.80-6.92 (m, 2H), 7.07-7.17 (m, 2H), 7.28-7.37 (m, 5H), 7.42-7.47 (m, 1H) y 7.95-7.98 (m, 1H).

¹³C NMR (rotámetros, 125 MHz, CDCl₃): δ 14.01, 22.51, 26.78, 26.85, 27.28, 28.56, 28.85, 28.93, 31.65, 31.70, 38.22, 39.94, 40.25, 41.57, 41.60, 45.16, 46.48, 47.94, 103.53 (t), 104.26(t), 111.50(br), 111.71(br), 119.65(d), 120.37(d), 127.05, 128.95 (br), 129.61, 129.68, 131.15, 131.66(d), 131.76(d), 132.41, 132.80, 132.88, 133.85, 134.03, 140.43, 160.58 (dd), 160.91(dd), 162.21(dd), 162.53(dd), 170.46, 171.44 y 171.54.

Ejemplo 3

a) Ácido (4-{[2-(metoxycarbonil)bencil]oxi}fenil)acético

Ácido 4-hidroxifenilacético (760 mg, 4.995 mmol) se disolvió en etanol (99.5%, 20 ml). Se agregó hidróxido de potasio (560.5 mg, 9.99 mmol). La mezcla se agitó a temperatura de la sala durante 30 minutos. Seguidamente se introdujo éster metílico de ácido 2-bromometilbenzoico (1144.2 mg, 4.995 mmol). La mezcla resultante se calentó a reflujo durante 2 horas y luego se evaporó en vacío a sequedad. Se agregaron agua y acetato de etilo en el residuo y las fases se separaron. La fase acuosa se acidificó con 10% ácido clorhídrico, pH~5, y luego se extrajo con acetato de etilo. La fase orgánica se secó con sulfato de magnesio y se evaporó en vacío a sequedad. Cromatografía del residuo en una columna (ISOLUTE® SI, 5g/6ml) usando DCM, MeOH/DCM (1:99) como eluente produjo el producto deseado (262 mg), rendimiento 17.5%.

¹H NMR (500 MHz, CDCl₃): δ 3.61 (s, 2H), 3.91 (s, 3H), 5.50 (s, 2H), 6.97 (d, 2H), 7.22 (d, 2H), 7.39 (t, 1H), 7.57 (t, 1H), 7.76 (d, 1H) y 8.04 (d, 1H).

b) Metil 2-[(4-{2-[bencil(hexil)amino]-2-oxoetil}fenoxi)metil]benzoato

a9
20

Ácido (4-{{2-(metoxicarbonil)bencil}oxi}fenil)acético (50 mg, 0.166 mmol) se disolvió en DCM (2 ml), se agregó N-hexilbencilamina (38.2 mg, 0.2 mmol), luego EDC (38.3 mg, 0.2 mmol) y luego DMAP (24.4 mg, 0.2 mmol). La mezcla se agitó a temperatura de la sala de un día para otro. Se agregaron 1% HCl (1 ml) y agua (1 ml) en la mezcla. Las dos fases se separaron usando un Tubo de Filtro Whatman. La solución orgánica obtenida se evaporó en vacío y quedó el producto oleoso (71 mg). Éste se usó entonces en el siguiente paso.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.86-0.91 (m, 3H), 1.22-1.32 (m, 6H), 1.47-1.58(m, 2H), 3.21, 3.39 (t, t, 2H), 3.65, 3.75 (s, s, 2H), 3.93 (s, 3H), 4.53, 4.64 (s, s, 2H), 5.51, 5.52 (s, s, 2H), 6.96, 6.99 (d, d, 2H), 7.16 (d, 2H), 7.23-7.42 (m, 6H), 7.59 (t, 1H), 7.78 (d, 1H) y 8.06 (d, 1H).

c) Ácido 2-[(4-{2-[bencil(hexil)amino]-2-oxoetil}fenoxi)metil]benzoico

Metil 2-[(4-{2-[bencil(hexil)amino]-2-oxoetil}fenoxi)metil]benzoato (70 mg, 0.148 mmol) en THF (2 ml) se enfrió en un baño helado. Se añadió por goteo hidróxido de litio (7.08 mg, 0.296 mmol) en agua (1 ml). A continuación se retiró el baño de enfriamiento y la mezcla se agitó de un día para otro. HPLC mostró que la reacción no había concluido. Se agregó más hidróxido de litio (0.2M, 0.5 ml). La mezcla de reacción se agitó durante 4 días más. Luego se evaporó en vacío para retirar el THF. El residuo se acidificó con 1% ácido clorhídrico, pH=3-4, y se extrajo con acetato de etilo. Se secó la fase orgánica (sulfato de magnesio) y se evaporó. Cromatografía del residuo en una columna (ISOLUTE® SI, 2g/6 ml) usando DCM, MeOH/DCM (1:99, y luego 2:98) como eluyente produjo 24 mg el producto deseado, rendimiento 35%.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.86-0.90 (m, 3H), 1.21-1.30 (m, 6H), 1.46-1.58(m, 2H), 3.21, 3.39 (t, t, 2H), 3.68, 3.77 (s, s, 2H), 4.53, 4.65 (s, s, 2H), 5.53, 5.54 (s, s, 2H), 6.95, 6.98 (d, d, 2H), 7.14-7.17 (m, 2H), 7.22-7.33 (m, 4H), 7.35-7.43 (m, 2H), 7.60 (t, 1H), 7.80 (d, 1H) y 8.16 (d, 1H).

100
100

^{13}C NMR (rotámeros, 125 MHz, CDCl_3): δ 13.94, 13.97, 22.49, 22.53, 26.47, 26.57, 27.29, 28.36, 31.40, 31.50, 39.82, 40.12, 46.50, 47.43, 48.28, 51.31, 68.21, 115.15, 126.25, 126.85, 127.20, 127.24, 127.36, 127.48, 127.54, 127.97, 128.49, 128.87, 129.76, 129.89, 131.52, 133.18, 136.80, 137.57, 140.40, 157.59, 170.60, 171.76 y 172.03.

Ejemplo 4

a) Metil 2-[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil}fenoxi)metil]-benzoato

N-(2,4-Difluorobencil)-*N*-heptilamina (106 mg, 0.44 mmol) se agregó en ácido (4-{[2-(metoxicarbonil)bencil]oxi}fenil)acético (120 mg, 0.4 mmol) en DCM (10 ml) y se siguió por EDC (84.3 mg, 0.44 mmol) y luego DMAP (54 mg, 0.44 mmol). La mezcla se agitó a temperatura de la sala de un día para otro, y después se lavó con 1% ácido clorhídrico, agua y salmuera y se secó con sulfato de magnesio y se evaporó. Cromatografía del residuo en una columna (ISOLUTE[®]SI, 5g/15 ml) usando DCM y MeOH/DCM (0.5:99.5) como eluyente produjo 155 mg producto deseado, rendimiento 74%.

^1H NMR (rotámeros, 500 MHz, CDCl_3): δ 0.88-0.92 (m, 3H), 1.23-1.33 (m, 8H), 1.49-1.57 (m, 2H), 3.24, 3.34 (t, t, 2H), 3.66, 3.72 (s, s, 2H), 3.92 (s, 3H), 4.53, 4.62 (s, s, 2H), 5.50, 5.51 (s, s, 2H), 6.77-6.89 (m, 2H), 6.95, 6.98 (d, d, 2H), 6.99-7.04, 7.29-7.33 (m, m, 1H), 7.17, 7.20 (d, d, 2H), 7.39(t, 1H), 7.57 (t, 1H), 7.75-7.79 (m, 1H) y 8.05 (d, 1H).

b) Ácido 2-[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil}fenoxi)metil]benzoico

Hidróxido de litio (13.3 mg, 0.554 mmol) en agua (1.5 ml) se agregó en 70335 (sic) metil 2-[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil}fenoxi)metil]benzoato (145 mg, 0.277 mmol) disuelto en THF (3 ml). La mezcla se puso entonces en un horno microondas (Smith

Synthesizer) a 150 °C durante 7 minutos y luego se evaporó para retirar el THF. El residuo se acidificó con 1% ácido clorhídrico, pH~4 y luego se extrajo con acetato de etilo (x2). Las porciones orgánicas se combinaron, se lavaron con salmuera, se secaron con sulfato de magnesio y luego se evaporaron. Cromatografía del residuo en una columna (ISOLUTE® SI, 2g/6ml) usando DCM, luego MeOH/DCM (0.5:99.5, luego 1:99) como eluente produjo 94 mg de producto deseado, rendimiento 67%.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.86-0.91 (m, 3H), 1.22-1.32 (m, 8H), 1.48-1.56 (m, 2H), 3.23, 3.34 (t, t, 2H), 3.68, 3.73 (s, s, 2H), 4.52, 4.63 (s, s, 2H), 5.53 (s, br, 2H), 6.77-6.87 (m, 2H), 6.93- 6.97 (m, 2H), 6.99-7.04, 7.27-7.33 (m, m, 1H), 7.16-7.20 (m, 2H), 7.41 (t, 1H), 7.58-7.62 (m, 1H), 7.78 (d, 1H) y 8.15(d, 1H).

¹³C NMR (rotámetros, 125 MHz, CDCl₃): δ 14.00, 22.51, 26.75, 26.84, 27.26, 28.54, 28.86, 28.94, 31.64, 31.70, 39.75, 40.08, 41.39, 45.05, 46.30, 47.98, 68.21, 103.67 (t), 104.12 (t), 111.52 (d), 115.17, 119.80 (d), 120.52 (d), 126.97, 127.04, 127.21, 128.81 (br), 129.78, 129.85, 131.52, 133.16, 140.33, 157.65, 160.48 (dd), 160.85 (dd), 162.13 (dd), 162.46 (dd), 171.01, 171.93 y 171.99.

