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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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División de Nuevas Creaciones

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54. **TITULO**

DERIVADOS DEL ACIDO FENILPROPIONICO SUSTITUIDO COMO AGONISTAS DE

RECEPTOR α HUMANO ACTIVADO POR PROLIFERACION DE PEROXISOMAS (PPAR)

51. **CLASIFICACION INTERNACIONAL**

71. **SOLICITANTE**

ASTRAZENECA AB

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SODERTALJE, SUECIA

74. **APODERADO**

RAMIRO CASTRO DUQUE

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

PETITORIO

1

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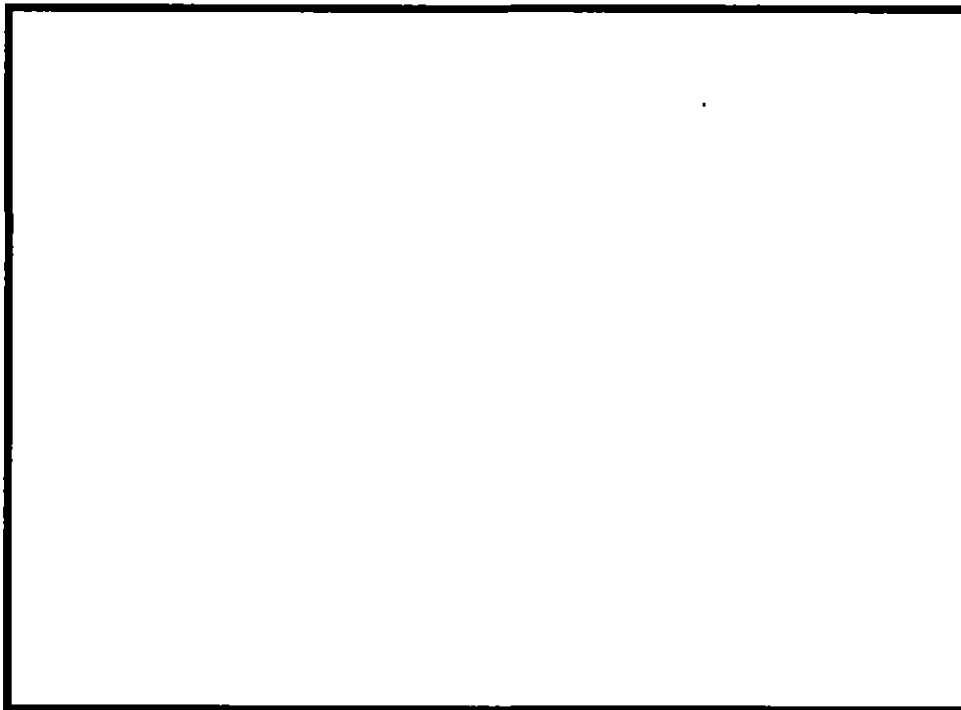
1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: ASTRAZENECA AB Dirección: S-151 85 Sodertälje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail:		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE 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>170.322 TP 1003</u>
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5 PCT (86) Solicitud Internacional No. <u>PCT/GB02/05738</u> Fecha <u>18-12-2002</u> Publicación Internacional No. <u>WO 03/051821 A1</u> Fecha <u>26-06-2003</u>			
Título (54): <u>DERIVADOS DEL ÁCIDO FENILPROPIÓNICO SUSTITUIDO COMO AGONISTAS DE RECEPTOR α HUMANO ACTIVADO POR PROLIFERADOR DE PEROXISOMAS (PPAR)</u>			
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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.			

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$422.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- ☒ Documento de cesión del Invenor 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 Solicitud de concesión de la patente

NOMBRE: RAMIRO CASTRO DUEÑE

FIRMA

C.C. 170.322 de Bogotá T.P. 4003 del C.S.I.

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

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BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	21740989	17/05/2004	22,697,000.00

***** CONCEPTO *****

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

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

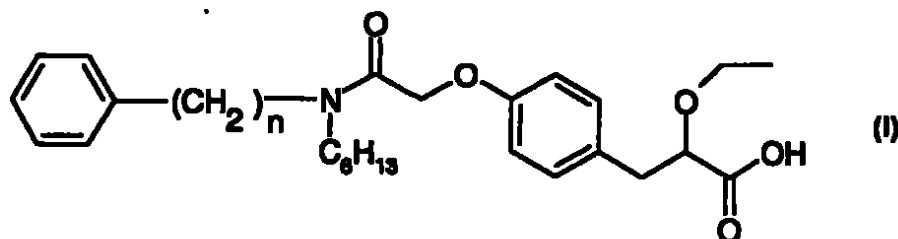
(84) Designated States (regional): ARIPO patent (GH, GM, KR, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI,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

Published:

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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: SUBSTITUTED PHENYLPROPIONIC ACID DERIVATIVES AS AGONISTS TO HUMAN PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR ALPHA (PPAR)



(57) Abstract: The present invention provides the S enantiomer of a compound of formula (I) wherein n is 1 or 2 as well as pharmaceutically acceptable salts, solvates, crystalline forms and prodrugs thereof, to processes for preparing such compounds, to their utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance, to methods for their therapeutic use and to pharmaceutical compositions containing them.

WO 03/051821 A1

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**SUBSTITUTED PHENYLPROPIONIC ACID DERIVATIVES AS
AGONISTS TO HUMAN PEROXISOME PROLIFERATOR-ACTIVATED
RECEPTOR ALPHA (PPAR)**

Field of the invention

The present invention relates to certain novel (2S)-3-(4-{2-[amino]-2-oxoethoxy}phenyl)-
2-ethoxypropionic acid derivatives, to processes for preparing such compounds, to their
the utility in treating clinical conditions including lipid disorders (dyslipidemias) whether
or not associated with insulin resistance and other manifestations of the metabolic
syndrome, to methods for their therapeutic use and to pharmaceutical compositions
containing them.

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Background of the invention

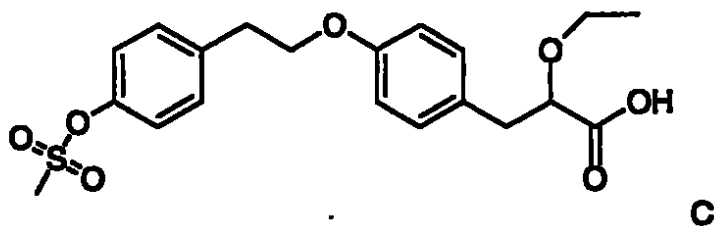
The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of
manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly
type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia
observed as deranged lipoprotein levels 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
patients with the metabolic syndrome and thus to correct the dyslipidaemia which is
considered to cause the accelerated progress of atherosclerosis. However, currently this is
not a universally accepted diagnosis with well-defined pharmacotherapeutic indications.

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The S-enantiomer of the compound of formula C below

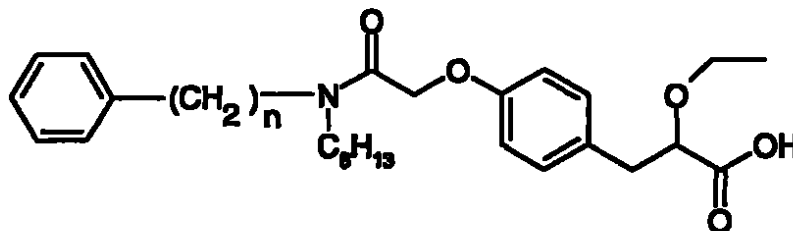
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2-ethoxy-3-[4-(2-[4-methanesulfonyloxyphenyl]ethoxy)phenyl]propanoic acid, is disclosed in PCT Publication Number WO99/62872. This compound is reported to be a modulator of peroxisome proliferator-activated receptors (PPAR, for a review of the PPARs see T. M. Willson et al, J Med Chem 2000, Vol 43, 527) and has combined PPAR α /PPAR γ agonist activity (Structure, 2001, Vol 9, 699, P. Cronet et al). This compound is effective in treating conditions associated with insulin resistance.

Surprisingly a series of compounds has now been found which are highly potent PPAR α modulators.

Description of the invention

The present invention provides the S enantiomer of a compound of formula I



wherein n is 1 or 2 and pharmaceutically acceptable salts, solvates, crystalline forms and prodrugs thereof.

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

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the activity of the compound of formula I into which the prodrugs are converted. Prodrugs 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:

- 5 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);
- 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);
- 10 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.

- In vivo* cleavable esters are just one type of prodrug of the parent molecule. An *in vivo*
- 15 hydrolysable (or cleavable) ester of a compound of the formula (I) that contains a carboxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters, for example, methoxymethyl; C₁₋₆alkanoyloxymethyl esters, for example, pivaloyloxymethyl; phthalidyl esters;
- 20 C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters, for example, 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example, 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters, for example, 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

- 25 The compounds of formula I have activity as medicaments. In particular the compounds of formula I are highly potent agonists of PPAR α . In addition the compounds of formula I are also agonists of PPAR γ . The term agonists as used herein, includes partial agonists.

Specific compounds of the invention are:

- 30 (2S)-3-(4-{2-[Benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid; and
(2S)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid ;

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and pharmaceutically acceptable salts, solvates and crystalline forms thereof.

In the present specification the expression "pharmaceutically acceptable salts" is intended to define but is not limited to base salts such as the alkali metal salts, alkaline earth metal salts, ammonium salts, salts with basic amino acids, and salts with organic amines.

9

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms. Certain compounds of the present invention may exist as tautomers. It is to be understood that the present invention

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encompasses all such tautomers.

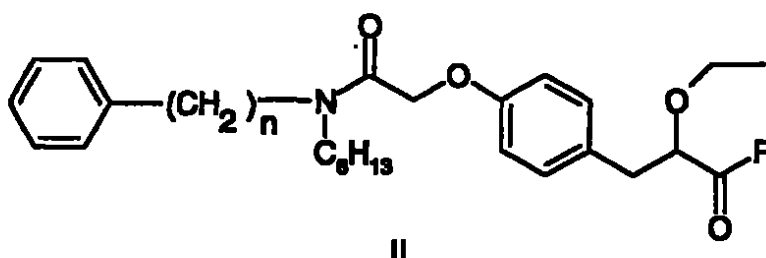
Methods of preparation

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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.

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Compounds of formula I may be prepared by reacting the S-enantiomer of a compound of formula II



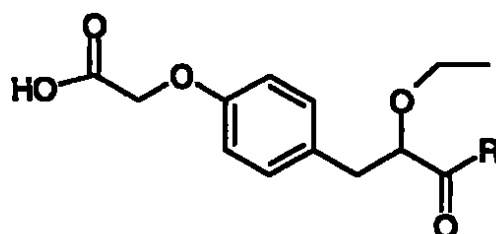
25

in which n is as previously defined and R 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. 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

a' /

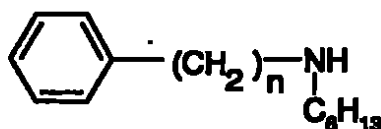
art. One such protecting group is where R represents a C₁₋₆alkoxy group or an arylalkoxy group eg benzyloxy, such that COR represents an ester. Such esters can be reacted with a de-protecting agent e.g. a hydrolysing agent, for example lithium hydroxide in a mixture of THF and water, at a temperature in the range of 0-100°C to give compounds of formula I.

Compounds of formula II may be prepared by reacting the S-enantiomer of a compound of formula III



III

in which R is as previously defined with a compound of formula IV



IV

in which n is as previously defined in an inert solvent, for example dichloromethane, in the presence of a coupling agent, for example a carbodiimide, eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylaminopyridine, at a temperature in the range of -25°C to 150°C.

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

Compounds of formula II and III are useful intermediates in the preparation of compounds of formula I and are believed to be novel. Compounds of formula II and III are herein claimed as a further aspect of the present invention. The S-enantiomers

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of compounds of formula II and III are preferred. 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 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).

