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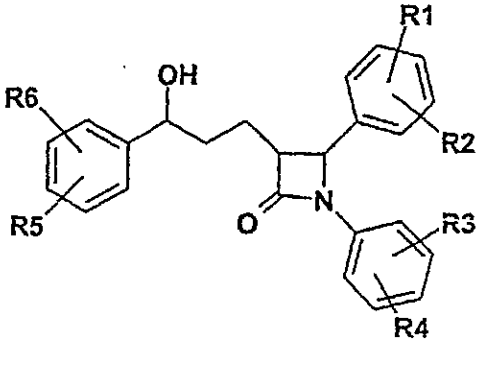
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(54) Title: DIPHENYL AZETIDINONES SUBSTITUTED BY ACIDIC GROUPS, METHOD FOR THEIR PRODUCTION, MEDICAMENTS CONTAINING SAID COMPOUNDS AND USE THEREOF

(54) Bezeichnung: SÄUREGRUPPEN-SUBSTITUIERTE DIPHENYLAZETIDINONE, VERFAHREN ZU DEREN HERSTELLUNG, DIESE VERBINDUNGEN ENTHALTENDE ARZNEIMITTEL UND DEREN VERWENDUNG

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(I)

(57) Abstract: The invention relates to compounds of formula (I), in which R1, R2, R3, R4, R5 and R6 are defined as cited, in addition to their physiologically compatible salts. The compounds are suitable for use e.g. as hypolipidaemics.

(57) Zusammenfassung: Die Erfindung betrifft Verbindungen der Formel (I), worin R1, R2, R3, R4, R5 , and R6 die angegebenen Bedeutungen haben, sowie deren physiologisch verträgliche Salze. Die Verbindungen eignen sich z.B. als Hypolipidämika.

Description

Diphenyl azetidinones substituted by acidic groups, method for their production, medicaments containing said compounds and use thereof

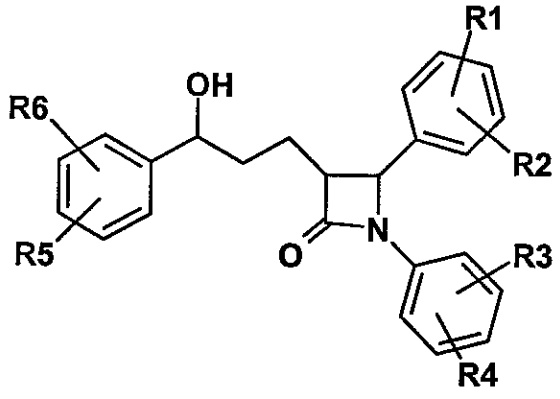
The invention relates to acid-group-substituted diphenylazetidinones, to their physiologically acceptable salts and to derivatives having physiological functions.

Diphenylazetidinones (such as, for example, ezetimibe) and their use for treating hyperlipidemia and arteriosclerosis and hypercholesterolemia have already been described [cf. Drugs of the Future 2000, 25(7):679-685) and US 5,756,470].

It was an object of the invention to provide further compounds having a therapeutically utilizable hypolipidemic action. In particular, it was an object to find novel compounds which, compared to the compounds described in the prior art, are absorbed to a very low extent. Very low absorption is to be understood as meaning an intestinal absorption of less than 10%, preferably less than or equal to 5%.

In particular, absorption of the novel compounds must be less than that of ezetimibe. Pharmaceutically active compounds which are absorbed to a low extent generally have considerably fewer side-effects.

Accordingly, the invention relates to compounds of the formula I



I

in which

R1, R2, R3, R4, R5, R6 independently of one another are $(C_0\text{-}C_{30})$-alkylene-$(LAG)_n$, where n may be 1 – 5 and where one or more carbon atoms of the alkylene radical may be replaced by $-S(O)_n-$, where n = 0 – 2, -O-, -(C=O)-, -(C=S)-, -CH=CH-, -C≡C-, -N($(C_1\text{-}C_6)$-alkyl)-, -N(phenyl), -N($(C_1\text{-}C_6)$-alkyl-phenyl)- , -N(CO-$(CH_2)_{1\text{-}10}$-COOH)- or -NH-;

H, F, Cl, Br, I, CF_3, NO_2, N_3, CN, COOH, COO$(C_1\text{-}C_6)$-alkyl, $CONH_2$, CONH$(C_1\text{-}C_6)$-alkyl, CON[$(C_1\text{-}C_6)$-alkyl]$_2$, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, O-$(C_1\text{-}C_6)$-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine;
C(=NH)(NH_2), PO_3H_2, SO_3H, SO_2-NH_2, $SO_2NH(C_1\text{-}C_6)$-alkyl, $SO_2N[(C_1\text{-}C_6)\text{-alkyl}]_2$, S-$(C_1\text{-}C_6)$-alkyl, S-$(CH_2)_n$-phenyl, SO-$(C_1\text{-}C_6)$-alkyl, SO-$(CH_2)_n$-phenyl, SO_2-$(C_1\text{-}C_6)$-alkyl, SO_2-$(CH_2)_n$-phenyl, where n may be 0 – 6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl, NH_2;
NH_2, NH-$(C_1\text{-}C_6)$-alkyl, N($(C_1\text{-}C_6)$-alkyl)$_2$, NH$(C_1\text{-}C_7)$-acyl, phenyl, O-$(CH_2)_n$-phenyl, where n may be 0 – 6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O-$(C_1$-

C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, SO_2-CH_3, COOH, COO-(C_1-C_6)-alkyl, $CONH_2$;

$(LAG)_n$ is -$(CH_2)_{1-10}$-SO_3H, -$(CH_2)_{0-10}$-P(O)(OH)$_2$, $(CH_2)_{0-10}$-O-P(O)(OH)$_2$, -$(CH_2)_{0-10}$-COOH and n may be 1 - 5;

where in each case at least one of the radicals R1 to R6 must have the meaning (C_0-C_{30})-alkylene-$(LAG)_n$, where n = 1 – 5 and where one or more carbon atoms of the alkylene radical are replaced by –S(O)$_n$-, where n = 0 – 2, -O-, -(C=O)-, -(C=S)-, -CH=CH-, -C≡C-, -N((C_1-C_6)-alkyl)-, -N(phenyl)-, -N((C_1-C_6)-alkyl-phenyl)-, -N(CO-$(CH_2)_{1-10}$-COOH)- or -NH-,
and their pharmaceutically acceptable salts;

except for the compound 2-{[4-(4-{1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)butyl]methylamino}ethanesulfonic acid and those compounds in which the radicals R1 - R6 have the meaning -O-$(CH_2)_{1-10}$-COOH, (C_1-C_6)-alkylene-COOH or -COOH.

Preference is given to compounds of the formula I where at least one of the radicals R1 to R6 has the meaning (C_0-C_{30})-alkylene-(LAG), where one or more carbon atoms of the alkylene radical may be replaced by -O-, -(C=O)-, -N((C_1-C_6)-alkyl)-, -N(CO-$(CH_2)_{1-10}$-COOH)- or -NH-.

