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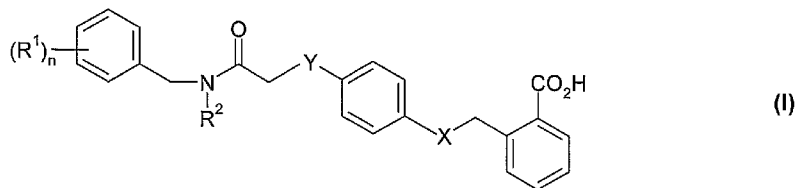
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(54) Title: THERAPEUTIC AGENTS



(57) Abstract: A *tert*-butylammonium salt or an adamantylammonium salt of a compound of formula I wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different; R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen; Y is absent or represents methylene; and X is O or S.

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THERAPEUTIC AGENTS**Field of the invention**

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

Background of the invention

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

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

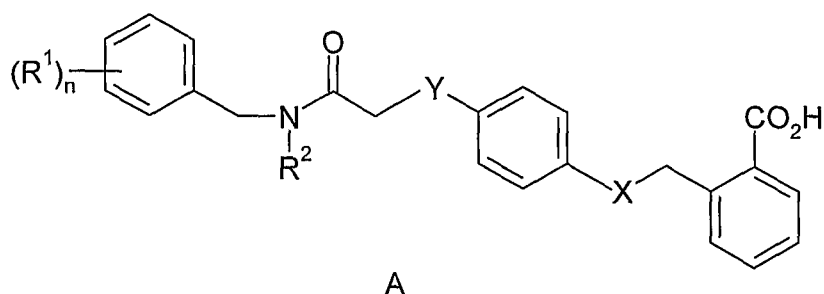
In clinical medicine there is awareness of the need to increase the insulin sensitivity in IRS
suffering patients and thus to correct the dyslipidaemia which is considered to cause the
25 accelerated progress of atherosclerosis. However, currently this is not a universally well
defined disease.

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

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

5 WO 2004/000790 (PCT/GB02/05743) discloses compounds of formula A



wherein n is 0, 1 or 2 and R¹ represents halo, a C₁₋₄alkyl group which is optionally substituted by one or more fluoro, a C₁₋₄alkoxy group which is optionally substituted by one or more fluoro and wherein when n is 2 the substituents R¹ may be the same or different; R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen; Y is absent or represents methylene; and X is O or S; and pharmaceutically acceptable salts and prodrugs thereof have utility in treating clinical conditions associated with insulin resistance.

These compounds are effective in treating conditions associated with insulin resistance. Specific pharmaceutically-acceptable salts of compounds of the formula A are not disclosed in WO 2004/000790. Further, no information is provided in relation to how crystalline forms of compounds of the formula A, and particularly salts thereof, may be prepared. Compounds of formula A exemplified in WO 2004/000790 are isolated as the free acids. However, these compounds have a physical consistency which is not suitable for use in pharmaceutical formulations. Therefore there exists a need for a solid form of these compounds that has physical and chemical properties suitable for use in pharmaceutical formulations. Many salts were tried but most of these either could not be formed in the solid state or were amorphous with a low glass transition temperature. Salts with suitable properties for pharmaceutical formulation have now been found.

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In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound.

Further, in the manufacture of drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of drug is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active ingredients are also very important factors. The drug substance, and compositions containing it, should preferably be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, hygroscopicity and solubility).

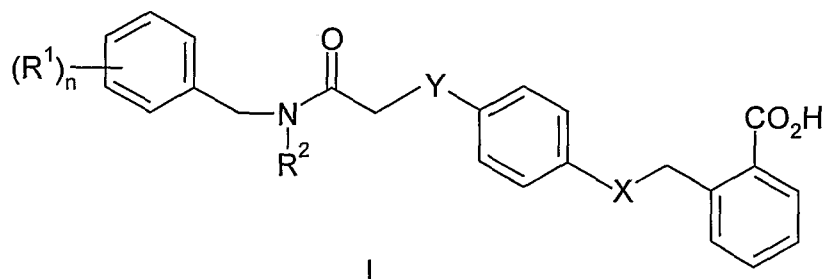
Moreover, it is also important to be able to provide the drug in a form which is as chemically pure as possible.

The skilled person will appreciate that, typically, if a drug can be readily obtained in a stable form, such as a stable crystalline form, advantages may be provided, in terms of ease of handling, ease of preparation of suitable pharmaceutical formulations, and a more reliable solubility profile.