Ejemplo 5

a) *N*-(2,4-difluorobencil)-*N*-heptil-3-(4-hidroxifenil)propanamida

Ácido 3-(4-hidroxifenil)propiónico (108 mg, 0.650 mmol) se disolvió en DMF. Se agregó *N*-(2,4-difluorobencil)-*N*-heptilamina (164.7 mg, 0.682 mmol). La mezcla se enfrió en un baño helado. TBTU (219 mg, 0.682 mmol) se agregó y se siguió por DIPEA (0.238 ml, 1.365 mmol). La mezcla se agitó de un día para otro y se dejó aumentar la temperatura a la temperatura de la sala. Se agregaron acetato de etilo y solución acuosa de carbonato hidrogenado de sodio (sat.), y luego se separaron las dos fases. La fase acuosa se extrajo con acetato de etilo. Las fases orgánicas se combinaron y se secaron con sulfato de magnesio y se evaporaron. Cromatografía del residuo en una columna (ISOLUTE® SI, 5g/15 ml)

usando DCM y luego MeOH/DCM (1:99) como eluente produjo 223 mg del producto deseado, rendimiento 88%.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.86-0.90 (m, 3H), 1.21-1.31 (m, 8H), 1.47-1.53 (m, 2H), 2.60, 2.67 (t, t, 2H), 2.85-2.96 (m, 2H), 3.15, 3.32 (t, t, 2H), 4.41, 4.60 (s, s, 2H), 6.75-6.85 (m, 4H), 6.90-6.96, 7.12-7.18 (m, m, 1H) y 7.00, 7.04 (d, d, 2H).

b) Metil 2-[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil}fenoxi)metil]-benzoato

N-(2,4-difluorobencil)-*N*-heptil-3-(4-hidroxifenil)propanamida (195 mg, 0.501 mmol), éster metílico de ácido 2-bromometilbenzoico (120.4 mg, 0.526 mmol) y carbonato de potasio anhidro (103 mg, 0.751 mmol) se mezclaron en acetonitrilo (15 ml). La mezcla se calentó a reflujo de un día para otro y luego se evaporó a sequedad. Se agregaron agua y acetato de etilo y las dos fases se separaron. Se secó la fase orgánica (sulfato de magnesio) y se evaporó. Cromatografía del residuo en una columna (ISOLUTE® SI, 2g/6ml) usando heptano/DCM (50:50), luego DCM y luego MeOH/DCM (0.5:99.5) como eluente produjo 187 mg del producto deseado, rendimiento 69.5%.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.87-0.91 (m, 3H), 1.21-1.31 (m, 8H), 1.44-1.56 (m, 2H), 2.56-2.69 (m, 2H), 2.91-3.01 (m, 2H), 3.14, 3.32 (t, t, 2H), 3.92 (s, 3H), 4.43, 4.59 (s, s, 2H), 5.49 (s, 2H), 6.75-6.97 (m, 4H), 7.08-7.28 (m, 3H), 7.38 (t, 1H), 7.56 (t, 1H), 7.76 (d, 1H) y 8.04 (d, 1H),

c) Ácido 2-[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil}fenoxi)metil]benzoico

Hidróxido de litio (13.3 mg, 0.554 mmol) en agua (1 ml) se agregó en metil 2-[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil}fenoxi)metil]benzoato (149 mg, 0.277 mmol) disuelto en THF (2 ml). La mezcla se puso entonces en un horno microondas (Smith Synthesizer) a 150 °C durante 7

minutos y luego se evaporó para retirar THF. El residuo se acidificó con 1% ácido clorhídrico, pH~4, y se extrajo con acetato de etilo (x2). Los extractos orgánicos se combinaron y se lavaron con salmuera y se secaron con sulfato de magnesio y luego se evaporaron. Cromatografía del residuo en una columna (ISOLUTE® SI, 2g/6ml) usando DCM, luego MeOH/DCM (1:99) como eluyente produjo 121 mg del producto deseado, rendimiento 83%.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.89-0.93 (m, 3H), 1.24-1.33 (m, 8H), 1.49-1.58 (m, 2H), 2.64-2.74 (m, 2H), 2.97-3.03 (m, 2H), 3.17, 3.37 (t, 2H), 4.46, 4.65 (s, s, 2H), 5.58, 5.59 (s, s, 2H), 6.78-6.87 (m, 2H), 6.94-6.97 (m, 2H), 6.99-7.04, 7.27-7.31 (m, m, 1H), 7.14, 7.17 (d, d, 2H), 7.42-7.45 (m, 1H), 7.61-7.64 (m, 1H), 7.82-7.85 (m, 1H) y 8.19-8.22 (d, 1H),

¹³C NMR (rotámetros, 125 MHz, CDCl₃): δ 13.96, 22.46, 22.49, 26.67, 26.85, 27.38, 28.57, 28.80, 28.94, 30.69, 30.84, 31.58, 31.67, 35.01, 35.26, 41.63, 44.76, 44.78, 46.43, 47.78, 68.15, 103.60(t), 104.07(t), 111.41(dd), 111.49 (dd), 114.91, 119.74 (d), 120.45 (d), 126.86, 127.12, 128.53 (br), 129.40, 131.49, 131.58, 133.15, 133.32, 140.54, 157.12, 160.33 (dd), 160.81 (dd), 162.07 (dd), 162.33 (dd), 171.07, 173.04 y 173.11.

Ejemplo 6

a) Ácido 3-(4-mercaptofenil)propanoico (2.0 g, 10.97 mmol) se disolvió en THF seco (60 ml) y se enfrió a 0° C. Se agregó hidruro de sodio (0.64 g, 24.1 mmol). La muestra se agitó durante 30 minutos; se agregó gota a gota metil 2-(bromometil)benzoato (2.77 g, 12.07 mmol) disuelto en THF seco (10 ml). Se dejó calentar la solución a temperatura de la sala y se agitó de un día para otro. La adición gota a gota de agua (10 ml) desactivó el hidruro de sodio restante. El disolvente se retiró por evaporación, y el residuo se acidificó a pH 3 (HCl 1%). La fase acuosa se lavó con EtOAc (3 X 10 ml). Las fases orgánicas se combinaron, se secaron (MgSO₄) y se evaporaron. El crudo se purificó por HPLC preparativa (iniciada con

acetonitrilo/solución amortiguadora 60/40 y luego se incrementó la concentración de acetonitrilo a 100%; la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Las fracciones que contenían el producto se agruparon y el acetonitrilo se retiró mediante evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El retiro del disolvente mediante evaporación produjo 2.26 gramos de ácido 3-(4-{[2-(metoxicarbonil)bencil]tio}fenil)propanoico (rendimiento 62.3%).

¹H NMR (500 MHz, CDCl₃): δ 2.66 (t, 2H), 2.92 (t, 2H), 3.90 (s, 3H), 4.51 (s, 2H), 7.10 (d, 2H), 7.19 (d, 1H), 7.25 (d, 2H), 7.29 (t, 1H), 7.36 (t, 1H) y 7.94 (d, 1H).

b) Metil 2-[[[4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil}fenil]tio]-metil]benzoato

N-(2,4-difluorobencil)-*N*-heptilamina (0.64 g, 2.65 mmol) se disolvió en DMF (10 ml), se agregó ácido 3-(4-{[2-(metoxicarbonil)bencil]tio}fenil)propanoico (0.80 g, 2.41 mmol) y la mezcla se enfrió a 0° C. Se agregaron *N*-[(1*H*-1,2,3-benzotriazol-1-iloxi)-(dimetilamino)metilen]-*N*-metilmetanaminio tetrafluoroborato (0.85 g, 2.65 mmol) y diisopropiletilamina (0.65 g, 5.05 mmol). La mezcla se dejó calentar a la temperatura de la sala y se agitó de un día para otro. Se agregó EtOAc (15 ml) y la fase orgánica se lavó con dos porciones de carbonato hidrogenado de sodio (aq., 10 ml). El EtOAc se retiró por evaporación y el crudo se purificó por HPLC preparativa (iniciada con acetonitrilo/solución amortiguadora 60/40 y luego la concentración de acetonitrilo se aumentó a 100%, la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto y el

acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El disolvente se retiró por evaporación y produjo 1.10 gramos de metil 2-{[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil}fenil)tio]metil}benzoato (rendimiento 82.2%).

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.89 (t, 3H), 1.22-1.32 (m, 8H), 1.47-1.55 (m, 2H), 2.55, 2.66 (t, t, 2H), 2.95-3.01 (m, 2H), 3.16, 3.33 (t, t, 2H), 3.89, 3.90 (s, s, 3H), 4.44, 4.60 (s, s, 2H), 4.50, 4.51 (s, s, 2H), 6.76-6.85 (m, 2H), 6.92-6.96, 7.20-7.25 (m, m, 4H), 7.07, 7.12 (d, d, 2H), 7.27-7.31 (m, 1H), 7.32-7.34 (m, 1H) y 7.91-7.92 (m, 1H).

c) Ácido 2-{[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil}fenil)tio]-metil}benzoico

Metil 2-{[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil}fenil)tio]-metil}benzoato (1.05 g, 1.89 mmol) se disolvió en EtOH (95%, 5 ml), se agregó hidróxido de potasio (0.21 g, 3.77 mmol). La reacción se llevó a cabo en un horno microondas de un solo nódulo (7 min, 150° C). El desarrollo mediante la adición de EtOAc (5 ml) y lavado con HCl (2 X 5 ml, 1M). La fase orgánica se secó (MgSO₄) y el disolvente se retiró por evaporación para producir 0.96 gramos de ácido 2-{[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil}fenil)tio]metil}benzoico (rendimiento 94.3%).

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.88-0.92 (m, 3H), 1.24-1.33 (m, 8H), 1.50-1.57 (m, 2H), 2.64, 2.69 (t, t, 2H), 2.95-3.00 (m, 2H), 3.20, 3.34 (t, t, 2H), 4.48, 4.62 (s, s, 2H), 4.55, 4.56 (s, s, 2H), 6.79-6.87 (m, 2H), 6.98-7.03, 7.27-7.30 (m, m, 2H), 7.06-7.10 (m, 2H), 7.22-7.24 (m, 2H), 7.31-7.36 (m, 1H), 7.41-7.46 (m, 1H) y 8.03 (d, 1H).

¹³C NMR (rotámetros, 125 MHz, CDCl₃): δ 14.01, 22.51, 22.54, 26.74, 26.90, 27.42, 28.63, 28.86, 28.98, 30.92, 31.18, 31.64, 31.72, 34.65, 38.23, 38.28, 41.58, 44.82, 46.44, 47.77, 103.46 (t), 104.14 (t), 111.52 (dd), 111.58 (dd), 119.74 (dd), 120.51 (dd), 127.09, 128.55, 128.63, 129.03, 131.16, 131.49, 131.55, 131.78 (dd), 132.30, 132.50, 132.96, 140.04, 140.11, 140.59, 140.68, 160.47 (dd), 160.88 (dd), 162.16 (dd), 162.44 (dd), 170.88 (br), 172.56 y 172.59.

Ejemplo 7

a) *N*-(2,3-dimetoxibencil)butan-1-amina (0.59 g, 2.65 mmol) se disolvió en DMF (10 ml), se agregó ácido 3-(4-hidroxifenil)propanoico (0.4 g, 2.41 mmol), y la mezcla se enfrió a 0° C. Se agregaron *N*-[(1*H*-1,2,3-benzotriazol-1-iloxi)(dimetilamino)metilen]-*N*-metilmetanaminio tetrafluoroborato (0.85 g, 2.65 mmol) y diisopropiletilamina (0.65 g, 5.05 mmol). La mezcla se dejó calentar a temperatura de la sala y se agitó de un día para otro. Se agregó EtOAc (15 ml) y la fase orgánica se lavó con dos porciones de carbonato hidrogenado de sodio (aq., 10 ml). El EtOAc se retiró mediante evaporación y el crudo se purificó por HPLC preparativa (iniciada con acetonitrilo/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%, la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, caudal 40 ml/min). Las fracciones que contenían el producto se agruparon y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El disolvente se retiró por evaporación y produjo 1.08 gramos de *N*-butil-*N*-(2,3-dimetoxibencil)-3-(4-hidroxifenil)propanamida (rendimiento 82.3%).

