159159

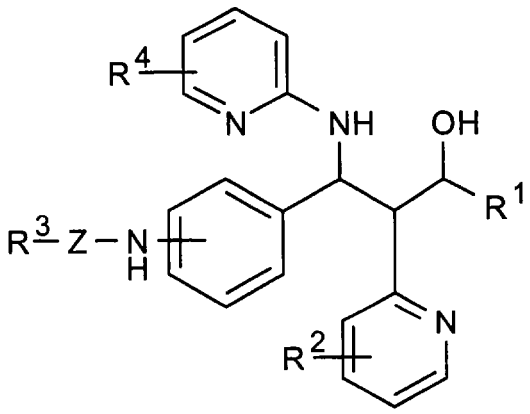
Description

Combination products of aryl-substituted propanolamine derivatives with other active ingredients and the use thereof

EP 1 117 645 discloses propanolamine derivatives with hypolipidemic effect.

The invention was based on the object of providing compositions of matter or combination products of propanolamine derivatives of the formula I with other active ingredients which display a synergistic effect. It was particularly intended that the hypolipidemic effect of the propanolamine 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 propanolamine derivatives of the formula I



I

in which

R^1 is phenyl, heteroaryl, unsubstituted or optionally substituted by one to three mutually independent radicals, where the aromatic or heteroaromatic system may be substituted one to three times by

G00002

fluorine, chlorine, bromine, iodine, OH, CF_3, $-NO_2$, CN, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, NH_2, $-NH-R^9$, $-N(R^9)R^{10}$, CHO, -COOH, $-COOR^{11}$, $-(C=O)-R^{12}$, (C_1-C_6)-alkyl-OH, (C_1-C_6)-alkyl(-OH)-phenyl, (C_1-C_6)-alkyl-CF_3, (C_1-C_6)-alkyl-NO_2, (C_1-C_6)-alkyl-CN, (C_1-C_6)-alkyl-NH_2, (C_1-C_6)-alkyl-$NH-R^9$, (C_1-C_6)-alkyl-$N(R^9)R^{10}$, (C_1-C_6)-alkyl-CHO, (C_1-C_6)-alkyl-COOH, (C_1-C_6)-alkyl-$COOR^{11}$, (C_1-C_6)-alkyl-$(C=O)-R^{12}$, $-O-(C_1-C_6)$-alkyl-OH, $-O-(C_1-C_6)$-alkyl-CF_3, $-O-(C_1-C_6)$-alkyl-NO_2, $-O-(C_1-C_6)$-alkyl-CN, $-O-(C_1-C_6)$-alkyl-NH_2, $-O-(C_1-C_6)$-alkyl-$NH-R^9$, $-O-(C_1-C_6)$-alkyl-$N(R^9)R^{10}$, $-O-(C_1-C_6)$-alkyl-CHO, $-O-(C_1-C_6)$-alkyl-COOH, $-O-(C_1-C_6)$-alkyl-$COOR^{11}$, $-O-(C_1-C_6)$-alkyl-$(C=O)-R^{12}$, $-N-SO_3H$, $-SO_2-CH_3$, $-O-(C_1-C_6)$-alkyl-$O-(C_1-C_6)$-alkyl-phenyl, (C_1-C_6)-alkylthio, pyridyl, it being possible for one or more hydrogen atom(s) in the alkyl radicals to be replaced by fluorine, and it being possible for phenyl and pyridyl in turn to be monosubstituted by methyl, methoxy or halogen;

R^2 is H, OH, CH_2OH, OMe, CHO, NH_2;

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 one of the saccharide protective groups, $HO-SO_2-$, $(HO)_2-PO-$;

R^4 is H, methyl, F, OMe;

R^9 to R^{12} are, independently of one another, H, C_1-C_8-alkyl;

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

n is 0 or 1;

m is 0 or 1;

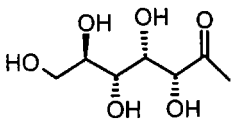
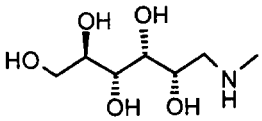
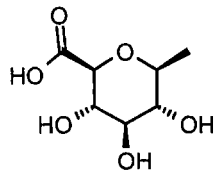
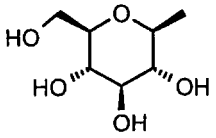
and the pharmaceutically acceptable salts and physiologically functional derivatives thereof, with other active ingredients, preferably orally active hypoglycemic active ingredients.