Description of the invention

The present invention provides a *tert*-butylammonium salt or an adamantylamine salt of a compound of formula I

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

R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen;

Y is absent or represents methylene; and

X is O or S.

Further values of R¹, R², Y and X in compounds of Formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one aspect X is O.

In a second aspect X is S.

In a third aspect Y is methylene.

In a fourth aspect Y is absent.

In a fifth aspect R¹ is halo, a C₁₋₄alkyl group or a C₁₋₄alkoxy group and n is 0, 1 or 2.

Particularly R¹ is fluoro, methoxy, or isopropyl when n is 1 or 2. Particularly n is 0.

In a sixth aspect R² represents a C₅₋₇alkyl group.

The term C₂₋₈alkyl denotes a straight-chain or branched saturated aliphatic hydrocarbon having from 2 to 8 carbon atoms. Examples of said alkyl include ethyl, n-propyl, iso-

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propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl, hexyl, heptyl and octyl.

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

The compounds of formula I have activity as medicaments as described in
WO2004/00790.

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

- 10 2-[(4-{3-[benzyl(hexyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid *tert*-
butylammonium salt;
- 2-{[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl)thio]methyl}benzoic
acid *tert*-butylammonium salt;
- 2-[(4-{2-[benzyl(hexyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid *tert*-
15 butylammonium salt;
- 2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid
tert-butylammonium salt;
- 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid
tert-butylammonium salt;
- 20 2-{[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]methyl}benzoic
acid *tert*-butylammonium salt;
- 2-[(4-{3-[butyl(2,3-dimethoxybenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid
tert-butylammonium salt;
- 2-[(4-{3-[(2,3-dimethoxybenzyl)(heptyl)-amino]-3-oxopropyl}phenoxy)methyl]benzoic
25 acid *tert*-butylammonium salt;
- 2-[(4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy)methyl]-
benzoic acid *tert*-butylammonium salt;
- 2-[(4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid
tert-butylammonium salt;
- 30 2-[(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid *tert*-
butylammonium salt;

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

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

5 2-{[(3-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl)thio]methyl}benzoic acid *tert*-butylammonium salt;

2-{[(4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethyl}phenyl)thio]methyl}benzoic acid *tert*-butylammonium salt;

10 2-[(4-{3-[benzyl(hexyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid adamantylammonium salt;

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

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

15 2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid adamantylammonium salt;

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

20 2-{[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]methyl}benzoic acid adamantylammonium salt ;

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

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

25 2-[(4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy)methyl]-benzoic acid adamantylammonium salt;

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

30 2-[(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid adamantylammonium salt;

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

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- 2-({[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethyl)phenyl]thio}-methyl)benzoic acid adamantylammonium salt;
- 2-{{[3-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl]thio}methyl}benzoic acid adamantylammonium salt; and
- 5 2-{{[4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethyl}phenyl]thio}methyl}benzoic acid adamantylammonium salt.

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

10

Methods of preparation

The compound of the invention may be prepared as outlined below. However, the invention is not limited to these methods.

- 15 The salts may be prepared by reacting an acid with *tert*-butylamine or adamantylamine in an inert solvent, for example ethanol, methanol, propan-2-ol, ethyl acetate, dichloromethane, toluene, acetone or mixtures thereof or a mixture of acetone or ethanol or methanol or propan-2-ol and water, at a temperature in the range of 0-100°C and isolating the solid salt. The salt may be isolated by cooling the reaction solution and
- 20 optionally seeding the solution with the desired product and/or concentrating the solution. Optionally the product may be isolated by adding an antisolvent to a solution of the product in an inert solvent. The solid may be collected by methods known to those skilled in the art for example filtration or centrifugation.
- 25 In one embodiment the acid was dissolved in ethyl acetate (preferably the minimum volume required to dissolve the acid at room temperature although some gentle warming may be applied to facilitate dissolution) and 2 equivalents of *tert*-butylamine were added to the solution at room temperature. The ethyl acetate and the *tert*-butylamine were slowly evaporated at room temperature from the open flask and a solid precipitated. When the
- 30 volume of solvent had decreased sufficiently the product *tert*-butylammonium salt was collected by filtration and dried under vacuum at room temperature.

