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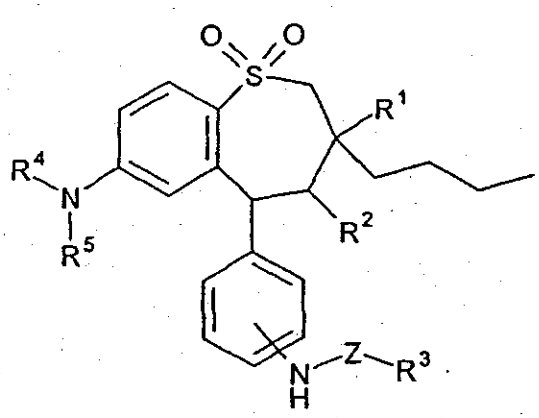
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(54) Title: COMBINED PREPARATIONS, CONTAINING 1,4-BENZOTHIEPINE-1,1-DIOXIDE DERIVATIVES AND OTHER ACTIVE SUBSTANCES, AND THE USE THEREOF

(54) Bezeichnung: KOMBINATIONSPRÄPARATE VON 1,4- BENZOTHIEPIN-1,1-DIOXIDDERIVATENMIT WEITEREN WIRKSTOFFEN UND DEREN VERWENDUNG

WO 03/018024 A1



(I)

(57) Abstract: The invention relates to mixtures of substances, containing propanolamine derivatives of formula I, in which the radicals have the indicated meanings, their physiologically acceptable salts and physiologically functional derivatives as well as other active substances.

(57) Zusammenfassung: Die Erfindung betrifft Stoffgemische der Propanolaminderivate der Formel I, worin die Reste die angegebenen Bedeutungen haben, sowie derer physiologisch verträgliche Salze, physiologisch funktionellen Derivate mit weiteren Wirkstoffen.

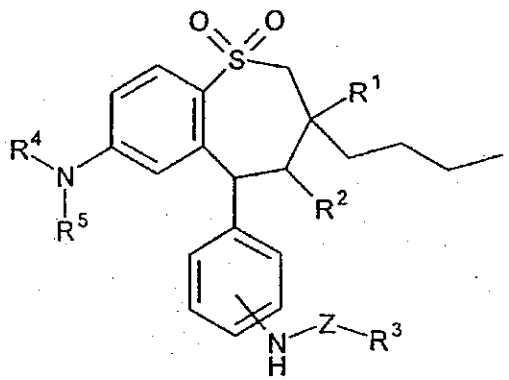
Description

Combination products of 1,4-benzothiepine 1,1-dioxide derivatives with other active ingredients and the use thereof

1,4-Benzothiepine 1,1-dioxide derivatives and the use thereof for the treatment of hyperlipidemia and of arteriosclerosis and hypercholesterolemia have been described [cf. US 6,221,897].

The invention was based on the object of providing compositions of matter or combination products of 1,4-benzothiepine 1,1-dioxide derivatives of the formula I with other active ingredients which display a synergistic effect. It was particularly intended that the hypolipidemic effect of the 1,4-benzothiepine 1,1-dioxide derivatives of the formula I in the combination products be increased to a disproportionately large extent by the synergistic effect with other active ingredients.

The invention therefore relates to compositions of matter of the 1,4-benzothiepine 1,1-dioxide derivatives of the formula I



I

in which

R^1 is methyl, ethyl, propyl, butyl;

R^2 is H, OH, NH_2, NH-(C_1-C_6)-alkyl;

R^3 is saccharide residue, disaccharide residue, trisaccharide residue, tetrasaccharide residue, where the saccharide residue, disaccharide

residue, trisaccharide residue or tetrasaccharide residue is optionally substituted one or more times by a saccharide protective group; amino acid residue, diamino acid residue, triamino acid residue, tetraamino acid residue, where the amino acid residue, diamino acid residue, triamino acid residue or tetraamino acid residue is optionally substituted one or more times by an amino acid protective group;

R^4 is methyl, ethyl, propyl, butyl;

R^5 is methyl, ethyl, propyl, butyl;

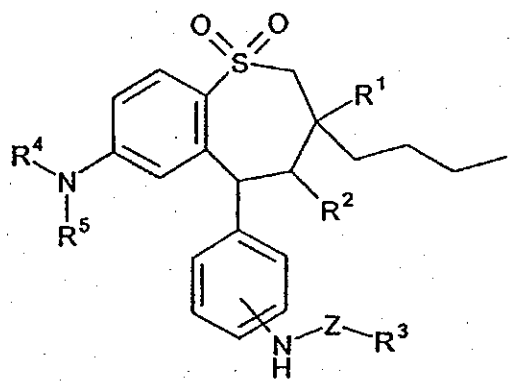
Z is $-(C=O)_n-C_0-C_{16}$-alkyl, $-(C=O)_n-C_0-C_{16}$-alkyl-NH-, $-(C=O)_n-C_0-C_{16}$-alkyl-O-, $-(C=O)_n-C_1-C_{16}$-alkyl-$(C=O)_m$, a covalent bond;

n is 0 or 1;

m is 0 or 1;

and the pharmaceutically acceptable salts and physiologically functional derivatives thereof, with other active ingredients, preferably orally active hypoglycemic active ingredients.