Particular preference is given to compounds of the formula I where one of the radicals R1 or R3 has the meaning (C_0-C_{30})-alkylene-(LAG), where one or more carbon atoms of the alkylene radical may be replaced by -O-, -(C=O)-, -N(CH_3)-, or -NH-.

Very particular preference is given to compounds of the formula I where one of the radicals R1 or R3 has the meaning -$(CH_2)_{0-1}$-Y-W-(C_0-C_{25})-alkylene-Y'-W'-(LAG); where one or more carbon atoms of the alkylene radical may be replaced by oxygen atoms and where Y and W independently of one another may be NH, NCH_3, C=O,

O, a bond or $S(O)_n$, where n = 0 - 2, and Y' and W' independently of one another may be NH, NCH_3, C=O, O, a bond or $S(O)_n$, where n = 0 - 2, or Y-W or Y'-W' in each case together may be a bond.

Preference is furthermore given to compounds of the formula I where the group LAG is a carboxylic acid radical or a sulfonic acid radical.

Owing to their increased solubility in water, compared to the parent compounds, pharmaceutically acceptable salts are particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds according to the invention are salts of inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, metaphosphoric acid, nitric acid, sulfonic acid and sulfuric acid, and of organic acids, such as acetic acid, benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gluconic acid, glycolic acid, isothionic acid, lactic acid, lactobionic acid, maleic acid, malic acid, methanesulfonic acid, succinic acid, p-toluenesulfonic acid, tartaric acid and trifluoroacetic acid, for example. For medical purposes, very particular preference is given to using the chloride salt. 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).

The scope of the invention also includes salts having a pharmaceutically unacceptable anion, which salts may be useful intermediates for preparing or purifying pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

Here, the term "derivative having physiological function" refers to any physiologically acceptable derivative of a compound according to the invention, for example an ester, that is able, upon administration to a mammal, for example man, to form such a compound or an active metabolite (directly or indirectly).

A further aspect of this invention are prodrugs of the compounds according to the invention. Such prodrugs can be metabolized in vivo to give a compound according to the invention. These prodrugs may or may not be active in their own right.

The compounds according to the invention can also be present in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. The scope of the invention includes all polymorphous forms of the compounds according to the invention, which form a further aspect of the invention.

Hereinbelow, all references to "compound(s) of the formula (I)" refer to a compound or compounds of the formula (I) as described above, and to their salts, solvates and derivatives having physiological function, as described herein.

The compounds of the formula I and their pharmaceutically acceptable salts and derivatives having physiological function are ideal medicaments for treating an impaired lipid metabolism, in particular hyperlipidemia. The compounds of the formula I are also suitable for modulating the serum cholesterol concentration and for preventing and treating arteriosclerotic manifestations.

The compound(s) of the formula (I) can also be administered in combination with other active compounds.

The amount of a compound of the formula (I) required to achieve the desired biological effect depends on a number of factors, for example on the specific compound chosen, on the intended use, on the mode of administration and on the clinical condition of the patient. In general, the daily dose is in the range from 0.1 mg to 100 mg (typically from 0.1 mg to 50 mg) per day per kilogram of bodyweight, for example 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 abovementioned weight data relate to the weight of the diphenyl-azetidinone-ion derived from the salt. For the prophylaxis or therapy of the abovementioned conditions, the compounds of the formula (I) can be used

themselves as the compound, but preferably they are present in the form of a pharmaceutical composition with an acceptable carrier. The carrier must of course be acceptable in the sense that it is compatible with the other constituents of the composition and is not harmful to the health of the patient. The carrier can be a solid or a liquid or both and is preferably formulated with the compound as an individual dose, for example as a tablet, which can contain from 0.05% to 95% by weight of the active compound. Further pharmaceutically active substances can also be present, including further compounds of the formula (I). The pharmaceutical compositions according to the invention can be prepared by one of the known pharmaceutical methods, which essentially consist in mixing the constituents with pharmacologically acceptable carriers and/or auxiliaries.

Pharmaceutical compositions according to the invention are those which are suitable for oral or peroral (e.g. sublingual) administration, although the most suitable manner of administration is dependent in each individual case on the nature and severity of the condition to be treated and on the type of the compound of the formula (I) used in each case. Coated formulations and coated delayed-release formulations are also included in the scope of the invention. Acid-resistant and enteric formulations are preferred. Suitable enteric coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration can be present in separate units, such as, for example, capsules, cachets, lozenges or tablets, which in each case contain a specific amount of the compound of the formula (I); as a powder or granules; as a solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. As already mentioned, these compositions can be prepared according to any suitable pharmaceutical method which includes a step in which the active compound and the carrier (which can consist of one or more additional constituents) are brought into contact. In general, the compositions are prepared by uniform and homogeneous mixing of the active compound with a liquid and/or finely divided solid carrier, after which the product, if

necessary, is shaped. For example, a tablet can thus be prepared by pressing or shaping a powder or granules of the compound, if appropriate with one or more additional constituents. Pressed tablets can be produced by tableting the compound in free-flowing form, such as, for example, a powder or granules, if appropriate mixed with a binder, lubricant, inert diluent and/or a (number of) surface-active/ dispersing agent(s) in a suitable machine. Shaped tablets can be produced by shaping the pulverulent compound moistened with an inert liquid diluent in a suitable machine.

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

Suitable other active compounds for the combination preparations are:
all antidiabetics mentioned in Rote Liste 2001, Chapter 12. They can be combined with the compounds of the formula I according to the invention in particular to achieve a synergistically enhanced action. The active compound combination can be administered either by separate administration of the active compounds to the patient or in the form of combination preparations comprising a plurality of active compounds in a pharmaceutical preparation.

Antidiabetics include insulin and insulin derivatives, such as, for example, Lantus® or HMR 1964, GLP-1 derivatives, such as, for example, those disclosed by Novo Nordisk A/S in WO 98/08871, and oral hypoglycemic active compounds.
The oral hypoglycemic active compounds preferably include sulfonylureas, biguadines, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers, such as, for example, those disclosed by Novo Nordisk A/S in WO 97/26265 and WO 99/03861, insulin sensitizers, inhibitors of liver enzymes involved in stimulating gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds

which modulate lipid metabolism, such as antihyperlipidemic active compounds and antilipidemic active compounds, compounds which reduce food intake, PPAR and PXR agonists and active compounds 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 HMGCoA 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 a PPAR alpha agonist, 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.

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, Bay 13-

9952, BMS-201038, R-103757.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a bile acid absorption inhibitor, such as, for example, HMR 1453.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, such as, for example, Bay 194789.

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer, 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 gliclazide.

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 by Dr. Reddy's Research Foundation in WO 97/41097, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl-methoxy]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 compound which acts on the ATP-dependent potassium channel of

beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, gliazide or repaglinide.

In one embodiment, the compounds of the formula I are administered in combination with more than one of the abovementioned compounds, for example in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazon, insulin and lovastatin, etc.