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In a second embodiment the acid was dissolved in ethyl acetate (preferably the minimum volume required to dissolve the acid at room temperature although some gentle warming may be applied to facilitate dissolution) and a solution of adamantylamine in dichloromethane was added. The solvents were slowly evaporated at room temperature
5 from the open flask and a solid precipitated. When the volume of solvent had decreased sufficiently the product adamantylammonium salt was collected by filtration and dried under vacuum at room temperature.

The expression "inert solvent" refers to a liquid in which the acid and the amine are both
10 soluble that does not react with either of these starting materials. Particularly an equivalent of the amine is used. Alternatively excess of the amine may be used for example 1% -100 %molar excess.

The starting acids may be prepared as described in WO 2004/000790. The pharmaceutical
15 activity of the salts may be demonstrated by using the assays described in WO 2004/000790.

Pharmacological properties

The compounds of the invention are useful for the prophylaxis and/or treatment of
20 clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type
2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This
25 dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

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

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

20

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

The present invention provides a method of treating or preventing dyslipidemias, the
25 insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the administration of a compound of formula I to a mammal (particularly a human) in need thereof.

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

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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
5 manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

Combination Therapy

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

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

25

In another aspect of the invention, the compound of the invention may be administered in association with another PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma and /or delta agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha
30 and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO

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98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to BMS 298585,
5 clofibrate, fenofibrate, bezafibrate, gemfibrozil and ciprofibrate; GW 9578, pioglitazone, rosiglitazone, rivoglitazone, balaglitazone, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxy-phenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

10

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,
15 phenbutamide, tolcyclamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. Therefore the present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this paragraph. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated
20 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.

20

Alternatively smaller doses may be used as a result of the benefits derived from the combination. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to
25 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
30 sodium or calcium, or a solvate thereof, or a solvate of such a salt. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly

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preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[N-methyl-N-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid
5] 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 Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now
10 known under its generic name rosuvastatin.

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

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

20 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).

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
25 94/24087, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO98/07749, WO 98/38182, WO 98/40375, WO 98/56757, WO 99/32478, WO 99/35135, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 00/47568, WO 00/61568, WO 01/68637, WO 01/68096, WO 02/08211, WO 00/38725, WO 00/38726, WO 00/38727,
30 WO 00/38728, WO 00/38729, DE 19825804, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 489 423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595, EP 869 121, EP 864 582, and EP 1 070 703, and the contents of these patent applications,

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particularly the compounds described in claim 1 and the named examples, are incorporated herein by reference.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8- $\{N-[(R)-\alpha-[(N-((S)-1\text{-carboxy-2-(R)-hydroxypropyl})\text{carbamoyl}]\text{benzyl})\}\text{carbamoylmethoxy}\}$ -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*-(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 invention optionally together with a pharmaceutically acceptable diluent

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or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

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

a phytosterol compound for example stanols;
probucol;

an omega-3 fatty acid for example OmacorTM;

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

an antihypertensive compound for example an angiotensin converting enzyme (ACE)

inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker for example metoprolol, a mixed

20 alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

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

aspirin;

25 a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

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

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-

30 blooded animal, such as man in need of such therapeutic treatment.

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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 the invention include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, 5 ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphan-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, 10 mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE 15 inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of 20 such salts or a prodrugs thereof for use in combination with a compound of the invention include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

25 Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the invention in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this 30 combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt 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 the invention 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 the invention 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 the invention 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 the invention 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 the invention 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.

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According to another feature of the invention there is provided the use of a compound of the invention 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 invention 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 invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Examples

1. Preparation of 2-({[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethyl)phenyl]thio}methyl)benzoic acid adamantylammonium salt.

2-({[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethyl)phenyl]thio}methyl)-benzoic acid (0.3 g) was dissolved in ethyl acetate in a round bottom flask.

Adamantylamine (0.093 g) was dissolved in dichloromethane and added to the flask. The solvents were allowed to slowly evaporate at room temperature until a smaller volume remained. The crystals of product that formed were isolated by filtration and dried under vacuum overnight. Melting point 170 °C.

2. Preparation of 2-({[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethyl)phenyl]thio}methyl)benzoic acid *tert*-butylammonium salt.

