

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



DELEGATURA PROPIEDAD INDUSTRIAL

Division de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

21 EXPEDIENTE No 04-68143

54 TITULO DERIVADOS DE ACIDO 3-FENIL-2-ARILALQUILITIO PROPIONICO COMO
ANTAGONISTAS SELECTIVOS DE PPAR-ALFA

51 CLASIFICACION INTERNACIONAL _____

71 SOLICITANTE ASTRAZENECA AB

DOMICILIO SODENTALJE SUECIA

74 APODERADO RAMIRO CASTRO DUQUE

22 SANTAFE DE BOGOTA, D C _____

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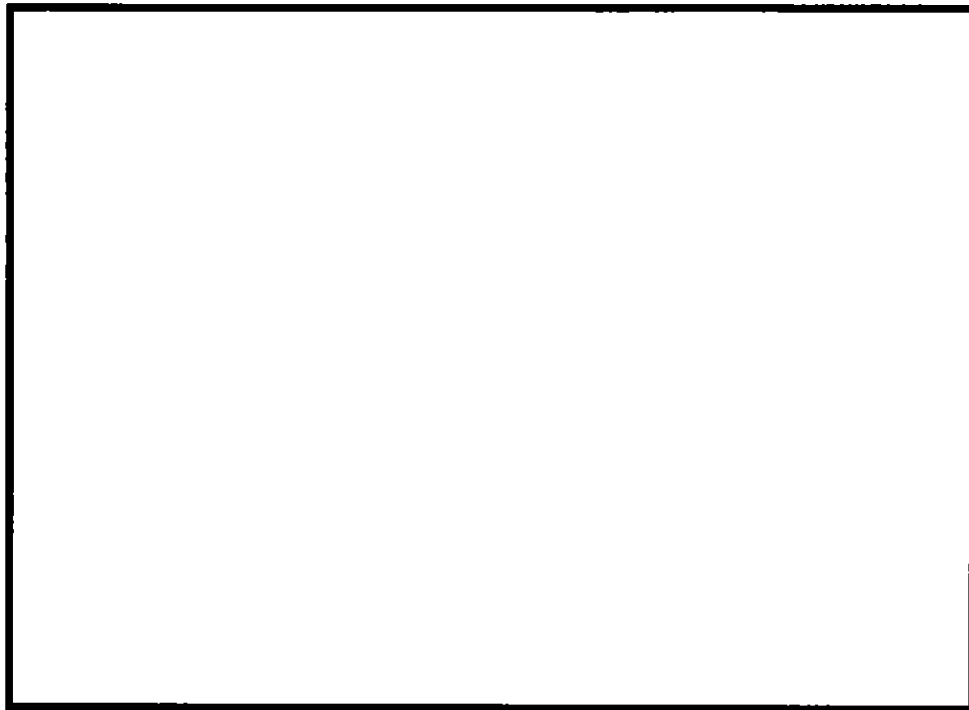
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☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
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2 SOLICITANTE (71)	Nombre: ASTRAZENECA AB Dirección: S-151 85 Sodertälje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: 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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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 acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente:

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170422 de Bogotá T.P. 1003 del C.S.U.

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

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***** CONCEPTO *****

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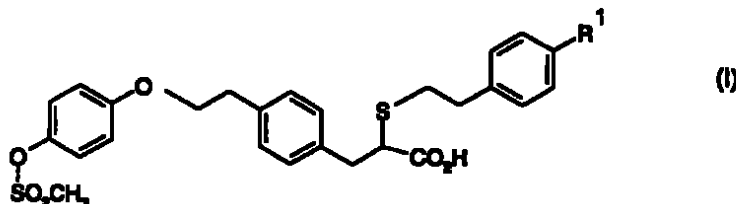
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ning of each regular issue of the PCT Gazette.

(54) Title: 3-PHENYL-2-ARYLALKYLTHIOPROPIONIC ACID DERIVATIVES AS SELECTIVE AGONISTS OF PPAR-ALPHA



(57) Abstract: A compound of formula (I); wherein R¹ represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, 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, to methods for their therapeutic use and to pharmaceutical compositions containing them.

**3-PHENYL-2-ARYLALKYLTHIOPROPIONIC ACID DERIVATIVES
AS SELECTIVE ANTAGONISTS OF PPAR-ALPHA**

Field of the invention

5 The present invention relates to certain novel 3-phenyl-2-arylalkylthiopropionic 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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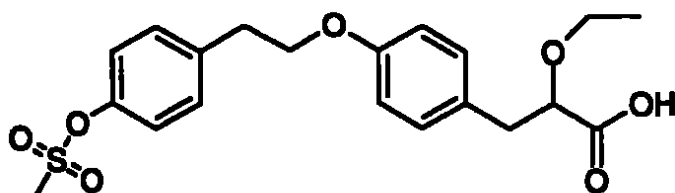
Background of the invention

The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly
15 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.

20 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.

25 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.

30 The S-enantiomer of the compound of formula C below

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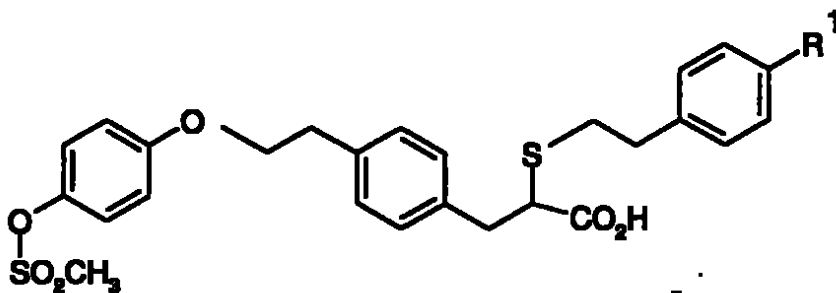
C

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 selective PPAR α modulators.

Description of the invention

The present invention provides a compound of formula I



I

wherein R¹ represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof.

It will be appreciated by those skilled in the art the compounds of formula I contain an optically active centre and therefore can exist as enantiomers which can be separated as described later. It is expected that most, if not all, of the activity of the compounds of formula I resides in one enantiomer: either the S or the R enantiomer or the (+) or the (-)

enantiomer. The enantiomers which are more active in the assays which are described later are preferred forms of the present invention. It will be understood that the present invention includes all mixtures of this active enantiomer with the other enantiomer, for example the racemic mixture, which is a useful intermediate for the active enantiomer.

5

The active enantiomers may be isolated by separation of racemate for example by fractional crystallization, resolution or HPLC on a chiral column (for example a ChiralpakTM AD 250x50 column). Alternatively the active enantiomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause
10 racemisation or epimerisation, or by derivatisation with a chiral reagent.

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. The term "prodrug" also includes derivatives of the
15 hydroxy substituent (when R¹ represents hydroxy) which are converted in a mammal, particularly a human, into the hydroxy group or a salt or conjugate thereof. It should be understood that, whilst not being bound by theory, it is believed that most of the activity associated with the prodrugs arises from the activity of the compound of formula I into which the prodrugs are converted. Prodrugs can be prepared by routine methodology well
20 within the capabilities of someone skilled in the art. Various prodrugs of carboxy and hydroxy are known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology. 42: 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and
25 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).

30 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* hydrolysable (or cleavable) ester of a compound of the formula (I) that contains a carboxy

or a hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters, for example, methoxymethyl; C₁₋₆alkanoyloxymethyl esters, for example, pivaloyloxymethyl; phthalidyl esters; C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters, for example, 1-cyclohexyl-carbonyloxyethyl; 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. An *in vivo* hydrolysable (or cleavable) ester of a compound of the formula (I) that contains a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxy carbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

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

Specific compounds of the invention are:

2-([2-(4-chlorophenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid; preferably either the (R)- enantiomer or the (S)- enantiomer;

- 2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid; preferably either the (R)- enantiomer or the (S)- enantiomer;
- 2-([2-(4-fluorophenyl)ethyl]thio)-3-[4-(2-{4- [(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid; preferably either the (R)- enantiomer or the (S)- enantiomer;
- (-)-2-([2-(4-chlorophenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid and
- (-)-2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;
- and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof.

It will be understood by those skilled in the art that where (-) occurs in the above list that the compound indicated has a negative rotation when measured using the conditions and concentration described in the experimental section. It should be understood that salts of the parent acid are included even if a particular salt exhibits a (+) rotation provided that the absolute configuration of the salt is the same as the configuration of the (-)-parent acid.

Specific enantiomers of the invention are selected from one or more of the following:

- (R)- 2-([2-(4-chlorophenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;
- (S)-2-([2-(4-chlorophenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;
- (R)-2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;
- (S)-2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;
- (R)-2-([2-(4-fluorophenyl)ethyl]thio)-3-[4-(2-{4- [(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;
- (S)- 2-([2-(4-fluorophenyl)ethyl]thio)-3-[4-(2-{4- [(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;

(-)-2-[[2-(4-chlorophenyl)ethyl]thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid and

(-)-2-[[2-(4-hydroxyphenyl)ethyl]thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;

5 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.

10

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

15

encompasses all such tautomers.

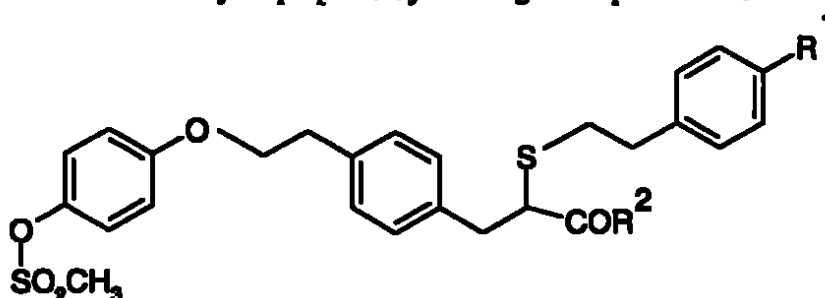
Methods of preparation

The compounds of the invention may be prepared as outlined below. However, the

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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.

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

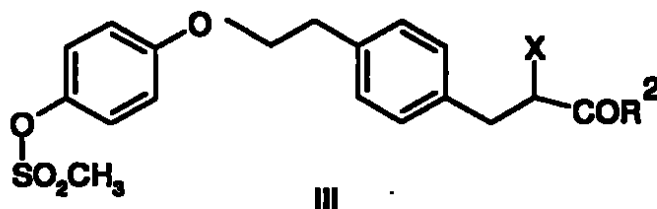


II

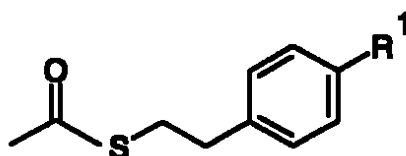
25

in which R^1 is as previously defined and R^2 represents a protecting group for 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 reagent. The protecting group may also be a resin, such as Wang resin or 2-chlorotrityl chloride resin. Protecting groups may be removed in accordance to techniques which are well known to those skilled in the art. One such protecting group is where R^2 represents C_{1-6} alkoxy group or an arylalkoxy group eg benzyloxy, such that COR^2 represents an ester. Such esters can be reacted with a de-protecting reagent 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 a compound of formula III

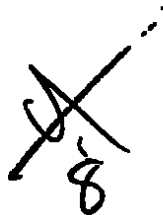


in which R^2 is as previously defined and X is a leaving group for example halo e.g. chloro with a compound of formula IV



in which R^1 is as previously defined or a protected hydroxy group for example R^1 is benzyloxy.