In a further embodiment, the compounds of the formula I are administered in combination with CART agonists, NPY agonists, MC3 and MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3-agonists, MCH (melanine-concentrating hormone) antagonists, CCK agonists, serotonin reuptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone-releasing compounds, TRH agonists, decoupling protein 2 or 3 modulators, leptin agonists, DA agonists (bromocriptine, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR-β agonists.

In one embodiment of the invention, the further active compound is leptin.

In one embodiment, the further active compound is dexamphetamine or amphetamine.

In one embodiment, the further active compound is fenfluramine or dexfenfluramine.

In another embodiment, the further active compound is sibutramine.

In one embodiment, the further active compound is Orlistat.

In one embodiment, the further active compound is mazindol or phentermine.

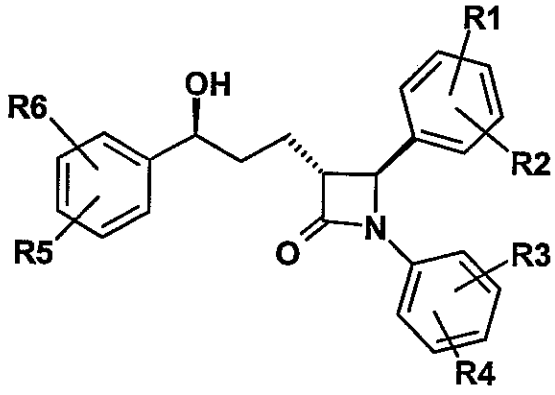
In one embodiment, the compounds of the formula I are administered in combination with fiber, preferably insoluble fiber, such as, for example, Caromax®. The combination with Caromax® can be given in one preparation or by separate administration of compounds of the formula I and Caromax®. Here, Caromax® can also be administered in the form of food, such as, for example, in bakery goods or muesli bars. Compared to the individual active compounds, the combination of

compounds of the formula I with Caromax® is, in addition to an enhanced action, in particular with respect to the lowering of LDL cholesterol, also characterized by its improved tolerability.

It goes without saying that each suitable combination of the compounds according to the invention with one or more of the compounds mentioned above and optionally one or more further pharmacologically active substances is included in the scope of the present invention.

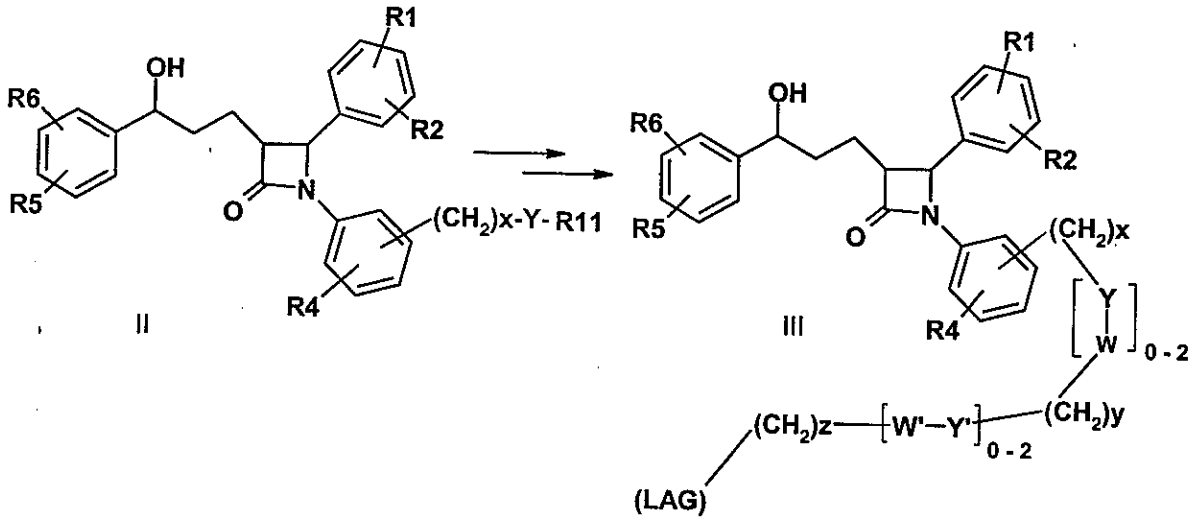
The invention furthermore provides both stereoisomer mixtures of the formula I and the pure stereoisomers of the formula I, and diastereomer mixtures of the formula I and the pure diastereomers. The mixtures are separated by chromatographic means.

Preference is given to both racemic and enantiomerically pure compounds of the formula I of the following structure:



Amino protective groups that are preferably used are the benzyloxycarbonyl (Z) radical, which can be removed by catalytic hydrogenation, the 2-(3,5-dimethyloxyphenyl)propyl(2)oxycarbonyl(Ddz) or trityl (Trt) radical, which can be removed by weak acids, the t-butylcarbamate (BOC) radical, which can be removed by 3M hydrochloric acid, and the 9-fluorenylmethyloxycarbonyl (Fmoc) radical, which can be removed using secondary amines.

The invention furthermore relates to a process for preparing diphenylazetidinone derivatives of formula I.



Y can be S, O, (C=O), (C=S), CH=CH, C≡C, N($(C_1$-$C_6)$-alkyl), N(phenyl), N($(C_1$-$C_6)$-alkyl-phenyl), N(CO-$(CH_2)_{1-10}$-COOH) or NH;
R11 can be H or, if Y = (C=O) or (C=S), OH;
W, Y' and W' can, independently of one another and of Y, be $-S(O)_n-$, where n = 0 – 2, -O-, -(C=O)-, -(C=S)-, -CH=CH-, -C≡C-, -N($(C_1$-$C_6)$-alkyl)-, -N(phenyl), -N($(C_1$-$C_6)$-alkyl-phenyl)-, -N(CO-$(CH_2)_{1-10}$-COOH)- or -NH- or a bond;
x, y and z independently of one another can be 0 to 10.

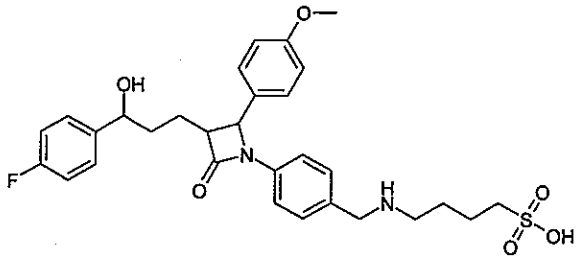
In compound II, -(CH_2)x-Y-R11 can alternatively also be attached to one of the other two phenyl rings.

The process for preparing compounds of the formula I comprises reacting, for example, an amine or a hydroxy compound of the formula II with an alkylating or acylating agent which, preferably in the omega position, carries a further functionality- if appropriate in protected form. This functionality is (after deprotection) used for attaching (LAG), for example with the formation of ether, amine or amide bonds.