In a first aspect of the present invention, there is provided a composition of matter comprising compounds of the formula I



I

in which

R^1 is methyl, ethyl, propyl, butyl;

R^2 is H, OH, NH_2, NH-(C_1-C_6)-alkyl;

R^3 is saccharide residue, disaccharide residue, trisaccharide residue, tetrasaccharide residue, where the saccharide residue, disaccharide residue, trisaccharide residue or tetrasaccharide residue is optionally substituted one or more times by a saccharide protective group; amino acid residue, diamino acid residue, triamino acid residue, tetraamino acid residue, where the amino acid residue, diamino acid residue, triamino acid residue or tetraamino acid residue is optionally substituted one or more times by an amino acid protective group,

R^4 is methyl, ethyl, propyl, butyl;

R^5 is methyl, ethyl, propyl, butyl;

Z is $-(C=O)_n-C_0-C_{16}$-alkyl, $-(C=O)_n-C_0-C_{16}$-alkyl-NH-, $-(C=O)_n-C_0-C_{16}$-alkyl-O-, $-(C=O)_n-C_1-C_{16}$-alkyl-$(C=O)_m$, a covalent bond;

n is 0 or 1;

m is 0 or 1;

and the pharmaceutically acceptable salts and physiologically functional derivatives thereof, with other active ingredients.

Preferred compositions of matter comprise the compounds of the formula I in which one or more radical(s) has or have the following meaning:

R^1 ethyl, propyl, butyl;

R^2 is H, OH, NH_2, NH-(C_1-C_6)-alkyl;

R^3 is saccharide residue, disaccharide residue, where the saccharide residue or disaccharide residue is optionally substituted one or more times by a saccharide protective group;
amino acid residue, diamino acid residue, where the amino acid residue or diamino acid residue is optionally substituted one or more times by

an amino acid protective group;

R^4 is methyl, ethyl, propyl, butyl;

R^5 is methyl, ethyl, propyl, butyl;

Z is $-(C=O)_n-C_0-C_{16}$-alkyl, $-(C=O)_n-C_0-C_{16}$-alkyl-NH-, $-(C=O)_n-C_0-C_{16}$-alkyl-O-, $-(C=O)_n-C_1-C_{16}$-alkyl-$(C=O)_m$, a covalent bond;

n is 0 or 1;

m is 0 or 1;

and the physiologically tolerated acid addition salts thereof.

Particularly preferred compositions of matter comprise the following compound of the formula I in which the meanings are:

R^1 ethyl;

R^2 OH;

R^3 saccharide residue, where the saccharide residue is optionally substituted one or more times by a saccharide protective group; diamino acid residue, where the diamino acid residue is optionally substituted one or more times by an amino acid protective group

R^4 methyl;

R^5 methyl;

Z $-(C=O)-C_0-C_4$-alkyl, a covalent bond;

and the physiologically tolerated acid addition salts thereof.

Pharmaceutically acceptable salts are, because of their greater solubility in water compared with the initial or basic compounds, particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic and sulfuric acids, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic, tartaric and trifluoroacetic acids. The chloride salt is particularly preferably used for medical purposes. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

Salts with a pharmaceutically unacceptable anion likewise belong in the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the invention, e.g. an ester which is able on administration to a mammal, such as, for example, a human, to form (directly or indirectly) such a compound or an active metabolite thereof.

Prodrugs of the compounds are another embodiment. Such prodrugs can be metabolized in vivo to give a compound according to the invention. These prodrugs may or may not be active themselves.

The compounds of the formula I can also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All the polymorphous forms of the compounds according to the invention are included in the scope of the invention and are a further aspect of the invention.
All references to "compound(s) according to formula (I)" in the following text relate to compound(s) of the formula (I) as described above and their salts, solvates and

physiologically functional derivatives as described herein.

Saccharide residues mean compounds derived from aldoses and ketoses which have 3 to 7 carbon atoms and may belong to the D or L series; these include amino saccharides, sugar alcohols or saccharic acids. Examples which may be mentioned are glucose, mannose, fructose, galactose, ribose, erythrose, glyceraldehyde, sedoheptulose, glucosamine, galactosamine, glucuronic acid, galacturonic acid, gluconic acid, galactonic acid, mannonic acid, glucamine, 3-amino-1,2-propanediol, glucaric acid and galactaric acid.

Disaccharides means saccharides composed of two saccharide units. Di-, tri-, or tetrasaccharides are produced by acetal-like linkage with 2 or more sugars. The linkages may moreover occur in the α or β form. Examples which may be mentioned are lactose, maltose and cellobiose.

If the saccharide is substituted, the substitution preferably takes place on the hydrogen atom of an OH group of the sugar.

Suitable protective groups for the hydroxyl groups of the saccharides are essentially the following: benzyl, acetyl, benzoyl, pivaloyl, trityl, tert-butyldimethylsilyl, benzylidene, cyclohexylidene or isopropylidene protective groups.

The term amino acids or amino acid residues mean e.g. the stereoisomeric forms, i.e. D or L forms, of the following compounds:

alanine	glycine	proline
cysteine	histidine	glutamine
aspartic acid	isoleucine	arginine
glutamic acid	lysine	serine
phenylalanine	leucine	threonine
tryptophan	methionine	valine
tyrosine	asparagine	

2-aminoadipic acid 2-aminoisobutyric acid

3-aminoadipic acid	3-aminoisobutyric acid
beta-alanine	2-aminopimelic acid
2-aminobutyric acid	2,4-diaminobutyric acid
4-aminobutyric acid	desmosine
piperidic acid	2,2-diaminopimelic acid
6-aminocaproic acid	2,3-diaminopropionic acid
2-aminoheptanoic acid	N-ethylglycine
2-(2-thienyl)-glycine	3-(2-thienyl)-alanine
penicillamine	sarcosine
N-ethylasparagine	N-methylisoleucine
hydroxylysine	6-N-methyllysine
allo-hydroxylysine	N-methylvaline
3-hydroxyproline	norvaline
4-hydroxyproline	norleucine
isodesmosine	ornithine
allo-isoleucine	
N-methylglycine	

The abbreviated names for the amino acids follow the generally customary names (cf. Schröder, Lübke, The Peptides, Vol. I, New York 1965, pages XXII-XXIII; Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Volume XV/1 and 2, Stuttgart 1974). The amino acid pGlu is pyroglutamyl, Nal is 3-(2-naphthyl)alanine, azagly-NH2 is a compound of the formula NH2-HN-CONH2 and D-Asp is the D form of aspartic acid. According to their chemical nature, peptides are amides and decompose into amino acids on hydrolysis.