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.85-0.89 (m, 3H), 1.20-1.30 (m, 2H), 1.44-1.53 (m, 2H), 2.60, 2.65 (t, t, 2H), 2.88, 2.94 (t, t, 2H), 3.13, 3.33

(t, t, 2H), 3.78, 3.80 3.83, 3.85 (s, s, s, s, 6H), 4.43, 4.68 (s, s, 2H), 6.57, 6.67 (d, d, 1H), 6.74-6.86 (m, 3H) y 6.95-7.05 (m, 3H).

b) *N*-butil-*N*-(2,3-dimetoxibencil)-3-(4-hidroxifenil)propanamida (50 mg, 0.13 mmol) y metil 2-(bromometil)benzoato (0.034 g, 0.15 mmol) se disolvieron en acetonitrilo (10 ml) y se agregó carbonato de potasio (37 mg, 0.27 mmol). La mezcla se agitó a 60° C durante tres horas. Se agregó trisamina con soporte polimérico (0.3 eqv) y se agitó de un día para otro. El polímero se extrajo por filtración y el disolvente se eliminó por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con tres porciones de agua. Luego de secar el crudo (MgSO₄), el disolvente se había retirado por evaporación. El residuo se purificó por HPLC preparativa (iniciada con acetonitrilo/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%, la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El retiro del disolvente por evaporación produjo 15 mg de metil 2-[(4-{3-[butil(2,3-dimetoxibencil) amino]-3-oxopropil}fenoxi)metil]benzoato (21.4%).

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.89-0.95 (m, 3H), 1.24-1.35 (m, 2H), 1.48-1.57 (m, 2H), 2.62, 2.69 (t, t, 2H), 2.95, 3.01 (t, t, 2H), 3.17, 3.36 (t, t, 2H), 3.83, 3.86, 3.89, 3.90, 3.93, 3.94 (s, s, s, s, s, s, 9H), 4.48, 4.71 (s, s, 2H), 5.50, 5.52 (s, s, 2H), 6.62, 6.75 (d, d, 1H), 6.84-6.97 (m, 3H), 7.00-7.04 (m, 1H), 7.11, 7.19 (d, d, 2H), 7.38-7.42 (m, 1H), 7.56-7.60 (m, 1H), 7.78 (t, 1H) y 8.04-8.07 (m, 1H).

c) Metil 2-[(4-{3-[butil(2,3-dimetoxibencil)amino]-3-oxopropil}fenoxi)metil]-benzoato (15 mg, 0.029 mmol) se disolvió en THF/agua (2/1, 2 ml) y

se agregó LiOH (1.4 mg, 0.058 mmol). La reacción se efectuó en un horno microondas de un solo nódulo (150° C, 7 min). El desarrollo se hizo agregando EtOAc (10 ml) y lavando la fase orgánica con dos porciones de HCl (2 X 5 ml, 1 M). Se secó la fase orgánica (MgSO₄) y el disolvente se retiró por evaporación para producir 13 mg de ácido 2-[(4-{3-[butil(2,3-dimetoxibencil)amino]-3-oxopropil}fenoxi)metil]benzoico (rendimiento 89%).

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.89-0.95 (m, 3H), 1.24-1.35 (m, 2H), 1.48-1.57 (m, 2H), 2.62, 2.69 (t, t, 2H), 2.95, 3.01 (t, t, 2H), 3.17, 3.36 (t, t, 2H), 3.83, 3.85, 3.88, 3.89 (s, s, s, s, 6H), 4.48, 4.71 (s, s, 2H), 5.50, 5.52 (s, s, 2H), 6.62, 6.75 (d, d, 1H), 6.84-6.97 (m, 3H), 7.00-7.04 (m, 1H), 7.11, 7.19 (d, d, 2H), 7.38-7.42 (m, 1H), 7.56-7.60 (m, 1H), 7.78 (t, 1H) y 8.04-8.07 (m, 1H).

¹³C NMR (rotámetros, 125 MHz, CDCl₃): δ 13.76, 13.85, 20.02, 20.21, 29.55, 30.30, 30.69, 30.84, 30.96, 35.13, 35.34, 42.60, 46.17, 46.37, 47.20, 55.69, 55.75, 60.35, 61.74, 68.20, 111.23, 111.79, 114.88, 114.96, 118.79, 120.88, 124.15, 124.21, 126.81, 127.18, 127.26, 129.46, 130.51, 131.25, 131.52, 133.23, 133.65, 140.59, 146.50, 147.17, 152.48, 152.61, 157.02, 157.10, 170.79, 172.93 y 173.25.

Ejemplo 8

a) *N*-(2,3-Dimetoxibencil)-*N*-heptilamina (0.70 g, 2.65 mmol) se disolvió en DMF (10 ml), se agregó ácido 3-(4-hidroxifenil)propanoico (0.4 g, 2.41 mmol), y la mezcla se enfrió a 0°C. Se agregaron *N*-[(1*H*-1,2,3-benzotriazol-1-iloxi)(dimetilamino)metilen]-*N*-metilmetanaminio tetrafluoroborato (0.85 g, 2.65 mmol) y diisopropiletilamina (0.65 g, 5.05 mmol). La mezcla se dejó calentar a temperatura de la sala y se agitó de un día para otro. Se agregó EtOAc (15 ml) y la fase orgánica se lavó con dos porciones de carbonato hidrogenado de sodio (aq., 10 ml). El EtOAc se

T10 109

retiró mediante evaporación y el crudo se purificó por HPLC preparativa (iniciada con acetonitrilo/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%, la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El disolvente se retiró por evaporación y produjo 0.98 gramos de *N*-(2,3-dimetoxibencil)-*N*-heptil-3-(4-hidroxifenil)propanamida (rendimiento 70%).

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.85-0.89 (m, 3H), 1.20-1.30 (m, 8H), 1.47-1.56 (m, 2H), 2.62, 2.67 (t, t, 2H), 2.89, 2.95 (t, t, 2H), 3.14, 3.33 (t, t, 2H), 3.79, 3.80, 3.84, 3.85 (s, s, s, s, 6H), 4.45, 4.69 (s, s, 2H), 6.58, 6.68 (d, d, 1H), 6.74-6.88 (m, 3H) y 6.96-7.05 (m, 3H).

b) *N*-(2,3-dimetoxibencil)-*N*-heptil-3-(4-hidroxifenil)propanamida 0.196 g, 0.47 mmol) y metil 2-(bromometil)benzoato (0.12 g, 0.52 mmol) se disolvieron en acetonitrilo (10 ml) y se agregó carbonato de potasio (131 mg, 0.95 mmol). La mezcla se agitó a 60° C durante tres horas. Se agregó trisamina con soporte polimérico (0.3 eqv) y se agitó de un día para otro. El polímero se extrajo por filtración, el disolvente se eliminó por evaporación, adición de EtOAc (10 ml) y la fase orgánica se lavó con tres porciones de agua. Luego de secar el crudo (MgSO₄) y después de haber retirado el disolvente por evaporación, el crudo se purificó por HPLC preparativa (iniciada con acetonitrilo/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%; la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Las fracciones que contenían el producto se agruparon y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos

porciones de salmuera y se secó (MgSO_4). El retiro del disolvente por evaporación produjo 39 mg de metil 2-[(4-{3-[(2,3-dimetoxibencil)(heptil)amino]-3-oxopropil}fenoxi)metil]benzoato (rendimiento 14.6%).

^1H NMR (rotámetros, 500 MHz, CDCl_3): δ 0.86-0.89 (m, 3H), 1.19-1.30 (m, 8H), 1.46-1.55 (m, 2H), 2.60, 2.66 (t, t, 2H), 2.93, 2.98 (t, t, 2H), 3.14, 3.33 (t, t, 2H), 3.80, 3.83, 3.86, 3.87, 3.90, 3.91 (s, s, s, s, s, s, 9H), 4.45, 4.68 (s, s, 2H), 5.48, 5.49 (s, s, 2H), 6.59, 6.73 (d, d, 1H), 6.81-7.01 (m, 4H) 7.08, 7.16 (d, d, 2H) 7.35-7.39 (m, 1H), 7.53-7.57 (m, 1H), 7.76 (t, 1H) y 8.01-8.04 (m, 1H).

c) Metil 2-[(4-{3-[(2,3-dimetoxibencil)(heptil)amino]-3-oxopropil}fenoxi)metil]-benzoato (39 mg, 0.069 mmol) se disolvió en THF/agua (2/1, 2 ml) y se agregó LiOH (3.3 mg, 0.14 mmol). La reacción se realizó en un horno microondas de un solo nódulo (150° C, 7 min). El desarrollo se hizo agregando EtOAc (10 ml) y lavando la fase orgánica con dos porciones de HCl (2 X 5 ml, 1 M). Se secó la fase orgánica (MgSO_4) y el disolvente se retiró por evaporación para producir 30 mg se ácido 2-[(4-{3-[(2,3-dimetoxibencil)(heptil)-amino]-3-oxopropil}fenoxi)metil]benzoico (rendimiento 78.9).

^1H NMR (rotámetros, 500 MHz, CDCl_3): δ 0.84-0.87 (m, 3H), 1.20-1.28 (m, 8H), 1.45-1.55 (m, 2H), 2.63, 2.69 (t, t, 2H), 2.93, 2.99 (t, t, 2H), 3.13, 3.33 (t, t, 2H), 3.79, 3.81, 3.84, 3.85 (s, s, s, s, 6H), 4.45, 4.69 (s, s, 2H), 5.52, 5.53 (s, s, 2H), 6.60, 6.72 (d, d, 1H), 6.79-7.01 (m, 4H) 7.08, 7.16 (d, d, 2H) 7.36-7.41 (m, 1H), 7.55-7.60 (m, 1H), 7.79 (t, 1H) y 8.13-8.16 (m, 1H).

^{13}C NMR (rotámetros, 125 MHz, CDCl_3): δ 14.04, 22.52, 22.56, 26.77, 26.96, 27.45, 28.60, 28.92, 29.03, 30.83, 30.97, 31.66, 31.75, 35.16, 35.36, 42.61, 46.42, 46.46, 47.45, 55.69, 55.75, 60.35, 60.73, 68.19, 111.26, 111.83, 114.88, 114.95, 118.84, 120.91, 124.14, 124.20, 126.85, 127.15,

127.22, 129.46, 130.52, 131.26, 131.51, 133.19, 133.66, 140.61, 146.59, 147.19, 152.48, 152.60, 157.02, 157.11, 170.77, 172.92 y 173.23.