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

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 a pharmaceutical acceptable organic or inorganic base addition 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

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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 pharmaceutically acceptable derivatives 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 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

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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 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 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.

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.

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X**Combination Therapy**

The compounds of the invention may be combined with another therapeutic agent that is
5 useful in the treatment of disorders associated with the development and progress of
atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and
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
10 also be combined with therapeutic agents used to treat complications related to micro-
angiopathies.

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
15 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
inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is
repaglinide or nateglinide.

20 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 agonist, or pharmaceutically acceptable salts,
25 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),
30 623-634 (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 NN622/Ragaglitazar, BMS

298585, WY-14643, clofibrate, fenofibrate, bezafibrate, gemfibrozil and ciprofibrate; GW 9578, ciglitazone, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-(4-methanesulphonyloxyphenyl)ethoxy)-phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

In addition the combination of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chlorpropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glicoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcyclamide 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 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, nivistatin, 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-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-

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methyl-*N*-(methylsulfonyl)-amino]pyrimidin-5-yl](3*R*,5*S*)-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]-
pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts
5 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.

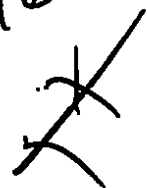
In the present application, the term "cholesterol-lowering agent" also includes chemical
10 modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and
metabolites, whether active or inactive.

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

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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
96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818,
WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO
20 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810,
WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO
00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051,
EP 864 582, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595 and
EP624596 and the contents of these patent applications are incorporated herein by
25 reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are
benzothiepinines, 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
30 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.

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One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-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:

- 5 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-1'-phenyl-1'-[*N'*-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 10 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 15 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;
- 20 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;
- 25 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;
- 30 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

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

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

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

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

10 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

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

15 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;

20 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;

25 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;

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

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

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

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

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

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- a phytosterol compound for example stanols;
probucol;
an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);
5 an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;
10 a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ;
a Melanin concentrating hormone (MCH) antagonist;
a PDK inhibitor; or
modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;
15 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such
20 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, encovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril,
25 enalaprilat, enapril, epicaptopril, foroxymithine, fosafenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphan-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride,
30 quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE

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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.

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

Therefore in an additional feature of the invention, there is provided a method for 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
15 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.

20 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
25 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
30 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

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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.

- 5 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.

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

- a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) 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
- 15 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:

- 20 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
- 25 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
- 30 a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in

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

5 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 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.

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

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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, 25 400, 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.

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Abbreviations

DMSO dimethyl sulfoxide
THF tetrahydrofuran

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	Pd/C	palladium on charcoal
	DMAP	dimethylaminopyridine
	t	triplet
	s	singlet
5	d	doublet
	q	quartet
	m	multiplet
	bs	broad singlet
	dm	doublet of multiplet
10	bt	broad triplet
	dd	doublet of doublet

Example 1(2S)-3-(4-(2-(benzyloxy)-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid15 (i) Ethyl (2S)-3-(4-(2-(benzyloxy)-2-oxoethoxy)phenyl)-2-ethoxypropanoate

To a solution of ethyl (2S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (23.8 g, 100 mmol, prepared as described in WO99/62872) in acetonitrile (200 mL) was added anhydrous potassium carbonate (31.9 g, 231 mmol) followed by benzyl bromoacetate (17.4 mL, 110 mmol) and the reaction mixture was refluxed overnight. The reaction mixture was allowed to cool to room temperature, insoluble salts were filtered off and the solution was concentrated *in vacuo*. The residue was taken up in ethyl acetate (300 mL), and the organic phase was washed with aqueous NaHCO₃ (3 x 100 mL) and brine (100 mL), dried over anhydrous MgSO₄, and concentrated *in vacuo*. Purification on silica gel with methylene chloride as the eluent and collection of pure fractions yielded 22.4 g (58%) of a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 1.16 (t, 3H), 1.22 (t, 3H), 2.93–2.97 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.64 (s, 2H), 5.23 (s, 2H), 6.82 (d, 2H), 7.15 (d, 2H), 7.32–7.39 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): δ 14.3, 15.2, 38.6, 60.9, 65.6, 66.3, 67.0, 80.4, 114.6, 128.5, 128.6, 128.7, 130.6, 135.3, 156.7, 169.0, 172.6.

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20(ii) 4-[(2S)-2,3-Diethoxy-3-oxopropyl]phenoxy}acetic acid

To a solution of ethyl (2S)-3-{4-[2-(benzyloxy)-2-oxoethoxy]phenyl}-2-ethoxypropanoate
(22.33 g, 57.8 mmol) in freshly distilled THF (290 mL) was added Pd/C (10%, 3.1 g) and the
reaction mixture was hydrogenated under atmospheric pressure at room temperature
overnight. The mixture was filtered through a plug of Celite and the filtrate was concentrated
in vacuo to afford 16.6 g (97%) of a light yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 1.15 (t, 3H), 1.21 (t, 3H), 2.93–2.98 (m, 2H), 3.35 (m, 1H),
3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.65 (s, 2H), 6.84 (d, 2H), 7.17 (d, 2H), 8.48 (bs,
1H)

¹³C NMR (100 MHz, CDCl₃): δ 14.3, 15.1, 38.5, 61.0, 65.1, 66.4, 80.3, 114.6, 130.7, 130.9,
156.4, 172.7, 173.7

(iii) Ethyl (2S)-3-(4-{2-[benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.110 g, 0.37
mmol) in methylene chloride (3.7 mL) were added N-hexyl-benzylamine (0.079 g, 0.41
mmol) and DMAP (0.045 g, 0.37 mmol) followed by 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydrochloride (0.071 g, 0.37 mmol) and the reaction
mixture was stirred at room temperature overnight. The mixture was diluted with methylene
chloride (25 mL), and the organic phase was washed with 5% HCl (3 x 25 mL), aqueous
NaHCO₃ (25 mL), and brine (25 mL), dried over Na₂SO₄, and concentrated *in vacuo*.
Purification on a prepacked column of silica gel (Isolute® SPE Column, 5 g Si/25 mL) with
methanol (0–1% gradient) in methylene chloride as the eluent yielded 0.139 g (80%) of a
colourless oil.

¹H NMR (400 MHz, CDCl₃): δ 0.81–0.90 (m, 3H), 1.11–1.32 (m, 12H), 1.46–1.62 (m, 2H),
2.88–3.00 (m, 2H), 3.21–3.29 and 3.29–3.40 (2m, 3H, rotamers), 3.59 (m, 1H), 3.95 (m, 1H).

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4.10–4.19 (m, 2H), 4.60 and 4.61 (2s, 2H, rotamers), 4.65 and 4.73 (2s, 2H, rotamers), 6.77 and 6.87 (2d, 2H, rotamers), 7.07–7.37 (m, 7H).

¹³C NMR (100 MHz, CDCl₃): δ 13.9, 14.2, 15.1, 22.5, 26.5, 27.1, 28.4, 31.4, 31.5, 38.4, 46.3, 46.5, 48.2, 50.5, 60.7, 66.1, 67.5, 67.8, 80.3, 114.4, 114.5, 126.6, 127.3, 127.6, 128.0, 128.5, 128.8, 130.2, 130.2, 130.4, 130.5, 136.6, 137.2, 156.8, 156.9, 168.0, 168.1, 172.4. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

(iv) (2S)-3-(4-(2-[Benzyl(hexyl)amino]-2-oxoethoxy)phenyl)-2-ethoxypropanoic acid

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To a solution of ethyl (2S)-3-(4-(2-[benzyl(hexyl)amino]-2-oxoethoxy)phenyl)-2-ethoxypropanoate (0.080 g, 0.17 mmol) in THF (8.6 mL) was added 4.3 mL of a 0.10 M LiOH solution and the reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with 2M HCl and extracted with ethyl acetate (3 x 25mL). The combined organic phase was washed with brine (25 mL), dried over Na₂SO₄, and concentrated *in vacuo* to afford 0.068 g (90%) of a colourless oil.

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¹H NMR (400 MHz, CDCl₃): δ 0.80–0.92 (m, 3H), 1.11–1.18 (m, 3H), 1.18–1.33 (m, 6H), 1.46–1.63 (m, 2H), 2.87–3.11 (m, 2H), 3.20–3.30 and 3.32–3.45 (2m, 3H, rotamers), 3.61 (m, 1H), 4.01 (m, 1H), 4.61 and 4.63 (2s, 2H, rotamers), 4.67 and 4.75 (2s, 2H, rotamers), 6.77 and 6.88 (2d, 2H, rotamers), 7.10–7.40 (m, 7H), 8.79 (bs, 1H).

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¹³C NMR (100 MHz, CDCl₃): δ 14.0, 15.1, 22.6, 26.6, 27.1, 28.4, 31.5, 31.5, 31.6, 38.1, 46.5, 46.6, 48.5, 50.7, 66.7, 67.4, 67.7, 79.9, 114.6, 114.7, 126.7, 127.5, 127.8, 128.2, 128.7, 129.0, 130.1, 130.1, 130.6, 130.7, 136.5, 137.0, 156.9, 157.0, 168.5, 168.6, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

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29Example 2(2S)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid5 (i) Ethyl (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)
propanoate

To a solution of {4-[(2S)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.110 g, 0.37 mmol) in methylene chloride (3.7 mL) were added N-hexyl-2-phenylethylamine (0.080 g, 0.39 mmol) and DMAP (0.045 g, 0.37 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.071 g, 0.37 mmol), and the reaction mixture was stirred at room temperature overnight. The mixture was diluted with methylene chloride (25 mL), and the organic phase was washed with 5% HCl (3 x 25 mL), aqueous NaHCO₃ (25 mL) and brine (25 mL), dried over Na₂SO₄ and concentrated *in vacuo*.
15 Purification on a prepacked column of silica gel (Isolute® SPE Column, 5 g Si/25 mL) with methanol (0-1% gradient) in methylene chloride as the eluent yielded 0.125 g (70%) of a colourless oil.

¹H NMR (400 MHz, CDCl₃): δ 0.82-0.92 (m, 3H), 1.16 (t, 3H), 1.19-1.33 (m, 9H), 1.45-1.65 (m, 2H), 2.82-2.90 (m, 2H), 2.91-2.98 (m, 2H), 3.12-3.21 and 3.29-3.42 (2m, 3H, rotamers) 3.50-3.65 (m, 3H), 3.95 (m, 1H), 4.16 (q, 2H), 4.39 and 4.65 (2s, 2H, rotamers), 6.75 and 6.86 (2d, 2H, rotamers), 7.10-7.34 (m, 7H).

¹³C NMR (100 MHz, CDCl₃): δ 14.0, 14.1, 14.3, 15.1, 22.6, 26.5, 26.7, 27.4, 29.0, 31.5, 31.6, 33.9, 35.3, 38.5, 45.9, 48.1, 48.3, 48.9, 60.8, 66.2, 67.5, 80.4, 114.5, 126.4, 126.9, 128.5, 128.9, 130.1, 130.2, 130.5, 130.5, 138.3, 139.2, 156.9, 157.0, 167.6, 167.8, 172.5. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

(ii) (2S)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

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To a solution of ethyl (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate (0.081 g, 0.17 mmol) in THF (8.6 mL) was added 4.3 mL of a

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0.10 M LiOH solution and the reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with 2M HCl and extracted with ethyl acetate (3 x 25mL). The combined organic phase was washed with brine (25 mL), dried over Na₂SO₄, and concentrated *in vacuo* to afford 0.073 g (96%) of a colourless oil.