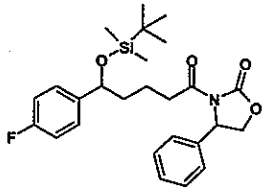
The examples below serve to illustrate the invention in more detail, without limiting the invention to the products and embodiments described in the examples.

Example I

4-{4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzylamino}butane-1-sulfonic acid (6):



a) 3-[5-(tert-butyldimethylsilanyloxy)-5-(4-fluorophenyl)-pentanoyl]-4-phenyl-oxazolidin-2-one (1):



27 g of 3-[5-(4-fluorophenyl)-5-hydroxypentanoyl]-4-phenyloxazolidin-2-one, 13.6 g of tert-butyldimethylsilyl chloride and 10.2 g of imidazole are dissolved in 36 ml of dimethylformamide and stirred at 60°C for 90 min. After the reaction has ended, the mixture is dissolved in ethyl acetate and extracted two times with water. The organic phase is dried over magnesium sulfate, filtered and concentrated under reduced pressure. This gives 3-[5-(tert-butyldimethylsilanyloxy)-5-(4-fluorophenyl)-pentanoyl]-4-phenyloxazolidin-2-one (1) of molecular weight 471.65 ($C_{26}H_{34}FNO_4Si$); MS (ESI): 340.28 (MH^+ - $HOSi(CH_3)_2C(CH_3)_3$).

b) 4-[5-(tert-butyldimethylsilanyloxy)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-(2-oxo- 4-phenyloxazolidine-3-carbonyl)pentylamino]benzonitrile (2):

16.2 g of 3-[5-(tert-butyldimethylsilanyloxy)-5-(4-fluorophenyl)-pentanoyl]-4-phenyl-oxazolidin-2-one are dissolved in 350 ml of dichloromethane. 19.8 ml of Hünig base and 10.14 g of 4-[(4-methoxyphenylimino)methyl]benzonitrile are added, and the solution is cooled to –10°C. 8.52 ml of trimethylsilyl triflate are added to the cooled solution, and the mixture is stirred at –10°C for 30 min. The solution is then cooled to –30°C, and 44 ml of titanium tetrachloride solution are added. The reaction mixture is stirred at from –30 to -40°C for 2 h. The solution is then allowed to warm to room temperature and the reaction solution is washed successively with 200 ml of 2N sulfuric acid, 300 ml of 20% strength sodium hydrogen sulfite solution and sat. sodium chloride solution. The organic phase is dried over magnesium sulfate and concentrated under reduced pressure, and the residue is purified on silica gel using n-heptane/ethyl acetate 3/1. This gives 4-[5-(tert-butyldimethylsilanyloxy)-5-(4-fluoro-phenyl)-1-(4-methoxyphenyl)-2-(2-oxo-4-phenyloxazolidine-3-carbonyl)pentyl-amino]benzonitrile (2) of molecular weight 707.93 ($C_{41}H_{46}FN_3O_5Si$); MS (ESI): 590.51 ($MH^+ - C_7H_5N_2$).

c) 4-[3-[3-(tert-butyldimethylsilanyloxy)-3-(4-fluorophenyl)propyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzonitrile (3):

13.2 g of 4-[5-(tert-butyldimethylsilanyloxy)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-(2-oxo-4-phenyloxazolidine-3-carbonyl)pentylamino]benzonitrile are dissolved in 380 ml of methyl tert-butylether, 18.6 ml of N,O-bis(trimethylsilyl)acetamide and 1.86 ml of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran are added and the mixture is stirred at room temperature for 2 h. After the reaction has ended, 10 ml of acetic acid are added, the reaction mixture is concentrated under reduced pressure and the residue is purified on silica gel using toluene/ethyl acetate 50/1. This gives 4-[3-[3-(tert-butyldimethylsilanyloxy)-3-(4-fluorophenyl)propyl]-2-(4-

methoxyphenyl)-4-oxoazetidin-1-yl]-benzonitrile (3) of molecular weight 544.75 ($C_{32}H_{37}FN_2O_3Si$); MS (ESI): 545.56 ($M+H^+$).

d) 4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]- benzonitrile (4):

3.5 g of 4-[3-[3-(tert-butyldimethylsilanyloxy)-3-(4-fluorophenyl)propyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-benzonitrile are dissolved in 65 ml of tetrahydrofuran, 0.74 ml of acetic acid and 8.03 ml of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran are added and the mixture is stirred at room temperature for 2 h. Another 4.82 ml of the tetrabutylammonium fluoride solution are then added, and the mixture is stirred at reflux temperature for another 3 h. The cooled reaction mixture is concentrated under reduced pressure and the residue is purified by silica gel chromatography using n-heptane/ethyl acetate 2/1. This gives 4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-benzonitrile (4) of molecular weight 430.48 ($C_{26}H_{23}FN_2O_3$); MS (ESI): 431.24 ($M+H^+$).

e) 1-(4-Aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-methoxyphenyl)-azetidin-2-one (5):

1.22 g of 4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-benzonitrile are dissolved in 90 ml of ethanol, 10 ml of conc. ammonia solution and an excess of Raney nickel are added, and the mixture is stirred at 60°C and a hydrogen pressure of 10 bar for 8 h. Overnight, the reaction mixture cools to room temperature, and the next day, the catalyst is removed, the filtrate is concentrated under reduced pressure and the residue is purified by silica gel chromatography using dichloromethane/methanol/ammonia solution 10/1/0.1. This gives 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-

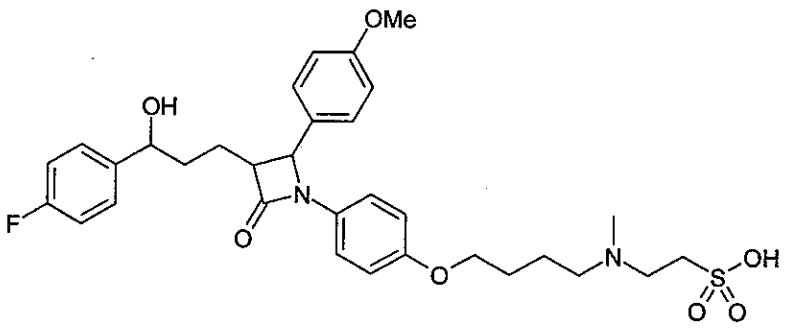
methoxyphenyl)-azetidin-2-one (5) of molecular weight 434.51 ($C_{26}H_{27}FN_2O_3$); MS (ESI): 418.2 ($MH^+ - NH_3$)..

f) 4-{4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxo-azetidin-1-yl]benzylamino}butane-1-sulfonic acid (6):

At room temperature, 87 mg of the above benzylamine are dissolved in 3 ml of dry acetonitrile, 40 µl of 1,4-butanesultone are added and the mixture is heated under reflux for 12 h. The cooled reaction solution is concentrated under reduced pressure and purified chromatographically (silica gel; dichloromethane/methanol 85/15 + 10% water). This gives 4-{4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzylamino}butane-1-sulfonic acid (6) of molecular weight 570.69 ($C_{30}H_{35}FN_2O_6S$); MS (ESI): 553.28 ($MH^+ - H_2O$).