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, III and IV are believed to be novel and are claimed herein as useful intermediates in the preparation of compounds of formula I.

- 5 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
10 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).

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

Pharmaceutical preparations

20

- 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
25 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.

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

- 10 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

- 15 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
20 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)
25 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
30 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 antidyshlipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-
5 angiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of their insulin sensitizing effect the compounds of formula I are also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term
10 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
15 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.

20

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.

25

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.

30 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.

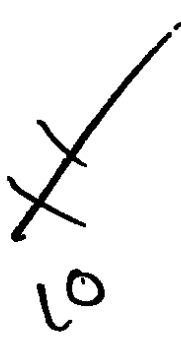
9 Combination Therapy

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

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The compounds of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial
20 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.

In another aspect of the invention, the compound of formula I, or a pharmaceutically
25 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, 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
30 thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5),



623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference.

Particularly a PPAR alpha and/or gamma agonist refers to 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.

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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, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolclamide 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.

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Alternatively smaller doses may be used as a result of the benefits derived from the combination.

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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, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt. A particular statin is atorvastatin, or a

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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, 5 [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[N-methyl-N-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European 10 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 15 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).

20 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 25 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 30 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 suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and
5 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-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:
10 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-
15 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-
20 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;
25 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-
30 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;
- 5 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{ α -[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 10 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)-
- 15 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-
- 20 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-
- 25 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;

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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-methylsulphonyl)-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;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-[(*R*)- α -(*N*-[(*R*)-1-carboxy-2-

methylthio-ethyl) carbamoyl]-4-hydroxybenzyl) carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

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

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

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

benzothiadiazepine;

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

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

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

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

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

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

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

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

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

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

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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
5 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;
- 10 a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and nicheritrol;
- a phytosterol compound for example stanols;
- probucol;
- an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB
15 2,184,122 and US 4,929,629);
- an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic
20 or a vasodilator;
- 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
- 25 modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;
- or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.
- 30 Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with a compound of formula I include but are not limited to, the following compounds:

alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, 5 fosenopril, fosenopril 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, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, 10 spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

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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 20 angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the 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, 25 such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt 30 or a prodrug thereof.

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

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

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

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

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

- a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- 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 a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in 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.

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.

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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~~X~~**Examples**

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

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

Abbreviations

10	DMSO	dimethyl sulfoxide
	EtOAc	ethyl acetate
	DMF	<i>N,N</i> -dimethylformamide
	THF	tetrahydrofuran
15	MeCN	acetonitrile
	MeOH	methanol
	TFA	trifluoroacetic acid
	NH ₄ OAc	ammonium acetate
	t	triplet
20	s	singlet
	d	doublet
	q	quartet
	m	multiplet
	bs	broad singlet

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Example 1**2-[2-(4-Chlorophenyl)ethyl]thio]-3-[4-(2-[4-
[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoic acid****5 (i) [2-(4-Chlorophenyl)ethyl]ethanethioate**

1-(2-Chloroethyl)-4-chlorobenzene (0.700 g, 4.00 mmol), thioacetic acid (0.320 g, 4.20 mmol) and triethylamine (0.425 g, 4.20 mmol) were dissolved in MeOH (8 ml). The solution was warmed with microwaves for 900 seconds at 150 °C. The mixture was used in the next step without purification.

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(ii) 2-[2-(4-Chlorophenyl)ethyl]thio]-3-[4-(2-[4-**[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoic acid**

The reaction vessel was flushed with argon. To a part 0.8 ml (0.400 mmol) of the mixture from the reaction step above was added under stirring sodium methanethiolate (56.5 mg, 0.800 mmol) in MeOH (0.2 ml). After an hour methyl 2-chloro-3-[4-(2-[4-
15 [(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoate (0.200 g, 0.484 mmol, prepared as described in Example 2) in acetonitrile (0.800 ml) was added. The mixture was stirred for 16 h under an argon atmosphere and then centrifuged under vacuum at 35 °C. 2 ml 0.5 M LiOH solution (THF/water 7:1) was added and the mixture was stirred vigorously for 20
20 h. After acidification with 12 M HCl (100 µl) the stirring was continued for another hour. The crude product was filtered through a Teflon™ filter and further purified using preparative HPLC (0.2 % TFA/MeCN, gradient). The pooled fractions were centrifuged under vacuum giving 18 mg of the desired product (yield 7%).

¹H-NMR (400 MHz, CDCl₃): 2.75-2.95 (m, 5H), 3.06 (t, 2H), 3.10 (s, 3H), 3.16 (dd, 1H),
25 3.45 (dd, 1H), 4.14 (d, 2H), 6.87 (d, 2H), 7.05 (d, 2H), 7.11-7.27 (m, 8H).

**(iii) (-)-2-[2-(4-chlorophenyl)ethyl]thio]-3-[4-(2-[4-[(methylsulfonyl)oxy]-
phenoxy)ethyl]phenyl]propanoic acid**

30 The (-)-enantiomer of 2-[2-(4-chlorophenyl)ethyl]thio]-3-[4-(2-[4-[(methylsulfonyl)-oxy]phenoxy)ethyl]phenyl]propanoic acid was separated from the racemate by chiral

chromatography. A Chiralpak AD JP003 (250 x 20 mm i.d.) column was used and ethanol/formic acid 100/0.1% as mobile phase. The racemate (2 g) was dissolved in ethanol (20 mg/ml) and was injected onto the column. The first eluting peak was collected and UV-detected. The product (0.9 g) was obtained with an enantiomeric purity = 99.2%.

The optical rotation was found to be $[\alpha]^{20}_D = -29^\circ$ by dissolving the enantiomer in ethanol to give a concentration of 0.5 g/100ml. The optical rotation was measured at 20 °C using the sodium line at 589 nm.

¹H NMR (500 MHz, CD₃OD): 7.18-7.25 (6H, m), 7.15 (2H, d), 7.13 (2H, d), 4.16 (2H, t), 3.45 (1H, t), 3.14 (3H, s), 3.11 (1H, m), 3.04 (2H, t), 2.77-2.90 (5H m).

Example 2

2-([2-(4-Hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-
[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoic acid

(i) Methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate

2-(4-Aminophenyl)ethanol (11g, 81mmol) and 32ml conc HCl was dissolved in acetone and cooled to 0°C. Sodium nitrite (5.6g, 81mmol) in 20ml water was added dropwise. The temperature was kept under 0°C. After one hour, methyl acrylate (70g, 808mmol) and CuI (1.6g, 8mmol) were added (<0°C). The reaction mixture was stirred at room temperature overnight.

The solvent was evaporated and water was added. The water phase was extracted three times with EtOAc, the organic phases were pooled and washed with water, dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by flash chromatography using a 65:35 mixture of EtOAc and heptane as eluent. Further purification by preparative HPLC (using a gradient of CH₃CN/ 5%CH₃CN-waterphase containing 0.1M NH₄OAc as eluent) gave 9.7g product (yield 49%) as an oil.

¹H NMR (400MHz, CDCl₃): 2.84 (t, 3H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 3.84 (t, 3H), 4.43 (t, 1H), 7.17 (d, 4H)

(ii) Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate

Triphenylphosphine (2.4g, 9mmol) was added to a solution of methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate (2.1g, 8.5mmol) and 4-(benzyloxy)phenol (1.7g, 8mmol) in 20ml toluene under nitrogen atmosphere. The solution was warmed to 55°C and diisopropyl azodicarboxylate (1.8g, 9mmol) was added. The reaction mixture was stirred at 55°C overnight.

The mixture was allowed to cool and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using a 80:20 mixture of heptane and EtOAc as eluent to yield 2.28g of the desired product (yield 61%) as colourless crystals.

¹HNMR (400MHz, CDCl₃): 3.05 (t, 2H), 3.16 (dd, 1H), 3.36 (dd, 1H), 3.75 (s, 3H), 4.12 (t, 2H), 4.45 (t, 1H), 5.01 (s, 2H), 6.82 (m, 2H), 6.90 (m, 2H), 7.13-7.27 (m, 4H), 7.29-7.47 (m, 5H).

(iii) Methyl 2-chloro-3-[4-{2-(4-hydroxyphenoxy)ethyl}phenyl]propanoate

Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate (1.0g, 2.4mmol) and dimethyl sulfide (0.9g, 14mmol) was dissolved in 60ml CH₂Cl₂. Boron trifluoride etherate (2.0g, 14mmol) was added dropwise to the stirred solution. The reaction mixture was stirred for two days at room temperature. Another equivalent (0.4g, 2.87mmol) boron trifluoride etherate was added and the stirring was continued overnight. Water was added. The phases were separated and the aqueous phase was extracted twice with CH₂Cl₂. The organic phases were pooled, washed (water, brine), dried (Na₂SO₄) and evaporated under reduced pressure. Further purification by preparative HPLC using a gradient of CH₃CN/ 5% CH₃CN-waterphase containing 0.1M NH₄OAc gave 0.55g of the desired product (yield 52%) as an oil.

¹HNMR (400MHz, CDCl₃): 3.04 (t, 2H), 3.16 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 4.10 (t, 2H), 4.40 (t, 1H), 6.75 (m, 4H), 7.12-7.29 (m, 4H).

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X

(iv) Methyl 2-chloro-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy]ethyl)phenyl]propanoate

Methyl 2-chloro-3-[4-[2-(4-hydroxyphenoxy)ethyl]phenyl]propanoate (334mg, 1.0mmol) and triethylamine (303mg, 3.0mmol) was dissolved in 20ml dichloromethane and cooled to -20°C under nitrogen atmosphere. Methanesulfonyl chloride (114mg, 1.0mmol) was added dropwise. The mixture was allowed to reach room temperature. After 2 hours dichloromethane was added, the mixture was washed (water, brine), dried (Na₂SO₄) and evaporated under reduced pressure to yield 394mg pure product (yield 96%).

¹HNMR (400MHz, CDCl₃): 3.02-3.11 (m, 5H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.74 (s, 3H), 4.14 (t, 2H), 4.44 (t, 1H), 5.29 (s, 2H), 6.88 (d, 2H), 7.14-7.25 (m, 6H).

(v) Methyl 2-([2-[4-(benzyloxy)phenyl]ethyl]thio)-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy]ethyl)phenyl]propanoate

2-[4-(Benzyloxy)phenyl]ethanethiol (334mg, 1.4mmol), methyl 2-chloro-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy]ethyl)phenyl]propanoate (394mg, 0.95mmol) and potassium carbonate (189mg, 1.4mmol) were dissolved in 14ml dry DMF and stirred under nitrogen atmosphere at room temperature overnight.