¹H NMR (400 MHz, CDCl₃): δ 0.82–0.93 (m, 3H), 1.15 (t, 3H), 1.20–1.35 (m, 6H), 1.47–1.62 (m, 2H), 2.80–2.99 (m, 3H), 3.00–3.09 (m, 1H), 3.11–3.21 and 3.31–3.44 (2m, 3H, rotamers), 3.50–3.67 (m, 3H), 4.01 (m, 1H), 4.40 and 4.66 (2s, 2H, rotamers), 6.75 and 6.85 (2d, 2H, rotamers), 7.10–7.35 (m, 7H), 8.86 (bs, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 14.0, 14.1, 15.1, 22.6, 22.6, 26.6, 26.7, 27.3, 28.9, 31.5, 31.6, 33.8, 35.2, 38.1, 46.1, 48.3, 48.4, 49.0, 66.7, 67.4, 79.9, 114.6, 126.4, 127.0, 128.6, 128.9, 130.0, 130.1, 130.6, 130.7, 138.2, 139.1, 156.9, 157.0, 168.1, 168.2, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

BIOLOGICAL ACTIVITY

Formulations

Compounds were dissolved in DMSO to obtain 16 mM stock solutions. Before assays, 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.

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 mM L-alanyl-L-glutamine, 10% fetal calf serum, at 5% CO₂. Phosphate buffered saline (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.

29

PLASMID CONSTRUCTS FOR HETEROLOGOUS EXPRESSION

Standard recombinant DNA techniques were carried out as described by Ausubel (7). The Luciferase reporter vector, pGL5UAS (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.

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.

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 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
pSGGALmPP γ	murine PPAR γ	U09138, nt 652-1577

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

TRANSIENT TRANSFECTIONS

Frozen stocks of cells from passage number six were thawed and expanded to passage
5 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 1.8×10^6 cells/ml. After addition of DNA, the cell suspension was incubated on ice for approximately 5 minutes before electroporation at 230 V, 960 μ F in Biorad's Gene Pulser™ in 0.5 ml batches. A total of 50 μ g DNA was added to each
10 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).

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
15 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 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
20 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 treatment, the FCS was centrifuged and filter sterilised in order to remove remnants of charcoal and resin.

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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.

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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 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 murine PPAR γ . 5,8,11,14-Eicosatetrayonic acid (ETYA) was used as reference substance for human PPAR α .

Calculations and analysis

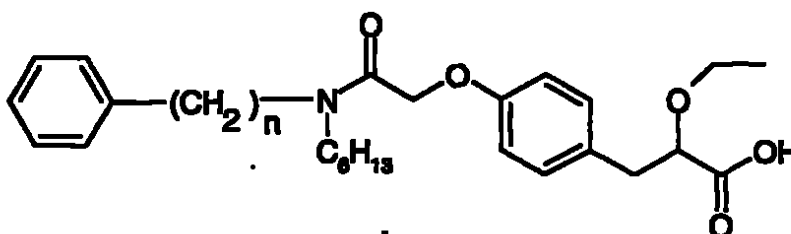
For calculation of EC₅₀ values, a concentration-effect curve was established. Values used were derived from the average of two or three independent measurements (after subtraction of the background average value) and were expressed as the percentage of the maximal activation obtained by the reference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

The compounds of formula I have an EC₅₀ of less than 0.5 μ mol/l for PPAR α and preferred compounds have an EC₅₀ of less than 0.05 μ mol/l for PPAR α . The compounds of formula I are a select group of compounds in that they are more potent with respect to PPAR α than with respect to PPAR γ . It is believed that this relationship is important with respect to the pharmacological activity of the compounds and to their therapeutic profile.

In addition the compounds of the present invention exhibit improved DMPK (Drug Metabolism and Pharmacokinetic) properties, for example they exhibit improved metabolic stability *in vitro*, and also exhibit favourable dose response curves *in vivo*. The compounds also have a promising toxicological profile.

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CLAIMS

1. The S enantiomer of a compound of formula I



wherein n is 1 or 2 and pharmaceutically acceptable salts, solvates, crystalline forms and prodrugs thereof.

2. A compound selected from:

- 10 (2S)-3-(4-{2-[Benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid ;
(2S)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;
and pharmaceutically acceptable salts, solvates and crystalline forms thereof.

- 15 3. (2S)-3-(4-{2-[Benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid and
pharmaceutically acceptable salts, solvates and crystalline forms thereof.

4. (2S)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid
and pharmaceutically acceptable salts, solvates and crystalline forms thereof.

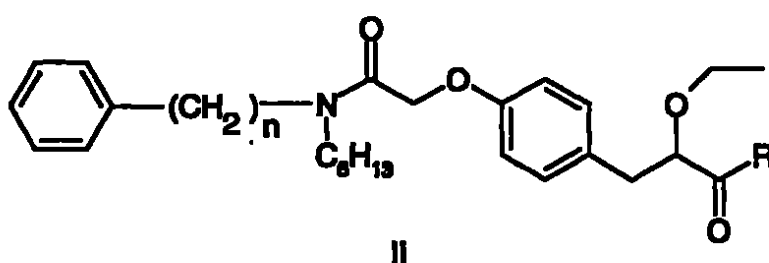
- 20 5. A pharmaceutical formulation comprising a compound according to any one of claims
1-4 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

6. A method of treating or preventing lipid disorders (dyslipidemia) whether or not
associated with insulin resistance comprising the administration of a compound according
25 to any one of claims 1-4 to a mammal in need thereof.

7. The use of a compound according to any one of claims 1-4 in the manufacture of a medicament for the treatment of lipid disorders (dyslipidemia) whether or not associated with insulin resistance.

8. A method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of formula I according to any one of claims 1-4 to a mammal in need thereof.

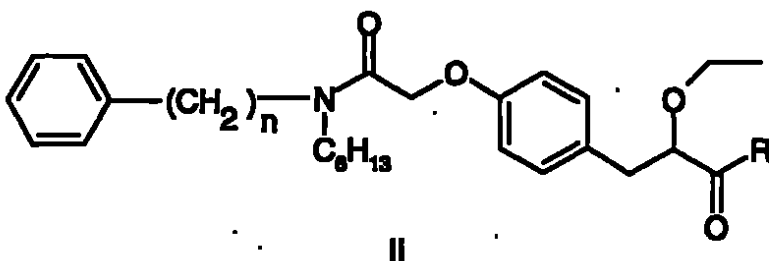
9. A process for the preparation of a compound of formula I comprising reacting a compound of formula II



in which n is as previously defined and R represents a protecting group for carboxylic hydroxy group with a de-protecting agent.

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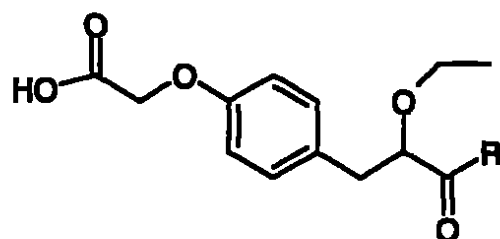
10. A compound of formula II



20 in which n is as previously defined and R represents a protecting group for carboxylic hydroxy group with a de-protecting agent.

11. A compound of formula III

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in which R is as previously defined.

- 5 12. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 4 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 obesity.
- 10 13. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 4 combined with another PPAR modulating agent.
14. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 4 combined with a cholesterol-lowering agent.
- 15 15. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 4 combined with a HMG-CoA reductase inhibitor.
16. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 4 combined with atorvastatin or a pharmaceutically acceptable salt, solvate, crystalline form or prodrug thereof.
- 20 17. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 4 combined with rosuvastatin or a pharmaceutically acceptable salt thereof.
- 23 18. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 4 combined with an IBAT inhibitor.

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19. A pharmaceutical composition according to claim 18 wherein the IBAT inhibitor is selected from 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'-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

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

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

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

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

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N'-(2-

carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/05738

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C235/20 A61K31/16 A61P3/00

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 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data bases consulted during the international search (name of data base and, where practical, search terms used)

PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 26, 1 July 2002 (2002-07-01) & JP 2001 261612 A (MITSUI CHEMICALS INC), 26 September 2001 (2001-09-26) abstract	1,5,7,12
A	WO 00 59889 A (OGUCHI MINORU ; SANKYO CO (JP); FUJITA TAKASHI (JP); HONMA HIDEHITO) 12 October 2000 (2000-10-12) abstract	1,5,7,12
A	WO 00 61582 A (OGUCHI MINORU ; SANKYO CO (JP); FUJITA TAKASHI (JP); HONMA HIDEHITO) 19 October 2000 (2000-10-19) abstract	1,5,7, 11,12
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document claiming the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

18 March 2003

Date of mailing of the international search report

28/03/2003

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

P. 1/6B 02/05738

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 75103 A (KYORIN SEIYAKU KK ;MURAKAMI KOJI (JP); IDE TOMOHIRO (JP); NOMURA M) 14 December 2000 (2000-12-14) abstract	1,5,7,12
A,P	WO 02 44130 A (KYORIN SEIYAKU KK ;MURAKAMI KOUJI (JP); NOMURA MASAHIRO (JP); TAKA) 6 June 2002 (2002-06-06) abstract	1,5,7,12
A,P	WO 02 44127 A (KYORIN SEIYAKU KK ;MURAKAMI KOUJI (JP); NOMURA MASAHIRO (JP); MIYA) 6 June 2002 (2002-06-06) abstract	1,5,7,12
A,P	WO 02 083616 A (SUGAWARA TOMOKADU ;SANKYO CO (JP); ENDO TAKESHI (JP); KUROBE HIROS) 24 October 2002 (2002-10-24) abstract	1,5,7,12

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,10,19 all partially

Present claims 1, 10 and 19 relate to an extremely large number of possible compounds or pharmaceutical compositions due to the term "prodrug" or the expression "protecting group for carboxylic hydroxy group" comprised in those claims respectively. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products/apparatus/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formulae (I) and (II) according to claims 1 and 10 wherein the protecting group is an ester according to page 3 of the description. It is stressed that prodrugs of compounds of formula (I) have not been searched since their structure is not defined nor disclosed.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/05738

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 6 and 8 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 for which the search has been carried out.
2. ☒ Claims Nos.: 1,10,19 all partially
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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

Information on patent family members

Int. Appl. No.
PCT/GB 02/05738

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2001261612	A	26-09-2001	NONE
WO 0059889	A	12-10-2000	AU 3670700 A 23-10-2000 BR 0009593 A 18-06-2002 CN 1353694 T 12-06-2002 CZ 20013593 A3 13-03-2002 EP 1167357 A1 02-01-2002 HU 0200895 A2 28-11-2002 WO 0059889 A1 12-10-2000 JP 2001097955 A 10-04-2001 NO 20014849 A 27-11-2001 TR 200102908 T2 22-04-2002
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WO 02083616	A	24-10-2002	WO 02083616 A1 24-10-2002 JP 2002371033 A 26-12-2002

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(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL
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(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional



(43) Fecha de Publicación Internacional
26 de junio de 2003 (26.06.2003)

(10) Número de Publicación Internacional

PCT

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

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

(84) Países designados (regional): Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eurselática (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, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

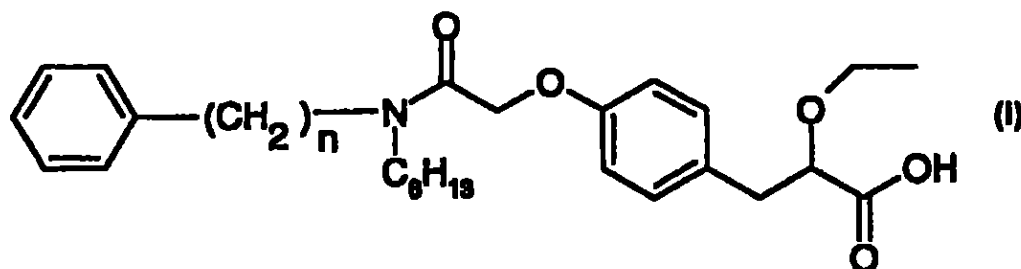
(71) Solicitante (para MG únicamente): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

Publicado:
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(72) Inventores, o
(75) Inventores/Solicitantes (para US únicamente): ALSTERMARK LINDSTEDT, Eva-Lotta [SE/SE]; Moindal, S-431 83 (SE). OLSSON, Anna, Christina [SE/SE]; Moindal, S-431 83 (SE). LI, Lanna [SE/SE]; Moindal, S-431 83 (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 FENILPROPIÓNICO SUSTITUIDO COMO AGONISTAS DE RECEPTOR α HUMANO ACTIVADO POR PROLIFERADOR DE PEROXISOMAS (PPAR)



(57) Extracto: La presente invención provee el S enantiómero de un compuesto de fórmula (I) en donde n es 1 ó 2 así como sales farmacéuticamente aceptables, solvatos, formas cristalinas y profármacos del mismo, [se refiere] a procesos para preparar tales compuestos, a su utilidad en tratar condiciones clínicas incluidos trastornos de lípidos (dislipidemias) asociados o no con resistencia a la insulina, a métodos para su uso terapéutico y a composiciones farmacéuticas que los contienen.