Diamino acid residue, triamino acid residue, tetraamino acid residue are understood as meaning peptides which are composed of 2 to 4 of the abovementioned amino acids.

Suitable protective groups (see, for example, T.W. Greene, "Protective Groups in Organic Synthesis") employed for amino acids are primarily:
Arg(Tos), Arg(Mts), Arg(Mtr), Arg(PMV), Asp(OBzl), Asp(OBut), Cys(4-MeBzl), Cys(Acm), Cys(SBut), Glu(OBzl), Glu(OBut), His(Tos), His(Fmoc), His(Dnp), His(Trt),

Lys(Cl-2), Lys(Boc), Met(O), Ser(Bzl), Ser(But), Thr(Bzl), Thr(But), Trp(Mts), Trp(CHO), Tyr(Br-Z), Tyr(Bzl) or Tyr(but).

Amino protective groups used are preferably the benzyloxycarbonyl(Z) radical which is removable by catalytic hydrogenation, the 2-(3,5-dimethyloxyphenyl)prop-2-yloxycarbonyl (Ddz) or trityl (Trt) radical which can be eliminated by weak acids and the 9-fluorenylmethyloxycarbonyl (Fmoc) radical which can be eliminated by secondary amines.

The amount of a compound of formula (I) and of other active ingredients necessary to achieve the desired biological effect with the combination depends on a number of factors, e.g. the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.1 mg to 100 mg (typically from 0.1 mg to 50 mg) per day per kilogram of body weight, e.g. 0.1-10 mg/kg/day. Tablets or capsules may contain, for example, from 0.01 to 100 mg, typically from 0.02 to 50 mg. In the case of pharmaceutically acceptable salts, the aforementioned weight data are based on the weight of the aminopropanol ion derived from the salt. The compositions of matter are, however, preferably in the form of a pharmaceutical composition with a convertible carrier. The carrier must, of course, be compatible in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compounds as single dose, for example as tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula (I). The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods which consist essentially of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral and peroral (e.g. sublingual) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the particular compound of formula (I) used. Coated formulations and coated slow-release formulations are also within the scope of the

invention. Acid- and gastric juice-resistant formulations are preferred. Suitable gastric juice-resistant coatings comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration may be in the form of separate units such as, for example, capsules, cachets, lozenges or tablets, each of which contain a defined amount of the compound of the formula (I) and of the other active ingredients; as powders or granules; as a solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. These compositions are generally produced by a uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or shaping a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets may be produced by tableting the compound in free-flowing form, such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent in a suitable machine. Shaped tablets can be produced by shaping the compound which is in powder form and has been moistened with an inert liquid diluent in a suitable machine.

Pharmaceutical compositions suitable for peroral (sublingual) administration include lozenges which contain a compound of formula (I) and the other active ingredient with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Other active ingredients which are suitable for the combination products are: all antidiabetics mentioned in the Rote Liste 2001, chapter 12. They can be combined with compounds of the invention of formula I in particular for synergistic improvement of the effect. Administration of the active ingredient combination can

take place either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. Most of the active ingredients listed below are disclosed in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

Antidiabetics include insulin and insulin derivatives such as, for example, Lantus® (see www.lantus.com) or HMR 1964, fast-acting insulins (see US 6,221,633), GLP-1 derivatives such as, for example, those disclosed in WO 98/08871 of Novo Nordisk A/S, and orally active hypoglycemic active ingredients.

The orally active hypoglycemic active ingredients include, preferably, sulfonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1-agonists, potassium channel openers such as, for example, those disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S, insulin sensitizers, inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds which alter lipid metabolism, such as antihyperlipidemic active ingredients and antilipidemic active ingredients, compounds which reduce food intake, PPAR and PXR agonists and active ingredients which act on the ATP-dependent potassium channel of the beta cells.

In a second aspect of the present invention, there is provided the use of the composition of matter as defined above for administration as medicament for the prophylaxis or treatment of lipid metabolism disorders or metabolic syndrome.

In a third aspect of the present invention, there is provided a use of compounds of the formula I as defined above in combination with at least one other active ingredient, in the manufacture of a medicament, wherein the medicament is suitable for administration of the compounds of the formula I and at least one other active ingredients closely in time, preferably within 10 minutes.

In a fourth aspect of the present invention, there is provided a use of compounds of the formula I as defined above in combination with at least one other active ingredient, in the manufacture of a medicament for the prophylaxis or treatment of lipid metabolism disorders, wherein the medicament is suitable for administration of the compounds of the formula I and at least one other active ingredient closely in time, preferably within 10 minutes.

In a fifth aspect of the present invention, there is provided a process for producing a composition of matter as defined above, which comprises mixing the active ingredients with a pharmaceutically suitable carrier and converting this mixture into a form suitable for administration.