Ejemplo 9

a) *N*-(3-etoxipropil)-*N*-(4-isopropilbencil)amina

Se disolvió *p*-iso-propilbenzaldehído (1.007 g, 6.798 mmol) en metanol (5 ml). Se agregó ortoformato de trimetilo (5 ml). A continuación se agregó 3-etoxipropilamina (681 mg, 6.6 mmol) y se siguió por ácido acético (0.2 ml). Luego de reposar a temperatura de la sala de un día para otro, se agregó DCM (5 ml) y se siguió por borohidruro en un soporte polimérico (5.28 g, 13.2 mmol). La muestra se agitó a temperatura de la sala durante 4 días y luego se filtró. El filtrado se evaporó. El residuo se disolvió en acetonitrilo, se dividió luego en dos porciones y se cargó en 2 columnas (ISOLUTE® PRS, 10g/70 ml, humectadas con acetonitrilo). Se eluyó con acetonitrilo, luego metanol y luego metanol (NH₃ sat.). Las fracciones del producto se combinaron y se evaporaron. Se obtuvo un producto oleoso 1.283 g, rendimiento 83%.

¹H NMR (300 MHz, CDCl₃): δ 1.19 (t, 3H), 1.25 (d, 6H), 1.75-1.84 (m, 2H), 2.73 (t, 2H), 2.85-2.94 (m, 1H), 3.43-3.52 (m, 4H), 3.75 (s, 2H), 7.18 (d, 2H) y 7.24 (d, 2H).

b) *N*-(3-etoxipropil)-*N*-(4-isopropilbencil)amina (0.62 g, 2.65 mmol) se disolvió en DMF (10 ml), se agregó ácido 3-(4-hidroxifenil)propanoico (0.4 g, 2.41 mmol), y la mezcla se enfrió a 0° C. Se agregaron *N*-[(1*H*-1,2,3-benzotriazol-1-iloxi)(dimetilamino)-metilen]-*N*-metilmetanaminio tetrafluoroborato (0.85 g, 2.65 mmol) y diisopropiletilamina (0.65 g, 5.05 mmol). La mezcla se dejó calentar a temperatura de la sala y se agitó de un día para otro. Se agregó EtOAc (15 ml) y la fase orgánica se lavó con dos porciones de carbonato hidrogenado de sodio (aq., 10 ml). El EtOAc se retiró mediante evaporación y el crudo se purificó por HPLC preparativa

12
/

(iniciada con acetonitrilo/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%, la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El disolvente se retiró por evaporación y produjo 1.0 gramos de *N*-(3-etoxipropil)-3-(4-hidroxifenil)-*N*-(4-isopropilbencil)propanamida (rendimiento 75.8%).

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 1.16-1.21 (m, 3H), 1.26, 1.27 (d, 6H), 1.75-1.80, 1.84-1.90 (m, m, 2H), 2.64, 2.74 (t, t, 2H), 2.86-3.00 (m, 3H), 3.33, 3.37 (t, t, 2H), 3.41-3.50 (m, 4H), 4.43, 4.62 (s, s, 2H), 6.80-6.84 (m, 2H) y 6.97-7.22 (m, 6H).

c) *N*-(3-etoxipropil)-3-(4-hidroxifenil)-*N*-(4-isopropilbencil)propanamida (0.18 g, 0.47 mmol) y metil 2-(bromometil)benzoato (0.12 g, 0.52 mmol) se disolvieron en acetonitrilo (10 ml) y se agregó carbonato de potasio (131 mg, 0.95 mmol). La mezcla se agitó a 60°C durante tres horas. Se agregó trisamina con soporte polimérico (0.3 eqv) y se agitó de un día para otro. El polímero se extrajo por filtración, el disolvente se eliminó por evaporación, la adición de EtOAc (10 ml) y la fase orgánica se lavó con tres porciones de agua. Luego de secar el crudo (MgSO₄) y haberse retirado el disolvente por evaporación, se purificó el crudo por HPLC preparativa (iniciada con acetonitrilo/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%); la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El retiro del disolvente por evaporación produjo 0.16 gramos de metil 2-[(4-{3-[(3-etoxipropil)(4-

isopropilbencil)amino]-3-oxopropil} fenoxi)metil]benzoato (rendimiento 63.5%).

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 1.17, 1.21 (t, t, 3H), 1.27, 1.28 (d, d, 6H), 1.75-1.80, 1.84-1.89 (m, m, 2H), 2.63, 2.73 (t, t, 2H), 2.89-3.04 (m, 3H), 3.32, 3.37 (t, t, 2H), 3.41-3.50 (m, 4H), 3.93, 3.94 (s, s, 3H), 4.46, 4.61 (s, s, 2H), 5.51, 5.53 (s, s, 2H), 6.92, 6.95 (d, d, 2H), 7.04-7.22 (m, 6H), 7.40 (t, 1H), 7.58 (t, 1H), 7.78-7.80 (m, 1H) y 8.05-8.07 (m, 1H).

d) Metil 2-[(4-{3-[(3-etoxipropil)(4-isopropilbencil)amino]-3-oxopropil} fenoxi)-metil]benzoato (0.16 g, 0.30 mmol) se disolvió en THF/agua (2/1, 2 ml) y se agregó LiOH (14.4 mg, 0.60 mmol). La reacción se efectuó en un horno microondas de un solo nódulo (150° C, 7 min). El desarrollo se hizo agregando EtOAc (10 ml) y lavando la fase orgánica con dos porciones de HCl (2 X 5 ml, 1 M). Se secó la fase orgánica (MgSO₄) y el disolvente se retiró por evaporación para producir 0.108 gramos de ácido 2-[(4-{3-[(3-etoxipropil)(4-isopropilbencil)amino]-3-oxopropil} fenoxi)metil]benzoico (rendimiento 69.3%).

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 1.15, 1.19 (t, t, 3H), 1.23-1.25 (m, 6H), 1.74-1.79, 1.84-1.89 (m, m, 2H), 2.66, 2.76 (t, t, 2H), 2.86-3.03 (m, 3H), 3.30, 3.36 (t, t, 2H), 3.40-3.50 (m, 4H), 4.44, 4.61 (s, s, 2H), 5.55, 5.56 (s, s, 2H), 6.90-6.94 (m, 2H), 7.02-7.20 (m, 6H), 7.40 (t, 1H), 7.57-7.60 (m, 1H), 7.79-7.82 (m, 1H) y 8.15-8.18 (m, 1H).

¹³C NMR (rotámetros, 125 MHz, CDCl₃): δ 15.15, 23.98, 27.78, 28.61, 30.93, 31.01, 33.73, 35.07, 35.38, 43.86, 44.13, 47.96, 51.26, 66.06, 66.22, 66.82, 67.98, 68.13, 114.77, 126.03, 126.38, 126.72, 126.97, 127.90, 129.31, 131.31, 132.88, 133.23, 133.39, 133.84, 134.56, 140.30, 140.38, 147.71, 148.05, 156.90, 170.48, 173.02 y 173.26.

114
X**Ejemplo 10****a) N-(2,4-difluorobencil)-N-propilamina**

2,4-Difluorbenzaldehído (1.003 g, 7.055 mmol) se disolvió en metanol (5 ml). Se agregó ortoformato de trimetilo (5 ml). A continuación se agregó propilamina (401 mg, 6.784 mmol) y se siguió por ácido acético (0.2 ml). Luego de 1 hora, se agregó DCM (5 ml) y se siguió por borohidruro con soporte polimérico (2.5mmol/g, 5.42 g, 13.55 mmol). La muestra se agitó a temperatura de la sala durante 4 días y luego se filtró. El filtrado se evaporó. El residuo se disolvió en acetonitrilo, se dividió luego en dos porciones y se cargó en dos columnas (ISOLUTE®PRS, 10g/70 ml, humectadas con acetonitrilo). Se eluyó con acetonitrilo, luego metanol y luego metanol (NH₃ sat.). Las fracciones del producto se combinaron y se evaporaron. Se obtuvo un producto oleoso (892 mg), rendimiento 71%.

¹H NMR (400 MHz, CDCl₃): δ 0.91 (t, 3H), 1.47-1.56 (m, 2H), 2.57 (t, 2H), 3.79 (s, 2H), 6.75-6.85 (m, 2H) y 7.27-7.33 (m, 1H).

b) N-(2,4-difluorobencil)-3-(4-hidroxifenil)-N-propilpropanamida

Ácido 3-(4-Hidroxifenil)propionico (245 mg, 1.474 mmol) en DMF (5 ml) se enfrió en un baño helado. Se agregó N-(2,4-difluorobencil)-N-propilamina (300.4 mg, 1.622 mmol) y luego TBTU (521 mg, 1.622 mmol) seguido por DIPEA (400 mg, 3.096 mmol). La mezcla se agitó a temperatura de la sala de un día para otro. Se agregó solución acuosa de carbonato hidrogenado de sodio (sat.). La mezcla se extrajo con acetato de etilo (x2). Los extractos se combinaron y se secaron (sulfato de magnesio) y se evaporaron. Cromatografía del residuo en una columna (ISOLUTE® SI, 5g/25 ml) usando DCM/heptano (50:50), DCM y luego MeOH/DCM (1:99, luego 2:98) como eluyente produjo 336 mg del producto deseado, rendimiento 68%.

¹H NMR (rotámetros, 300 MHz, CDCl₃): δ 0.82-0.88 (m, 3H), 1.45-1.58 (m, 2H), 2.59, 2.65 (t, t, 2H), 2.88-2.98 (m, 2H), 3.11, 3.27 (t, t, 2H), 4.40, 4.59 (s, s, 2H), 6.71-7.03 (m, 6H), 7.07-7.16 (m, 1H) y 7.79 (s, br, 1H).

c) Metil 2-[(4-{3-[(2,4-difluorobencil)(propil)amino]-3-oxopropil} fenoxi) metil]benzoato

N-(2,4-Difluorobencil)-3-(4-hidroxifenil)-*N*-propilpropanamida (290 mg, 0.87 mmol) se disolvió en acetonitrilo (10 ml). Se agregó éster metílico de ácido 2-bromometil-benzoico (209 mg, 0.913 mmol) seguido por carbonato de potasio anhidro (180 mg, 1.305 mmol). La mezcla se calentó a reflujo de un día para otro y luego se evaporó a sequedad. Se agregaron agua y acetato de etilo y las dos fases se separaron. Se secó la fase orgánica (sulfato de magnesio) y se evaporó. Cromatografía del residuo en una columna (ISOLUTE®SI, 20g/70ml) usando DCM y luego MeOH/DCM (1:99) como eluyente produjo 184 mg del producto deseado, rendimiento 44%.