WO 03/051821 A1

**DERIVADOS DE ÁCIDO FENILPROPIÓNICO SUSTITUIDO COMO
AGONISTAS DE RECEPTOR α HUMANO ACTIVADO POR
PROLIFERADOR DE PEROXISOMAS (PPAR)**

Campo de la invención

La presente invención se relaciona con ciertos derivados novedosos de ácido (2S)-3-(4-{2-[amino]-2-oxoetoxi}fenil)-2-etoxipropanoico, con procesos para preparar tales compuestos, con su capacidad en tratar afecciones clínicas, incluidos trastornos de lípidos (dislipidemias), asociados o no con resistencia a la insulina y otras manifestaciones del síndrome metabólico, con métodos para su empleo terapéutico y con composiciones farmacéuticas que los contienen.

Antecedentes de la invención

El síndrome metabólico, incluida la diabetes sacarina tipo II, se refiere a un grupo de manifestaciones incluida la resistencia a la insulina con hiperinsulinemia concomitante, posiblemente diabetes sacarina tipo 2, hipertensión arterial, obesidad (visceral) central, dislipidemia observada como niveles desordenados de lipoproteína, caracterizados típicamente por VLDL elevadas (lipoproteínas de muy baja densidad), partículas LDL densas pequeñas y concentraciones HDL (lipoproteína de alta densidad) reducidas y fibrinólisis reducida.

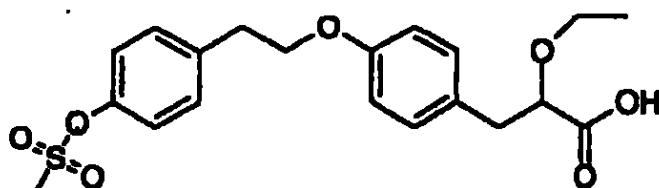
La investigación epidemiológica reciente ha documentado que individuos con resistencia a la insulina corren un riesgo fuertemente redoblado de morbimortalidad cardiovascular, que sufren en forma especial de infarto del miocardio y apoplejía. En la diabetes sacarina tipo 2 las afecciones relacionadas con aterosclerosis causan hasta el 80% de todas las muertes.

En la medicina clínica existe una conciencia de la necesidad de aumentar la sensibilidad a la insulina en pacientes con el síndrome metabólico y corregir

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así la dislipidemia, que se considera que causa la evolución acelerada de la aterosclerosis. No obstante, en la actualidad éste no es un diagnóstico universalmente aceptado con indicaciones farmacoterapéuticas bien definidas.

El S-enantiómero del compuesto de fórmula C mencionada a continuación



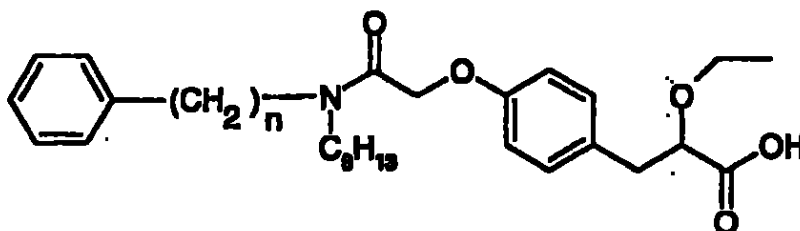
C

ácido 2-etoxi-3-[4-(2-{4-metanosulfoniloxifenil}etoxi)fenil]propanoico se divulga en la Publicación PCT Número WO99/62872. Se informa que este compuesto es un modulador de receptores activados por proliferador de peroxisomas (PPAR, para una reseña de los PPARs véase T. M. Willson et al., J Med Chem 2000, Vol 43, 527) y posee actividad agonista PPAR α /PPAR γ combinada (Structure, 2001, Vol 9, 699, P. Cronet et al.). Este compuesto es efectivo para tratar afecciones con resistencia a la insulina.

Sorpresivamente se ha encontrado ahora una serie de compuestos que son moduladores PPAR α altamente potentes.

Descripción de la invención

La presente invención provee el S enantiómero de un compuesto de fórmula I



I

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~~47~~

en donde n es 1 ó 2 y sales farmacéuticamente aceptables, solvatos, formas cristalinas y profármacos del mismo.

El término "profármaco" como se emplea es esta especificación incluye derivados del grupo de ácido carboxílico que se convierten en un mamífero, particularmente un humano, en el grupo de ácido carboxílico o una sal o conjugado del mismo. Debe entenderse que, sin estar atado por la teoría, se cree que la mayor parte de la actividad asociada con los profármacos proviene de la actividad del compuesto de fórmula I, en el cual se convierten los fármacos. Los profármacos pueden prepararse por metodología rutinaria adecuadamente dentro de las habilidades de un experto en el arte. En el arte se conocen diferentes profármacos de carboxilo. Para ejemplos de tales derivados de profármacos, véase:

- 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);
- 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).

Los documentos anteriores de a - e se incorporan aquí por referencia.

Ésteres escindibles *in vivo* son precisamente un tipo de profármaco de la molécula original. Un éster hidrolizable (o escindible) *in vivo* de un compuesto de la fórmula (I) que contiene el grupo carboxilo es, por ejemplo, un éster farmacéuticamente aceptable, que se hidroliza en el cuerpo humano o animal para producir el ácido precursor. Ésteres apropiados farmacéuticamente aceptables para carboxilo incluyen ésteres de C₁₋₆alcoximetilo, por ejemplo, metoximetilo; ésteres de C₁₋

ϵ alcanoiloximetilo, por ejemplo, pivaloiloximetilo; ésteres de ftalidilo; ésteres de C_{3-8} cicloalcoxicarbonilo C_{1-6} alquilo, por ejemplo, 1-ciclohexilcarboniloxietilo; ésteres de 1,3-dioxolen-2-onilmetilo, por ejemplo, 5-metil-1,3-dioxolen-2-onilmetilo; y ésteres de C_{1-6} alcoxicarboniloxietilo, por ejemplo, 1-metoxycarboniloxietilo; y pueden formarse en cualquier grupo carboxilo en los compuestos de esta invención.

Los compuestos de fórmula I tienen actividad como medicamentos. En particular, los compuestos de fórmula I son agonistas altamente potentes de PPAR α . Adicionalmente, los compuestos de fórmula I son también agonistas de PPAR γ . El término agonistas, como se emplea aquí, incluye agonistas parciales.

Compuestos específicos de la invención son:

Ácido (2S)-3-(4-{2-[(bencil)(hexil)amino]-2-oxoetoxi}fenil)-2-etoxipropanoico; y ácido (2S)-2-etoxi-3-(4-{2-[hexil(2-feniletíl)amino]-2-oxoetoxi}fenil)-2-etoxipropanoico;

y sales farmacéuticamente aceptables, solvatos y formas cristalinas de los mismos.

En la presente especificación la expresión "sales farmacéuticamente aceptables" tiene como finalidad definir, pero no se limita a, sales de base tales como sales de metal alcalino, sales de metal alcalinotérreo, sales de amonio, sales con aminoácidos básicos, y sales con aminas orgánicas.

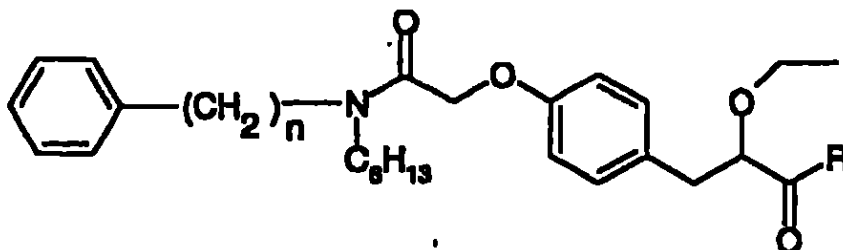
Se entenderá que ciertos compuestos de la presente invención pueden existir en formas solvatadas, por ejemplo hidratadas, así como formas no solvatadas. Hay que entender que la presente invención abarca todas esas formas solvatadas. Ciertos compuestos de la presente invención pueden existir como tautómeros. Hay que entender que la presente invención comprende todos esos tautómeros.

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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; los compuestos pueden prepararse asimismo según se describe en el arte previo para compuestos relacionados estructuralmente. Las reacciones pueden llevarse a cabo de acuerdo con procedimientos estándar o como se describe en la sección experimental.

Los compuestos de fórmula I pueden prepararse haciendo reaccionar el S-enantiómero de un compuesto de fórmula II

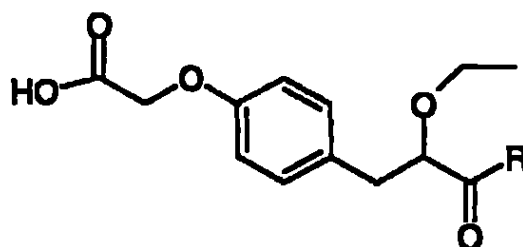


En la cual, como se definió en la cual n es como se define previamente y R representa un grupo protector para un grupo hidroxilo carboxílico como se describe en el texto estándar "Protective Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts, con un agente desprotector. El grupo protector puede ser también una resina, tal como una resina Wang o una resina de cloruro de 2-clorotritilo. Los grupos protectores pueden retirarse de acuerdo con técnicas que son bien conocidas por los expertos en el arte. Un grupo protector similar es donde R representa un grupo C_{1-6} alcoxilo o un grupo arilalcoxilo, verbigracia benciloxilo, tal que COR representa un éster. Tales ésteres pueden hacerse reaccionar con un reactivo desprotector, verbigracia un agente hidrolizante, por ejemplo hidróxido de litio en una mezcla de THF y agua, a una temperatura en el rango de 0-100°C para producir compuestos de fórmula I.

Compuestos de fórmula II pueden prepararse haciendo reaccionar el S-

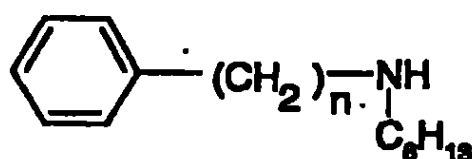
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enantiómero de un compuesto de fórmula III



III

en el cual R es, como se define previamente, con un compuesto de fórmula IV



IV

en la cual n es como se define previamente en un solvente inerte, por ejemplo diclorometano, en la presencia de un agente de acoplamiento, por ejemplo una carbodimida, verbigracia 1-(3-dimetilamino-propil)-3-etilcarbodiimida, y de manera opcional en la presencia de un catalizador, por ejemplo un catalizador básico, verbigracia 4-dimetilaminopiridina, a una temperatura en el rango de -25°C a 150°C.

Compuestos de fórmula III y IV pueden prepararse por métodos descritos en los Ejemplos o por métodos análogos conocidos por los expertos en el arte.

Compuestos de fórmula II y III son intermedios útiles en la preparación de compuestos de fórmula I, y se cree que son novedosos. Compuestos de fórmula II y III se reivindican aquí como un aspecto adicional de la presente invención. Se prefieren los S-enantiómeros de compuestos de fórmula II y III. Los compuestos de la invención pueden aislarse de sus mezclas de reacción usando técnicas tradicionales.