In one embodiment, the compounds of the formula I may be administered in combination with an HMG-CoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin.

In one embodiment, the compounds of the formula I may be administered in combination with a cholesterol absorption inhibitor such as, for example, ezetimibe, tiqueside, pamaqueside.

In one embodiment, the compounds of the formula I may be administered in combination with a PPAR gamma agonist such as, for example, rosiglitazone, pioglitazone, JTT-501, GI 262570.
In one embodiment, the compounds of the formula I may be administered in combination with PPAR alpha agonists such as, for example,
GW 9578, GW 7647.

In one embodiment, the compounds of the formula I may be administered in combination with a mixed PPAR alpha/gamma agonist such as, for example, GW 1536, AVE 8042, AVE 8134, AVE 0847, or as described in PCT/US00/ 11833, PCT/US00/ 11490, DE10142734.4.

In one embodiment, the compounds of the formula I may be administered in combination with a fibrate such as, for example, fenofibrate, clofibrate, bezafibrate.

In one embodiment, the compounds of the formula I may be administered in combination with an MTP inhibitor such as, for example, implitapide, BMS-201038, R-103757.

In one embodiment, the compounds of the formula I may be administered in combination with bile acid absorption inhibitors (see, for example, US 6,245,744 or US 6,221,897) such as, for example, HMR 1741.

In one embodiment, the compounds of the formula I may be administered in combination with a CETP inhibitor such as, for example, JTT-705.

In one embodiment, the compounds of the formula I may be administered in combination with a polymeric bile acid adsorbent such as, for example, cholestyramine, colesevelam.

In one embodiment, the compounds of the formula I may be administered in combination with an LDL receptor inducer (see US 6,342,512) such as, for example, HMR1171, HMR1586.

In one embodiment, the compounds of the formula I may be administered in combination with an ACAT inhibitor such as, for example, avasimibe.
In one embodiment, the compounds of the formula I may be administered in combination with an antioxidant such as, for example, OPC–14117.

In one embodiment, the compounds of the formula I may be administered in combination with a lipoprotein lipase inhibitor such as, for example, NO-1886.

In one embodiment, the compounds of the formula I may be administered in combination with an ATP-citrate lyase inhibitor such as, for example, SB-204990.

In one embodiment, the compounds of the formula I may be administered in combination with a squalene synthetase inhibitor such as, for example, BMS-188494.

In one embodiment, the compounds of the formula I may be administered in combination with a lipoprotein(a) antagonist such as, for example, CI-1027 or nicotinic acid.

In one embodiment, the compounds of the formula I may be administered in combination with a lipase inhibitor such as, for example, orlistat.

In one embodiment, the compounds of the formula I may be administered in combination with insulin.

In one embodiment, the compounds of the formula I may be administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

In one embodiment, the compounds of the formula I may be administered in combination with a biguanide such as, for example, metformin.

In another embodiment, the compounds of the formula I may be administered in combination with a meglitinide such as, for example, repaglinide.

In one embodiment, the compounds of the formula I may be administered in combination with a thiazolidinedione such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 of Dr. Reddy's Research

Foundation, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]-phenyl]methyl]-2,4-thiazolidinedione.

In one embodiment, the compounds of the formula I may be administered in combination with an α-glucosidase inhibitor such as, for example, miglitol or acarbose.

In one embodiment, the compounds of the formula I may be administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

In one embodiment, the compounds of the formula I may be administered in combination with more than one of the aforementioned compounds, e.g. in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

In a further embodiment, the compounds of the formula I may be administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.:Hormone and Metabolic Research (2001), 33(9), 554-558), NPY antagonists, e.g. naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)-methyl]cyclohexylmethyl}amide; hydrochloride (CGP 71683A)), MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acids [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxo-ethyl]amide; (WO 01/91752)), orexin antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea; hydrochloride (SB-334867-A)), H3 agonists (3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208)); TNF agonists, CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (e.g. urocortin), urocortin agonists, β3-agonists (e.g. 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]ethanol; hydrochloride (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (e.g. {2-[4-(4-chloro-2,5-dimethoxy-phenyl)-5-(2-cyclohexylethyl)thiazol-2-ylcarbamoyl]-5,7- dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525)); serotonin reuptake inhibitors (e.g. dexfenfluramine), mixed serotoninergic and noradrenergic compounds (e.g.

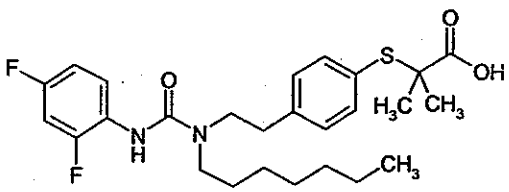
WO 00/71549), 5HT agonists e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111), bombesin agonists, galanin antagonists, growth hormone (e.g. human growth hormone), growth hormone-releasing compounds (6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (WO 01/85695)), TRH agonists (see, for example, EP 0 462 884), uncoupling protein 2 or 3 modulators, leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881), DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors (e.g. WO 00/40569), PPAR modulators (e.g. WO 00/78312), RXR modulators or TR-β agonists.

In one embodiment of the invention, the other active ingredient may be leptin, see, for example, "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2(10), 1615-1622.