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 is phenyl, thiazolyl, oxazolyl, isoxazolyl, it being possible for the aromatic or heteroaromatic system to be substituted one to two times by fluorine, chlorine, bromine, (C_1-C_8)-alkyl;

R^2 is H, OH, CH_2OH, OMe, CHO, NH_2;

R^3 is

where the saccharide residue is optionally substituted one or more times by one of the saccharide protective groups, HO-SO_2-;

R^4 is H, methyl, F, OMe;

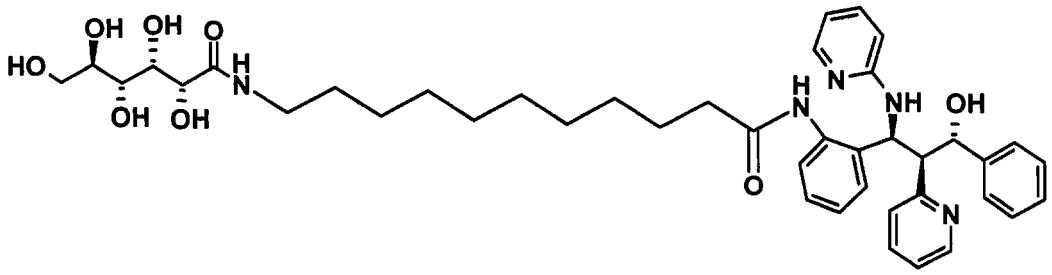
Z is -NH-C_6-C_{12}-alkyl-C=O-, -O-C_6-C_{12}-alkyl-C=O-, -$(C=O)_m$-C_6-C_{12}-alkyl-$(C=O)_n$;

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:



and the physiologically tolerated acid addition salts thereof.

Heteroatoms particularly suitable in the abovementioned heteroaryl groups are, for example, O, S, N.

Unless otherwise defined, the heteroaromatic rings have 1-15 carbon atoms and 1-6 heteroatoms, preferably 1-5 C atoms and 1-2 heteroatoms.
Examples of suitable heteroaryl groups mentioned in the foregoing definitions are thiophene, furan, pyridine, pyrimidine, indole, quinoline, oxazole, isoxazole, thiazole or isothiazole.

The term alkyl means straight-chain or branched hydrocarbon chains.

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 mean 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 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	N-methylglycine
N-ethylasparagine	N-methylisoleucine
hydroxylysine	6-N-methyllysine
allo-hydroxylysine	N-methylvaline
3-hydroxyproline	norvaline
4-hydroxyproline	norleucine
isodesmosine	ornithine
allo-isoleucine	11-aminoundecanoic acid

The term amino acid protective groups means suitable groups protecting the functional groups of the side chains of the amino acid residues (see, for example, T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd Edition, John Wiley and Sons, New York 1991). Those mainly used are: t-butyloxycarbonyl (BOC), 9-fluorenylmethoxycarbonyl (Fmoc), benzyloxycarbonyl (Z), 2-(3,5-dimethoxyphenyl)prop-2-yloxycarbonyl (Ddz), methyl, t-butyl, trityl, s-t-butyl.

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, sulfamic 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 of the formula I, e.g. an ester which is able on administration to a mammal, such as, for example, a human, to form (directly or indirectly) a compound of the formula I or an active metabolite thereof.

Physiologically functional derivatives also include prodrugs of the compounds of the

invention. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.

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

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR gamma agonist such as, for example, rosiglitazone, pioglitazone, JTT-501, GI 262570.

In one embodiment of the invention, the compounds of the formula I are administered in combination with PPAR alpha agonists such as, for example, GW 9578, GW 7647.

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

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

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

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

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ACAT inhibitor such as, for example, avasimibe.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant such as, for example, OPC--14117.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor such as, for example,

NO-1886.