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Los expertos en el arte se darán cuenta de que, con el fin de obtener compuestos de la invención en una manera alternativa y, en algunas ocasiones, más conveniente, los pasos del proceso individual, mencionados más arriba en el texto, pueden realizarse en diferente orden, y/o las reacciones individuales pueden llevarse a cabo en una etapa diferente en toda la ruta general (es decir, pueden efectuarse transformaciones químicas sobre intermedios diferentes a los asociados más arriba con una reacción particular).

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

Preparaciones farmacéuticas

Los compuestos de la invención se administrarán normalmente por vías orales, parenterales, intravenosas, intramusculares, subcutáneas o en otras vías inyectables, por vía bucal, rectal, vaginal, transdérmica y/o nasal y/o por inhalación, en la forma de preparaciones farmacéuticas que comprenden el ingrediente activo ya sea como ácido libre, o una sal de adición de base, orgánica o inorgánica, farmacéuticamente aceptable, en una forma de administración 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 el tratamiento terapéutico de humanos son alrededor de 0.0001-100 mg/kg de peso corporal, preferiblemente 0.001-10 mg/kg de peso corporal.

Las formulaciones orales preferidas son particularmente tabletas o cápsulas, que pueden formularse por métodos conocidos por los expertos en el arte para proporcionar dosis del compuesto activo en el rango de 0.5mg a

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500mg por ejemplo 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg y 250mg.

De acuerdo con un aspecto adicional de la invención, se provee en consecuencia una formulación farmacéutica que incluye cualquiera de los compuestos de la invención, o derivados farmacéuticamente aceptables de los mismos, en mezcla con auxiliares, 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, inducida o inherente, a la insulina (resistencia a la insulina) y trastornos metabólicos asociados (también conocido 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 en forma característica con la resistencia a la insulina. Esta dislipidemia, también conocida como el perfil lipoproteínico aterogénico, se caracteriza por ácidos grasos no esterificados, moderadamente elevados, partículas ricas en triglicéridos lipoproteína de muy baja densidad (VLDL) elevada, niveles Apo B elevados, niveles de lipoproteína de baja densidad (HDL) asociados con bajos niveles de partículas apoAI y niveles Apo B elevados en la presencia de partículas de lipoproteínas de baja densidad (LDL) pequeñas, densas, fenotipo B.

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

Se espera que el tratamiento con los presentes compuestos disminuya la

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morbimortalidad cardiovascular asociada con la aterosclerosis debido a sus propiedades antidislipídicas, así como antiinflamatorias. Los estados de enfermedad cardiovascular incluyen macro-angiopatías de diferentes órganos 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 eviten o retrasen el desarrollo de la diabetes tipo 2 del síndrome metabólico y la diabetes del embarazo. Por lo tanto, se espera que se retrase el desarrollo de complicaciones a largo plazo asociadas con hiperglucemia crónica en diabetes sacarina tales como las micro-angiopatías causantes de nefropatía, lesión retinal 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 el síndrome de ovario poliquístico, obesidad, cáncer y estados de enfermedad inflamatoria, incluidos trastornos neurodegenerativos tales como deterioro cognitivo leve, enfermedad de Alzheimer, enfermedad 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 sufren 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 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 otros agentes terapéuticos que son útiles en el tratamiento de trastornos asociados con el desarrollo y evolución de la aterosclerosis tales como hipertensión, hiperlipidemias, dislipidemias, diabetes y obesidad. Los compuestos de la invención pueden combinarse con otro agente terapéutico que disminuye la proporción de LDL:HDL o un agente que produce una caída en los niveles circulantes de colesterol LDL. En pacientes con diabetes sacarina, los compuestos de la invención pueden combinarse igualmente con agentes terapéuticos usados para tratar complicaciones relacionadas con micro-angiopatías.

Los compuestos de la invención pueden emplearse junto con otras terapias para el tratamiento del síndrome metabólico o diabetes tipo 2 y sus complicaciones asociadas; éstos 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 una sal

farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, puede administrarse en asociación con otro agente modulador PPAR. Agentes moduladores PPAR incluyen, pero no se limitan a, agonista PPAR alfa y/o gamma, o sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos de los mismos. Agonistas PPAR alfa y/o gamma apropiados, sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos de los mismos, 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 de un Experto sobre Patentes Terapéuticas, 10 (5), 623-634 (en particular, los compuestos descritos en las solicitudes de patente listadas en la página 634) y J Med Chem, 2000, 43, 527 todas las cuales se incorporan aquí por referencia. Particularmente un agonista PPAR alfa y/o gamma se refiere a NN622/Ragaglitazar, BMS 298585, WY-14643, clofibrato, fenofibrato, bezafibrato, gemfibrozil y ciprofibraty; GW 9578, ciglitazona, troglitazona, pioglitazona, rosiglitazona, eglitazona, proglitazona, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 y GW 2433. Particularmente un agonista PPAR alfa y/o gamma se refiere a ácido (S)-2-etoxi-3-[4-(2-{4-metanosulfoniloxifenil}etoxi)-fenil]propanoico y sales farmacéuticamente aceptables del mismo.

Adicionalmente la combinación de la invención puede emplearse en conjunción con una sulfonilurea por ejemplo: glimepirida, glibenclamida (gliburida), gliclazida, glipizida, gliquidona, cloropropamida, tolbutamida, acetohexamida, glicopiramida, carbutamida, glibonurida, glisoxepida, glibutiazol, glibuzol, glihexamida, glimidina, glipinamida, fenbutamida, tolcilamida y tolazamida. Preferiblemente la sulfonilurea es glimepirida o glibenclamida (gliburida). Más preferiblemente la sulfonilurea es glimepirida. Por lo tanto, la presente invención incluye la administración de un compuesto de la presente invención en conjunción con uno, dos o más terapias existentes descritas en este acápite. Las dosis de las otras

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terapias existentes para el tratamiento de diabetes tipo 2 y sus complicaciones asociadas serán las conocidas en el arte y aprobadas para uso por las entidades normativas 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 además un compuesto de la presente invención en combinación con un agente reductor de colesterol. Los agentes reductores de colesterol mencionados en esta solicitud incluyen, pero no se limitan a, inhibidores de HMG-CoA reductasa (3-hidroxi-3-metilglutaril coenzima A reductasa). Apropiadamente el inhibidor de la 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 una sal de sodio o calcio, o un solvato del, o un solvato de tal sal. Una estatina particular es atorvastatina, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de las mismas. Una estatina más particular es sal de calcio de atorvastatina. Una estatina particular preferida es, sin embargo, un compuesto con el nombre químico 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 solvato del mismo, 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. Esta última estatina es conocida bajo su nombre genérico rosuvastatina.

En la presente solicitud, el término "agente reductor de colesterol" incluye

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asimismo las modificaciones químicas de los inhibidores de HMG-CoA reductasa, tales como ésteres, profármacos y metabolitos, sean activos o inactivos.

La presente invención incluye además un compuesto de la presente invención en combinación con un inhibidor del sistema de transporte de ácidos biliares 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 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595 y EP624596 y los contenidos de estas solicitudes de patente se incorporan aquí por referencia.

Clases particulares de inhibidores IBAT adecuados para empleo en la presente invención son benzotiazepinas, y los compuestos descritos en las reivindicaciones, particularmente la reivindicación 1, de WO 00/01687, WO 96/08484 y 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 adecuada de inhibidores IBAT son las 1,2,5-benzotiadiazepinas.

Un compuesto adecuado particular que posee actividad inhibidora IBAT es ácido (3*R*,5*R*)-3-butil-3-etil-1,1-dioxido-5-fenil-2,3,4,5-tetrahidro-1,4-benzotiazepin-8-il β-D-glucopiranosidurónico (EP 864 582). Otros inhibidores IBAT apropiados incluyen una de:

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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-carboxipentil)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-

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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;

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

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

1,1-dioxo-3,3-dibutil-5-fenil-7-metoxi-8-[*N*-{(R)- α -[*N'*-(2-sulfoetil)

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carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

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

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

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

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

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

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

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

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

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

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

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-{(S)-1-[N-((S)-2-hidroxi-1-carboxietil)carbamoil]propil}carbamoil]bencil}
carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-((S)-1-carboxi-2-metilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;
1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(N-{(R)- α -[N-((S)-1-carboxipropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;
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 una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de las mismas.

De acuerdo con otro aspecto adicional de la presente invención se proveed un tratamiento de combinación que comprende la administración de una cantidad efectiva de un compuesto de la fórmula I, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, de manera opcional junto con diluyente o vehículo farmacéuticamente aceptables, con la administración simultánea, secuencial o separada de uno o más de los siguientes agentes seleccionados de:

Un inhibidor 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, los cuales 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 las cuales se incorporan aquí por referencia;

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

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

un compuesto de a fitosterol por ejemplo estanoles; probucol;

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

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

un antagonista CB₁ o agonista inversa, por ejemplo como se describe en WO 01/70700 y EP 65635;

un antagonista de hormona concentradora de melanina (MCH);

un inhibidor PDK; o

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

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

Inhibidores ACE particulares o sales farmacéuticamente aceptables, solvatos, solvato de tales sales o profármacos de los mismos, incluidos metabolitos activos, que pueden emplearse en combinación con un

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compuesto de fórmula I incluyen, pero no se limitan a, los siguientes compuestos: alacepril, alatriopril, altiopril cálcico, 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, lyciumin A, lyciumin 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. Inhibidores 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.

Antagonistas preferidos de angiotensina II, sales farmacéuticamente aceptables, solvatos, solvato de tales sales o profármacos de los mismos para uso en combinación con un compuesto de fórmula I incluyen, pero no se limitan a, los compuestos: candesartán, candesartan cilexetil, losartán, valsartán, irbesartán, tasosartán, telmisartán y eprosartán. Antagonistas particularmente preferidos de angiotensina II o derivados farmacéuticamente aceptables de los mismos 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 una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, en administración simultánea, secuencial o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de los mismos.

Por lo tanto, 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 una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, en administración simultánea, secuencial o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de los mismos.

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica que comprende un compuesto de fórmula I, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, y uno de los demás compuestos descritos en esta sección de combinación o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de los mismos, en asociación con un diluyente o vehículo farmacéuticamente aceptables.

De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende un compuesto de fórmula I, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, y uno de los demás compuestos descritos en esta sección de combinación o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de los mismos.

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De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende:

- a) un compuesto de fórmula I, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, en una primera formulación unitaria;
- b) uno de los demás compuestos descritos en esta sección de combinación o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de los mismos; en una segunda formulación unitaria; y
- c) medios recipientes para contener dichas formulaciones 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 una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, junto con un diluyente o vehículo farmacéuticamente aceptables, en una primera formulación unitaria;
- b) uno de los demás compuestos descritos en esta sección de combinación o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de los mismos, en una segunda formulación unitaria; y
- c) medios recipientes para contener dichas formulaciones primera y segunda.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de la fórmula I, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, y uno de los demás compuestos descritos en esta sección de combinación, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de los mismos, en la manufactura de un medicamento para uso en el tratamiento del 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 una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, y uno de los demás compuestos descritos en esta sección de combinación, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de los mismos, en la manufactura de un medicamento para uso en el tratamiento de afecciones hiperlipidélicas en una 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 una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, de manera opcional junto con un diluyente o vehículo farmacéuticamente aceptables, con la administración simultánea, secuencial o separada de una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de los mismos, de manera opcional junto con un diluyente o vehículo farmacéuticamente aceptables 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 espectrómetros Varian Mercury 300 o Varian UNITY plus 400, 500 ó 600, que funcionaban a frecuencias ^1H de 300, 400, 500 y 600 MHz, respectivamente, y a frecuencias ^{13}C de 75, 100, 125 y 150 MHz, respectivamente. Se efectuaron mediciones en escala delta (δ).