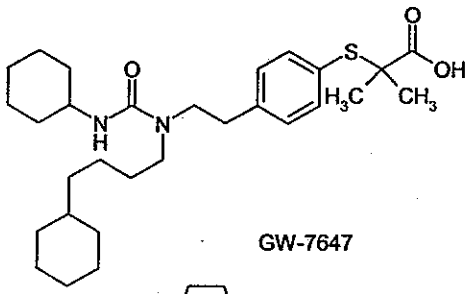
In one embodiment, the other active ingredient may be dexamphetamine or amphetamine.
In one embodiment, the other active ingredient may be fenfluramine or dexfenfluramine.
In yet another embodiment, the other active ingredient may be sibutramine.
In one embodiment, the other active ingredient may be orlistat.
In one embodiment, the other active ingredient may be mazindol or phentermine.

In one embodiment, the compounds of the formula I may be administered in combination with dietary fiber materials, preferably insoluble dietary fiber materials (see, for example, Carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6.) Caromax is a carob-containing product supplied by Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main)). Combination with Caromax® is possible in one preparation or by a separate administration of compounds of the formula I and Caromax®. Caromax® can moreover be administered in the form of foodstuffs such as, for example, in bakery products or muesli bars. Combination of compounds of the formula I with Caromax® not only improves the effect, in particular in LDL-cholesterol lowering, compared with the

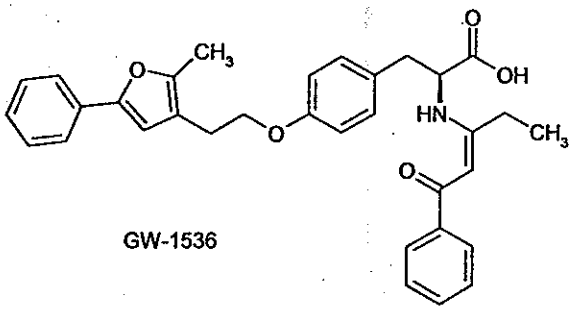
individual active ingredients, but is also tolerated better.



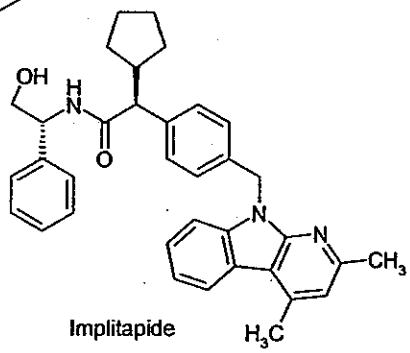
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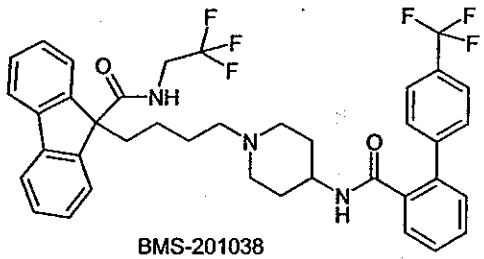
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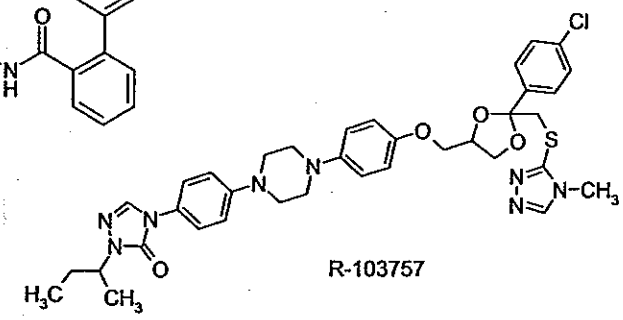
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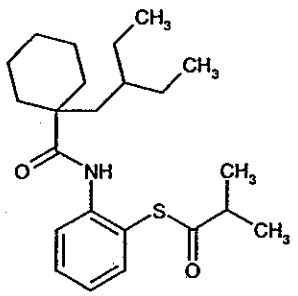
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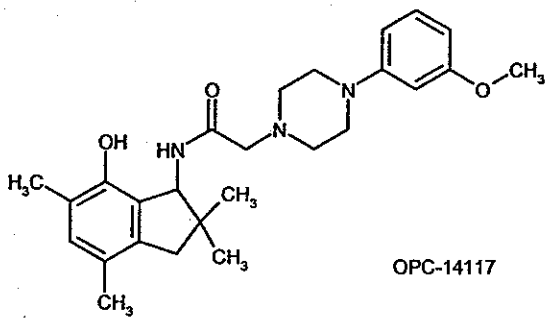
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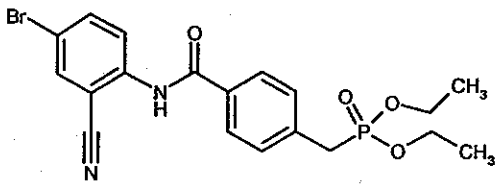
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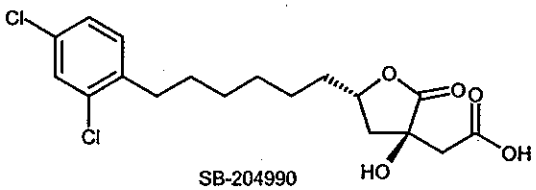
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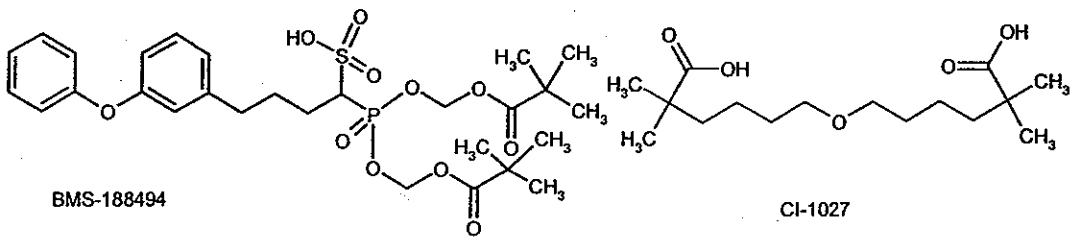
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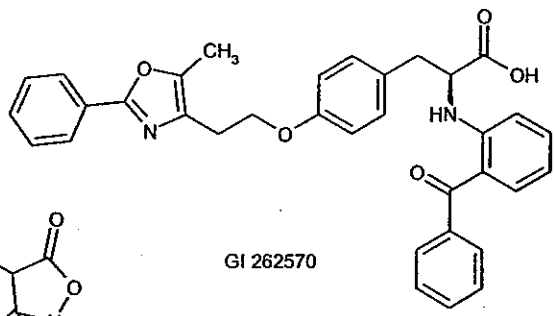