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

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

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

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with insulin.
In one embodiment, the compounds of the formula I are administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.
In one embodiment, the compounds of the formula I are administered in combination with a biguanide such as, for example, metformin.

In another embodiment, the compounds of the formula I are administered in combination with a meglitinide such as, for example, repaglinide.
In one embodiment, the compounds of the formula I are 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 are administered in combination with an α-glucosidase inhibitor such as, for example, miglitol or acarbose.

In one embodiment, the compounds of the formula I are 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 are 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.

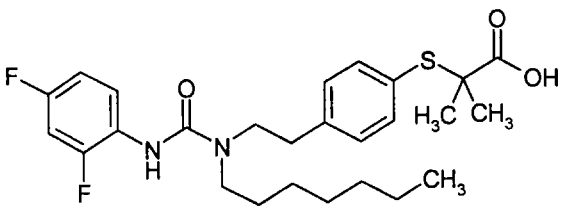
In a further embodiment, the compounds of the formula I are administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.:Hormone and Metabolic Research (2001), 33(9), 554-558), 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-tetrahydronaphthalen-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.

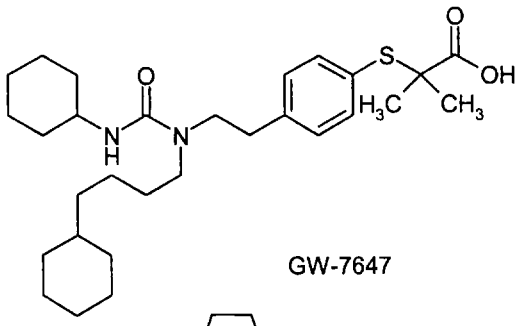
In one embodiment of the invention, the other active ingredient is leptin, see, for example, "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2(10), 1615-1622.

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

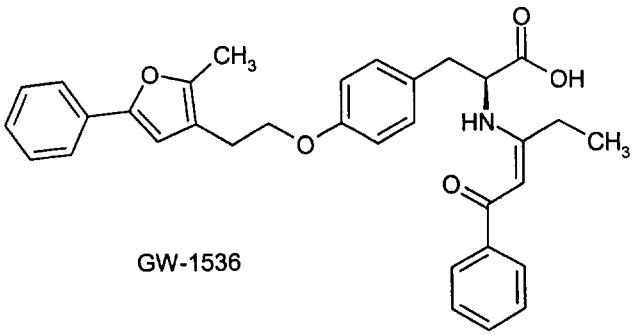
In one embodiment, the compounds of the formula I are administered in combination with dietary fiber materials, preferably insoluble dietary fiber materials (see, for example, Carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 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.