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

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Abreviaturas

DMSO	Sulfóxido de dimetilo
THF	Tetrahidrofurano
Pd/C	Paladio sobre carbón
DMAP	Dimetilaminopiridina
t	Triplete
s	Singlete
d	Doblete
q	Cuartete
m	Multiplete
bs	Singlete amplio
dm	Doblete de multiplete
bt	Triplete amplio
dd	Doblete de doblete

Ejemplo 1

Ácido (2S)-3-(4-{2-[bencil(hexil)amino]-2-oxoetoxi}fenil)-2-
etoxipropanoico

(i) Etil(2S)-3-{4-[2-(benciloxi)-2-oxoetoxi]fenil}-2-etoxipropanoato

A una solución de etil (2S)-2-etoxi-3-(4-hidroxifenil)propanoato (23.8 g, 100 mmol, preparado como se describe en WO99/62872) en acetonitrilo (200 mL) se agregó carbonato de potasio anhidro (31.9 g, 231 mmol) seguido por bromoacetato de bencilo (17.4 mL, 110 mmol) y la mezcla de reacción se hizo refluir de un día para otro. La mezcla de reacción se dejó enfriar a temperatura de la sala, se extrajeron por filtración las sales insolubles y la solución se concentró *in vacuo*. El residuo se absorbió en acetato de etilo (300 mL), y la fase orgánica se lavó con NaHCO₃ acuoso (3 x 100 mL) y salmuera (100 mL), se secó sobre MgSO₄ anhidro, y se concentró *in vacuo*. La purificación en gel de sílice con cloruro de metileno como el eluyente y la recolección de las fracciones puras produjeron 22.4 g

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(58%) de un aceite amarillo.

^1H NMR (400 MHz, CDCl_3): δ 1.16 (t, 3H), 1.22 (t, 3H), 2.93-2.97 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.64 (s, 2H), 5.23 (s, 2H), 6.82 (d, 2H), 7.15 (d, 2H), 7.32-7.39 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 15.2, 38.6, 60.9, 65.6, 66.3, 67.0, 80.4, 114.6, 128.5, 128.6, 128.7, 130.6, 135.3, 156.7, 169.0, 172.6.

(ii) Ácido {4-[(2S)-2,3-dietoxi-3-oxopropil]fenoxi}acético

A una solución de (2S)-3-{4-[2-(benciloxi)-2-oxoetoxi]fenil}-2-etoxipropanoato de etilo (22.33 g, 57.8 mmol) en THF recién destilado (290 mL) se agregó Pd/C (10%, 3.1 g) y la mezcla de reacción se hidrogenó bajo presión atmosférica a temperatura de la sala de un día para otro. La mezcla se filtró a través de un tapón de celita y el filtrado se concentró *in vacuo* para proporcionar 16.6 g (97%) de un aceite marailllo pálido.

^1H NMR (400 MHz, CDCl_3): δ 1.15 (t, 3H), 1.21 (t, 3H), 2.93-2.98 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.65 (s, 2H), 6.84 (d, 2H), 7.17 (d, 2H), 8.48 (bs, 1H)

^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 15.1, 38.5, 61.0, 65.1, 66.4, 80.3, 114.6, 130.7, 130.9, 156.4, 172.7, 173.7

(iii) (2S)-3-(4-{2-[bencil(hexil)amino]-2-oxoetoxi}fenil)-2-etoxipropanoato de etilo

A una solución de ácido {4-[(2S)-2,3-dietoxi-3-oxopropil]fenoxi}acético (0.110 g, 0.37 mmol) en cloruro de metileno (3.7 mL) se agregaron *N*-hexil-bencilamina (0.079 g, 0.41 mmol) y DMAP (0.045 g, 0.37 mmol)

seguido por clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0.071 g, 0.37 mmol) y la mezcla de reacción se agitó a temperatura de la sala de un día para otro. La mezcla se diluyó con cloruro de metileno (25 mL) y la fase orgánica se lavó con 5% HCl (3 x 25 mL), NaHCO₃ acuoso (25 mL) y salmuera (25 mL), se secó sobre Na₂SO₄, y se concentró *in vacuo*. La purificación en una columna pre-empacada de gel de sílice (Isolute® SPE Column, 5 g Si/25 mL) con metanol (0-1% gradiente) en cloruro de metileno como el eluyente produjo 0.103 g (58%) de un aceite incoloro.

¹H NMR (400 MHz, CDCl₃): δ 0.81-0.90 (m, 3H), 1.11-1.32 (m, 12H), 1.46-1.62 (m, 2H), 2.88-3.00 (m, 2H), 3.21 y 3.29 y 3.29-3.40 (2m, 3H, rotámeros), 3.59 (m, 1H), 3.95 (m, 1H), 4.10-4.19 (m, 2H), 4.60 y 4.61 (2s, 2H, rotámeros), 4.65 y 4.73 (2s, 2H, rotámeros), 6.77 y 6.87 (2d, 2H, rotámeros), 7.07-7.37 (m, 7H)

¹³C NMR (100 MHz, CDCl₃): δ 13.9, 14.2, 15.1, 22.5, 26.5, 27.1, 28.4, 31.4, 31.5, 38.4, 46.3, 46.5, 48.2, 50.5, 60.7, 66.1, 67.5, 67.8, 80.3, 114.4, 114.5, 126.6, 127.3, 127.6, 128.0, 128.5, 128.8, 130.2, 130.2, 130.4, 130.5, 136.6, 137.2, 156.8, 156.9, 168.0, 168.1, 172.4. (El número de picos es mayor que el número de átomos de carbono debido a rotámeros.)

(iv) Ácido (2S)-3-(4-{2-[bencil(hexil)amino]-2-oxoetoxi}fenil)-2-etoxipropanoico

A una solución de (2S)-3-(4-{2-[bencil(hexil)amino]-2-oxoetoxi}fenil)-2-etoxipropanoato de etilo (0.080 g, 0.17 mmol) en THF (8.6 mL) se agregó 4.3 mL de una solución 0.10 M LiOH y la mezcla de reacción se agitó a temperatura de la sala de un día para otro. La mezcla de reacción se acidificó con 2M HCl y se extrajo con acetato de etilo (3 x 25mL). La fase orgánica combinada se lavó con salmuera (25 mL), se secó sobre Na₂SO₄, y se concentró *in vacuo* para proporcionar 0.068 g (90%) de un aceite

incoloro.

^1H NMR (400 MHz, CDCl_3): δ 0.80-0.92 (m, 3H), 1.11-1.18 (m, 3H), 1.18-1.33 (m, 6H), 1.46-1.63 (m, 2H), 2.87-3.11 (m, 2H), 3.20-3.30 y 3.32-3.45 (2m, 3H, rotámeros), 3.61 (m, 1H), 4.01 (m, 1H), 4.61 y 4.63 (2s, 2H, rotámeros), 4.67 y 4.75 (2s, 2H, rotámeros), 6.77 y 6.88 (2d, 2H, rotámeros), 7.10-7.40 (m, 7H), 8.79 (bs, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 15.1, 22.6, 26.6, 27.1, 28.4, 31.5, 31.5, 31.6, 38.1, 46.5, 46.6, 48.5, 50.7, 66.7, 67.4, 67.7, 79.9, 114.6, 114.7, 126.7, 127.5, 127.8, 128.2, 128.7, 129.0, 130.1, 130.1, 130.6, 130.7, 136.5, 137.0, 156.9, 157.0, 168.5, 168.6, 175.6. (El número de picos es mayor que el número de átomos de carbono debido a rotámeros.)

Ejemplo 2

Ácido (2S)-2-etoxi-3-(4-{2-[hexil(2-feniletíl)amino]-2-oxoetoxi}fenil)propanoico

(i) (2S)-2-etoxi-3-(4-{2-[hexil(2-feniletíl)amino]-2-oxoetoxi}fenil)propanoato de etilo

A una solución de ácido {4-[(2S)-2,3-dietoxi-3-oxopropil]fenoxi}acético (0.110 g, 0.37 mmol) en cloruro de metileno (3.7 mL) se agregaron N-hexil-2-feniletilamina (0.080 g, 0.39 mmol) y DMAP (0.045 g, 0.37 mmol) seguido por clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (0.071 g, 0.37 mmol), y la mezcla de reacción se agitó a temperatura de la sala de un día para otro. La mezcla se diluyó con cloruro de metileno (25 mL), y la fase orgánica se lavó con 5% HCl (3 x 25 mL), NaHCO_3 acuoso (25 mL) y salmuera (25 mL), se secó sobre Na_2SO_4 , y se concentró *in vacuo*. La purificación en una columna pre-empacada de gel de sílice (Isolute® SPE Column, 5 g Si/25 mL) con

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metanol (0-1% gradiente) en cloruro de metileno como el eluyente produjo 0.125 g (70%) de un aceite incoloro.

^1H NMR (400 MHz, CDCl_3): δ 0.82-0.92 (m, 3H), 1.16 (t, 3H), 1.19-1.33 (m, 9H), 1.45-1.65 (m, 2H), 2.82-2.90 (m, 2H), 2.91-2.98 (m, 2H), 3.12-3.21 y 3.29-3.42 (2m, 3H, rotámeros) 3.50-3.65 (m, 3H), 3.95 (m, 1H), 4.16 (q, 2H), 4.39 y 4.65 (2s, 2H, rotámeros), 6.75 y 6.86 (2d, 2H, rotámeros), 7.10-7.34 (m, 7H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 14.1, 14.3, 15.1, 22.6, 26.5, 26.7, 27.4, 29.0, 31.5, 31.6, 33.9, 35.3, 38.5, 45.9, 48.1, 48.3, 48.9, 60.8, 66.2, 67.5, 80.4, 114.5, 126.4, 126.9, 128.5, 128.9, 130.1, 130.2, 130.5, 130.5, 138.3, 139.2, 156.9, 157.0, 167.6, 167.8, 172.5; (El número de picos es mayor que el número de átomos de carbono debido a rotámeros.)

(ii) Ácido (2S)-2-etoxi-3-(4-{2-[hexil(2-feniletíl)amino]-2-oxoetoxi} fenil) propanoico

A una solución de (2S)-2-etoxi-3-(4-{2-[hexil(2-feniletíl)amino]-2-oxoetoxi} fenil)propanoato de etilo (0.081 g, 0.17 mmol) en THF (8.6 mL) se agregó 4.3 mL de una solución 0.10 M LiOH y la mezcla de reacción se agitó a temperatura de la sala de un día para otro. La mezcla de reacción se acidificó con 2M HCl y se extrajo con acetato de etilo (3 x 25mL). La fase orgánica combinada se lavó con salmuera (25 mL), se secó sobre Na_2SO_4 , y se concentró *in vacuo* para proporcionar 0.073 g (96%) de un aceite incoloro.

^1H NMR (400 MHz, CDCl_3): δ 0.82-0.93 (m, 3H), 1.15 (t, 3H), 1.20-1.35 (m, 6H), 1.47-1.62 (m, 2H), 2.80-2.99 (m, 3H), 3.00-3.09 (m, 1H), 3.11-3.21 y 3.31-3.44 (2m, 3H, rotámeros), 3.50-3.67 (m, 3H), 4.01 (m, 1H), 4.40 y 4.66 (2s, 2H, rotámeros), 6.75 y 6.85 (2d, 2H, rotámeros), 7.10-7.35 (m, 7H), 8.86 (bs, 1H).

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N
K

^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 14.1, 15.1, 22.6, 22.6, 26.6, 26.7, 27.3, 28.9, 31.5, 31.6, 33.8, 35.2, 38.1, 46.1, 48.3, 48.4, 49.0, 66.7, 67.4, 79.9, 114.6, 126.4, 127.0, 128.6, 128.9, 130.0, 130.1, 130.6, 130.7, 138.2, 139.1, 156.9, 157.0, 168.1, 168.2, 175.6. (El número de picos es mayor que el número de átomos de carbono debido a rotámeros.)