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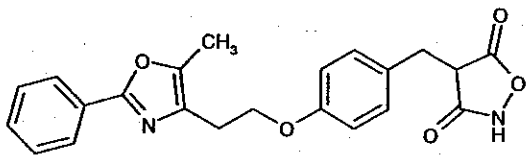


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It is self-evident that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is to be regarded as covered by the scope of protection of the present invention.

The combination products or compositions of matter comprising compounds of the formula I represent ideal medicaments for the treatment of lipid metabolism disorders

and/or carbohydrate metabolism disorders, especially hyperlipidemia and metabolic syndrome. The combination products are likewise suitable for influencing the serum cholesterol level and for the prevention and treatment of arteriosclerotic manifestations.

The following preparations serve to illustrate the invention without, however, restricting it.

Example A

Soft gelatin capsules containing 100 mg of active ingredients per capsule:

	per capsule
active ingredients	100 mg
triglyceride mixture fractionated from coconut fat	400 mg
capsule contents	500 mg

Example B

Emulsion containing 60 mg of active ingredients per 5 ml:

	per 100 ml of emulsion
active ingredients	1.2 g
neutral oil	q.s.
sodium carboxymethylcellulose	0.6 g
polyoxyethylene stearate	q.s.
glycerol, pure	0.2 to 2.0 g
flavoring	q.s.
water (deionized or distilled)	ad 100 ml

Example C

Rectal drug form containing 40 mg of active ingredients per suppository:

	per suppository
active ingredients	40 mg
suppository base	ad 2 g

Example D

Tablets containing 40 mg of active ingredients per tablet:

	per tablet
lactose	600 mg
corn starch	300 mg
soluble starch	20 mg
magnesium stearate	40 mg
	1000 mg

Example E

Coated tablet containing 50 mg of active ingredients per coated tablets:

	per coated tablet
active ingredients	50 mg
corn starch	100 mg
lactose	60 mg
sec. calcium phosphate	30 mg
soluble starch	5 mg
magnesium stearate	10 mg
colloidal silica	5 mg
	260 mg

Example F

The following formulations are suitable for producing the contents of hard gelatin capsules:

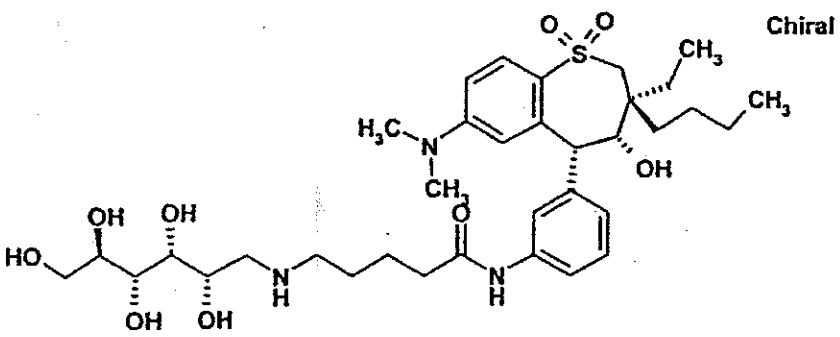
a)	active ingredients	100 mg
	corn starch	300 mg
		400 mg
b)	active ingredients	140 mg
	lactose	180 mg
	corn starch	180 mg
		500 mg

Example G

Drops can be produced using the following formulation (100 mg of active ingredient in 1 ml = 20 drops):

active ingredients	10 g
methyl benzoate	0.07 g
ethyl benzoate	0.03 g
ethanol, 96%	5 ml
demineralized water	ad 100 ml

The synergistic effect of the combinations of compounds of the formula I with other active ingredients was tested in an animal experiment. For this purpose, the following compound (C1) from the group of compounds of the formula I was tested:



Hamsters were used for the biological testing of the combination products of the invention.

Male Syrian hamsters (Mesocricetus auratus) from 8 to 10 weeks of age were used for the experiment. The animals received a standard feed (Teklad 8604M) supplemented with 0.1% cholesterol. An additional normal control group received only standard feed.

The test substances were administered orally by gavage once a day on 12 consecutive days, and the control group was treated with the vehicle.

Feces were collected on days 5 and 6 of the experiment for bile acid analysis.

Retroorbital blood was taken from the animals on day 10 of the experiment, and the lipid levels in the plasma were determined. Radioactive tracers were administered orally to the animals on day 11 of the experiment to determine the cholesterol absorption in analogy to the method described by Zilversmith et al. On day 11 of the experiment, the animals were sacrificed, and the animals' livers were removed for cholesterol analysis and preparation of microsomes. The 7α-hydroxylase activity was determined in the liver microsomes ex vivo by a modified method of Hylemon et al.