Example II

2-[(4-{4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]phenoxy}butyl)methylamino]ethylsulfonic acid (8):

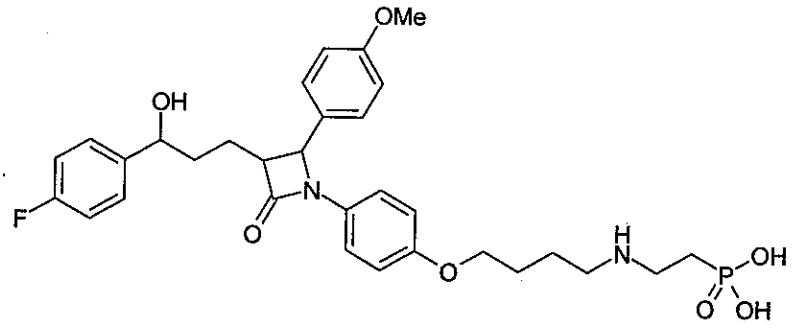


130 mg of 3-[3-(4-fluorophenyl)-3-hydroxypropyl]-1-[4-(4-fluorobutoxy)phenyl]-4-(4-methoxyphenyl)azetidin-2-one (7) are dissolved in 6 ml of absolute methanol. 120 mg of N-methyltaurine in 2 ml of water and 60 mg of potassium carbonate are then added. The mixture is stirred at 50°C for 24 h. The reaction mixture is concentrated using a rotary evaporator and the residue is purified by preparative chromatography. Freeze-drying gives the product (50 mg) as an oil.

$C_{32}H_{39}FN_2O_7S$ ESIMS m/z: 614 (M^+)

Example III

[2-(4-{4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]phenoxy}butylamino)ethyl]phosphonic acid (9):

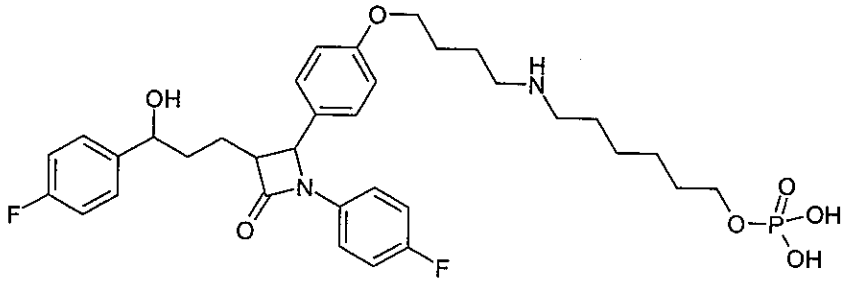


200 mg of 3-[3-(4-fluorophenyl)-3-hydroxypropyl]-1-[4-(4-fluorobutoxy)phenyl]-4-(4-methoxyphenyl)azetidin-2-one (7) are dissolved in 6 ml of absolute methanol. 165 mg of 1-aminoethylphosphate and 247 mg of potassium carbonate dissolved in 3 ml of water are then added. The mixture is stirred at 90°C for 8 h. The reaction mixture is concentrated using a rotary evaporator and the residue is purified by preparative chromatography. Freeze-drying gives the product (47 mg) as an oil.

$C_{31}H_{38}FN_2O_7P$ ESIMS m/z: 600 (M^+)

Example IV

Phosphoric acid mono-{6-[4-(4-{1-(4-fluorophenyl)-3-[3-(4-fluorofluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)butylamino]hexyl}ester (10):

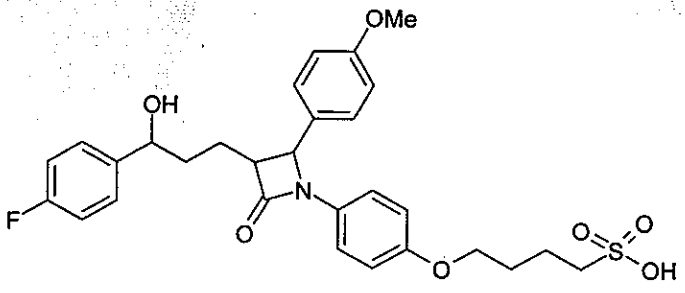


115 mg of 1-(4-fluorofluorophenyl)-3-[3-(4-fluorofluorophenyl)-3-hydroxypropyl]-4-[4-(2-fluoromethoxyethoxy)phenyl]azetidin-2-one (7) are dissolved in 6 ml of absolute methanol. 130 mg of 6-amino-1-hexyl phosphate in 1.5 ml of water and 107 mg of potassium carbonate are then added. The mixture is stirred at 70°C overnight. The reaction mixture is concentrated using a rotary evaporator and the residue is purified by preparative chromatography. Freeze-drying gives the product as an oil.

$C_{34}H_{43}F_2N_2O_7P$ ESIMS m/z: 660 (M^+)

Example V

4-{4-[3-[3-(4-fluorofluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]phenoxy}butane-1-sulfonic acid (12):



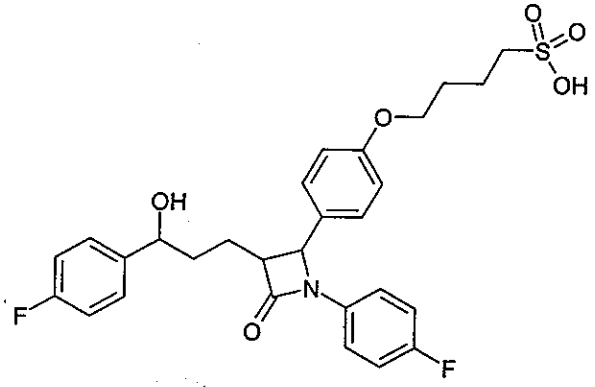
160 mg of 3-[3-(4-fluorofluorophenyl)-3-hydroxypropyl]-1-(4-hydroxyphenyl)-4-(4-methoxyphenyl)azetidin-2-one (11) are dissolved in 4 ml of absolute dimethylformamide. 210 mg of powdered potassium carbonate and 42 mg of 1,4,-butanesultone are added. The mixture is stirred at room temperature overnight. The reaction solution is concentrated under oil pump vacuum, taken up in dichloromethane and washed 1x with water. The aqueous phase is acidified with 2N hydrochloric acid and extracted 2x with dichloromethane. The combined organic phases are dried over sodium sulfate and concentrated. The residue is chromatographed on a 10 g SiO_2 cartridge (dichloromethane/

methanol = 5/1). The product (72 mg) is obtained as an oil.