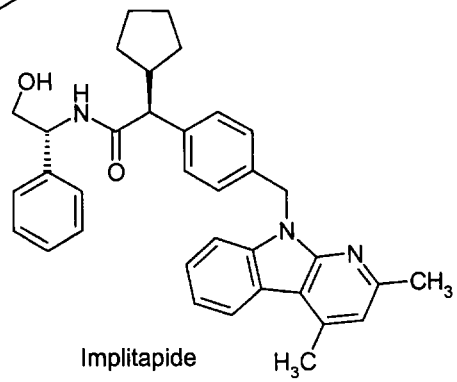
GW-9578



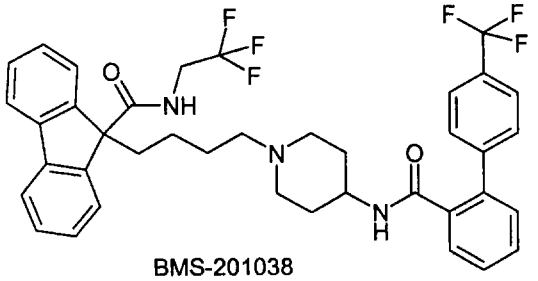
GW-7647



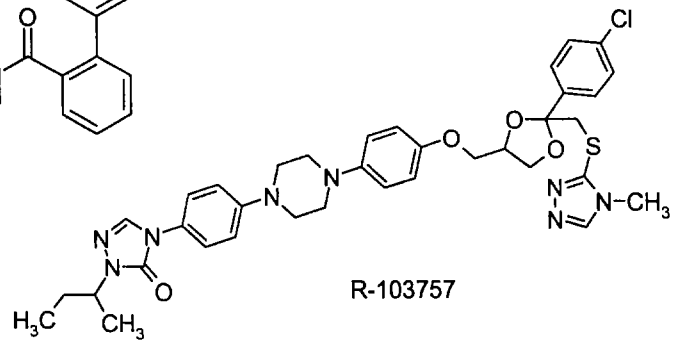
GW-1536



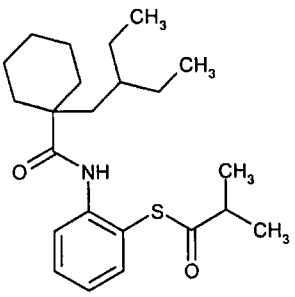
Implitapide



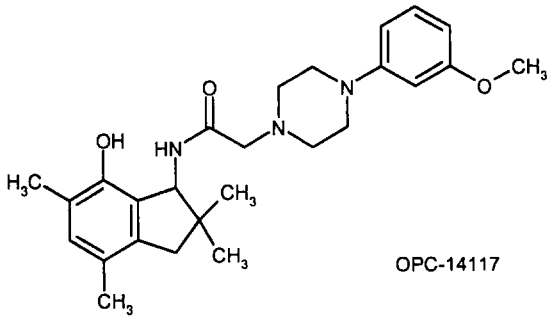
BMS-201038



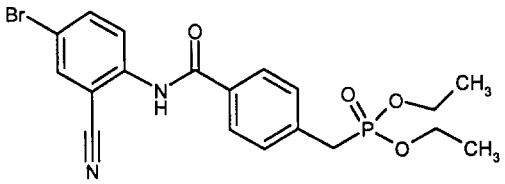
R-103757



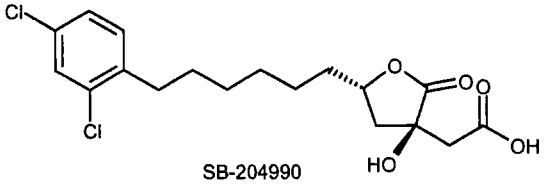
JTT-705



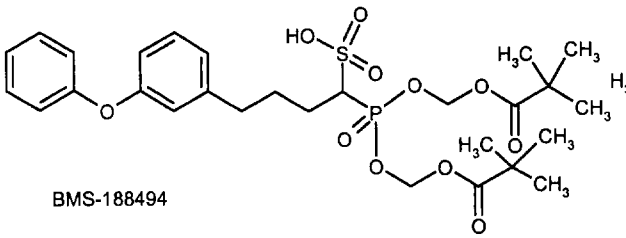
OPC-14117



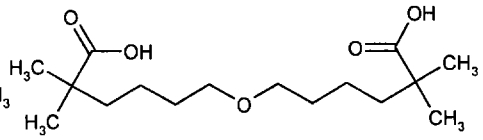
NO-1886



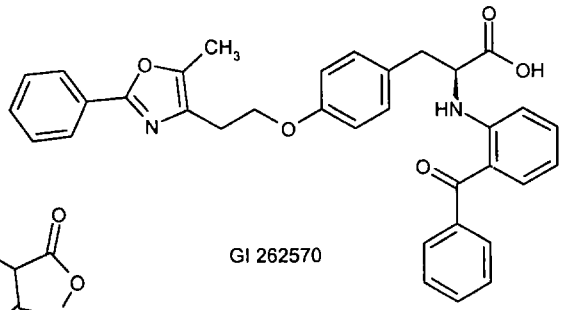
SB-204990



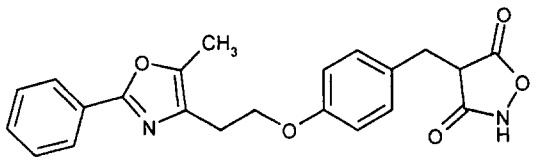
BMS-188494



CI-1027



GI 262570



JTT-501

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 tablets containing 50 mg of active ingredients per coated tablet:

	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:

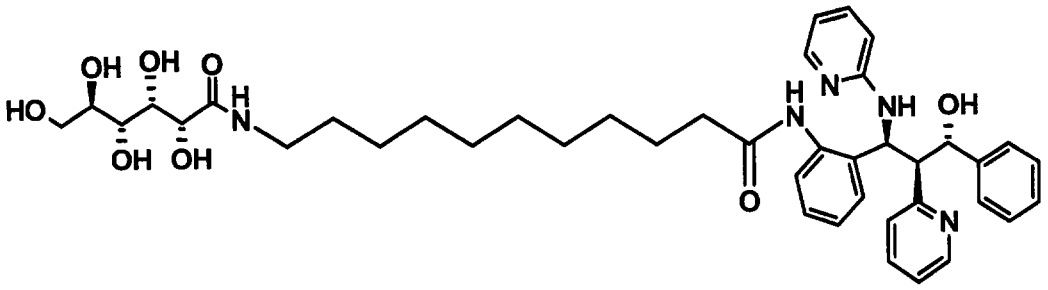
a)	active ingredients	100 mg
	corn starch	300 mg
		400 mg
b)	active ingredients	140 mg
	lactose	180 mg
	corn starch	180 mg
		500 mg

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:



Compound (C1)

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 13 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.

Combination of compound C1 with Caromax®

				Product mg/200 ml
1 Teklad		normal ctr. I	n = 6 -6	-
2 Teklad	+ 0.1% CH	hyperlip. ctr. (0.1% CH)	n = 6 -12	-
3 Teklad	+ 0.1% CH	30 mg/kg/d C1	n = 6 -18	600
4 Teklad	+ 0.1% CH	5% Caromax in the feed	n = 6 -24	
5 Teklad	+ 0.1% CH	30 mg/kg/d C1 + 5% Caromax (feed)	n = 6 -30	600

The substances are dissolved in Solutol (50°C) in a final concentration of 5%.
The solutions are then suspended with 0.4% potato starch.
Administration takes place 1× a day with 10 ml/kg

Feed: Teklad 8604M batch: 030610M

Experimental animals: Male Syrian hamsters (Mesocricetus auratus) supplied by Harlan
80-100 g at the start of adaptation

Measured parameters:
Feed consumption
Animal weight (weekly)
Safety parameters (CH; TG, ALAT/ASAT; AP; HDL/LDL)

Preliminary value and 2 days before end of the experiment (isoflurane anesthesia) by retroorbital blood sampling

Liver weight

Liver cholesterol (HPLC) = 1 × 500 mg in EtOH/KOH (sample is also used for CH synthesis)

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

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:

Feed/product	Cholesterol mmol/L	STD	%	Triglycerides mmol/L	STD	%	LDL-cholesterol mmol/L	STD	%	HDL-cholesterol mmol/L	STAB W	%	Liver Cholesterol mg/g	STD	%	Sterol biosynthesis dpm/g/h	STD	%
Normal ctr. I	**2.91**	±0.14	**72**	**1.53**	±0.24	**105**	**0.46**	±0.05	**39**	**2.16**	±0.08	**86**	**2.80**	±0.37	**10**	**409**	±296	**100**
Hyperlip. ctr. (0.1% CH)	**4.02**	±0.19	**100**	**1.46**	±0.34	**100**	**1.17**	±0.14	**100**	**2.52**	±0.15	**100**	**27.11**	±6.04	**100**	**50**	±12	**12**
+ 0.1% CH 30 mg/kg/d C1	**3.58**	±0.23	**89**	**1.49**	±0.16	**102**	**0.88**	±0.10	**75**	**2.42**	±0.23	**96**	**14.72**	±2.16	**54**	**73**	±18	**18**
+ 0.1% CH 5% Caromax in feed	**3.63**	±0.48	**90**	**1.34**	±0.58	**92**	**1.05**	±0.33	**89**	**2.38**	±0.34	**95**	**20.50**	±3.73	**76**	**45**	±18	**11**
+ 0.1% CH 30 mg/kg/d C1+ 5% Caromax (Feed)	**2.51**	±0.33	**62**	**1.34**	±0.26	**92**	**0.45**	±0.08	**39**	**1.82**	±0.20	**72**	**4.14**	±0.92	**15**	**216**	±114	**53**