¹H NMR (rotámetros, 500 MHz, CDCl₃): δ 0.85-0.92 (m, 3H), 1.52-1.60 (m, 2H), 2.61, 2.68 (t, t, 2H), 2.95-3.01 (m, 2H), 3.15, 3.32 (t, t, 2H), 3.92, 3.93 (s, s, 3H), 4.45, 4.62 (s, s, 2H), 5.51, 5.52 (s, s, 2H), 6.77-6.86 (m, 2H), 6.92-6.99, 7.23-7.27 (m, m, 3H), 7.12, 7.16 (d, d, 2H), 7.38-7.42 (m, 1H), 7.57 (t, 1H) 7.78 (d, 1H) y 8.04-8.07 (m, 1H).

d) Ácido 2-[(4-{3-[(2,4-difluorobencil)(propil)amino]-3-oxopropil} fenoxi) metil]benzoico

Una mezcla de metil 2-[(4-{3-[(2,4-difluorobencil)(propil)amino]-3-oxopropil} fenoxi)-metil]benzoato (0.184 g, 0.382 mmol) e hidróxido de litio (0.018 g, 0.76 mmol) en THF (2 ml) y agua (2 ml) se calentó a 150 grados durante 7 minutos. La mezcla se diluyó con agua, se acidificó con ácido clorhídrico y se extrajo con cloruro de metileno. Los extractos combinados se secaron con sulfato de magnesio y se evaporaron para

producir ácido 2-[(4-{3-[(2,4-difluorobencil)(propil)amino]-3-oxopropil} fenoxi)metil]benzoico.

¹HNMR (400 MHz, CDCl₃): δ 0.85 (t, 3), 1.4-1.6 (m, 2), 2.6-2.7 (m, 2), 2.9-3.0 (m, 2), 3.05-3.15 y 3.25-3.35 (multipletes, rotámeros, 2), 4.4 y 4.6 (singletes, rotámeros, 2), 5.5 (m, 2), 6.7-6.8 (m, 2), 6.9-7.0 (m, 2), 7.05-7.2 (m, 2), 7.4 (t, 1), 7.6 (t, 1), 7.8 (d, 1), 8.15 (d, 1).

Ejemplo 11

a) Metil 2-([4-(2-{etil[4-(trifluorometil)bencil]amino}-2-oxoetil)fenil]tio} metil)benzoato

Etil [4-(trifluorometil)bencil]amina (284 mg, 1.40 mmol) y ácido (4-{[2-(metoxicarbonil)bencil]tio}fenil)acético (443 mg, 1.40 mmol, véase Ejemplo 2 b) se mezclaron en DMF (15 ml). Se agregó TBTU (472 mg, 1.47 mmol) y luego DIPEA (190 mg, 1.47 mmol). La mezcla se agitó a temperatura de la sala durante 1 hora. Se agregó EtOAc (20 ml). La mezcla se lavó entonces con solución acuosa de carbonato hidrogenado de sodio (sat.), 1% HCl, agua (x2) y salmuera, se secó con sulfato de magnesio y se evaporó. Quedó el compuesto del título (663 mg), rendimiento 94%.

¹H NMR (rotámeros, 500 MHz, CDCl₃): δ 1.08-1.15 (m, 3H), 3.31, 3.45 (q, q, 2H), 3.63, 3.76 (s, s, 2H), 3.92 (s, 3H), 4.52-4.66 (m, 4H), 7.09-7.40 (m, 8H), 7.56, 7.62 (d, d, 2H) y 7.94 (d, 2H).

b) Ácido 2-([4-(2-{etil[4-(trifluorometil)bencil]amino}-2-oxoetil)fenil]tio} metil)benzoico

Metil 2-([4-(2-{etil[4-(trifluorometil)bencil]amino}-2-oxoetil)fenil]tio} metil) benzoato (640 mg, 1.276 mmol) se disolvió en THF (20 ml). Se agregó hidróxido de litio (61 mg, 2.552 mmol) en agua (10 ml). La mezcla se agitó a temperatura de la sala y la reacción fue seguida por LC-MS.

117
X
X
X

Después de 24 horas, se agregaron más hidróxido de litio (30 mg) y agua (10 ml). Luego de un total de 70 horas, la LC-MS mostró que la reacción había concluido. La mezcla se evaporó para retirar THF. El residuo se lavó con éter dietílico, luego se acidificó con 10% HCl, pH=2, y se extrajo con EtOAc (x2). Los extractos se combinaron y se lavaron con salmuera, se secaron con sulfato de magnesio y se evaporaron. Cromatografía del residuo en una columna (ISOLUTE SI, 5g/25 ml), usando DCM y luego MeOH/DCM (0.5:99.5, luego 1:99) como eluyente, produjo el compuesto del título (510 mg), rendimiento 82%.

¹H NMR (rotámetros, 300 MHz, CDCl₃): δ 1.07-1.15 (m, 3H), 3.31, 3.45 (q, q, 2H), 3.64, 3.77 (s, s, 2H), 4.54 (s, 2H), 4.55, 4.66 (s, s, 2H), 7.05-7.40 (m, 8H), 7.55, 7.60 (d, d, 2H) y 7.97 (d, 2H).

¹³C NMR (rotámetros, 75 MHz, CDCl₃): δ 12.60, 13.80, 38.17, 38.25, 40.00, 40.44, 41.63, 42.40, 47.94, 50.61, 118-134 (multiplete complejo), 140.32, 140.70, 141.50, 170.48 171.20.

Ejemplo 12

Ácido 2-[(4-{2-[etil(2-fluorobencil)amino]-2-oxoetil}fenoxi)metil]benzoico.

a) *N*-(2-Fluorobencil)etanamina (0.554 g, 3.615 mmol) se disolvió en DMF (10 ml). Se agregó ácido (4-hidroxifenil)acético (0.500 g, 3.286) y la mezcla se enfrió a 0°C. Se agregaron *N*-[(1*H*-1,2,3-benzotriazol-1-iloxi)(dimetilamino)metilen]-*N*-metilmetanaminio tetrafluoroborato (1.161 g, 3.615 mmol) y *N*-etil-*N,N*-diisopropilamina (0.892 g, 6.901 mmol). La solución se agitó de un día para otro a temperatura de la sala. Se agregó EtOAc (20 ml) y la fase orgánica se lavó con dos porciones de Na₂CO₃ (2 X 20 ml, aq.). La fase orgánica se secó (MgSO₄) y el disolvente se retiró por evaporación. El crudo se purificó por HPLC preparativa (iniciada con acetonitrilo isocrático/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%, la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto, y el acetonitrilo se retiró por

118

evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO_4) y el disolvente se retiró por evaporación para producir 0.69 g de *N*-etil-*N*-(2-fluorobencil)-2-(4-hidroxifenil)acetamida (rendimiento 73.1%).

$^1\text{HNMR}$ (Rotámetros, 500 MHz, CDCl_3): δ 1.12 (m, 3H), 3.35-3.5 (m, 2H), 3.62-3.72 (m, 2H), 4.57-4.78 (m, 2H), 6.7 (t, 2H), 6.98-7.38 (m, 6H).

b) *N*-Etil-*N*-(2-fluorobencil)-2-(4-hidroxifenil)acetamida (0.381 g, 1.327 mmol) y metil 2-(bromometil)benzoato (0.334 g, 1.460 mmol) se disolvieron en acetonitrilo (10 ml) y se agregó carbonato de potasio (0.367 g, 2.654 mmol). La mezcla se agitó a 65° C durante tres horas. Cuando se consumió la *N*-etil-*N*-(2-fluorobencil)-2-(4-hidroxifenil)acetamida, se agregó PS-trisamina (0.3 eqv) y la solución se agitó de un día para otro a temperatura de la sala. El polímero se extrajo por filtración y se eliminó acetonitrilo por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de agua, se secó (MgSO_4) y el disolvente se retiró por evaporación para producir 0.545 g de metil 2-[(4-{2-[etil(2-fluorobencil)amino]-2-oxoetil}fenoxi)metil]benzoato (rendimiento 94.3%).

$^1\text{HNMR}$ (Rotámetros, 300 MHz, CDCl_3): δ 1.12 (m, 3H), 3.23-3.35 (m, 2H), 3.6-3.75 (m, 2H), 3.88 (s, 3H), 4.45-4.70 (m, 2H), 5.45 (s, 2H), 6.84-7.35 (m, 9H), 7.5 (t, 1H), 7.72 (d, 1H), 8.0 (d, 1H).

c) Metil 2-[(4-{2-[etil(2-fluorobencil)amino]-2-oxoetil}fenoxi)metil]benzoato (0.545 g, 1.251 mmol) se disolvió en EtOH (5 ml) y se agregó hidróxido de potasio (0.105 g, 1.877 mmol). La reacción se efectuó en un horno microondas de un solo nódulo (7 min, 150° C). El desarrollo se efectuó retirando el solvente por evaporación, adición de HCl (20 ml, 1 M) y la fase acuosa se lavó con dos porciones de EtOAc (20 ml). Se agruparon las fases orgánicas y el disolvente se retiró por evaporación. El crudo se purificó por HPLC preparativa (comenzando con acetonitrilo isocrático/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%, la solución amortiguadora fue una

mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El disolvente se retiró por evaporación para producir 0.124 g de ácido 2-[(4-{2-[etil(2-fluorobencil) amino]-2-oxoetil}fenoxi)metil]benzoico (23.5%).

¹HNMR (Rotámetros, 500 MHz, CDCl₃): δ 1.12 (m, 3H), 3.25-3.5 (m, 2H), 3.65-3.8 (m, 2H), 4.5-4.75 (m, 2H), 5.52 (m, 2H), 6.84-7.45 (m, 9H), 7.55 (t, 1H), 7.78 (d, 1H), 8.13 (d, 1H).

Ejemplo 13

Ácido 2-[(4-{3-[etil(2-fluorobencil)amino]-3-oxopropil}fenoxi)metil]benzoico.

a) *N*-(2-Fluorobencil)etanamina (0.554 g, 3.615 mmol) se disolvió en DMF (10 ml). Se agregó ácido 3-(4-hidroxifenil)propanoico (0.546 g, 3.286 mmol) y la mezcla se enfrió a 0°C. Se agregaron *N*-[(1*H*-1,2,3-benzotriazol-1-iloxi)(dimetilamino)-metilen]-*N*-metilmetanaminio tetrafluoroborato (1.161 g, 3.615 mmol) y *N*-etil-*N,N*-diisopropilamina (0.892 g, 6.901 mmol). La solución se agitó de un día para otro a temperatura de la sala. Se agregó EtOAc (20 ml) y la fase orgánica se lavó con dos porciones de Na₂CO₃ (2 X 20 ml, aq.). La fase orgánica se secó (MgSO₄) y el disolvente se retiró por evaporación. El crudo se purificó por HPLC preparativa (iniciando con acetonitrilo isocrático/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%, la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄) y luego el disolvente se eliminó por evaporación para producir 0.803 g de *N*-etil-*N*-(2-fluorobencil)-3-(4-hidroxifenil)propanamida (rendimiento 81.1%).