The solvent was evaporated under reduced pressure and the residue was dissolved in toluene. The organic phase was washed (water, brine), dried (MgSO₄) and evaporated.

Further purification by preparative HPLC using a gradient of CH₃CN/5% CH₃CN-waterphase containing 0.1M NH₄OAc gave 477mg of the desired product (yield 75%).

¹HNMR (400MHz, CDCl₃): 2.76-2.89 (m, 4H), 2.95 (dd, 1H), 3.09 (m, 5H), 3.20 (dd, 1H), 3.53 (m, 1H), 3.70 (s, 3H), 4.15 (t, 2H), 5.06 (s, 2H), 6.91 (m, 4H), 7.07-7.24 (m, 8H), 7.31-7.48 (m, 5H).

(vi) Methyl 2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy]ethyl)phenyl]propanoate

To a solution of methyl 2-([2-[4-(benzyloxy)phenyl]ethyl]thio)-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy]ethyl)phenyl]propanoate (477mg, 0.8mmol) and 15ml dichloromethane, dimethyl sulfide (239mg, 3.8mol) and boron trifluoride etherate (545mg,

3.8mmol) were added. After 18 hours of stirring water was added to the reaction. The phases were separated and the aqueous phase was extracted twice with dichloromethane. The organic phases were pooled, dried (MgSO₄) and evaporated under reduced pressure. 274mg of the desired product (yield 67%) was obtained as an oil.

5 ¹HNMR (400MHz, CDCl₃): 2.70-2.85 (m, 4H), 2.91 (dd, 1H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.49 (m, 1H), 3.68 (s, 3H), 4.13 (t, 2H), 6.72 (d, 2H), 6.87 (d, 2H), 6.99 (d, 2H), 7.10-7.22 (m, 6H)

(vii) 2-([2-(4-Hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoic acid

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Methyl 2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoate (105mg, 0.2mmol) was dissolved in 6.5ml of a 7:1 mixture of THF and water and cooled on an ice-bath. Lithium hydroxide (9.4mg, 0.4mmol) was added. Water was added to the reaction mixture after 24 hours of stirring at room temperature. The THF was evaporated under reduced pressure and the residue was acidified with 1M hydrochloric acid. The water phase was extracted with EtOAc (x3), the organic phases were pooled, washed (water, brine), dried (MgSO₄) and evaporated. The crude product was purified using preparative HPLC (eluent: CH₃CN / 5% CH₃CN-waterphase containing 0.1M NH₄OAc) to give 74mg of the desired product (yield 97%) as an oil.

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¹HNMR (400MHz, CDCl₃): 2.68-2.95 (m, 5H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.47 (m, 1H), 4.12 (t, 2H), 6.70 (d, 2H), 6.86 (d, 2H), 6.97 (d, 2H), 7.12-7.21 (m, 6H).

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¹³CNMR (100MHz, CDCl₃): 33.8, 35.1, 35.5, 37.2, 37.3, 48.1, 69.3, 115.6, 115.8, 123.3, 129.3, 129.4, 129.9, 132.3, 136.2, 136.9, 142.8, 154.4, 158.0, 177.2.

(viii) (-)-2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoic acid

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The racemate of 2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoic acid was separated into its enantiomers using chiral

chromatography. A Chiralpak AD JDB01+ AS003 (336 x 100 mm i.d.) and ethanol/formic acid 100/0.01% was used as mobile phase. The racemate (9 g) was dissolved in ethanol and injected onto the column. The first eluting peak was collected and UV-detected. The product (4.1 g) was obtained with an enantiomeric purity >99%. The optical rotation was found to be $[\alpha]_D^{20} = -33^\circ$ by dissolving the enantiomer in methanol to give a concentration of 0.64 g/100ml. The optical rotation was measured at 20 °C using the sodium line at 589 nm.

^1H NMR (500 MHz, CD_3OD): 7.17-7.22 (6H, m), 6.99 (2H, d), 6.94 (2H, d), 6.69 (2H, d), 4.17 (2H, t), 3.46 (1H, t), 3.16 (3H, s), 3.13 (1H, dd), 3.05 (2H, t), 2.69-2.88 (5H, m).

Example 3

2-{[2-(4-Fluorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid

(i) [2-(4-fluorophenyl)ethyl]ethanethioate

To a solution of DMF (60ml) and thioacetic acid (2.1g, 28mmol), cooled in an ice-bath, was added cesium carbonate (9.1g, 28mmol). The reaction mixture immediately turned orange. 1-(2-Chloroethyl)-4-fluorobenzene (4g, 25mmol) was added, the ice-bath was removed and the reaction was stirred overnight. The solvent was evaporated and the residue was dissolved in EtOAc. The organic phase was washed (water), dried (NaSO_4) and evaporated under reduced pressure to yield 5g (99%) of the desired product as an oil.

^1H NMR (400MHz, CDCl_3): 2.33 (s, 3H), 2.83 (t, 2H), 3.09 (t, 2H), 6.98 (t, 2H), 7.17 (m, 2H).

^{13}C NMR (100MHz, CDCl_3): 30.8, 30.9, 35.3, 115.4, 115.6, 130.2, 130.3, 135.9, 160.7, 195.8.

(ii) Methyl 2-{[2-(4-fluorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoate

[2-(4-Fluorophenyl)ethyl]ethanethioate (96mg, 0.48mmol) was dissolved in 1ml methanol under nitrogen atmosphere. To this slurry was added sodium methanethiolate (33.9mg,

0.48mmol). After 30 minutes of stirring methyl 2-chloro-3-[4-(2-{4-[(methylsulfonyl)-oxy]phenoxy}ethyl)phenyl]propanoate (200mg, 0.48mmol) dissolved in 2ml CH₃CN was added. The resulting mixture was stirred overnight.

The solvent was evaporated and the residue was dissolved in EtOAc. The organic phase
5 was washed (water), dried (MgSO₄) and evaporated under reduced pressure.

Further purification by preparative HPLC (using a gradient of CH₃CN / 5%CH₃CN-waterphase containing 0.1M NH₄OAc) gave 82mg of the desired product (yield 32%).
¹HNMR (500MHz, CDCl₃): 2.82-3.00 (m, 5H), 3.10 (t, 2H), 3.14 (s, 3H), 3.22 (dd, 1H),
3.53 (m, 1H), 3.72 (s, 3H), 4.18 (t, 2H), 6.92 (d, 2H), 7.0 (t, 2H), 7.15 (m, 4H), 7.23 (m,
10 4H).

(iii) 2-{[2-(4-Fluorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid

15 Methyl 2-{[2-(4-fluorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoate (77mg, 0.14mmol) was dissolved in 2.5ml of a 4:1 mixture of THF and water and cooled on an ice-bath. Lithium hydroxide (6.9mg, 0.29mmol) was added. Water was added after 2 days of stirring at room temperature. The THF was evaporated under reduced pressure. The aqueous phase was acidified with 1M
20 HCl and extracted with EtOAc three times. The organic phases were pooled, washed (water, brine), dried (MgSO₄) and evaporated. The crude product was purified using preparative HPLC (eluent: CH₃CN / 5% CH₃CN-waterphase containing 0.1M NH₄OAc). 24mg of the desired product (yield 30%) was obtained as an oil.

¹HNMR (500MHz, CDCl₃): 2.82-3.00 (m, 5H), 3.10 (t, 2H), 3.14 (s, 3H), 3.21 (dd, 1H),
25 3.52 (m, 1H), 4.18 (t, 2H), 6.90 (d, 2H), 6.99 (t, 2H), 7.13 (m, 2H), 7.16-7.26 (m, 6H).

19
20**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.

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GENERAL CHEMICALS AND REAGENTS

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

10 **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.

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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.

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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

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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*/*Bam*HI fragments and cloned in frame to the GAL4 DNA binding
5 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
pSGGALhPPa	human PPAR α	S74349, nt 625-1530
pSGGALmPPa	murine PPAR α	X57638, nt 668-1573
pSGGALhPPg	human PPAR γ	U63415, nt 613-1518
pSGGALmPPg	murine PPAR γ	U09138, nt 652-1577

10 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
15 number eight before transfections. Confluent cells were trypsinised, washed and pelleted
by centrifugation at 270xg for 2 minutes. The cell pellet was resuspended in cold PBS to a
cell concentration of about 18 x 10⁶ 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 PulserTM in 0.5 ml batches. A total of 50 μ g DNA was added to each
20 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).

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

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.

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.

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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 EC_{50} 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. EC_{50} 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.

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The compounds of formula I have an EC_{50} of less than $5\mu\text{mol/l}$ for $PPAR\alpha$ and particular compounds have an EC_{50} of less than $1.0\mu\text{mol/l}$. Additionally in particular compounds the ratio of the EC_{50} ($PPAR\gamma$) : EC_{50} ($PPAR\alpha$) is greater than 25:1. It is believed that this ratio is important with respect to the pharmacological activity of the compounds and to their therapeutic profile.

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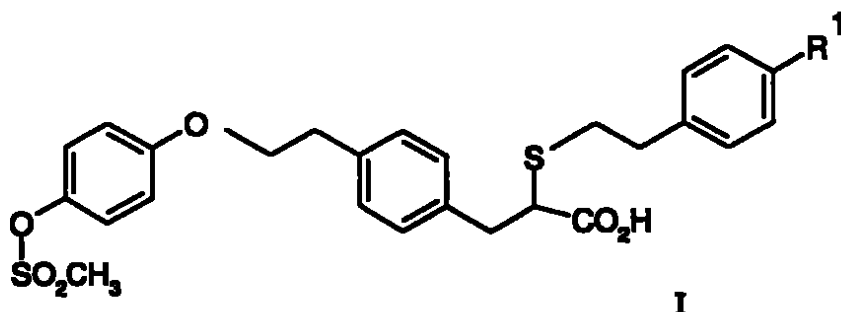
In addition the compounds of the present invention exhibit improved DMPK (Drug Metabolism and Pharmacokinetic) properties for example they exhibit improved metabolic stability *in vitro*. The compounds also have a promising toxicological profile.

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CLAIMS

1. A compound of formula I



wherein R¹ represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof.

2. A compound selected from

2-{[2-(4-chlorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;

- 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid; and

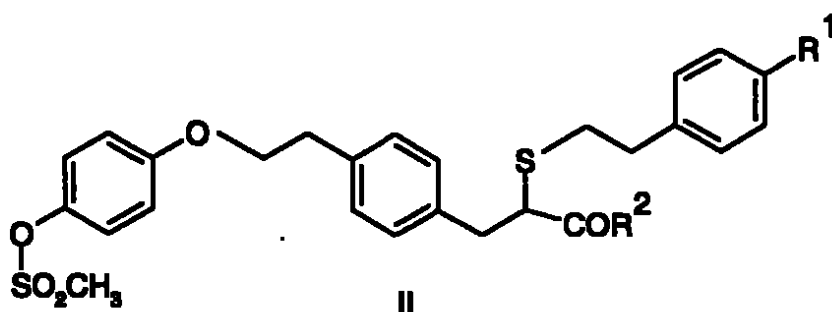
2-{[2-(4-fluorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid;

and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof.