ACTIVIDAD BIOLÓGICA

Formulaciones

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

PRODUCTOS QUÍMICOS Y REACTIVOS GENERALES

El reactivo del análisis de luciferasa se adquirió de Packard, USA. Las enzimas de restricción eran de Boehringer y la polimerasa Vent 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 re congelaron en lotes del 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 bovino fetal, a 5% CO_2 . Se empleó solución salina tamponada con fosfato (PBS) sin adición de calcio o magnesio. Todos los reactivos de cultivo de células eran de Gibco (USA) y se adquirieron placas de cultivo de 96 pozos de Wallach.

CONSTRUCTOS PLÁSMIDOS PARA EXPRESIÓN HETERÓLOGA

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

Los vectores de expresión utilizados se basaron en pSG5 (Stratagene). Todos los vectores contienen un fragmento EcoRI/NheI que codifica el dominio de unión de DN de GAL4 (que codifica las 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.

La secuencia de localización nucleares construyó usando oligonucleótidos traslapantes hibridados creando extremos adhesivos NheI/KpnI (5'-CTAGCGCTCCTAGAAGAAACGCAAGGTTGGTAC-3'). Los dominios de unión del ligando de PPAR α humano y de ratón y PPAR γ de humano y ratón se amplificaron con PCR como fragmentos KpnI/BamHI y se clonaron insertándolos al dominio de unión de ADN GAL4 y la secuencia de localización nuclear. La secuencia de todos los constructos de plásmidos usados se confirmó mediante secuenciación. Se emplearon los siguientes factores de expresión para las transfecciones transitorias:

vector	subtipo PPAR codificado	Secuencia de referencia ¹
pSGGALhPPa	PPAR α humano	S74349, nt 625-1530
pSGGALmPPa	PPAR α murino	X57638, nt 668-1573
pSGGALhPPg	PPAR γ humano	U63415, nt 613-1518

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pSGGALmPPg	PPAR γ murino	U09138, nt 652-1577
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se refiere a las posiciones de nucleótidos de la entrada de base de datos usadas para expresar el dominio de unión de ligando.

TRANSFECCIONES TRANSITORIAS

Cepas congeladas de células de número de pasaje seis se descongelaron y expandieron al número de pasaje ocho antes de las transfecciones. Se triptinizaron las células confluyentes, se lavaron y 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 del 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 Pulser™ en lotes de 0.5 ml. Un total de 50 μ g ADN se agregó a cada lote de 0.5 ml de células, incluidos 2.5 μ g de vector de expresión, 25 μ g vector reportero y 22.5 μ g ADN no especificado (pBluescript, Stratagene).

Luego de la electroporación, las células se diluyeron en 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 a las células recuperarse, las placas sembradas se incubaron a 37°C durante 3-4 horas antes de la adición de compuestos de prueba. En análisis para detectar PPAR α , el medio de células se suplementó con cuero fetal bovino filtrado en resina-carbón (FCS) con el fin de evitar la activación de fondo por componentes de ácidos grasos del FCS. El FCS filtrado en resina-carbón se produjo en la siguiente forma; para 500 ml de FCS inactivado por calor, se agregaron 10 g carbón y 25 g de Resina de Intercambio de Aniones Grado Analítico Bio-Rad, tamaño de malla 200-400, y la solución se mantuvo en un agitador magnético a temperatura de la sala de un día para

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A

otro. Al día siguiente, el FCS se centrifugó y se repitió el procedimiento de filtración durante 4-6 horas. Luego del segundo tratamiento, el FCS se centrifugó y el filtro se esterilizó con el fin de retirar los remanentes de carbón y resina.

PROCEDIMIENTO DE ANÁLISIS

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

Una vez ajustada la cantidad del medio de células a 75 μ l en cada pozo, se agregaron 50 μ l de solución de compuesto de prueba. Células transfectadas transitoriamente se expusieron a compuestos durante alrededor de 24 horas antes de realizar el análisis de detección de luciferasa. Para los análisis de luciferasa, se agregaron 100 μ l de un reactivo de análisis manualmente 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

Se utilizó la pioglitazona TZD como sustancia de referencia para la activación de PPAR γ humano y murino. Como sustancia de referencia para PPAR α humano se utilizó ácido 5,8,11,14-eicosatetrayónico (ETYA).

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 de fondo) y se expresaron como el porcentaje de la activación máxima obtenida por el compuesto de referencia. Se graficaron los valores contra el logaritmo de la concentración del compuesto de prueba. Los valores EC₅₀ se proyectaron por intercalación lineal entre los puntos de datos y calculando la

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concentración requerida para conseguir 50% de la activación máxima obtenida por el compuesto de referencia.

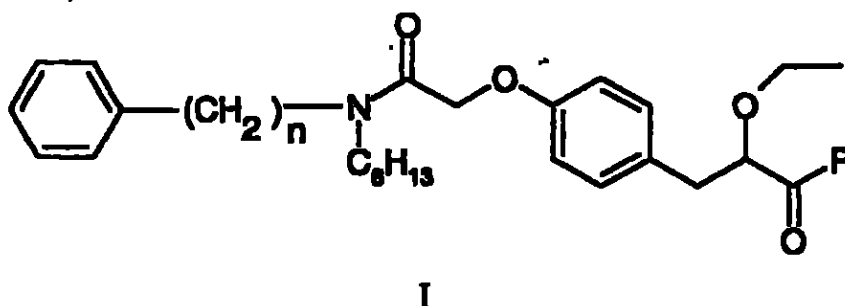
Los compuestos de fórmula I tienen un EC_{50} de menos de $0.5\mu\text{ mol/l}$ para $PPAR\alpha$ y compuestos preferidos tienen un EC_{50} de menos de $0.05\mu\text{ mol/l}$ para $PPAR\alpha$. Los compuestos de fórmula I son un grupo selecto de compuestos en que son más potentes con respecto a $PPAR\alpha$ que con respecto a $PPAR\gamma$. Se cree que esta relación es importante con respecto a la actividad farmacológica de los compuestos y a su perfil terapéutico.

Adicionalmente, los compuestos de la presente invención exhiben propiedades DMPK (Metabolismo y Farmacocinética de Medicamentos) mejoradas, por ejemplo exhiben una estabilidad metabólica mejorada *in vitro* y presentan además curvas favorables de respuesta a la dosis *in vivo*. Asimismo, los compuestos poseen un perfil toxicológico promisorio.

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REIVINDICACIONES

1. El S enantiómero de un compuesto de fórmula I



en donde n es 1 ó 2 y sales farmacéuticamente aceptables, solvatos, formas cristalinas y profármacos del mismo.

2. Un compuesto seleccionado de:

ácido (2S)-3-(4-{2-[bencil(hexil)amino]-2-oxoetoxi} fenil)-2-etoxipropanoico;

ácido (2S)-2-etoxi-3-(4-{2-[hexil(2-feniletíl)amino]-2-oxoetoxi} fenil)propanoico;

y sales farmacéuticamente aceptables, solvatos y formas cristalinas de los mismos.

3. Ácido (2S)-3-(4-{2-[bencil(hexil)amino]-2-oxoetoxi} fenil)-2-etoxipropanoico y sales farmacéuticamente aceptables, solvatos y formas cristalinas del mismo.

4. Ácido (2S)-2-etoxi-3-(4-{2-[hexil(2-feniletíl)amino]-2-oxoetoxi} fenil)propanoico y sales farmacéuticamente aceptables, solvatos y formas cristalinas del mismo.

5. Una formulación farmacéutica que comprende un compuesto de acuerdo

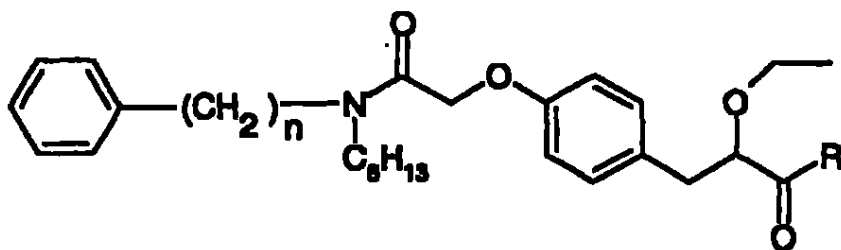
con una cualquiera de las reivindicaciones 1-4 en mezcla con auxiliares farmacéuticamente aceptables, diluyentes y/o vehículos.

6. Un método de tratar o prevenir trastornos de lípidos (dislipidemia) asociados o no con resistencia a la insulina, que comprende la administración de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-4 a un mamífero necesitado del mismo.

7. El uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-4 en la manufactura de un medicamento para el tratamiento de trastornos de lípidos (dislipidemia) asociados o no con resistencia a la insulina.

8. Un método de tratar o prevenir diabetes tipo 2, que comprende la administración de una cantidad efectiva de un compuesto de fórmula I de acuerdo con una cualquiera de las reivindicaciones 1-4 a un mamífero necesitado del mismo.

9. Un proceso para la preparación de un compuesto de fórmula I que comprende hacer reaccionar un compuesto de fórmula II

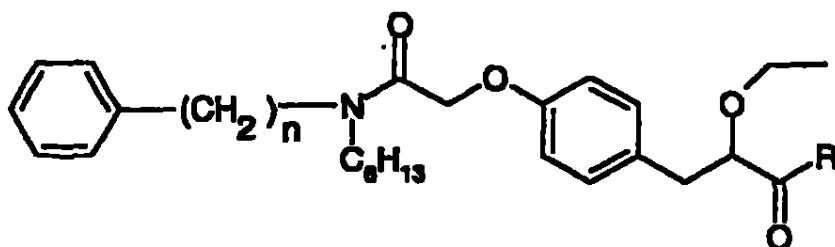


II

en la cual n es como se define previamente y R representa un grupo protector para el grupo hidroxí carboxílico con un agente desprotector.

10. Un compuesto de fórmula II

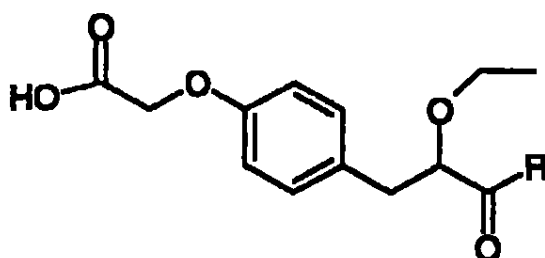
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II

en la cual n es como se define previamente y R representa un grupo protector para el grupo hidroxilo carboxílico con un agente desprotector.

11. Un compuesto de fórmula III



III

en la cual R es como se define previamente.

12. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 4 combinado 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.

13. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 4 combinado con otro agente modulador PPAR.

14. Una composición farmacéutica que comprende un compuesto como se

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reivindica en una cualquiera de las reivindicaciones 1 a 4 combinado con un agente reductor de colesterol.

15. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 4 combinado con un inhibidor de HMG-CoA reductasa.

16. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 4 combinado con atorvastatina o una sal farmacéuticamente aceptable, solvato, forma cristalina o profármaco del mismo.

17. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 4 combinado con rosuvastatina o una sal farmacéuticamente aceptable del mismo.

18. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 4 combinado con un inhibidor IBAT.

19. Una composición farmacéutica de acuerdo con la reivindicación 18 en donde el inhibidor IBAT se selecciona de 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-

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

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

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

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

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

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

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

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

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

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

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

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxi-2-metilpropil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-

tetrahidro-1,2,5-benzotiadiazepina;

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxibutil)carbamoil]-4-hidroxibencil}carbamoilmetoxi)-2,3,4,5-

tetrahidro-1,2,5-benzotiadiazepina;

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

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

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

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

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

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*-((R)-1-carboxi-2-metiltioetil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

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

1,1-dioxo-3,3-dibutil-5-fenil-7-metiltio-8-(*N*-{(R)- α -[*N*-((S)-1-carboxi-2-metilpropil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,2,5-benzotiadiazepina;

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

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 una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco de las mismas.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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

Applicant's or agent's file reference 100595/WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 02/ 05738	International filing date (day/month/year) 18/12/2002	Priority date (day/month/year) 19/12/2001
International Patent Classification (IPC) or national classification and IPC C07C235/20		
Applicant ASTRAZENECA AB ET AL.		