¹HNMR (Rotámetros, 500 MHz, CDCl₃): δ 1.1 (m, 3H), 2.58-2.72 (m, 2H), 2.83-3.0 (m, 2H), 3.2-3.5 (m, 2H), 4.45-4.7 (m, 2H), 6.78 (t, 2H), 6.95-7.35 (m, 6H).

b) *N*-Etil-*N*-(2-fluorobencil)-3-(4-hidroxifenil)propanamida (0.400 g, 1.327 mmol) y metil 2-(bromometil)benzoato (0.334 g, 1.460 mmol) se disolvieron en acetonitrilo (10 ml) y se agregó carbonato de potasio (0.367 g, 2.654 mmol). La mezcla se agitó a 65° C durante tres horas. Cuando se consumió la *N*-etil-*N*-(2-fluorobencil)-2-(4-hidroxifenil)acetamida, se agregó PS-trisamina (0.3 eqv) y la solución se agitó de un día para otro a temperatura de la sala. El polímero se extrajo por filtración y el acetonitrilo se eliminó por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de agua, se secó (MgSO₄) y el disolvente se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones en agua, se secó (MgSO₄) y el disolvente se retiró por evaporación. El crudo se purificó por HPLC preparativa (iniciando con acetonitrilo isocrático/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%, la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El disolvente se retiró por evaporación para producir 0.454 g de metil 2-[(4-{3-[etil(2-fluorobencil)amino]-3-oxopropil}fenoxi)metil]-benzoato (rendimiento 76.1%).

¹HNMR (Rotámetros, 400 MHz, CDCl₃): δ 1.08 (m, 3H), 2.52-2.68 (m, 2H), 2.9-3.03 (m, 2H), 3.18-3.45 (m, 2H), 3.88 (s, 3H), 4.45-4.7 (m, 2H), 5.45 (s, 2H), 6.82-7.28 (m, 8H), 7.36 (t, 1H), 7.53 (t, 1H), 7.73 (d, 1H), 8.0 (d, 1H).

c) Metil 2-[(4-{3-[etil(2-fluorobencil)amino]-3-oxopropil}fenoxi)metil]-benzoato (0.454 g, 1.001 mmol) se disolvió en EtOH (5 ml) y se agregó

121
227

hidróxido de potasio (0.085 g, 1.514 mmol). La reacción se efectuó en un horno microondas de un solo nódulo (7 min, 150° C). El desarrollo se efectuó retirando el disolvente por evaporación, adición de HCl (20 ml, 1 M) y la fase acuosa se lavó con dos porciones de EtOAc (20 ml). Se agruparon las fases orgánicas y el disolvente se retiró por evaporación. El crudo se purificó por HPLC preparativa (iniciando con acetonitrilo isocrático/solución amortiguadora 60/40 y luego se aumentó la concentración de acetonitrilo a 100%, la solución amortiguadora fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0.1 M, columna KR-100-7-C8, 50 mm X 250 mm, flujo 40 ml/min). Se agruparon las fracciones que contenían el producto y el acetonitrilo se retiró por evaporación. Se agregó EtOAc (10 ml) y la fase orgánica se lavó con dos porciones de salmuera y se secó (MgSO₄). El disolvente se retiró por evaporación para producir 0.079 g de ácido 2-[(4-{3-[etil(2-fluorobencil)amino]-3-oxopropil}-fenoxi)metil]benzoico (18.0%).

¹HNMR (Rotámetros, 500 MHz, CDCl₃): δ 1.12 (m, 3H), 2.60-2.75 (m, 2H), 3.03 (m, 2H), 3.23-3.50 (m, 2H), 4.45-4.73 (m, 2H), 5.57 (s, 2H), 6.88-7.35 (m, 8H), 7.41 (t, 1H), 7.60 (t, 1H), 7.80 (d, 1H), 8.18 (d, 1H).

Los siguientes Ejemplos se prepararon en una manera similar.

Ejemplo 14

Ácido 2-{[(3-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil}fenil)tio]metil}benzoico.

Ejemplo 15

Ácido 2-{[(4-{2-[(4-clorobencil)(etil)amino]-2-oxoetil}fenil)tio]metil}benzoico.

Actividad Biológica

Formulaciones

Los compuestos se disolvieron en DMSO para obtener soluciones madre de 16 mM. Antes de los análisis, las soluciones madre se diluyeron aún más en DMSO y medio de cultivo.

122
121

PRODUCTOS QUÍMICOS Y REACTIVOS GENERALES

El reactivo para ensayo de luciferasa se adquirió de Packard, USA. Las enzimas de restricción fueron de Boehringer y la Vent polimerasa de New England Biolabs.

ESTIRPES CELULARES Y CONDICIONES DEL CULTIVO DE CÉLULAS

U2-OS, (sarcoma osteogénico humano) se adquirió de ATCC, USA. Las células se expandieron y se volvieron a congelar en lotes de número de pasaje seis. Las células se cultivaron en Dulbecco's modified Eagle medium (DMEM) con 25 mM glucosa, 2 mM glutamina o 4 mM L-alanil-L-glutamina, 10% suero fetal bovino, a 5% CO₂. Se utilizó solución salina amortiguada con fosfato (PBS) sin adición de calcio o magnesio. Todos los reactivos para el cultivo de las células fueron de Gibco (USA) y las placas para cultivo de células de 96 pozos se adquirieron de Wallach.

CONSTRUCTOS DE PLÁSMIDO PARA EXPRESIÓN HETERÓLOGA

Se llevaron a cabo técnicas estándar de ADN recombinante como se describe por Ausubel (7). El vector indicador de luciferasa, pGL5UAS (el clon consta de cinco copias de la secuencia de fijación GAL4 DNA, 5'-CGACGGAGTACTGTCCTCCGAGCT-3', clonada en los sitios SacI/XhoI del pGL3-Promoter (Promega). El fragmento SacI/XhoI que portaba los sitios UAS se construyó usando oligonucleótidos traslapantes hibridados.

Los vectores de expresión utilizados se basan en pSG5 (Stratagene). Todos los vectores contienen un fragmento EcoRI/NheI que codifica el dominio de fijación de ADN de GAL4 (que codifica posiciones de aminoácidos 1-145 del número de acceso a la base de datos P04386) seguido por una fusión de inserción a un fragmento que codifica la secuencia de localización nuclear del antígeno T del Polyoma Virus. Las secuencia de localización nuclear se

construyó usando oligonucleótidos traslapantes hibridados que crean extremos pegajosos NheI/KpnI

(5'-CTAGCGCTCCTAGAAGAAACGCAAGGTTGGTAC-3'). Los

dominios de fijación de ligando de PPAR α humano y de ratón y PPAR γ de humano y de ratón se amplificaron por PCR como fragmentos KpnI/BamHI y se clonaron en la inserción al dominio de fijación de ADN GAL4 y la secuencia de localización nuclear. La secuencia de todos los constructos de plásmido utilizadas se confirmaron por secuenciación.

Los siguientes vectores de expresión se utilizaron para transfecciones transitorias:

vector	subtipo PPAR codificado	referencia de secuencia ¹
pSGGALhPPa	PPAR α humano	S74349, nt 625-1530
pSGGALmPPa	PPAR α de ratón	X57638, nt 668-1573
pSGGALhPPg	PPAR γ humano	U63415, nt 613-1518
pSGGALmPPg	PPAR γ de ratón	U09138, nt 652-1577

¹ se refiere a posiciones de nucleótidos de entrada a la base de datos usados para expresar el dominio de fijación de ligando.

TRANSFECCIONES TRANSITORIAS

Cepas congeladas de células de número de pasaje seis se descongelaron y se expandieron a número de pasaje ocho antes de las transfecciones. Se trataron con tripsina las células confluyentes, se lavaron y se microgranularon por centrifugación a 270xg durante 2 minutos. El microgránulo de células se resuspendió en PBS frío a una concentración de células de alrededor de 18×10^6 células/ml. Luego de la adición de ADN, la suspensión de células se incubó en hielo durante aproximadamente 5 minutos antes de la electroporación a 230 V, 960 μ F en Biorad's Gene PulserTM en lotes de 0.5 ml. Se agregó un total de 50 μ g ADN a cada lote

de 0.5 ml células, incluyendo 2.5 µg de vector de expresión, 25 µg de vector indicador y 22.5 µg de ADN no específico (pBluescript, Stratagene).

Luego de la electroporación, las células se diluyeron a una concentración de 320.000 células/ml en DMEM sin rojo fenol, y aproximadamente 25.000 células/pozo se sembraron en placas de 96 pozos. Con el fin de permitir que las células se recuperaran, las placas sembradas se incubaron a 37°C durante 3-4 horas antes de la adición de los compuestos de prueba. En los análisis para detección de PPAR α , el medio de las células se suplementó con suero fetal bovino (FCS) filtrado en resina-carbón con el fin de evitar activación de fondo por los componentes de ácido graso del FCS. El FCS filtrado en resina-carbón fue como sigue: para 500 ml de FCS inactivado por calor, se agregaron 10 g de carbón y 25 g Resina de Intercambio de Aniones Grado Analítico Bio-Rad (Bio-Rad Analytical Grade Anion Exchange Resin) malla 200-400, y la solución se mantuvo en un agitador magnético a temperatura de la sala de un día para otro. Al día siguiente, el FCS se centrifugó y se repitió el procedimiento de filtrado durante 4-6 horas. Luego del segundo tratamiento, el FCS se centrifugó y el filtro se esterilizó con el fin de eliminar los remanentes de carbón y resina.

PROCEDIMIENTO DE ANÁLISIS

Soluciones madre de compuestos en DMSO se diluyeron en rangos de concentración apropiados en placas maestras. De las placas maestras, los compuestos se diluyeron en medio de cultivo para obtener soluciones del compuesto de prueba para dosis finales.

Luego del ajuste de la cantidad de medio de células a 75 µl en cada pozo, se agregaron 50 µl de solución del compuesto de prueba. Células transfectadas transitoriamente se expusieron a los compuestos durante alrededor de 24 horas antes de que se realizara el análisis de detección de la luciferasa. Para análisis de luciferasa, se agregaron manualmente 100 µl de

reactivo de análisis a cada pozo y las placas se dejaron durante aproximadamente 20 minutos con el fin de permitir la lisis de las células. Luego de la lisis, se midió la actividad de la luciferasa en un contador 1420 Multiwell, Victor, de Wallach.

Compuestos de Referencia

La TZD pioglitazona se empleó como sustancia de referencia para la activación del PPAR γ humano y de ratón. Se usó ácido 5,8,11,14-eicosatetrayónico (ETYA) como sustancia de referencia para el PPAR α humano.