3. The compound (-)-2-{[2-(4-chlorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid.

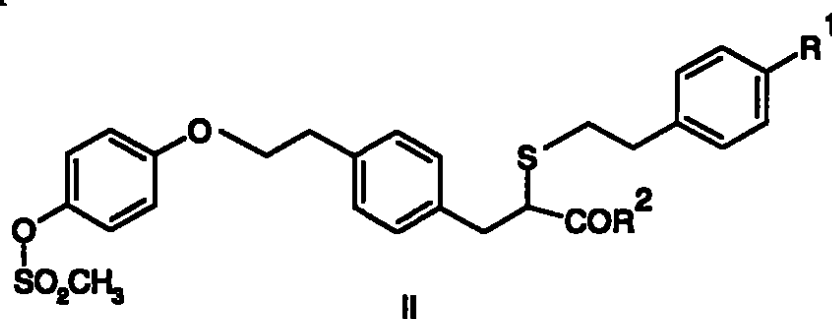
4. The compound (-)-2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-
[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid.
5. The (R)- enantiomer or the (S)- enantiomer of 2-([2-(4-fluorophenyl)ethyl]thio)-3-[4-
(2-{4- [(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid.
6. A pharmaceutical formulation comprising a compound according to any one of claims
1 to 5 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.
7. A pharmaceutical formulation comprising a compound according to any one of claims
1-5 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.
8. A method of treating or preventing lipid disorders (dyslipidemia) whether or not
associated with insulin resistance comprising the administration of a compound according
to any one of claims 1-5 to a mammal in need thereof.
9. The use of a compound according to any one of claims 1-5 in the manufacture of a
medicament for the treatment of lipid disorders (dyslipidemia) whether or not associated
with insulin resistance.
10. 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 1-5 to a
mammal in need thereof.
11. A process to prepare compounds of formula I reacting a compound of formula II

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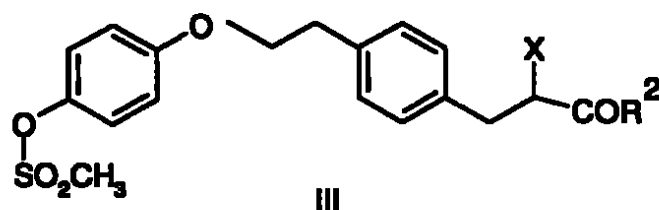
in which R^1 is as previously defined and represents R^2 represents a protecting group for carboxylic hydroxy group with a de-protecting reagent.

5 12. A compound of formula II



wherein R^1 is as previously described and R^2 represents a protecting group for carboxylic hydroxy.

10 13. A compound of formula III



in which R^2 is as previously defined and X is a leaving group.

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14. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 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.

15 15. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 combined with another PPAR modulating agent.

16. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 combined with a cholesterol-lowering agent.

10 17. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 combined with a HMG-CoA reductase inhibitor.

18. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 combined with atorvastatin or a pharmaceutically acceptable salt, solvate,
15 crystalline form or prodrug thereof.

19. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 combined with rosuvastatin or a pharmaceutically acceptable salt thereof.

20 20. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 combined with an IBAT inhibitor.

21. A pharmaceutical composition according to claim 20 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;
25 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-
30 benzothiazepine;

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

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

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

10 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-
15 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-
20 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-(R)-1-carboxy-2-
methylthio-ethyl]carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-
1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N-(S)-1-carboxy-2-(R)-
25 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;

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

Intern. Application No.
PCT/JP 02/05743A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C323/56 A61K31/192

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

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

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

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Classification of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 62872 A (ASTRA) 9 December 1999 (1999-12-09) cited in the application page 4; claims 1,5-11	1-13
A	WO 99 62871 A (ASTRA) 9 December 1999 (1999-12-09) examples 1,43,44	1-13

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

* Special categories of cited documents:

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

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to underlain 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.
"S" document member of the same patent family

Date of the actual completion of the international search

7 May 2003

Date of drafting of the international search report

22/05/2003

Name and mailing address of the ISA

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Authorized officer

English, R.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Claims Nos.: 1-21 (in part)

The scope of claims 1-21, in as far as the expressions "prodrug", "protecting group" and "leaving group" are concerned, is so unclear (Article 6 PCT) that a meaningful International Search is not possible with regard to these expressions. Nevertheless the search was complete for compounds of claims 12 and 13 in which the protecting group R2 is a methoxy group and for compounds of claim 13 in which the leaving group is a chlorine atom.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/05743

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 8,10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-21 (in part)
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 dependent 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

concerning on patent family members

Internet Application No
PCT/US 02/05743

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/05743

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		HR 20000782 A1	30-06-2001
		HU 0103376 A2	29-05-2002
		JP 2002516900 T	11-06-2002
		NO 20006115 A	07-02-2001
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(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional



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

(10) Número de Publicación Internacional

PCT

WO 03/051826 A1

(51) Clasificación Internacional de Patentes⁷: C07C 323/56, A61K 31/192

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(75) Inventores/Solicitantes (para US únicamente): ALSTERMARK LINDSTEDT, Eva-Lotta [SE/SE]; Moindal, S-431 83 (SE). BOJE, Anna, Maria, Peredottar [SE/SE]; Moindal, S-431 83 (SE). HOLM, Patrik [FI/SE]; Moindal, S-431 83 (SE).

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

(81) Países designados (nacional): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, 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.

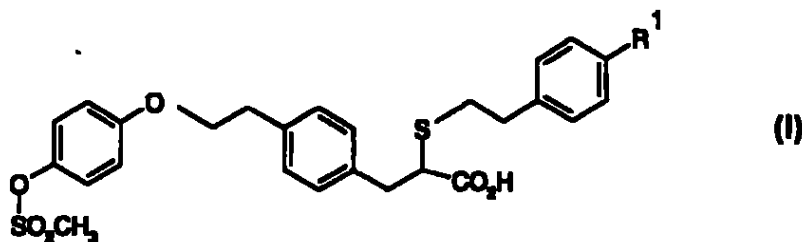
(84) Países designados (regional): Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eursalética (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF,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

Publicado:

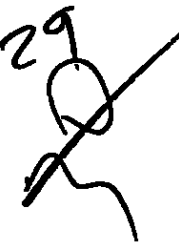
- con informe internacional de búsqueda
- antes del vencimiento del tiempo límite para modificar las reivindicaciones y para volver a publicar en el caso de recibo de modificaciones

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 3-FENIL-2-ARILALQUILTIOPROPIONICO COMO ANTAGONISTAS SELECTIVOS DE PPAR-ALFA



(57) Extracto: Un compuesto de fórmula (I); en donde R¹ representa cloro, fluoro o hidroxilo, así como isómeros ópticos y racematos del mismo, así como sales farmacéuticamente aceptables, profármacos, solvatos y formas cristalinas de los mismos, a procesos (sic) para preparar tales compuestos, a su utilidad en tratar estados clínicos incluidos trastornos de lípidos (dialipidemias), asociados o no con la resistencia a la insulina, a métodos para su uso terapéutico y a composiciones farmacéuticas que los contienen.



DERIVADOS DE ÁCIDO 3-FENIL-2-ARILALQUILTIO PROPIÓNICO COMO ANTAGONISTAS SELECTIVOS DE PPAR- ALFA

Campo de la invención

La presente invención se relaciona con ciertos derivados novedosos de ácido 3-fenil-2-arilalquiltiopropiónico, 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.

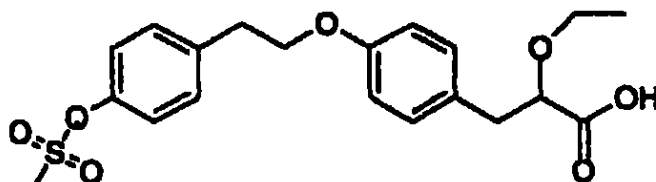
La investigación epidemiológica reciente ha documentado que individuos con resistencia a la insulina corren un riesgo fuertemente redoblado de morbimortalidad cardiovascular, que sufren en forma especial de infarto del miocardio y apoplejía. En la diabetes sacarina tipo 2 las afecciones relacionadas 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 afecciones farmacoterapéuticas bien definidas.

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



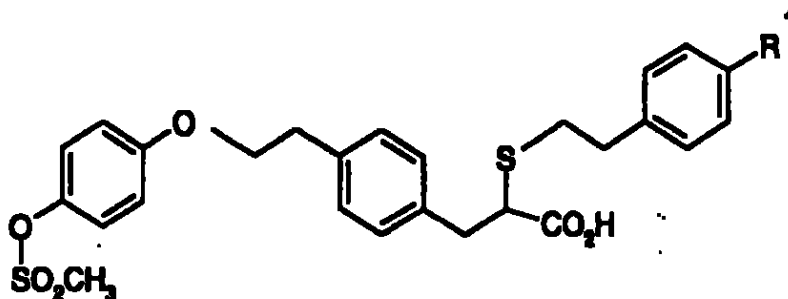
C

ácido 2-etoxi-3-[4-(2-{4-metanosulfonyloxyfenil}etoxi)fenil]propanoico se divulga en la Publicación PCT Número WO99/62872. Se informa que este compuesto es un modulador de receptores activadores de 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 un compuesto de fórmula I



I

en donde R¹ representa cloro, fluoro o hidroxilo, así como isómeros ópticos y

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racematos de los mismos, así como sales farmacéuticamente aceptables, solvatos, formas cristalinas del mismo.

Se reconocerá por los expertos en el arte que los compuestos de fórmula I contienen un centro óptimamente activo y, por lo tanto, pueden existir como enantiómeros que pueden separarse como se describe posteriormente. Se espera que la mayor parte, si no toda, la actividad de los compuestos de fórmula I reside en un enantiómero: cualquiera del enantiómero S o R o el enantiómero (+) o (-). Los enantiómeros que son más activos en los estudios descritos más adelante son formas preferidas de la presente invención. Se entenderá que la presente invención incluye todas las mezclas de este enantiómero activo con el otro enantiómero, por ejemplo la mezcla racémica, que es un intermedio útil para el enantiómero activo.

Los enantiómeros activos pueden aislarse por separación del racemato, por ejemplo por cristalización fraccionaria, resolución o HPLC en una columna quiral (por ejemplo una columna Chiralpak™ AD 250x50). Alternativamente, los enantiómeros activos pueden elaborarse mediante síntesis quiral a partir de materiales iniciales quirales bajo condiciones que no causarán racemización o epimerización, o mediante derivación con un reactivo quiral.