$C_{29}H_{32}FNO_7S$ ESIMS *m/z*: 557 (M^+)

Example VI

4-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-phenoxy)butane-1-sulfonic acid (13):

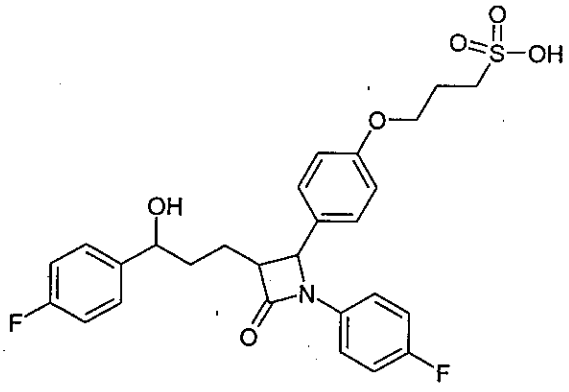


250 mg of 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one (7) are dissolved in 6 ml of absolute dimethylformamide. 337 mg of powdered potassium carbonate and 69 µl of 1,4,-butanesultone are added. The mixture is stirred at room temperature overnight. The reaction solution is filtered and concentrated under oil pump vacuum. The residue is chromatographed on a 10 g SiO_2 cartridge (dichloromethane/methanol = 5/1) and crystallized from diethyl ether. The product (131 mg) is obtained as a solid.

$C_{28}H_{29}F_2NO_6S$ ESIMS *m/z*: 546 (M^+)

Example VII

3-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-phenoxy)propan-1-sulfonin acid (14):

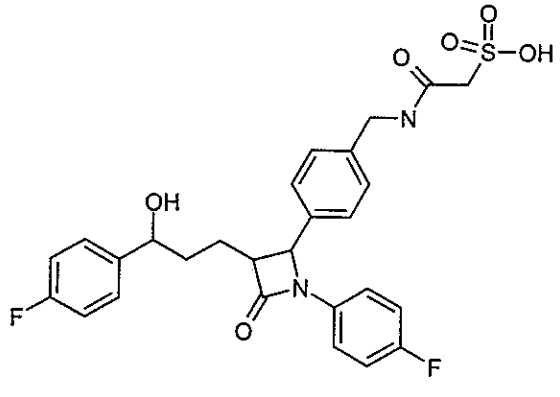


250 mg of 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one (7) are dissolved in 6 ml of absolute dimethylformamide. 337 mg of powdered potassium carbonate and 59 µl of 1,3,-propanesultone are added. The mixture is stirred at room temperature overnight. The reaction solution is filtered and concentrated under oil pump vacuum. The residue is chromatographed on a 10 g SiO_2 cartridge (dichloromethane/methanol = 5/1) and crystallized from diethyl ether. The product (250 mg) is obtained as a solid.

$C_{27}H_{27}F_2NO_6S$ ESIMS *m/z*: 532 (M^+)

Example VIII

(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)methanesulfonic acid (18):



a) 4-[5-(4-Fluorophenyl)-1-(4-fluorophenylamino)-5-hydroxy-2-(2-oxo-4-phenyloxazolidine-3-carbonyl)-pentyl]-benzonitrile (15):

Under argon, 2.5 g of 3-[5-(4-fluorophenyl)-5-hydroxypentanoyl]-4-phenyloxazolidin-2-one are dissolved in 30 ml of dichloromethane, 3.9 g of 4-[(4-fluorophenylimino)-methyl]-benzonitrile are added and the mixture is cooled to –10°C. 6.4 ml of diisopropylethylamine and, over a period of 30 min, 4.05 ml of trimethylsilyl chloride are added to this mixture so that the temperature does not exceed –5°C. The mixture is stirred at this temperature for 1 additional hour and then cooled to –25°C. 0.8 ml of titanium tetrachloride are then added slowly. The dark mixture is stirred at from –25 to –30°C overnight and then decomposed using 35 ml of a 7 percent strength solution of tartaric acid and then stirred at room temperature for another hour. 15 ml of a 20 percent strength solution of sodium bicarbonate are then added, and the mixture is again stirred for 1 hour. Following phase separation, the organic phase is washed with 30 ml of water, dried over magnesium sulfate and concentrated to about 10 ml. Following the addition of 2 ml of bistrimethylsilylacetamide, the mixture is heated at reflux for 30 min and then concentrated under reduced pressure. The residue is crystallized using ethyl acetate/heptane. The product is filtered off with suction and dried under reduced pressure. This gives the product of molecular weight 653.81 ($C_{37}H_{37}F_2N_3O_4Si$); MS (ESI+): 654.3 ($M+H^+$), 582.2 ($M+H^+ -Si(CH_3)_3$).

b) {1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzonitrile (16):

2 g of 4-[5-(4-Fluorophenyl)-1-(4-fluorophenylamino)-5-hydroxy-2-(2-oxo-4-phenyl-oxazolidine-3-carbonyl)-pentyl]-benzonitrile (15) are dissolved in 20 ml of methyl-tert-butyl ether and, together with 100 mg of tetrabutylammonium fluoride trihydrate and 1.3 ml of bistrimethylsilyl acetamide, heated at 40°C for about 1 h. The reaction is monitored by thin-layer chromatography. After the reaction has ended, 0.2 ml of glacial acetic acid is initially added and the mixture is stirred for 30 min and then concentrated. 20 ml of a mixture of isopropanol/2N sulfuric acid = 10:1 are added to

the residue, and the mixture is stirred for 1 hour. Following addition of a spatula tip of solid sodium bicarbonate, the mixture is again concentrated under reduced pressure, the residue is taken up in ethyl acetate and the organic phase is washed with water and dried, and the residue is, after removal of the solvent, purified by column chromatography (SiO_2, CH_2Cl_2/methanol = 100:1). This gives the product of molecular weight 418.45 ($C_{25}H_{20}F_2N_2O_2$); MS (DCI+): 419 ($M+H^+$).

c) 4-(4-Aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one (17):

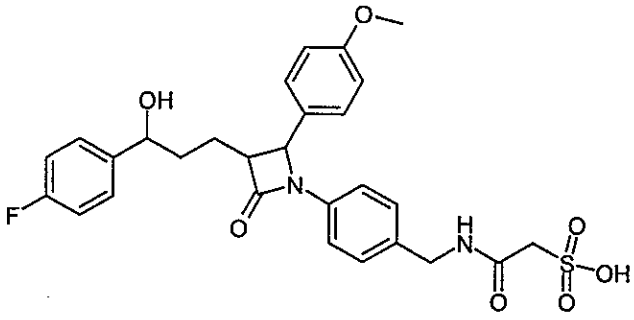
200 mg of {1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzonitrile (16) are dissolved in 20 ml of ethanol and, with 0.5 ml of conc. ammonia, hydrogenated over Raney nickel at a hydrogen pressure of 75 bar and at 25°C for 30 hours. The catalyst is filtered off with suction, the mixture is concentrated under reduced pressure and the residue is purified by column filtration (SiO_2, CH_2Cl_2/methanol/conc. NH_3 = 100:10:1). This gives the product of molecular weight 422.5 ($C_{25}H_{22}F_2N_2O_2$); MS (DCI+): 423 ($M+H^+$), 405 ($M+H^+ - H_2O$).

d) (4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)methanesulfonic acid (18):