Cálculos y análisis

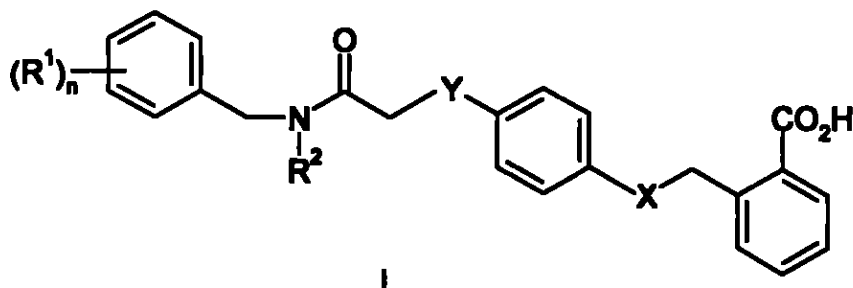
Para el cálculo de los valores EC₅₀, se estableció una curva concentración-efecto. Los valores utilizados se derivaron del promedio de dos o tres mediciones independientes (luego de restar el valor promedio del fondo) y se expresaron como el porcentaje de la activación máxima obtenida por el compuesto de referencia. Los valores se trazaron contra el logaritmo de la concentración del compuesto de prueba. Los valores EC₅₀ se estimaron por intercalación lineal entre los puntos de los datos y calculando la concentración requerida para lograr 50% de la activación máxima obtenida por el compuesto de referencia.

Los compuestos de Fórmula I tienen una EC₅₀ de menos de 50 $\mu\text{mol/l}$ para PPAR α y los compuestos preferidos tienen una EC₅₀ de menos de 5 $\mu\text{mol/l}$. Por ejemplo, las EC₅₀s de algunos de los Ejemplos para PPAR alfa humano son:

Ejemplo 5	0.163 $\mu\text{mol/l}$;
Ejemplo 10	0.168 $\mu\text{mol/l}$;
Ejemplo 11	0.026 $\mu\text{mol/l}$; y
Ejemplo 15	0.027 $\mu\text{mol/l}$.

126
127**Reivindicaciones**

1. Un compuesto de fórmula I



en donde n es 0, 1 ó 2 y R¹ representa halo, un grupo C₁₋₄alquilo el cual se sustituye de manera opcional por uno o más fluoro, un grupo C₁₋₄alcoxi, el cual se sustituye de manera opcional por uno o más fluoro y en donde cuando n es 2 los sustituyentes R¹ pueden ser los mismos o diferentes;

R² representa un grupo C₂₋₈alquilo que se interrumpe de manera opcional por oxígeno

Y está ausente o representa metileno; y

X es O ó S;

y sus sales farmacéuticamente aceptables y profármacos.

2. Un compuesto de acuerdo con la reivindicación 1 en la cual X es O.

3. Un compuesto de acuerdo con la reivindicación 1 en la cual X es S.

4. Un compuesto de acuerdo con cualquier reivindicación precedente en la cual Y es metileno.

5. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1, 2 ó 3 en la cual Y está ausente.

127

6. Un compuesto de acuerdo con cualquier reivindicación precedente en la cual R^1 es halo, un grupo C_{1-4} alquilo o un grupo C_{1-4} alcoxi y n es 0, 1 ó 2.

7. Un compuesto de acuerdo con cualquier reivindicación precedente en la cual R^1 es fluoro, metoxi, o isopropilo cuando n es 1 ó 2.

8. Un compuesto de acuerdo con cualquier reivindicación precedente en la cual n es 0.

9. Un compuesto de acuerdo con cualquier reivindicación precedente en la cual R^2 representa un grupo C_{5-7} alquilo.

10. Un compuesto seleccionado de:

ácido 2-[(4-{3-[bencil(hexil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-{[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenil)tio]metil}benzoico;

ácido 2-[(4-{2-[bencil(hexil)amino]-2-oxoetil} fenoxi)metil]benzoico;

ácido 2-[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-{[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil} fenil)tio]metil}benzoico;

ácido 2-[(4-{3-[butil(2,3-dimetoxibencil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[(2,3-dimetoxibencil)(heptil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[(3-etoxipropil)(4-isopropilbencil)amino]-3-oxopropil} fenoxi)metil]-benzoico;

ácido 2-[(4-{3-[(2,4-difluorobencil)(propil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{2-[etil(2-fluorobencil)amin]-2-oxoetil} fenoxi)metil]benzoico;

129/129

ácido 2-[(4-{3-[etil(2-fluorobencil)amino]-3-oxopropil} fenoxi)metil] benzoico;

ácido 2-({[4-(2-{etil[4-(trifluorometil)bencil]amino}-2-oxoetil)fenil]tio}-metil)benzoico;

ácido 2-{[(3-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenil)tio]metil}benzoico; y

ácido 2-{[(4-{2-[(4-clorobencil)(etil)amino]-2-oxoetil} fenil)tio]metil} benzoico y sus sales farmacéuticamente aceptables.

11. Un compuesto de acuerdo con la reivindicación 2 seleccionado de:

ácido 2-[(4-{3-[bencil(hexil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{2-[bencil(hexil)amino]-2-oxoetil} fenoxi)metil]benzoico;

ácido 2-[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenoxi)metil] benzoico;

ácido 2-[(4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[butil(2,3-dimetoxibencil)amino]-3-oxopropil} fenoxi)metil] benzoico;

ácido 2-[(4-{3-[(2,3-dimetoxibencil)(heptil)-amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[(3-etoxipropil)(4-isopropilbencil)amino]-3-oxopropil} fenoxi)metil]-benzoico;

ácido 2-[(4-{3-[(2,4-difluorobencil)(propil)amino]-3-oxopropil} fenoxi)metil]benzoico;

ácido 2-[(4-{2-[etil(2-fluorobencil)amino]-2-oxoetil} fenoxi)metil]benzoico;

ácido 2-[(4-{3-[etil(2-fluorobencil)amino]-3-oxopropil} fenoxi)metil] benzoico;

y sus sales farmacéuticamente aceptables.

12. Un compuesto de acuerdo con la reivindicación 3 seleccionado de:

ácido 2-{[(4-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil} fenil)tio]metil}benzoico;

ácido 2-{{{4-{3-[(2,4-difluorobencil)(heptil)amino]-3-oxopropil}fenil}tio}metil}benzoico;

ácido 2-{{{4-{2-{etil[4-(trifluorometil)bencil]amino}-2-oxoetil}fenil}tio}-metil}benzoico;

ácido 2-{{{3-{2-[(2,4-difluorobencil)(heptil)amino]-2-oxoetil}fenil}tio}metil}benzoico; y

ácido 2-{{{4-{2-[(4-clorobencil)(etil)amino]-2-oxoetil}fenil}tio}metil}benzoico

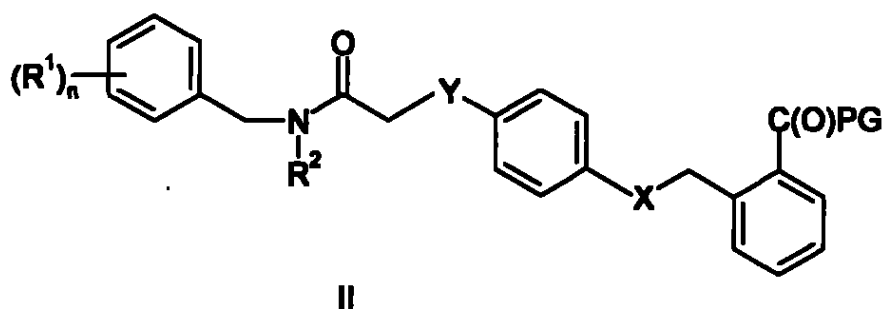
y sus sales farmacéuticamente aceptables.

13. Una formulación farmacéutica que comprende un compuesto de acuerdo con cualquier reivindicación precedente en mezcla con coadyuvantes, diluyentes y/o vehículos farmacéuticamente aceptables.

14. Un método de tratar o prevenir resistencia a la insulina que comprende la administración de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 a un mamífero necesitado del mismo.

15. El uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 en la manufactura de un medicamento para el tratamiento de resistencia a la insulina.

16. Un proceso para preparar un compuesto de fórmula I que comprende hacer reaccionar un compuesto de fórmula II



en la cual R^1 , R^2 , X y Y son como se definen previamente y PG representa un grupo protector para un grupo hidroxí carboxílico con un agente desprotector.

17. Un compuesto de fórmula II como se describe en la reivindicación 16.

18. Un tratamiento de combinación que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 en combinación con otro agente terapéutico que es útil en el tratamiento de trastornos asociados con el desarrollo y evolución de aterosclerosis, hipertensión, hiperlipidemias, dislipidemias, diabetes y obesidad.

130
X

PATENT COOPERATION TREATY

28 JAN 2003

45:90:953

131 TMA
77
1

From the

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Miller, T. K.
ASTRAZENECA
Global Intellectual Property
Mersey, Alderley Park
Macclesfield
Cheshire SK10 4TG
GRANDE BRETAGNE

CODE	DATE	NTD
ANKOM 28 JAN 2004		
NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT		
DATA ENTERED		
FINAL CHECK		

(PCT Rule 71.1)

Date of mailing
(day/month/year)

19/01/2004

Applicant's or agent's file reference

100680-1 WO

IMPORTANT NOTIFICATION

International application No.

PCT/GB03/02584

International filing date (day/month/year)

17/06/2003

Priority date (day/month/year)

20/06/2002

Applicant

ASTRAZENECA AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/

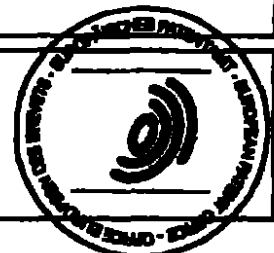


European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523636 epou d
Fax: (+49-89) 2399-4465

Authorized officer

PITTORRU R

Tel. (+49-89) 2399 2828



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalized Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 100680-1-WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB03/02584	International filing date (day/month/year) 17/06/2003	Priority date (day/month/year) 20/06/2002
International Patent Classification (IPC) or national classification and IPC G07G235/34		
Applicant ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

CODE	DATE	NTD
ANKOM 26 JAN 2004 GPS		
DATA ENTERED		
FINAL CHECK		

Date of submission of the demand 08/12/2003	Date of completion of this report 14/01/2004
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epou d Fax: (+49-89) 2399-4465	Authorized officer JONES M H Tel. (+49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No.