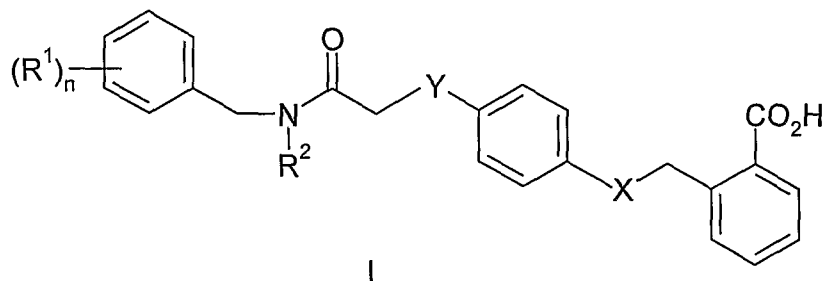
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2-([4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethyl)phenyl]thio)methyl)-
benzoic acid (14 g) was dissolved in ethyl acetate and t-butylamine added in excess (2 eq)
in a round bottom flask. Ethyl acetate and t-butylamine were slowly evaporated at room
temperature from the open flask and the salt precipitated. When a smaller volume remained
5 in the flask the crystals were isolated by filtration. The crystals were dried under vacuum at
room temperature during 12 h. Isolated amount 15 g. Melting point 105-107 °C. NMR
Includes two rotamers. ¹H NMR (400 MHz, CDCl₃, δ): 1.03-1.11 (2H), 1.24 (9H), 3.27 and
3.41 (2H), 3.57 and 3.70 (2H), 4.50 and 4.62 (2H), 4.60-4.64 (2H), 6.99-7.89 (12H).

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Claims

1. A *tert*-butylammonium salt or an adamantylammonium salt of a compound of formula I



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

R² represents a C₂₋₈alkyl group which is optionally interrupted by oxygen;

Y is absent or represents methylene; and

X is O or S.

2. A compound selected from one or more of the following:

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

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

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

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

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- 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid *tert*-butylammonium salt;
- 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenyl)thio]methyl}benzoic acid *tert*-butylammonium salt;
- 5 2-[(4-{3-[butyl(2,3-dimethoxybenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid *tert*-butylammonium salt;
- 2-[(4-{3-[(2,3-dimethoxybenzyl)(heptyl)-amino]-3-oxopropyl}phenoxy)methyl]benzoic acid *tert*-butylammonium salt;
- 2-[(4-{3-[(3-ethoxypropyl)(4-isopropylbenzyl)amino]-3-oxopropyl}phenoxy)methyl]-
- 10 benzoic acid *tert*-butylammonium salt;
- 2-[(4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid *tert*-butylammonium salt;
- 2-[(4-{2-[ethyl(2-fluorobenzyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid *tert*-butylammonium salt;
- 15 2-[(4-{3-[ethyl(2-fluorobenzyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid *tert*-butylammonium salt;
- 2-[(4-{2-[ethyl[4-(trifluoromethyl)benzyl]amino]-2-oxoethyl}phenyl)thio]-methyl}benzoic acid *tert*-butylammonium salt;
- 2-[(3-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl)thio]methyl}benzoic acid *tert*-butylammonium salt;
- 20 2-[(4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethyl}phenyl)thio]methyl}benzoic acid *tert*-butylammonium salt;
- 2-[(4-{3-[benzyl(hexyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid adamantylammonium salt;
- 25 2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenyl)thio]methyl}benzoic acid adamantylammonium salt;
- 2-[(4-{2-[benzyl(hexyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid adamantylammonium salt;
- 2-[(4-{2-[(2,4-difluorobenzyl)(heptyl)amino]-2-oxoethyl}phenoxy)methyl]benzoic acid
- 30 adamantylammonium salt;
- 2-[(4-{3-[(2,4-difluorobenzyl)(heptyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid adamantylammonium salt;

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

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

5 2-[(4-{3-[(2,3-dimethoxybenzyl)(heptyl)-amino]-3-oxopropyl}phenoxy)methyl]benzoic acid adamantylammonium salt;

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

10 2-[(4-{3-[(2,4-difluorobenzyl)(propyl)amino]-3-oxopropyl}phenoxy)methyl]benzoic acid adamantylammonium salt;

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

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

15 2-({[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethyl)phenyl]thio}-methyl)benzoic acid adamantylammonium salt;

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

20 2-{[(4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethyl}phenyl)thio]methyl}benzoic acid adamantylammonium salt.