Abbreviations: 0.1% CH = 0.1% cholesterol in the feed
5% Caromax = 5% Caromax added to the feed; equivalent to a dose of 5 000 mg/kg/day

Effect of ezetimibe (K00 04513) plus C1 on cholesterol absorption

Ezetimibe (K00 04513) is a cholesterol absorption inhibitor from Schering Plough

1	Teklad		Normal ctr.	n= 5 -5
2	Teklad	+ 0.1% CH	Cholesterol ctr.	n= 5 -10
3	Teklad	+ 0.1% CH	0.1 mg/kg/d K 00 04513	n= 5 -15
4	Teklad	+ 0.1% CH	0.3 mg/kg/d K 00 04513	n= 5 -20
5	Teklad	+ 0.1% CH	1 mg/kg/d K 00 04513	n= 5 -25
6	Teklad	+ 0.1% CH	3 mg/kg/d C1	n= 5 -30
7	Teklad	+ 0.1% CH	10 mg/kg/d C1	n= 5 -35
8	Teklad	+ 0.1% CH	30 mg/kg/d C1	n= 5 -40
9	Teklad	+ 0.1% CH	0.1 mg/kg/d K 00 04513 + 10 mg/kg/d C1	n= 5 -45
10	Teklad	+ 0.1% CH	0.3 mg/kg/d K 00 04513 + 3 mg/kg/d C1	n= 5 -50
11	Teklad	+ 0.1% CH	0.1 mg/kg/d K 00 04513 + 3 mg/kg/d C1	n= 5 -55
12	Teklad	+ 0.1% CH	0.3 mg/kg/d K 00 04513 + 10 mg/kg/d C1	n= 5 -60

K00 04513 employed as stock solution (1 mg/ml in EtOH)

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 1× in the morning 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; HDL/LDL)

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 absoroption

Oral administration of 2 μCi of ^{3}H-sitosterol/1 μCi of ^{14}C-cholesterol in 0.5 ml 1:1 tricaprin:tricaprylin

Feces collected on day 10-12

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

Table II:

Group	Feed/product	Plasma parameter												Liver			CH absorption	
		Cholesterol			Triglycerides			LDL			HDL			Cholesterol				
		mmo	STD	%	mmo	STD	%	mmo	ST	%	mmo	ST	%	mg/	ST	%	% absorption	% of ctr.
1	**Normal ctr.**	**2.95**	±0.1	**72**	**1.76**	±0.	**86**	**0.60**	±0.	**54**	**1.78**	±0.1	**83**	**3.7**	±0.	**34**	**49.0**	±100.0
2	**Cholesterol ctr.**	**4.09**	±0.1	**10**	**2.04**	±0.	**10**	**1.13**	±0.	**10**	**2.15**	±0.1	**100**	**11.**	±0.	**10**	**50.4**	±102.9
3	**+ 0.1% CH 0.1 mg/kg/d K 00 04513**	**3.73**	±0.3	**91**	**1.99**	±0.	**98**	**1.06**	±0.	**94**	**1.98**	±0.2	**92**	**11.**	±1.	**10**	**47.4**	±96.8
4	**+ 0.1% CH 0.3 mg/kg/d K 00 04513**	**2.99**	±0.4	**73**	**1.87**	±0.	**92**	**0.40**	±0.	**35**	**1.92**	±0.2	**89**	**2.0**	±0.	**18**	**15.6**	±31.8
5	**+ 0.1% CH 1 mg/kg/d K 00 04513**	**2.53**	±0.2	**62**	**1.79**	±0.	**88**	**0.23**	±0.	**20**	**1.71**	±0.1	**80**	**1.7**	±0.	**16**	**5.8**	±11.9
6	**+ 0.1% CH 3 mg/kg/d C1**	**3.92**	±0.4	**96**	**1.84**	±0.	**90**	**0.98**	±0.	**87**	**2.20**	±0.1	**10**	**10.**	±1.	**10**	**39.6**	±80.9