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

These annexes consists of a total of _____ sheets.

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

Date of submission of the demand 17/06/2003	Date of completion of this report 02/07/2003
Name and mailing address of the IPEA/  European Patent Office, Göttscheiner Str. 103 D-10969 Berlin - Germany Tel: (+49-30) 25901-0 Fax: (+49-30) 25901-840	Authorized officer DE BUNDEL E R J Tel. (+49-89) 2399 2828 

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

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

100595/WO

Original (for SUBMISSION) - printed on 17.12.2002 11:25:34 AM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.10.2002)
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	100595/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 ME 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 IE IT LU MC NL PT SE 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 BE 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 ME NO NZ OM PH PL PT RO RU SC SD SE SG SI 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

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100595/WO

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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)	ALSTERMARK LINDSTEDT, Eva-Lotte
III-2-5	Address:	Molndal S-431 83 Sweden
III-2-6	State of nationality	SE
III-2-7	State of residence	SE
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	BOIJE, Anna, Maria, Persdotter
III-3-5	Address:	Molndal S-431 83 Sweden
III-3-6	State of nationality	SE
III-3-7	State of residence	SE
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	HOLM, Patrik
III-4-5	Address:	Molndal S-431 83 Sweden
III-4-6	State of nationality	FI
III-4-7	State of residence	SE

PCT REQUEST

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100585/WO

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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	ASTRAZENECA
IV-1-2	Address:	Global Intellectual Property Mereside Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
IV-1-3	Telephone No.	+44 1625 230148
IV-1-4	Facsimile No.	+44 1625 510752
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AE 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 IE IT LU MC NL PT SE 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 NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

PCT REQUEST

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V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	19 December 2001 (19.12.2001)	
VI-1-2	Number	0104333-0	
VI-1-3	Country	SE	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VII-2	Request to use results of earlier search; reference to that search		
VII-2-1	Date	19 December 2001 (19.12.2001)	
VII-2-2	Number	SE 01/01590	
VII-2-3	Country (or regional Office)	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	33	-
IX-3	Claims	8	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	47	

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PCT REQUEST

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	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	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	Agent	
X-1-3	Capacity	AstraZeneca	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
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	
------	--	--

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 100595/WO	
International application No. PCT/GB2002/005738	International filing date (day/month/year) 18 December 2002 (18.12.2002)	(Earliest) Priority date (day/month/year) 19 December 2001 (19.12.2001)	
Title of invention SUBSTITUTED PHENYLPROPIONIC ACID DERIVATIVES AS AGONISTS TO HUMAN PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR ALPHA (PPAR)			
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 S-151 85 Södertälje Sweden		Telephone No. +44 1625 5130148	
		Facsimile No. +48 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 GB			
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.) ALSTERMARK LINDSTEDT, Eva-Lotte Molndal S-431 83 Sweden			
State (that is, country) of nationality: SE		State (that is, country) of residence: SE	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

OLSSON, Anna Christina
Molndal
S-431 83
Sweden

State (that is, country) of nationality:
SEState (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.)

LI, Lanna
Molndal
S-431 83
Sweden

State (that is, country) of nationality:
SEState (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.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐

Further applicants are indicated on another continuation sheet.

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.)GAINEY, Laurence David Scott
ASTRAZENECA
Global Intellectual Property
Mersey, Alderley Park
Macclesfield,
Cheshire, SK10 4TG
GB

Telephone No.

+44 1625 517081

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 (specify) | : | 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 (specify): |
| 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).

.....
GAINEY, Laurence David Scott 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:

Brigard & Castro

BOGOTA - COLOMBIA

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) ASTRAZENECA AB

domiciliado(s) en

domiciled in SE-131-Bodertalje, 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 enseñanzas, 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 ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.

domiciliado(s) en la Carrera 7 No. 16-58 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 vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they 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 pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm deal, 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. 16-58 Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

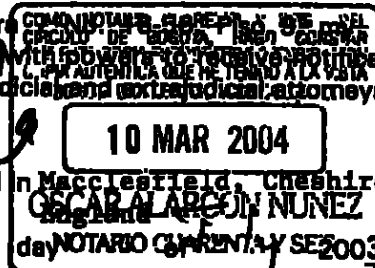
Granted and signed in Macclesfield, Cheshire,

this

Signature

Name KEVIN BILL

Title Director TB Services



110816

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy _____ de _____ de _____
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el
anterior documento, debidamente juramentado declaró
y dijo que él es

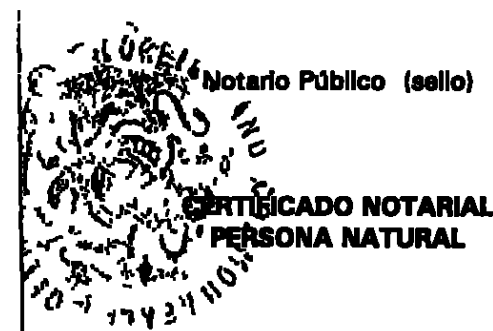
de

Sociedad legalmente constituida para un período de
duración que aún no ha terminado, que el declarante
está autorizado por dicha compañía para conferir este
poder, que el sello estampado por él al pie de tal poder,
en nombre y representación de la expresada compañía,
es el sello oficial de ella y que el objeto para el cual se
confiere este instrumento está comprendido dentro del
de la sociedad

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad

Estado de _____
en fecha _____

que quien confiere el presente poder es su
representante



oy _____ 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

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of _____
personally appeared before me

KEVIN BILLY
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

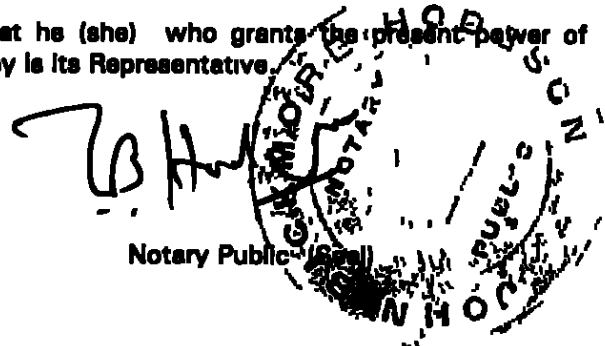
ATTORNEY
of ATRAZENECA AB

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 the
purpose for which this instrument is granted is
included within the corporate purpose of company

The undersigned Notary Public attests that he has seen
the documents that prove the existence of the
company

State of Sweden
under date of 1st January 2003

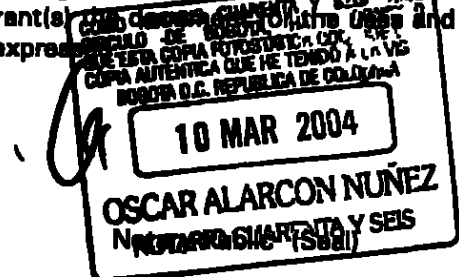
and that he (she) who grants the present power of
attorney is its Representative.



**NOTARIAL CERTIFICATE
NATURAL PERSON**

On this _____ day of _____ of _____
personally appeared before me

who is(are) known to me and who I attest executed
the foregoing document and he (they) declared he
(they) grant(s) the power of attorney for the uses and purposes
therein expressed



LEGALIZATION BY APOSTILLE IS REQUIRED

7

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

Thus 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/simbre de

Certified/Attesté

- 5 at London/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.

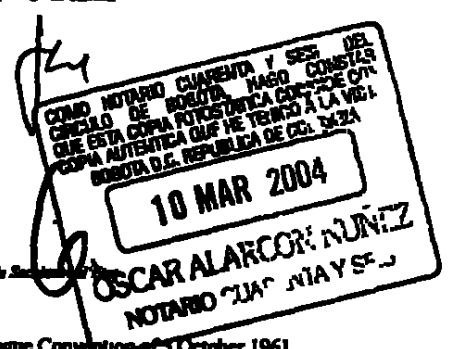
- 8. Number/sous No: **G348987**

- 9 Stamp

- 10. Signature: J Ireland

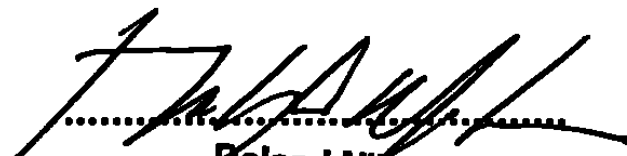
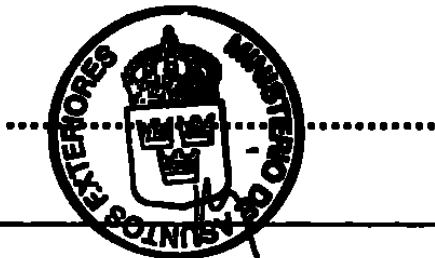


For the Secretary of State / Pour le Secrétaire d'Etat



If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961
it should be presented to the consular section of the mission representing that country

26

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 7 de junio de 2004****7. de Ministerio de Asuntos Exteriores****8. N° 3753****9. Timbre/Sello****10. Firma**
Roland Nilsson

ASSIGNMENT

The undersigned,

Eva-Lotte ALSTERMARK LINDSTEDT
Anna, Christina OLSSON
Lanna LI

domiciled in
Mölnadal, SE-431 83 Mölnadal, Sweden
Mölnadal, SE-431 83 Mölnadal, Sweden
Mölnadal, SE-431 83 Mölnadal, Sweden

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

SUBSTITUTED PHENYLPROPIONIC ACID DERIVATIVES AS AGONISTS TO HUMAN PEROXISOME
PROLIFERATOR-ACTIVATED RECEPTOR ALPHA (PPAR)

We state as well that we 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.


Eva-Lotte ALSTERMARK LINDSTEDT


Lanna LI

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.


Anna, Christina OLSSON

La infrascrita Anne-Marie Bonde, Notario Público
de Estocolmo, Suecia, certifica que
Eva-Lotte ALSTERMARK LINDSTEDT,
Anna, Christina OLSSON,
Lanna LI

han otorgado y firmado el documento que antecede.
Derechos Coronas Estocolmo, 2004-06-04
De oficio:





100

TRADUCCION DEL SELLO QUE SE ENCUENTRA EN EL DOCUMENTO DE CESIÓN DE DERECHOS SOBRE LA INVENCIÓN, OTORGADO POR LOS INVENTORES: EVA-LOTTE ALSTERMARK LINDSTEDT, ANNA CHRISTINA OLSSON Y LANNA LI, A LA SOCIEDAD ASTRAZENECA AB, DOMICILIADA EN S-151 85 SÖDERTÄLJE, SUECIA, DEL SUECO AL CASTELLANO.

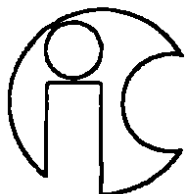
**ANNE-MARIE BONDE
NOTARIO PÚBLICO DE ESTOCOLMO**

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
Indicación de que se solicita la concesión de una patente	()	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
Descripción de la invención.	()	()
Dibujos de ser estos pertinentes.	()	()
Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA	()	()
INCOMPLETA	()	()
DISEÑO INDUSTRIAL	()	()
Indicación de que se solicita el registro de Diseño Industrial	()	()
Datos de identificación del solicitante o de la persona que presenta la solicitud	()	()
Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA	()	()
INCOMPLETA	()	()
ESQUEMA DE TRAZADO	()	()
Indicación de que solicita el registro de un Esquema de trazado.	()	()
Datos de identificación del solicitante o de la persona que presenta La solicitud	()	()
Representación gráfica del esquema de trazado	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA	()	()
INCOMPLETA	()	()

Firma Responsable:

Fecha



2020
Bogotá DC

Folio 102

Doctor(a)
RAMIRO CASTRO DUQUE
Apoderado(a)
ASTRAZENECA A.B.

REFERENCIA:	Radicación No.	04-67616
	Solicitud Internacional	PCT/GB2002/05738
	Fecha inicio fase nacional	19/07/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	1283
	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 la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 04 de Julio 2004


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202057