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. El término "profármaco" incluye asimismo derivados del sustituyente hidroxil (cuando R¹ representa hidroxil) los cuales se convierten en un mamífero, particularmente un humano, en el grupo hidroxil o una sal o conjugado del mismo. Debe entenderse que, sin ceñirse estrictamente a 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

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por metodología rutinaria adecuadamente dentro de las habilidades de un experto en el arte. En el arte se conocen diferentes profármacos de carboxilo e hidroxilo. 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 o hidroxilo es, por ejemplo, un éster farmacéuticamente aceptable, que se hidroliza en el cuerpo humano o animal para producir el ácido precursor o alcohol. Ésteres apropiados farmacéuticamente aceptables para carboxilo incluyen ésteres de C₁₋₆alcoximetilo, por ejemplo, metoximetilo; ésteres de C₁₋₆alcanoiloximetilo, por ejemplo, pivaloiloximetilo; ésteres de ftalidilo; ésteres de C₃₋₆cicloalcoxycarboniloxiC₁₋₆alquilo, por ejemplo, 1-ciclohexilcarboniloxietilo; ésteres de 1,3-dioxolen-2-onilmetilo, por ejemplo, 5-metil-1,3-dioxolen-2-onilmetilo; y ésteres de C₁₋₆alcoxycarboniloxietilo, por ejemplo, 1-metoxycarboniloxietilo; y pueden formarse en cualquier grupo carboxilo en los compuestos de esta invención. Un éster hidrolizable *in vivo* (o divisible) de un compuesto de la fórmula (I) que contiene un grupo hidroxilo incluye ésteres inorgánicos tales como ésteres de fosfato (incluidos ésteres cíclicos fosforamídicos) y éteres α -aciloxialquílicos y compuestos relacionados que, como resultado de la

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hidrólisis *in vivo* del éster se descomponen para producir el (los) grupo(s) hidroxil precursor(es). Ejemplos de éteres α -aciloxialquílicos incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi. Una selección de grupos que forman un éster hidrolizable *in vivo* para hidroxil incluyen alcanilo, benzoilo, fenilacetilo y bezoilo sustituido y fenilacetilo, alcóxicarbonilo (para producir ésteres de carbonato de alquilo), dialquilcarbamoilo y *N*-(dialquilaminoetil)-*N*-alquilcarbamoilo (para producir carbamatos), dialquilaminoacetilo y carboxiacetilo. Ejemplos de sustituyentes en benzoilo incluyen morfolino y piperazino enlazados de un átomo de nitrógeno de anillo mediante un grupo metileno a la posición 3- ó 4- del anillo benzoilo.

Los compuestos de fórmula I poseen actividad como medicamentos, en particular los compuestos de fórmula I son agonistas selectivos de PPAR α , es decir, su EC₅₀ para PPAR α es por lo menos diez veces menor que su respectivo EC₅₀ para PPAR γ en donde los EC₅₀ se miden y calculan como se describe en los análisis más adelante en este documento. Los compuestos de fórmula I son potentes y selectivos.

Compuestos específicos de la invención son:

ácido 2-{[2-(4-clorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico; preferiblemente cualquiera de los dos el (R)-enantiómero o el (S)-enantiómero;

ácido 2-{[2-(4-hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico; preferiblemente cualquiera de los dos el (R)-enantiómero o el (S)-enantiómero;

ácido 2-{[2-(4-fluorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico; preferiblemente cualquiera de los dos el (R)-enantiómero o el (S)-enantiómero;

ácido (-)-2-{[2-(4-clorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico y

ácido (-)-2-{[2-(4-hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-

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fenoxi}etil)fenil]propanoico;

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

Se entenderá por los expertos en el arte que donde ocurre (–) en el listado anterior el compuesto indicado tiene una rotación negativa cuando se mide usando las condiciones y la concentración descritas en la sección experimental. Debe entenderse que las sales del ácido precursor se incluyen incluso si una sal particular exhibe una rotación (+), con la condición que la configuración absoluta de la sal sea la misma que la configuración del ácido precursor (–).

Enantiómeros específicos de la invención se seleccionan de uno o más de los siguientes:

ácido (R)-2-{[2-(4-clorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico;

ácido (S)-2-{[2-(4-clorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico;

ácido (R)-2-{[2-(4-hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico;

ácido (S)-2-{[2-(4-hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico;

ácido (R)-2-{[2-(4-fluorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico;

ácido (S)-2-{[2-(4-fluorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico;

ácido (–)-2-{[2-(4-clorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico y

ácido (–)-2-{[2-(4-hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico;

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

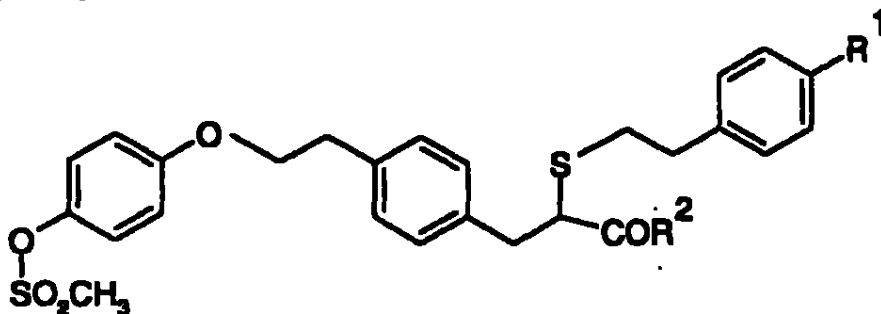
En la presente especificación la expresión "sales farmacéuticamente aceptables" tiene como finalidad definir, pero no se limita a, sales de base tales como sales de metal alcalino, sales de metal alcalinotérreo, sales de amonio, sales con aminoácidos básicos, y sales con aminas orgánicas.

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.

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 un compuesto de fórmula II

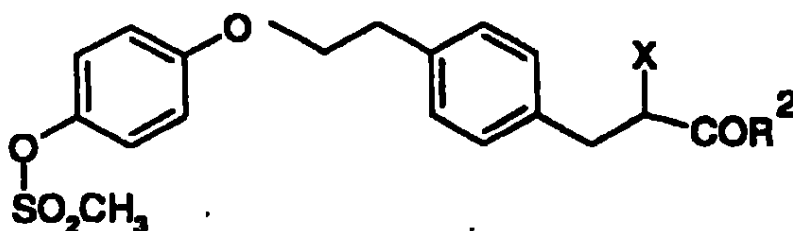


II

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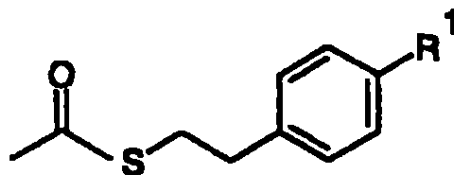
en la cual R^1 es como se define previamente y R^2 representa un grupo protector para un grupo hidroxí carboxílico como se describe en el texto estándar "Protective Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts, con un reactivo desprotector. El grupo protector puede ser también 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^2 representa un grupo C_{1-6} alcoxilo o un grupo arilalcoxilo, verbigracia benciloxi, tal que COR^2 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 par producir compuestos de fórmula I.

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



III

en el cual R^2 es, como se define previamente y X es un grupo saliente por ejemplo halo, verbigracia cloro, con un compuesto de fórmula IV



IV

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en la cual R^1 es como se define previamente o un grupo hidroxil protegido por ejemplo R^1 es benciloxi.

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.

Se cree que los compuestos de fórmula II, III y IV son novedosos y se reivindican aquí como intermedios útiles en la preparación de compuestos de fórmula I.

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

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

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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 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,

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X

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 morbimortalidad cardiovascular asociada con la aterosclerosis debido a sus propiedades antidislipídicas, así como antinflamatorias. 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

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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, Expert Opinion on Therapeutic Patents, 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 ciprofibrato; GW 9578, ciglitazona, troglitazona, pioglitazona, rosiglitazona, eglitazona, proglitazona, BRL-49634, KRP-297,

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3
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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 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 coenzyma A reductasa). Apropriadamente 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

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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 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,

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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 apropiados para uso 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:

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;

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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-

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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-hidroxi]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)(hidroxi)fosforil]etil}carbamoil)-4-hidroxi]bencil}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-hidroxi]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-carboxi-2-metiltio-etil]carbamoil]-4-hidroxi]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]-4-hidroxi]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]-4-hidroxi]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-carboxibutil)carbamoil]-4-hidroxi]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]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;

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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.

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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 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

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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, candesartán 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

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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.

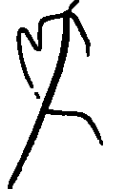
De acuerdo con un aspecto adicional de la presente invención se provee un estuche que comprende un compuesto de fórmula I, o una sal farmacéuticamente aceptable, solvato, solvato de tal sal o un profármaco del mismo, y uno de los demás compuestos descritos en esta sección de combinación o una sal farmacéuticamente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

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 hiperlipidémicas 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

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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.

Abreviaturas

DMSO	sulfóxido de dimetilo
EtOAc	acetato de etilo
DMF	<i>N,N</i> -dimetilformamida
THF	Tetrahidrofurano
MeCN	Acetonitrilo
MeOH	Metanol
TFA	ácido trifluoroacético
NH_4OAc	acetato de amonio
t	Triplete
s	Singlete
d	Doblete
q	Cuartete
m	Multiplete
bs	singlete amplio

Ejemplo 1

Ácido 2-{[2-(4-clorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]fenoxi}etil)fenil]propanoico

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X(i) [2-(4-Clorofenil)etil]etanotioato

1-(2-Cloroetil)-4-clorobenceno (0.700 g, 4.00 mmol), ácido tioacético (0.320 g, 4.20 mmol) y trietilamina (0,425 g, 4.20 mmol) se disolvieron en MeOH (8 ml). La solución se calentó con microondas durante 900 segundos a 150 °C. La mezcla se usó en el siguiente paso sin purificación.

(ii) ácido 2-{[2-(4-clorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi)etil]fenil]propanoico

El recipiente de reacción se enjuagó con argón. A una parte 0.8 ml (0.400 mmol) de la mezcla del anterior paso de reacción se agregó bajo agitación metanotiolato de sodio (56.5 mg, 0.800 mmol) en MeOH (0.2 ml). Pasada una hora se agregó 2-cloro-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi}etil)fenil]propanoato de metilo (0.200 g, 0.484 mmol, preparado como se describe en Ejemplo 2) en acetonitrilo (0.800 ml). La mezcla se agitó durante 16 horas bajo una atmósfera de argón y luego se centrifugó bajo vacío a 35 °C. Se agregó 2 ml 0.5 M solución LiOH (THF/agua 7:1) y la mezcla se agitó vigorosamente durante 20 horas. Después de la acidificación con 12 M HCl (100 µl) se continuó la agitación durante otra hora. El producto crudo se filtró a través de un filtro de Teflon™ y se purificó aún más usando HPLC preparativa (0.2 % TFA/MeCN, gradiente). Las fracciones agrupadas se centrifugaron bajo vacío produciendo 18 mg del producto deseado (rendimiento 7%).

¹H-NMR (400 MHz, CDCl₃): 2.75-2.95 (m, 5H), 3.06 (t, 2H), 3.10 (s, 3H), 3.16 (dd, 1H), 3.45 (dd, 1H), 4.14 (d, 2H), 6.87 (d, 2H), 7.05 (d, 2H), 7.11-7.27 (m, 8H).