7	**+ 0.1% CH 10 mg/kg/d C1**	**3.70**	±0.2	**90**	**2.35**	±0.	**11**	**0.78**	0.	**69**	**2.00**	±0.1	**93**	**9.5**	±1.	**86**	**49.1**	±100.1
8	**+ 0.1% CH 30 mg/kg/d C1**	**3.66**	±0.31	**89**	**2.02**	±0.47	**99**	**0.80**	±0.04	**71**	**2.02**	±0.28	**94**	**7.18**	±0.60	**65**	**38.3**	±78.2
9	**+ 0.1% CH 0.1 mg/kg/d K 00 04513 + 10 mg/kg/d C1**	**2.81**	±0.10	**69**	**1.51**	±0.33	**74**	**0.55**	±0.10	**49**	**1.74**	±0.10	**81**	**2.71**	±0.43	**25**	**17.1**	±34.9
10	**+ 0.1% CH 0.3 mg/kg/d K 00 04513 + 3 mg/kg/d C1**	**2.73**	±0.39	**67**	**1.71**	±0.44	**84**	**0.31**	±0.10	**28**	**1.84**	±0.16	**86**	**2.15**	±0.48	**20**	**10.4**	±21.2
11	**+ 0.1% CH 0.1 mg/kg/d K 00 04513 + 3 mg/kg/d C1**	**2.96**	±0.19	**72**	**1.82**	±0.25	**89**	**0.62**	±0.15	**55**	**1.75**	±0.12	**82**	**2.82**	±1.02	**26**	**23.2**	±47.4
12	**+ 0.1% CH 0.3 mg/kg/d K 00 04513 + 10 mg/kg/d C1**	**2.29**	±0.35	**56**	**0.99**	±0.40	**49**	**0.19**	±0.06	**17**	**1.71**	±0.21	**80**	**1.92**	±0.31	**17**	**9.5**	±19.5

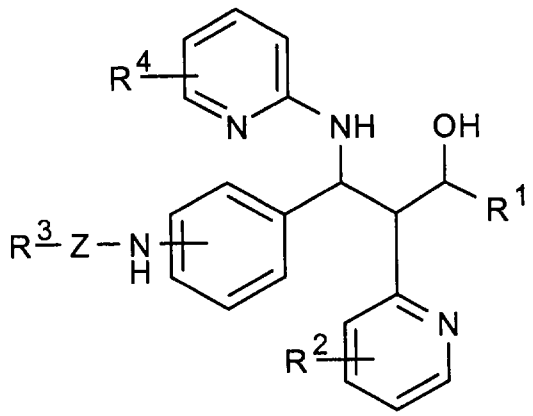
K 00 04513 = ezetimibe cholesterol absorption inhibitor, Schering Plough

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

Thus, for example, treatment with 0.1 mg/kg K 00 04513 (line 3) reduces the LDL-cholesterol to 94%, and treatment with 3 mg/kg C1 (line 6) reduces the LDL-cholesterol to 87%. Combination treatment with 0.1 mg/kg K 00 045 13 and 3 mg/kg C1 (line 10) reduces the LDL-cholesterol to 28%.

Patent claims:

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



I

in which

R^1 is phenyl, heteroaryl, unsubstituted or optionally substituted by one to three mutually independent radicals, where the aromatic or heteroaromatic system may be substituted one to three times by fluorine, chlorine, bromine, iodine, OH, CF_3, $-NO_2$, CN, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, NH_2, $-NH-R^9$, $-N(R^9)R^{10}$, CHO, -COOH, $-COOR^{11}$, $-(C=O)-R^{12}$, (C_1-C_6)-alkyl-OH, (C_1-C_6)-alkyl(-OH)-phenyl, (C_1-C_6)-alkyl-CF_3, (C_1-C_6)-alkyl-NO_2, (C_1-C_6)-alkyl-CN, (C_1-C_6)-alkyl-NH_2, (C_1-C_6)-alkyl-$NH-R^9$, (C_1-C_6)-alkyl-$N(R^9)R^{10}$, (C_1-C_6)-alkyl-CHO, (C_1-C_6)-alkyl-COOH, (C_1-C_6)-alkyl-$COOR^{11}$, (C_1-C_6)-alkyl-$(C=O)-R^{12}$, $-O-(C_1-C_6)$-alkyl-OH, $-O-(C_1-C_6)$-alkyl-CF_3, $-O-(C_1-C_6)$-alkyl-NO_2, $-O-(C_1-C_6)$-alkyl-CN, $-O-(C_1-C_6)$-alkyl-NH_2, $-O-(C_1-C_6)$-alkyl-$NH-R^9$, $-O-(C_1-C_6)$-alkyl-$N(R^9)R^{10}$, $-O-(C_1-C_6)$-alkyl-CHO, $-O-(C_1-C_6)$-alkyl-COOH, $-O-(C_1-C_6)$-alkyl-$COOR^{11}$, $-O-(C_1-C_6)$-alkyl-$(C=O)-R^{12}$, $-N-SO_3H$, $-SO_2-CH_3$, $-O-(C_1-C_6)$-alkyl-$O-(C_1-C_6)$-alkyl-phenyl, (C_1-C_6)-alkylthio, pyridyl, it being possible for one or more hydrogen atom(s) in the alkyl radicals to be replaced by fluorine, and it being possible for

phenyl and pyridyl in turn to be monosubstituted by methyl, methoxy or halogen;

R^2 is H, OH, CH_2OH, OMe, CHO, NH_2;

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, HO-SO_2-, $(HO)_2$-PO-;

R^4 is H, methyl, F, OMe;

R^9 to R^{12} are, independently of one another, H, C_1-C_8-alkyl;

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

n is 0 or 1;

m is 0 or 1;

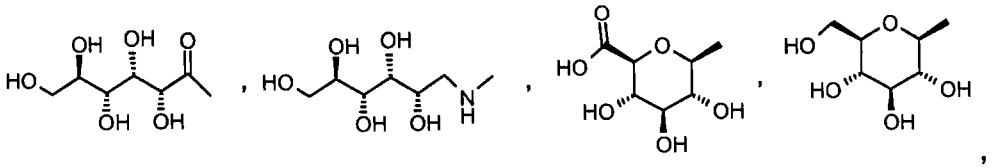
the pharmaceutically acceptable salts or physiologically functional derivatives thereof, and other active ingredients.

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

R^1 is phenyl, thiazolyl, oxazolyl, isoxazolyl, it being possible for the aromatic or heteroaromatic system to be substituted one to two times by fluorine, chlorine, bromine, $(C_1\text{-}C_8)$-alkyl;

R^2 is H, OH, CH_2OH, OMe, CHO, NH_2;

R^3 is



where the saccharide residue is optionally substituted one or more times by one of the saccharide protective groups, HO-SO_2-;

R^4 is H, methyl, F, OMe;

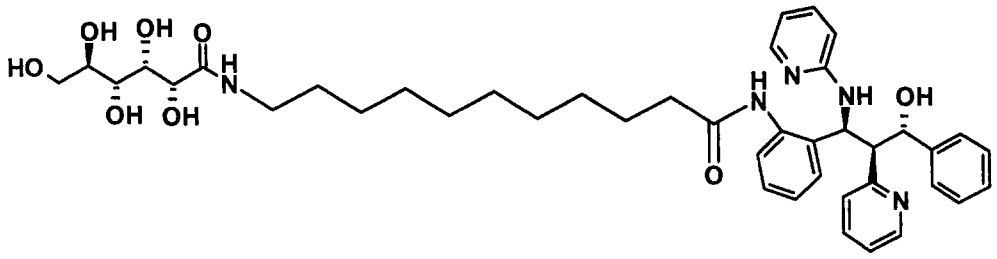
Z is -NH-C_6-C_{12}-alkyl-C=O-, -O-C_6-C_{12}-alkyl-C=O-, -$(C=O)_m$-C_6-C_{12}-alkyl-$(C=O)_n$;

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



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, cholesolvam, 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 method for administering 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, which comprises administering the compounds of the formula I and the at least one other active ingredient closely in time, preferably within 10 minutes.

14. A method for administering 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 for administration as medicament for the prophylaxis or treatment of lipid metabolism disorders, which comprises administering the compounds of the formula I and the 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.