PCT/GB03/02584

133
2h

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

PCT REQUEST

1/5

100680-1 WO

Duplicate of original printed on 05.06.2003 12:10:42 PM

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 01.07.2003)
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	100680-1 WO
I	Title of invention	THERAPEUTIC AGENTS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	AP: (GH GM KE LS MW NZ SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR 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 NZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address:	Sodertalje S-151 85 Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No.	+44 1625 230148
II-9	Facsimile No.	+44 1625 510752

PCT REQUEST

2/5

100880-1 WO

Duplicate of original printed on 06.06.2003 12:10:42 PM

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)	LI, Lanna
III-2-5	Address:	AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden
III-2-6	State of nationality	SE
III-2-7	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 Merreside Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
IV-1-3	Telephone No.	+44 1625 230148
IV-1-4	Facsimile No.	+44 1625 510752

PCT REQUEST

3/5

100880-1 WO

Duplicate of original printed on 05.06.2003 12:10:42 PM

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 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-8 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-8	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	20 June 2002 (20.06.2002)
VI-1-2	Number	0201935-4
VI-1-3	Country	SE

PCT REQUEST

4/5

100680-1 WO

Duplicate of original printed on 05.08.2003 12:10:42 PM

VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	20 December 2002 (20.12.2002)	
VI-2-2	Number	0203826-3	
VI-2-3	Country	SE	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	52	-
IX-3	Claims	4	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	62	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-13	Priority document(s)	Item(s) VI-1, VI-2	-
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	Thomas Kerr Miller	
X-1-3	Capacity	Agent	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
------	---	--

138
X

PCT REQUEST

100880-1 WO

Duplicate of original printed on 05.06.2003 12:10:42 PM

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
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

139
The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 100680-1 WO	
International application No. PCT/GB03/02584	International filing date (day/month/year) 17 June 2003 (17.06.2003)	(Earliest) Priority date (day/month/year) 20 June 2002 (20.06.2002)	
Title of invention ORTHO-SUBSTITUTED BENZOIC ACID DERIVATIVES FOR THE TREATMENT OF INSULIN RESISTANCE			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ASTRAZENECA AB SE-151 85 Södertälje Sweden		Telephone No. +44 1625 230148	
		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.) Li, Lanna AstraZeneca R&D Mölndal SE-431 83 Mölndal Sweden			
State (that is, country) of nationality: SE		State (that is, country) of residence: SE	
☒ Further applicants are indicated on a continuation sheet.			

140.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed 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.)*

Thomas Kerr MILLER
ASTRAZENECA
Global Intellectual Property
Meraside, Alderley Park
Macclesfield,
Cheshire, SK10 4TG
GB

Telephone No.

+44 1625 516036

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 filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (<i>specify</i>) | : | sheets |

For International Preliminary
Examining Authority use only

- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|---|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (<i>specify</i>): |
| 4. ☐ copy of general power of attorney;
reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

.....
Thomas Kerr MILLER et al
Global Intellectual Property, Patents, AstraZeneca AB

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due
to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months
from the priority date and item 4 or 5, below, does not apply.

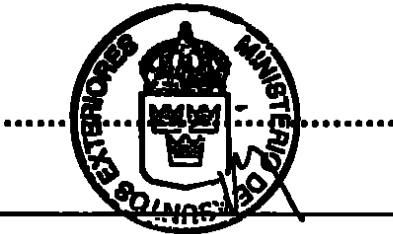
☐ The applicant has been
informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of
Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival
is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

**APOSTILLA****(Convention de La Haye du 5 octobre 1961)****1. Pais: Suecia****El presente documento oficial****2. ha sido firmado por Anne-Marie Bonde****3. en su calidad de Notario Público****4. y lleva el timbre/sello de Notario Público en Estocolmo****Atestado****5. en Estocolmo****6. el 3 de diciembre de 2004****7. de Ministerio de Asuntos Exteriores****8. N° 8681****9. Timbre/Sello****10. Firma**
.....
Eva Topfner Glückman

ASSIGNMENT

The undersigned,
LI, Lanna

domiciled in

AstraZeneca R&D Mölndal, SE-431 83 Mölndal,
Sweden

hereby state under oath to be the sole and true inventor
of

ORTHO-SUBSTITUTED BENZOIC ACID DERIVATIVES FOR THE TREATMENT OF INSULIN
RESISTANCE

state as well that assign, without reservations or
limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of
Sweden

domiciled in

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.

TRASPASO

abajo firmado

domiciliado en

decla bajo juramento ser único y verdadero inventor
de.

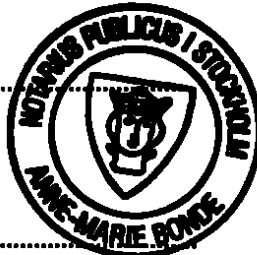
Declaro asimismo que cedo y
transfiero sin reserva ni limitación, a favor de la
sociedad

organizada y existente de conformidad con la leyes de

domiciliada en

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.

.....
LI, Lanna



CERTIFICADO NOTARIAL (INDIVIDUO)

NOTARIAL CERTIFICATE (INDIVIDUAL)

144

A los dos días del mes de diciembre
2004, comparecí personalmente ante mí,
Notario Publico,

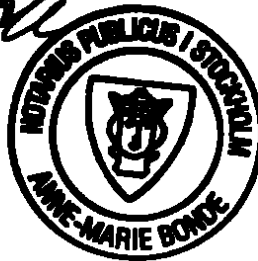
On this day of
2004 personally appeared before me, a Notary Public,

LANNA LI

a quien doy fé de conocer y me consta que
la persona descrita y firmante
del documento que precede, declarado ante mí que
otorga el mismo para los fines y propósitos que
en él se expresan.

to me known and known to me to be the person
described in and who executed the foregoing document,
and duly acknowledged to me that
executed the same for the uses and purposes
therein expressed.

NOTARY PUBLIC (Notario Público)
Anne-Marie Bonde



CERTIFICADO NOTARIAL (INDIVIDUO)

NOTARIAL CERTIFICATE (INDIVIDUAL)

A los días del mes de
2004, comparecí personalmente ante mí,
Notario Publico,

On this day of
2004 personally appeared before me, a Notary Public,

a quien doy fé de conocer y me consta que
la persona descrita y firmante
del documento que precede, declarado ante mí que
otorga el mismo para los fines y propósitos que
en él se expresan.

to me known and known to me to be the person
described in and who executed the foregoing document,
and duly acknowledged to me that
executed the same for the uses and purposes
therein expressed.



145
~~145~~

TRADUCCION DE LOS SELLOS QUE SE ENCUENTRAN EN EL
DOCUMENTO DE CESIÓN DE DERECHOS SOBRE LA INVENCIÓN,
OTORGADO POR LANNA LI, A LA SOCIEDAD ASTRAZENECA AB,
DOMICILIADA EN S-151 85 SÖDERTÄLJE, SUECIA, DEL SUECO AL
CASTELLANO.

ANNE-MARIE BONDE
NOTARIO PÚBLICO DE ESTOCOLMO

Brigard & Castro

BOGOTA - COLOMBIA

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) ASTRAZENECA AB

domiciliado(s) en

domiciled in SE-131-3odertalje, Sweden

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 enseññas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o 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 creyeran conducentes al resguardo de mis (nuestros) intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de confirmar en mi (nuestro) nombre todo lo actuado, así como la facultad de desistir, transigir, comprometer, y 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

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 appropriate to the safeguard of my (our) interest(s) and all the other necessary legal powers.

This power includes the faculty to ratify or confirm, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in Macclesfield, Cheshire,

this 18th day of July 2003

Signature

Name KEVIN BILL

Title Director, IP Services

120816

147

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORP RATION)

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.

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)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

On this 18th day of July 2003 of

to me known, and known to me to be the person who
signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the

ATTORNEY
of
ATRAZENECA 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.

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)

LEGALIZATION BY APOSTILLE IS REQUIRED.

148 P 1

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/stamp de

5. at London/A 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:

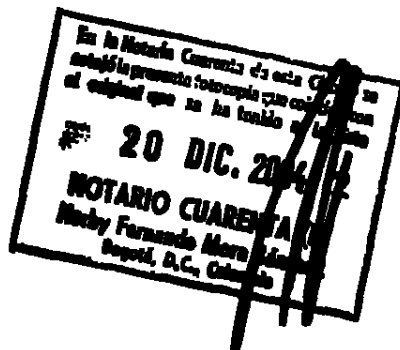
10. Signature: J. Ireland



[Handwritten signature]

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.



149

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 Sodertälje, 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.

AUTENTICACIÓN

(Convención de La Haya del 5 de Octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

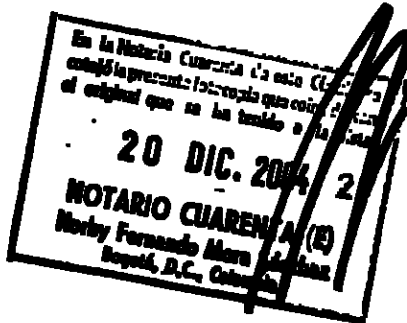
1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
2. Este documento público
 ha sido firmado por **J. B. Hodgson**
3. actuando en capacidad de **Notario Público**
4. lleva el sello de: **Dicho Notario Público**

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.



NOTARIA 32

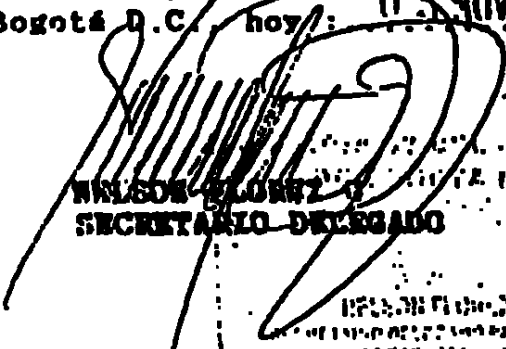
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

152
COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL
CIRCULO DE BOGOTA

CERTIFICO, QUE:

La presente nota es fiel copia del original tomada del registro
civil de defunciones serial indicativo número: ST 6224
que expido en la ciudad de Bogotá D.C. hoy: 11 de mayo de 2004


NELSON BLUM
SECRETARIO DELEGADO

151

SUPERINDUSTRIA Y COMERCIO
Rad cacion 83083518 00000000 Folios 132
Fecha (AMB) 2005-01 18 17 06 41
Tramite 011 PCT-PATENT 379 FASE NACT 411 PRESENTAC
Dependenci 2029 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	✓
Indicación de que solicita la concesión de un patente	()	() ✓
Datos de identificación del solicitante o de la persona que presenta la solicitud	()	() ✓
Descripción de la invención	()	() ✓
Dibujo de objeto pertinente	()	() ✓
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 fotográfica del Diseño Industrial 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 Nueva

Fecha

152

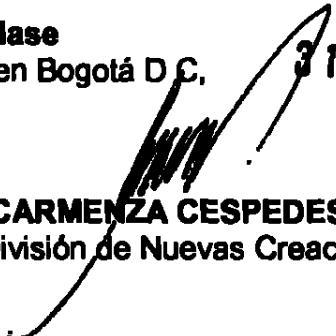
2020
Bogotá D C

Doctor(a)
JUAN PABLO CADENA SARMIENTO
Apoderado(a)
ASTRAZENECA.

REFERENCIA:	Radicación N°	05-3510
	Solicitud internacional	PCT/GB2003/002584
	Fecha límite inicio fase nacional	2005-03-07
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	1888
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía 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 artículo 40 de la Decisión 486.

Cúmplase
Dado en Bogotá D C, 31 ENE. 2005


ALIX CARMENZA CESPEDES DE VERGEL
Jefe División de Nuevas Creaciones (