(iii) ácido(-)-2-{[2-(4-clorofenil)etil]tio}-3-[4-(2-(4-[(metilsulfonyl)oxi]fenoxi)etil)fenil]propanoico

El (-)-enantiómero de ácido 2-{[2-(4-clorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi}etil)fenil]propanoico se separó del racemato por cromatografía quiral. Se empleó una columna Chiralpak AD JF003 (250 x

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20 mm i.d.) y etanol/ácido fórmico 100/0.1% como fase móvil. El racemato (2 g) se disolvió en etanol (20 mg/ml) y se inyectó en la columna. Se recogió el primer pico eluyente y se detectó con UV. El producto (0.9 g) se obtuvo con una pureza enantiomérica = 99.2%. Se encontró que la rotación óptica era $[\alpha]_D^{20} = -29^\circ$ disolviendo el enantiómero en etanol para producir una concentración de 0.5 g/100ml. La rotación óptica se midió a 20 °C usando la línea de sodio a 589 nm.

^1H NMR (500 MHz, CD_3OD): 7.18-7.25 (6H, m), 7.15 (2H, d), 7.13 (2H, d), 4.16 (2H, t), 3.45 (1H, t), 3.14 (3H, s), 3.11 (1H, m), 3.04 (2H, t), 2.77-2.90 (5H m).

Ejemplo 2

Ácido 2-{[2-(4-hidroxifenil)etil]tio}-3-[4-(2-(4-[(metilsulfonil)oxi]fenoxi)etil)fenil]propanoico

(i) 2-Cloro-3-[4-(2-hidroxietil)fenil]propanoato de metilo

2-(4-Aminofenil)etanol (11g, 81mmol) y 32ml de HCl concentrado se disolvió en acetona y se enfrió a 0°C. Se agregó gota a gota nitrito de sodio (5.6g, 81mmol) en 20ml de agua. La temperatura se mantuvo bajo 0°C. Pasada una hora, se agregaron acrilato de metilo (70g, 808mmol) y CuI (1.6g, 8mmol) (<0°C). La mezcla de reacción se agitó a la temperatura de la sala de un día para otro.

El solvente se evaporó y se agregó agua. Se extrajo la fase acuosa tres veces con EtOAc, las fases orgánicas se agruparon y se lavaron con agua, se secaron (MgSO_4) y se evaporaron bajo presión reducida. El producto crudo se purificó por cromatografía de destello usando una mezcla 65:35 de EtOAc y heptano como eluyente. La purificación adicional por HPLC preparativa (usando una gradiente de CH_3CN / 5% CH_3CN -fase acuosa que contenía 0.1M NH_4OAc como eluyente) proporcionó 9.7g de producto (rendimiento 49%) como un aceite. ^1H NMR (400MHz, CDCl_3): 2.84 (t,

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X

3H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 3.84 (t, 3H), 4.43 (t, 1H), 7.17 (d, 4H)

(ii) 3-(4-{2-[4-(Benciloxi)fenoxi]etil}fenil)-2-cloropropanoato de metilo

Trifenilfosfina (2.4g, 9mmol) se agregó a una solución de 2-cloro-3-[4-(2-hidroxietil)fenil]propanoato de metilo (2.1g, 8.5mmol) y 4-(benciloxi)fenol (1.7g, 8mmol) en 20ml de tolueno bajo atmósfera de nitrógeno. La solución se calentó a 55°C y se agregó azodicarboxilato de diisopropilo (1.8g, 9mmol). La mezcla de reacción se agitó a 55°C de un día para otro. La mezcla se dejó enfriar y el solvente se evaporó bajo presión reducida. El producto crudo se purificó por cromatografía de destello usando una mezcla 80:20 de heptano y EtOAc como eluyente para proporcionar 2.28g del producto deseado (rendimiento 61%) como cristales incoloros.

¹H NMR (400MHz, CDCl₃): 3.05 (t, 2H), 3.16 (dd, 1H), 3.36 (dd, 1H), 3.75 (s, 3H), 4.12 (t, 2H), 4.45 (t, 1H), 5.01 (s, 2H), 6.82 (m, 2H), 6.90 (m, 2H), 7.13-7.27 (m, 4H), 7.29-7.47 (m, 5H).

(iii) 2-Cloro-3-{4-[2-(4 hidroxifenoxi)etil]fenil}propanoato de metilo

3-(4-{2-[4-(Benciloxi)fenoxi]etil}fenil)-2-cloropropanoato de metilo (1.0g, 2.4mmol) y sulfuro de dimetilo (0.9g, 14mmol) se disolvió en 60ml CH₂Cl₂. Se agregó gota a gota etearato de trifluoruro de boro (2.0g, 14mmol) a la solución agitada. La mezcla de reacción se agitó durante dos días a la temperatura de la sala. Se agregó otro equivalente de etearato de trifluoruro de boro (0.4g, 2.87mmol) y se continuó la agitación de un día para otro. Se agregó agua. Se separaron las fases y la fase acuosa se extrajo dos veces con CH₂Cl₂. Las fases orgánicas se agruparon, se lavaron (agua, salmuera), se secaron (Na₂SO₄) y se evaporaron bajo presión reducida. La purificación adicional por HPLC preparativa usando un gradiente de CH₃CN/ 5% CH₃CN-fase acuosa que contenía 0.1M NH₄OAc aportó 0.55g del producto deseado (rendimiento 52%) como un aceite.

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¹H NMR (400MHz, CDCl₃): 3.04 (t, 2H), 3.16 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 4.10 (t, 2H), 4.40 (t, 1H), 6.75 (m, 4H), 7.12-7.29 (m, 4H).

(iv) 2-cloro-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi}etil)fenil]propanoato de metilo

2-Cloro-3-{4-[2-(4-hidroxifenoxi)etil]fenil}propanoato de metilo (334mg, 1.0mmol) y trietilamina (303mg, 3.0mmol) se disolvió en 20ml de diclorometano y se enfrió a -20°C bajo atmósfera de nitrógeno. Se agregó gota a gota cloruro de metanosulfonyl (114mg, 1.0mmol). Se dejó que la mezcla alcanzara la temperatura de la sala. Pasadas 2 horas se agregó diclorometano, la mezcla se lavó (agua, salmuera), se secó (Na₂SO₄) y se evaporó bajo presión reducida para proporcionar 394 mg de producto puro (rendimiento 96%).

¹H NMR (400MHz, CDCl₃): 3.02-3.11 (m, 5H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.74 (s, 3H), 4.14 (t, 2H), 4.44 (t, 1H), 5.29 (s, 2H), 6.88 (d, 2H), 7.14-7.25 (m, 6H).

(v) 2-({2-[4-(benciloxi)fenil]etil}tio)-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi}etil)fenil]propanoato de metilo

2-[4-(Benciloxi)fenil]etanotiol (334mg, 1.4mmol), 2-cloro-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi}etil)fenil]propanoato de metilo (394 mg, 0.95mmol) y carbonato de potasio (189mg, 1.4mmol) se disolvieron en 14ml de DMF seco y se agitaron bajo atmósfera de nitrógeno a la temperatura de la sala de un día para otro.

El solvente se evaporó bajo presión reducida y el residuo se disolvió en tolueno. La fase orgánica se lavó (agua, salmuera), se secó (MgSO₄) y se evaporó. La purificación adicional por HPLC preparativa usando una gradiente de CH₃CN/5% CH₃CN-fase acuosa que contenía 0.1M NH₄OAC aportó 477mg del producto deseado (rendimiento 75%). ¹H NMR (400MHz, CDCl₃): 2.76-2.89 (m, 4H), 2.95 (dd, 1H), 3.09 (m, 5H), 3.20

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(dd, 1H), 3.53 (m, 1H), 3.70 (s, 3H), 4.15 (t, 2H), 5.06 (s, 2H), 6.91 (m, 4H), 7.07-7.24 (m, 8H), 7.31-7.48 (m, 5H).

(vi) 2-{[2-(4-Hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]fenoxi}etil)fenil]propanoato de metilo

A una solución de 2-{[2-(4-benciloxi)fenil]etil}tio)-3-[4-(2-{4-[(metilsulfonil)oxi]fenoxi}etil)fenil]propanoato de metilo (477mg, 0.8mmol) y 15ml diclorometano, se agregaron sulfuro de dimetilo (239mg, 3.8mol) y etearato de trifluoruro de boro (545mg, 3.8mmol). Pasadas 18 horas de agitación se agregó agua a la reacción. Las fases se separaron y se extrajo la fase acuosa dos veces con diclorometano. Se agruparon las fases orgánicas, se secaron (MgSO_4) y se evaporaron bajo presión reducida. Se obtuvieron 274mg del producto deseado (rendimiento 67%) como un aceite. $^1\text{H NMR}$ (400MHz, CDCl_3): 2.70-2.85 (m, 4H), 2.91 (dd, 1H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.49 (m, 1H), 3.68 (s, 3H), 4.13 (t, 2H), 6.72 (d, 2H), 6.87 (d, 2H), 6.99 (d, 2H), 7.10-7.22 (m, 6H)

(vii) Ácido 2-{[2-(4-hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]fenoxi}etil)fenil]propanoico

2-{[2-(4-Hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]fenoxi}etil)fenil]propanoato de metilo (105mg, 0.2mmol) se disolvió en 6.5ml de una mezcla 7:1 de THF y agua y se enfriaron en un baño helado. Se agregó hidróxido de litio (9.4mg, 0.4mmol). Se agregó agua a la mezcla de reacción luego de 24 horas de agitación a la temperatura de la sala. El THF se evaporó bajo presión reducida y el residuo se acidificó con 1M ácido clorhídrico. Se extrajo la fase acuosa con EtOAc (x3), se agruparon las fases orgánicas, se lavaron (agua, salmuera), se secaron (MgSO_4) y se evaporaron. El producto crudo se purificó usando HPLC preparativa (eluyente: CH_3CN / 5% CH_3CN -fase acuosa que contenía 0.1M NH_4OAc) para proporcionar 74mg del producto deseado (rendimiento 97%) como un

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aceite.

^1H NMR (400MHz, CDCl_3): 2.68-2.95 (m, 5H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.47 (m, 1H), 4.12 (t, 2H), 6.70 (d, 2H), 6.86 (d, 2H), 6.97 (d, 2H), 7.12-7.21 (m, 6H).

^{13}C NMR (100MHz, CDCl_3): 33.8, 35.1, 35.5, 37.2, 37.3, 48.1, 69.3, 115.6, 115.8, 123.3, 129.3, 129.4, 129.9, 132.3, 136.2, 136.9, 142.8, 154.4, 158.0, 177.2.