A solution of 120 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (17), 48 µl of diisopropylethylamine in 1 ml of dimethylformamide is added to a solution of 40 mg of sulfoacetic acid, 110 µl of diisopropylcarbodiimide, 76 mg of hydroxybenzotriazole in 2 ml of dimethylformamide, and the mixture is stirred at room temperature for 12 h. The reaction solution is concentrated and separated by HPLC (Knauer Eurospher-100-10-C18, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 80/20 -> 10/90). This gives the product of molecular weight 544.58 ($C_{27}H_{26}F_2N_2O_6S_1$); MS (ESI) 527.10 ($M + H^+ - H_2O$)

Example IX

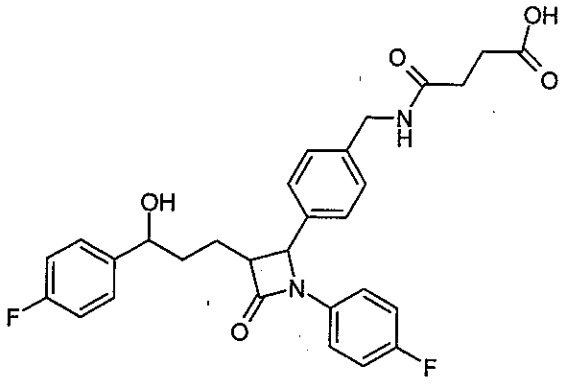
{4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-benzylcarbamoyl}methanesulfonic acid (19):



A solution of 60 mg of 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxy-propyl]-4-(4-methoxyphenyl)azetidin-2-one (5) in 1 ml of dimethylformamide is added to a solution of 20 mg of sulfoacetic acid, 55 µl of diisopropylcarbodiimide, 38 mg of hydroxybenzotriazole in 1 ml of dimethylformamide, and the mixture is stirred at room temperature for 12 h. The reaction solution is concentrated and separated by HPLC (Knauer Eurospher-100-10-C18, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 80/20 -> 10/90). This gives the product of molecular weight 556.61 ($C_{28}H_{29}F_1N_2O_7S_1$); MS (ESI) 539.05 ($M + H^+ - H_2O$)

Example X

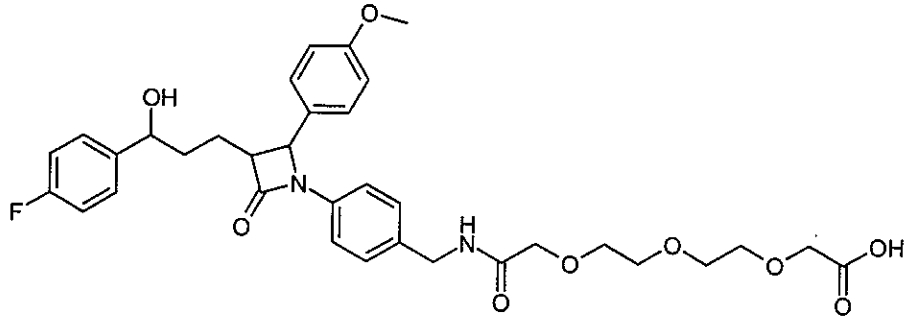
N-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzyl)succinaminic acid (20):



A solution of 100 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (17), 33 µl of triethylamine in 2 ml of dimethylformamide is added to a solution of 279 mg of succinic acid, 92 µl of diisopropylcarbodiimide, 80 mg of hydroxybenzotriazole in 2 ml of dimethylformamide, and the mixture is stirred at room temperature for 12 h. The reaction solution is concentrated and separated by HPLC (Knauer Eurospher-100-10-C18, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 80/20 -> 10/90). This gives the product of molecular weight 522.55 ($C_{27}H_{26}F_2N_2O_6S_1$); MS (ESI) 545.19 ($M + Na^+$)

Example XI

{2-[2-({4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzylcarbamoyl}methoxy)ethoxy]ethoxy}acetic acid (21):

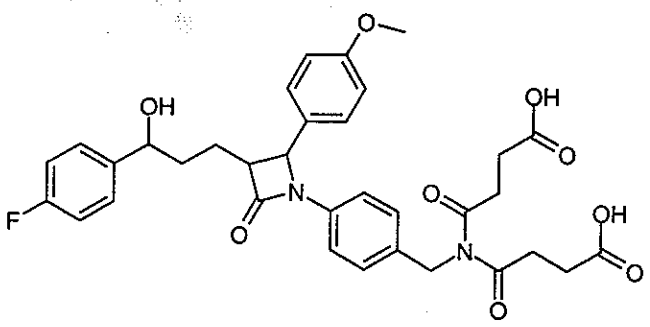


A solution of 64 mg of 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxy-

propyl]-4-(4-methoxyphenyl)azetidin-2-one (5), 21 µl of triethylamine in 1 ml of dimethylformamide are added to a solution of 327 mg of 3,6,9-trioxaundecanedioic acid, 57 µl of diisopropylcarbodiimide, 50 mg of hydroxybenzotriazole in 2 ml of dimethylformamide, and the mixture is stirred at room temperature for 12 h. The reaction solution is concentrated and separated by HPLC (Knauer Eurospher-100-10-C18, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 80/20 -> 10/90). This gives the product of molecular weight 638.70 ($C_{34}H_{39}F_1N_2O_9$); MS (ESI) 639.27 ($M + H^+$)

Example XII

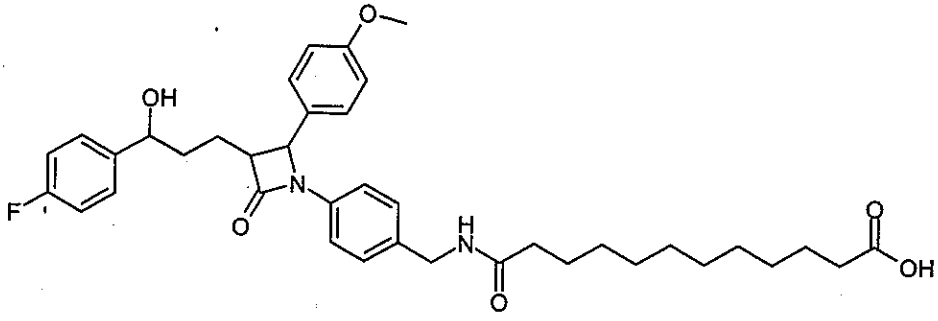
4-((3-Carboxypropionyl)-{4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzyl}amino)-4-oxobutyric acid (22):



A solution of 70 mg of 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-methoxyphenyl)azetidin-2-one (5), 23 µl of triethylamine in 1 ml of dimethylformamide is added to a solution of 190 mg of succinic acid, 63 µl of diisopropylcarbodiimide, 55 mg of hydroxybenzotriazole in 2 ml of dimethylformamide, and the mixture is stirred at room temperature for 12 h. The reaction solution is concentrated and separated by HPLC (Knauer Eurospher-100-10-C18, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 80/20 -> 10/90). This gives the product of molecular weight 634.4 ($C_{34}H_{35}F_1N_2O_9$); MS (ESI-neg.) 633.22 ($M - H^+$)