Effect of ezetimibe in combination with CI on cholesterol absorbtion
Duration of test: 10 days

1	Teklad		Normal Ctr.	n= 5
2	Teklad	+ 0.1% CH	Cholesterol Ctr.	n= 5
3	Teklad	+ 0.1% CH	0.1 mg/kg/d ezetimibe (K0004513)	n= 5
4	Teklad	+ 0.1% CH	0.1 mg/kg/d C1	n= 5
5	Teklad	+ 0.1% CH	0.3 mg/kg/d C1	n= 5
6	Teklad	+ 0.1% CH	1 mg/kg/d C1	n= 5
7	Teklad	+ 0.1% CH	0.1 mg/kg/d C1+ 0.1 mg/kg/d ezetimibe	n= 5
8	Teklad	+ 0.1% CH	0.3 mg/kg/d C1+ 0.1 mg/kg/d ezetimibe	n= 5
9	Teklad	+ 0.1% CH	0.1 mg/kg/d C1+ 0.1 mg/kg/d ezetimibe	n= 5

K00 04513 used as stock solution. (1mg/ml in ETOH)

The substances are dissolved in 2% ETOH in a final concentration of 5%.
The solutions are then suspended with 0.4% potato starch.
Administration takes place between 7-8 a.m. with 10 ml/kg

Feed: Teklad 8604M batch: 032201M

Experimental animals: Male Syrian hamsters (Mesocricetus auratus) supplied by Harlan, 100-120 g at the start of adaptation

Measured parameters:

Feed consumption
Animal weight (weekly)
Liver weight

Safety parameters (CH; TG; ALAT/ASAT; AP; CK; HDL/LDL -CH)

Liver cholesterol (HPLC) = 1 × 500 mg in ETOH/KOH

CYP7 activity (liver microsomes as group pool of 0.5 g each - preparation on day of experiment)

Feces collected on day 5-7 for bile acid determination

Cholesterol synthesis:

i.v. administration of ^{14}C-octanoate 10 μCi/100 g of animal 1 h before the end of the experiment (isoflurane anesthesia)

Removal of 2 × 500 mg of liver in EtOH/KOH

Table I:

Group	Feed/product	Plasma parameters						
		Cholesterol mmol/L	SD	%	Triglyceride mmol/L	SD	%	LDL mmol/L
1	Normal ctr.	2.84	±0.09	81	2.01	±0.23	124	0.60
2	Cholesterol ctr. + 0.1% CH	3.50	±0.27	100	1.62	±0.54	100	1.12
3	+ 0.1% CH 0.1mg/kg/d ezetimibe (K0004513)	3.44	±0.64	98	1.63	±0.36	100	1.04
4	+ 0.1% CH 0.1 mg/kg/d C1	4.20	±1.46	120	1.87	±0.30	115	1.06
5	+ 0.1% CH 0.3 mg/kg/d C1	4.01	±0.89	114	1.75	±0.23	108	1.18
6	+ 0.1% CH 1 mg/kg/d C1	3.23	±0.19	92	2.02	±0.57	124	0.92
7	+ 0.1% CH 0.1mg/kg/d C1 + 0.1 mg/kg/d ezetimibe	3.62	±0.18	103	2.08	±0.12	128	1.04
8	+ 0.1% CH 0.3 mg/kg/d C1 + 0.1 mg/kg/d ezetimibe	3.56	±0.94	101	2.11	±0.58	130	0.99
9	+ 0.1% CH 1 mg/kg/d C1 + 0.1 mg/kg/d ezetimibe	2.82	±0.05	81	1.84	±0.23	113	0.76

14 February 2006

Cholesterol absorption

Oral aministration of 2μCi ^{3}H-sitosterol/1μCi ^{14}C-cholesterol in 0,5ml 1:1

tricaprin: tricaprylin

Feces collected from day 8-10

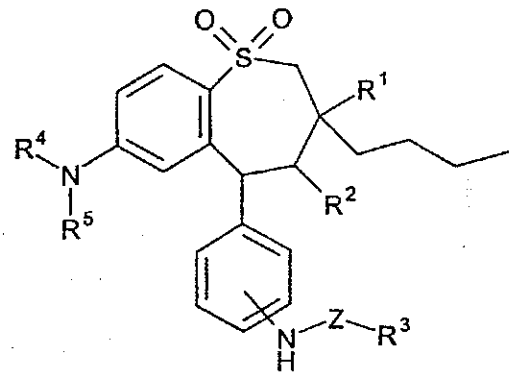
The feces are then dried and combusted for isotope determination in an Oximat (Packard)

It is evident from the table that the compounds of the formula I in combination with ezetimibe show a synergistic effect on the plasma parameters.

14 February 2006

Patent claims:

1. A composition of matter comprising compounds of the formula I



I

in which

R^1 is methyl, ethyl, propyl, butyl;

R^2 is H, OH, NH_2, NH-(C_1-C_6)-alkyl;

R^3 is saccharide residue, disaccharide residue, trisaccharide residue, tetrasaccharide residue, where the saccharide residue, disaccharide residue, trisaccharide residue or tetrasaccharide residue is optionally substituted one or more times by a saccharide protective group; amino acid residue, diamino acid residue, triamino acid residue, tetraamino acid residue, where the amino acid residue, diamino acid residue, triamino acid residue or tetraamino acid residue is optionally substituted one or more times by an amino acid protective group,

R^4 is methyl, ethyl, propyl, butyl;

R^5 is methyl, ethyl, propyl, butyl;

Z is -(C=O)$_n$-C$_0$-C$_{16}$-alkyl, -(C=O)$_n$-C$_0$-C$_{16}$-alkyl-NH-, -(C=O)$_n$-C$_0$-C$_{16}$-alkyl-O-, -(C=O)$_n$-C$_1$-C$_{16}$-alkyl-(C=O)$_m$, a covalent bond;

n is 0 or 1;

m is 0 or 1;

and the pharmaceutically acceptable salts and physiologically functional derivatives thereof, with other active ingredients.