(viii) Ácido (-)-2-{[2-(4-hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi}etil)fenil]propanoico

El racemato del ácido 2-{[2-(4-hidroxifenil)etil]tio}-3-[4-(2-{4-[(metilsulfonyl)-oxi]fenoxi}etil)fenil]propanoico se separó en sus enantiómeros usando cromatografía quiral. Se usó una columna Chiralpak AD JDB01+ AS003 (336 x 100 mm i.d.) y se usó etanol/ácido fórmico 100/0.01% como fase móvil. El racemato (9 g) se disolvió en etanol y se inyectó en la columna. El primer pico eluyente se recogió y se detectó con UV. El producto (4.1 g) se obtuvo con una pureza enantiomérica >99%. Se encontró que la rotación óptica era $[\alpha]^{20}_{\text{D}} = -33^\circ$ disolviendo el enantiómero en metanol para dar una concentración de 0.64 g/100ml. Se midió la rotación óptica a 20 °C usando la línea de sodio en 589 nm.

^1H NMR (500 MHz, CD_3OD): 7.17-7.22 (6H, m), 6.99 (2H, d), 6.94 (2H, d), 6.69 (2H, d), 4.17 (2H, t), 3.46 (1H, t), 3.16 (3H, s), 3.13 (1H, dd), 3.05 (2H, t), 2.69-2.88 (5H, m).

Ejemplo 3

Ácido 2-{[2-(4-fluorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi}-etil)fenil]propanoico

(i) [2-(4-Fluorofenil)etil]etanotioato

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A una solución de DMF (60ml) y ácido tioacético (2.1g, 28mmol), enfriado en un baño helado, se agregó carbonato de cesio (9.1g, 28mmol). La mezcla de reacción se volvió inmediatamente anaranjada. Se agregó 1-(2-cloroetil)-4-fluorobenceno (4g, 25mmol), se retiró el baño helado y la reacción se agitó de un día para otro. El solvente se evaporó y el residuo se disolvió en EtOAc. La fase orgánica se lavó (agua), se secó (NaSO₄) y se evaporó bajo presión reducida para proporcionar 5g (99%) del producto deseado como un aceite.

¹H NMR (400MHz, CDCl₃): 2.33 (s, 3H), 2.83 (t, 2H), 3.09 (t, 2H), 6.98 (t, 2H), 7.17 (m, 2H).

¹³CNMR (100MHz, CDCl₃): 30.8, 30.9, 35.3, 115.4, 115.6, 130.2, 130.3, 135.9, 160.7, 195.8.

(ii) 2-{[2-(4-Fluorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi}-etil)fenil]propanoato de metilo

[2-(4-Fluorofenil)etil]etanotioato (96mg, 0.48mmol) se disolvió en 1ml de metanol bajo atmósfera de nitrógeno. A esta lechada se agregó metanotiolato de sodio (33.9mg, 0.48mmol). Pasados 30 minutos de agitación, se agregó 2-cloro-3-[4-(2-{4-[(metilsulfonyl)oxi]fenoxi}etil)fenil]propanoato de metilo (200mg, 0.48mmol) disuelto en 2ml CH₃CN. La mezcla resultante se agitó de un día para otro.

El solvente se evaporó y el residuo se disolvió en EtOAc. La fase orgánica se lavó (agua), se secó (MgSO₄) y se evaporó bajo presión reducida. La purificación adicional por HPLC preparativa (usando una gradiente de CH₃CN / 5% CH₃CN-fase acuosa que contenía 0.1M NH₄OAc) proporcionó 82mg del producto deseado (rendimiento 32%).

¹H NMR (500MHz, CDCl₃): 2.82-3.00 (m, 5H), 3.10 (t, 2H), 3.14 (s, 3H), 3.22 (dd, 1H), 3.53 (m, 1H), 3.72 (s, 3H), 4.18 (t, 2H), 6.92 (d, 2H), 7.0 (t, 2H), 7.15 (m, 4H), 7.23 (m, 4H).

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(iii) Ácido 2-{[2-(4-fluorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]-fenoxi}etil)fenil]propanoico

2-{[2-(4-fluorofenil)etil]tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]-fenoxi}etil)fenil]propanoato de metilo (77mg, 0.14mmol) se disolvió en 2.5ml de una mezcla 4:1 de THF y agua y se enfrió en un baño helado. Se agregó hidróxido de litio (6.9mg, 0.29mmol). Se agregó agua tras 2 días de agitación a la temperatura de la sala. El THF se evaporó bajo presión reducida. La fase acuosa se acidificó con 1M HCl y se extrajo con EtOAc tres veces. Las fases orgánicas se agruparon, se lavaron (agua, salmuera), se secaron (MgSO₄) y se evaporaron. El producto crudo se purificó usando HPLC preparativa (eluyente: CH₃CN / 5% CH₃CN-fase acuosa que contenía 0.1M NH₄Oac). Se obtuvieron 24mg del producto deseado (rendimiento 30%) como un aceite.

¹H NMR (500MHz, CDCl₃): 2.82-3.00 (m, 5H), 3.10 (t, 2H), 3.14 (s, 3H), 3.21 (dd, 1H), 3.52 (m, 1H), 4.18 (t, 2H), 6.90 (d, 2H), 6.99 (t, 2H), 7.13 (m, 2H), 7.16-7.26 (m, 6H).

ACTIVIDAD BIOLÓGICA

Formulación

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

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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% CO₂. 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

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de localización nuclear. La secuencia de todos los constructores 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
pSGGALmPPg	PPAR γ murino	U09138, nt 652-1577

¹ 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 con fluyentes, 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 x 10⁶ 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 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

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✓
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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

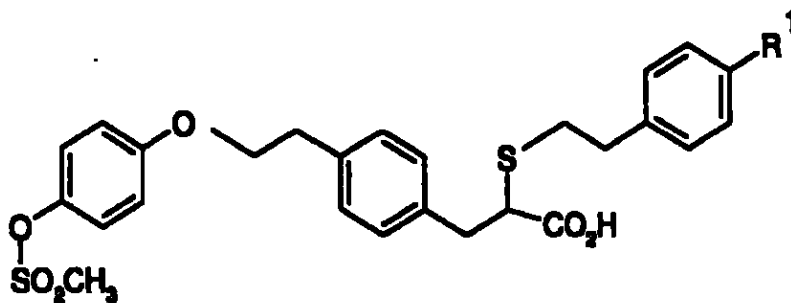
Para el cálculo de los valores EC₅₀, se estableció una curva concentración-efecto. Los valores utilizados se derivaron del promedio de dos o tres mediciones independientes (luego de restar el valor promedio de fondo) y se expresaron como el porcentaje de la activación máxima obtenida por el compuesto 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 concentración requerida para conseguir 50% de la activación máxima obtenida por el compuesto de referencia.

Los compuestos de fórmula I tienen un EC₅₀ de menos de 5 μ mol/l para PPAR α y compuestos particulares tienen un EC₅₀ de menos de 1.0 μ mol/l. Adicionalmente en compuestos particulares la relación del EC₅₀ (PPAR γ): EC₅₀ (PPAR α) es mayor que 25:1. 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*. Asimismo, los compuestos poseen un perfil toxicológico promisorio.

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6REIVINDICACIONES

1. Un compuesto de fórmula I



I

en donde R¹ representa cloro, fluoro o hidroxilo, así como isómeros ópticos y racematos del mismo, así como sales farmacéuticamente aceptables, profármacos, solvatos y formas cristalinas de los mismos.

2. Un compuesto seleccionado de:

ácido 2-{{2-(4-clorofenil)etil}tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]-fenoxi}etil)fenil]propanoico;

ácido 2-{{2-(4-hidroxifenil)etil}tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]-fenoxi}etil)fenil]propanoico; y

ácido 2-{{2-(4-fluorofenil)etil}tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]-fenoxi}etil)fenil]propanoico;

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

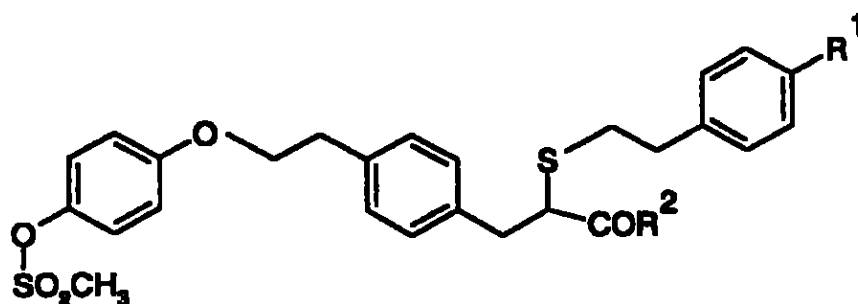
3. El compuesto ácido (-)-2-{{2-(4-clorofenil)etil}tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]-fenoxi}etil)fenil]propanoico.

4. El compuesto ácido (-)-2-{{2-(4-hidroxifenil)etil}tio}-3-[4-(2-{4-[(metilsulfonyl)oxi]-fenoxi}etil)fenil]propanoico.

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etil]tio}-3-[4-(2-{4-[(metilsulfonil)oxi]-fenoxi}etil)fenil]propanoico.

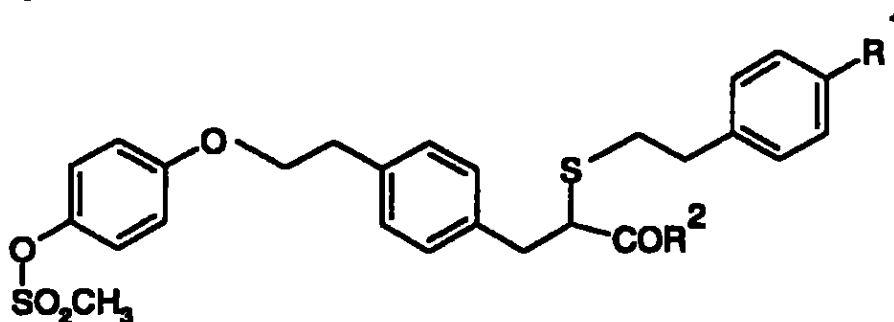
6. Una formulación farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 5 en mezcla con auxiliares farmacéuticamente aceptables, diluyentes y/o vehículos.
7. Una formulación farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-5 en mezcla con auxiliares farmacéuticamente aceptables, diluyentes y/o vehículos.
8. 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 1-5 a un mamífero necesitado del mismo.
9. El uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-5 en la manufactura de un medicamento para el tratamiento de trastornos de lípidos (dislipidemia) asociados o no con resistencia a la insulina.
10. 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 1-5 a un mamífero necesitado del mismo.
11. Un proceso para preparar compuestos de fórmula I haciendo reaccionar un compuesto de fórmula II

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II

en la cual R¹ es como se define previamente y R² representa un grupo protector para el grupo hidroxí carboxílico con un reactivo desprotector.

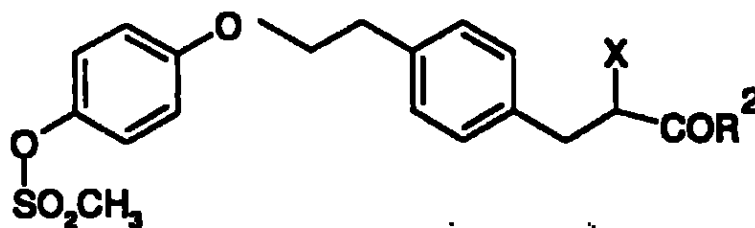
12. Un compuesto de fórmula II



II

en donde R¹ es como se describe previamente y R² representa un grupo protector para un hidroxí carboxílico.

13. Un compuesto de fórmula III



III

en la cual R² es como se define previamente y X es un grupo saliente.



14. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 5 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.

15. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 5 combinado con otro agente modulador PPAR.

16. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 5 combinado con un agente reductor de colesterol.

17. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 5 combinado con un inhibidor de HMG-CoA reductasa.

18. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 5 combinado con atorvastatina o una sal farmacéuticamente aceptable, solvato, forma cristalina o profármaco del mismo.

19. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 5 combinado con rosuvastatina o una sal farmacéuticamente aceptable del mismo.

20. Una composición farmacéutica que comprende un compuesto como se reivindica en una cualquiera de las reivindicaciones 1 a 5 combinado con un inhibidor IBAT.

21. Una composición farmacéutica de acuerdo con la reivindicación 20 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-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'*-(5-carboxipentil)carbamoil]bencil}carbamoilmetoxi)-2,3,4,5-tetrahidro-1,5-benzotiazepina;

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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-hidroxietyl} 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-hidroxi 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) (hidroxi) fosforil] etil} carbamoil)-4-hidroxi bencil] 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-

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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-

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A

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

AS: 94.317
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From the
 INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:		CODE		DATE	INTD	NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT	
ASTRAZENECA Global Intellectual Property Mercedes, Alderley Park Macclesfield, Cheshire, SK10 4TG GRANDE BRETAGNE				4TG			
		ANKOM 10 SEP 2003		GIPS		(PCT Rule 71.1)	
		DATA ENTERED		Date of mailing (day/month/year)		03/09/2003	
Applicant's or agent's file reference 100596/WO		FINAL CHECK		IMPORTANT NOTIFICATION			
International application No. PCT/GB 02/05743		International filing date (day/month/year) 18/12/2002		Priority date (day/month/year) 19/12/2001			
Applicant ASTRAZENECA AB		12 SEP 2003					

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

4. REMINDER

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

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

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

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

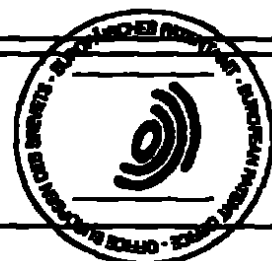
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PATENT COOPERATION TREATY

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 100596/WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IP/EA/416)	
International application No. PCT/GB 02/ 05743	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 G07C323/56		
Applicant ASTRAZENECA AB		

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.

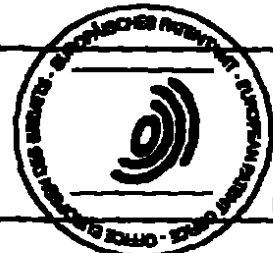
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the 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 29/08/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 eppnu d Fax: (+49-89) 2399-4465	Authorized officer VERHULST W Tel. (+49-89) 2399 2828



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/GB 02/ 05743

75
X

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

Original (for SUBMISSION) - printed on 17.12.2002 11:30:21 AM

100596/WO

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	100596/WO
I	Title of invention	THERAPEUTIC AGENTS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	AP: (GH GM KE LS MW NZ SD SL SZ TZ UG ZM ZW), EA: (AM AZ BY KG KZ MD RU TJ TM), EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR 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 BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MK MN MW MX NZ 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

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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100588/WO

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	ASTRAZENECA
IV-1-2	Address:	Global Intellectual Property Mereside Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
IV-1-3	Telephone No.	+44 1625 230148
IV-1-4	Facsimile No.	+44 1625 510752
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR 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

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	

PCT REQUEST

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100508/WO

	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	ASTRAZENECA	
X-1-2	Name of signatory	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
10-8	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	
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PCT (ANNEX - FEE CALCULATION SHEET)

100598/WO

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(This sheet is not part of and does not count as a sheet of the International application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form - PCT/RO/101 (Annex)	
0-4-1	PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.10.2002)
0-8	Applicant's or agent's file reference	100596/WO
2	Applicant	ASTRAZENECA AB, et al.
12	Calculation of prescribed fees	fee amount/multiplier Total amounts (GBP)
12-1	Transmittal fee T	$\Rightarrow$ 55
12-2-1	Search fee S	$\Rightarrow$ 592
12-2-2	International search to be carried out by	EP
12-3	International fee	
	Basic fee (first 30 sheets) b1	278
12-4	Remaining sheets	17
12-5	Additional amount (X)	6
12-6	Total additional amount b2	102
12-7	b1 + b2 = B	380
12-8	Designation fees	
	Number of designations contained in international application	95
12-9	Number of designation fees payable (maximum 5)	5
12-10	Amount of designation fee (X)	60
12-11	Total designation fees D	300
12-12	PCT-EASY fee reduction R	-86
12-13	Total international fee (B+D-R) I	$\Rightarrow$ 594
12-17	TOTAL FEES PAYABLE (T+S+H+P)	$\Rightarrow$ 1,241
12-18	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions	
	The receiving Office:	United Kingdom Patent Office (RO/GB)
12-20-1	Authorization to charge the total fees indicated above.	☒
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	☒
12-20-3	Authorization to charge the fee for priority document.	☒
12-21	Deposit account No.	D02934
12-22	Date	17 December 2002 (17.12.2002)

PCT (ANNEX - FEE CALCULATION SHEET)

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Original (for SUBMISSION) - printed on 17.12.2002 11:30:21 AM

100562/WS

12-23	Name and signature	ASTRAZENECA
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VALIDATION LOG AND REMARKS

13-2-3	Validation messages Names	Yellow Applicant 1.:City missing
		Yellow Applicant 3.:City missing
		Yellow Applicant 4.:City missing
		Yellow Applicant 5.:City missing
13-2-7	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
		Green? The international application contains no drawings. Please verify.
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

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PCT-EASY INFORMATION SHEET

(For applicant use only, DO NOT submit this sheet with the international application)

VALIDATION LOG

Yellow	Names
Yellow	Applicant 1.:City missing
Yellow	Applicant 3.:City missing
Yellow	Applicant 4.:City missing
Yellow	Applicant 5.:City missing
Yellow!	Contents
Green?	The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
Green?	The international application contains no drawings. Please verify.
Green?	Payment
Green?	Please ensure that you have a valid deposit account with the receiving Office selected.

Before submitting the International Application, please carefully verify that:

- the information contained on printed Request form is correct;
- Box X of the Request form and item 12-23 of the Annex to the Request form have been signed;
- all elements of the international application as indicated in Boxes VII and IX of the Request form have been attached; and,
- the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

ABSTRACT

A compound of formula I

(A chemical formula should be inserted here - please see paper copy enclosed)

wherein R₁? represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, 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, to methods for their therapeutic use and to pharmaceutical compositions containing them.

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).

81

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 100596/WO	
International application No. PCT/GB2002/005743	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 THERAPEUTIC AGENTS	
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.	

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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
Mereside, 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-151-3odertalje, Sweden

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.

Hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

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 desistirse 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 creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

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.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistirse, 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. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

This power includes the faculty to ratify or confirm dealt, 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. domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

Granted and signed in Macclesfield, Cheshire, England

hoy de de 200_

this day of July 2003

Firma

Signature

Nombre
Cargo

Name KEVIN BILL
Title Director, IP Services

120816

CERTIFICADO NOTARIAL (SOCIEDAD)

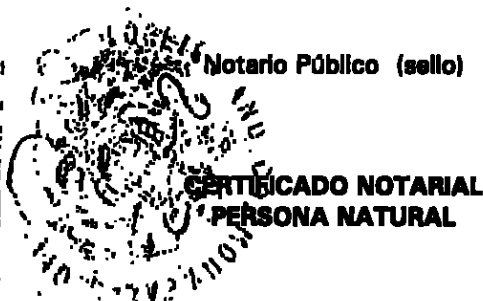
Hoy _____ de _____ de _____
 personalmente compareció ante mí _____
 a quien conozco, y de quien me consta que firmó el
 anterior documento, debidamente juramentado declaró
 y dijo que él es _____
 de _____

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

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

Estado de _____
 con fecha _____

y que quien confiere el presente poder es su
 representante.



Hoy _____ de _____ de _____, compareció(eron)
 ante mí _____

a quien (es) conozco y me consta que es(son) la(s)
 persona(s) firmante(s) del documento que precede y
 quien(es) declara(n) que otorgan el mismo para los
 fines y propósitos que en él se expresan.

Notario Público (sello)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

NOTARIAL CERTIFICATE (CORPORATION)

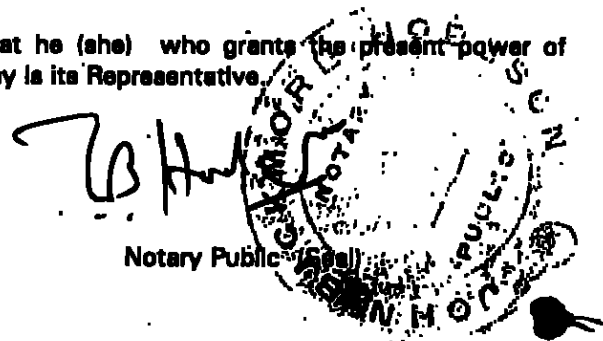
On this 18th day of July 2003 of _____
 personally appeared before me KEVIN BILLY
 to me known, and known to me to be the person who
 signed the foregoing instrument who being by me duly
 sworn did depose and say that he (she) is the
ATTORNEY
 of ATRAZENECA AB

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.

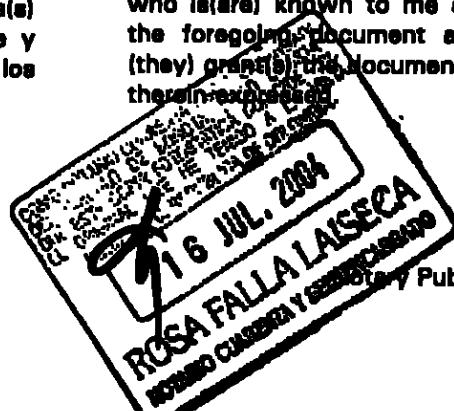
State of Sweden
 under date of 1st January 2003

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



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) this document for the uses and purposes
 therein expressed.



LEGALIZATION BY APOSTILLE IS REQUIRED.

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APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by J B Hodgson
a été signé par

3. Acting in the capacity of Notary Public
agissant en qualité de

4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

5. at London/Londres
Certified/Attesté
6. the/le 17 February 2004

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G348987**

9. Stamp:
timbre:

10. Signature: J. Ireland





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

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



REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
 TRAMITE

	USUARIO	RADIADOR
PATENTE DE INVENCION	()	()
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, D.C.,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
ASTRAZENECA AB.

Oficio N°
65054

ASUNTO:	Radicación N°	04-68143
	Solicitud internacional	PCT/GB2002/05743
	Fecha inicio fase nacional	19/07/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 27 AGO. 2004