2. A composition of matter as claimed in claim 1, wherein the meanings in formula I are

R^1 is ethyl, propyl, butyl;

R^2 is H, OH, NH_2 NH-(C$_1$-C$_6$)-alkyl;

R^3 is saccharide residue, disaccharide residue, where the saccharide residue or disaccharide residue is optionally substituted one or more times by a saccharide protective group;
amino acid residue, diamino acid residue, where the amino acid residue or diamino acid residue is optionally substituted one or more times by an amino acid protective group;

R^4 is methyl, ethyl, propyl, butyl;

R^5 is methyl, ethyl, propyl, butyl;

Z is -(C=O)$_n$-C$_0$-C$_{16}$-alkyl, -(C=O)$_n$-C$_0$-C$_{16}$-alkyl-NH-, -(C=O)$_n$-C$_0$-C$_{16}$-alkyl-O-, -(C=O)$_n$-C$_1$-C$_{16}$-alkyl-(C=O)$_m$, a covalent bond;

n is 0 or 1;

m is 0 or 1;

and the physiologically tolerated acid addition salts thereof.

3. A composition of matter as claimed in claim 1 or 2, wherein the compound of the formula I is

R^1 ethyl;

R^2 OH;

R^3 saccharide residue, where the saccharide residue is optionally substituted one or more times by a saccharide protective group; diamino acid residue, where the diamino acid residue is optionally substituted one or more times by an amino acid protective group;

R^4 methyl;

R^5 methyl;

Z -(C=O)-C_0-C_4-alkyl, a covalent bond;

and the physiologically tolerated acid addition salts thereof.

4. A composition of matter as claimed in one or more of claims 1 to 3, which comprises as other active ingredient one or more antidiabetics, hypoglycemic active ingredients, HMG-CoA reductase inhibitors, cholesterol absorption inhibitors, PPAR gamma agonists, PPAR alpha agonists, PPAR alpha/gamma agonists, fibrates, MTP inhibitors, bile acid absorption inhibitors, CETP inhibitors, polymeric bile acid adsorbents, LDL receptor inducers, ACAT inhibitors, antioxidants, lipoprotein lipase

inhibitors, ATP-citrate lyase inhibitors, squalene synthetase inhibitors, lipoprotein(a) antagonists, lipase inhibitors, insulins, sulfonylureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, active ingredients acting on the ATP-dependent potassium channel of the beta cells, CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonin reuptake inhibitors, mixed serotoninergic and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormones, growth hormone-releasing compounds, TRH agonists, uncoupling protein 2 or 3 modulators, leptin agonists, DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR-β agonists or amphetamines.

5. A composition of matter as claimed in one or more of claims 1 to 4, which comprises as other active ingredient one or more compounds which normalize lipid metabolism.

6. A composition of matter as claimed in one or more of claims 1 to 5, which comprises as other active ingredient normalizing lipid metabolism compounds from the group of statins, glitazones, PPAR alpha agonists, cholestyramine, cholestipol, colesolvam, adsorbent resins, fibrates, gemfibrozil, cholesterol absorption inhibitors, ezetimibe, tiqueside, pamaqueside, CETP inhibitors, MTP inhibitors, LDL receptor inducers, lipase inhibitors, orlistat.

7. A composition of matter as claimed in one or more of claims 1 to 6, which comprises cholesterol absorption inhibitor as other active ingredient.

8. A composition of matter as claimed in claim 7, which comprises ezetimibe,

tiqueside or pamaqueside as other active ingredient.

9. A composition of matter as claimed in one or more of claims 1 to 6, which comprises Caromax® as other active ingredient.

10. The use of the composition of matter as claimed in one or more of claims 1 to 9 for administration as medicament for the prophylaxis or treatment of lipid metabolism disorders or metabolic syndrome.

11. The use of the composition of matter as claimed in one or more of claims 1 to 9 for administration as medicament for the prophylaxis or treatment of hyperlipidemia.

12. The use of the composition of matter as claimed in one or more of claims 1 to 9 for administration as medicament for the prophylaxis or treatment of arteriosclerotic manifestations.

13. A use of compounds of the formula I as claimed in one or more of claims 1 to 3 in combination with at least one other active ingredient, in the manufacture of a medicament, wherein the medicament is suitable for administration of the compounds of the formula I and at least one other active ingredients closely in time, preferably within 10 minutes.

14. A use of compounds of the formula I as claimed in one or more of claims 1 to 3 in combination with at least one other active ingredient, in the manufacture of a medicament for the prophylaxis or treatment of lipid metabolism disorders, wherein the medicament is suitable for administration of the compounds of the formula I and at least one other active ingredient closely in time, preferably within 10 minutes.

15. A process for producing a composition of matter as claimed in one or more of claims 1 to 8, which comprises mixing the active ingredients with a pharmaceutically suitable carrier and converting this mixture into a form suitable for administration.