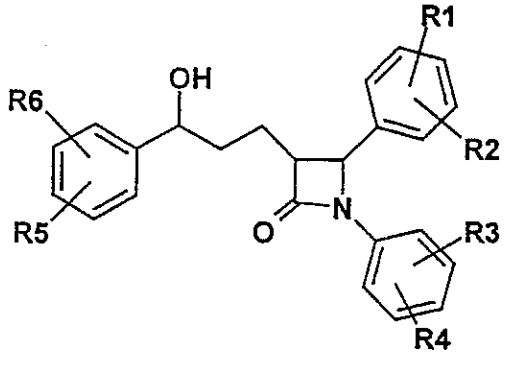
Example XIII

11-{4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzylcarbamoyl}undecanoic acid (23):

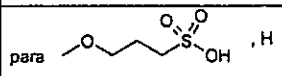
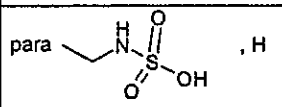
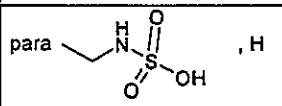
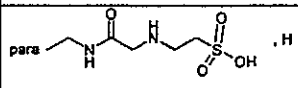
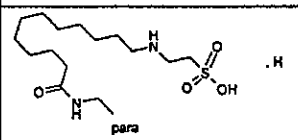
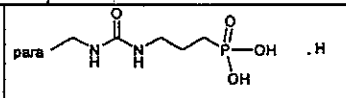
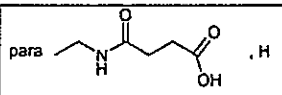
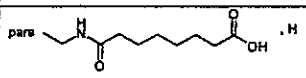
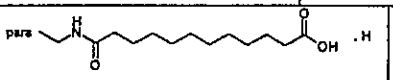
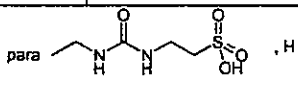
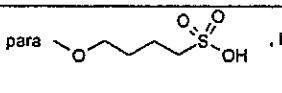


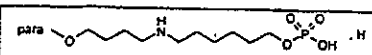
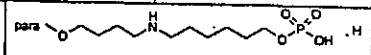
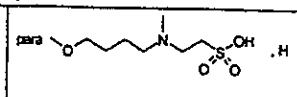
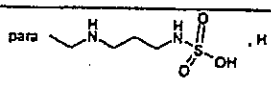
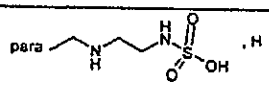
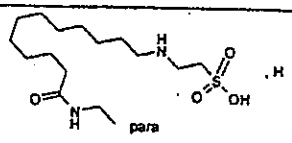
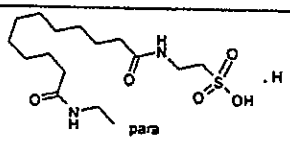
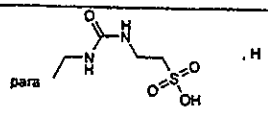
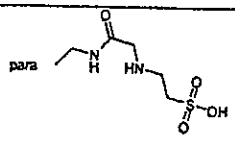
A solution of 70 mg of 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxy-propyl]-4-(4-methoxyphenyl)azetidin-2-one (5), 23 µl of triethylamine in 1 ml of dimethylformamide is added to a solution of 371 mg of dodecanedioic acid, 63 µl of diisopropylcarbodiimide, 55 mg of hydroxybenzotriazole in 2 ml of dimethylformamide, and the mixture is stirred at room temperature for 12 h. The reaction solution is concentrated and separated by HPLC(Knauer Eurospher-100-10-C18, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 80/20 -> 10/90). This gives the product of molecular weight 646.81 ($C_{38}H_{47}F_1N_2O_6$); MS (ESI) 647.35 ($M + H^+$)

Table 1: Compounds of the formula I



I

Ex.	R1, R2	R3, R4	R5, R6	Molecular weight of the free base or acid (calculated)	Molecular weight (found)
XIV		para-F, H	para-F, H	531.58	532.4 (MH^+)
XV		para-F, H	para-F, H	502.54	503.3 (MH^+)
XVI	para-F, H		para-F, H	514.58	515.4 (MH^+)
XVII	para-O-CH_3, H		para-F, H	599.68	599.21 (M^+)
XVIII	para-O-CH_3, H		para-F, H	739.95	740.42 (MH^+)
XIX	para-O-CH_3, H		para-F, H	599.60	600.34 (MH^+)
XX	para-O-CH_3, H		para-F, H	534.59	534.4 (MH^+)
XXI		para-F, H	para-F, H	578.66	561.25 (MH^+-H_2O)
XXII		para-F, H	para-F, H	634.77	617.31 (MH^+-H_2O)
XXIII	para-F, H		para-F, H	585.65	567.70 (MH^+-H_2O)
XXIV	para-O-CH_3, H		para-F, H	557.64	557.19 (M^+)

XXV		Para-F, H	para-F, H	660.70	660.28 (M^+)
XXVI	para-O-CH_3, H		para-F, H	600.62	600.24 (M^+)
XXVII	para-O-CH_3, H		para-F, H	614.73	597.32 (M-H_2O)$^{+1}$
XXVIII		para-F, H	para-F, H	559.64	560.4 (MH^+)
XXIX		para-F, H	para-F, H	545.61	546.3 (MH^+)
XXX		para-F, H	para-F, H	727.91	710.23 (MH^+-H_2O)
XXXI	para-O-CH_3, H		para-F, H	753.93	752.32 ($M-H^+$); measured in negative mode
XXXII		para-F, H	para-F, H	573.62	572.09 (M-H+); measured in negative mode
XXXIII		para-F, H	para-F, H	587.67	586.18 (M-H+); measured in negative mode

Using the method described below, the activity of the compounds of the formula I according to the invention was examined:

Effect on cholesterol absorption + ^{3}H-taurocholic acid excretion using fecal excrement of mice, rats or hamsters

NMRI mice, Wistar rats, or Golden Syrian hamsters (in groups of n=4-6) are kept in metabolic cages, where they are fed with a standard diet (Altromin, Lage (Lippe)). The afternoon prior to the administration of the radioactive tracers (^{14}C-cholesterol), the feed is removed and the animals are adapted to grates.

Additionally, the animals are labeled s.c. with ^{3}H-TCA (taurocholic acid) (for example 1 µCi/mouse up to 5 µCi/rat) 24 hours prior to the peroral administration of the test meal (^{14}C-cholesterol in Intralipid® 20, Pharmacia-Upjohn).

Cholesterol absorption test: 0.25 ml/mouse Intralipid ® 20 (Pharmacia-Upjohn) ((spiked with 0.25 µCi of ^{14}C-cholesterol in 0.1 mg of cholesterol) is administered perorally by gavage.

Test substances are prepared separately in 0.5% methylcellulose (Sigma)/5% Solutol (BASF, Ludwigshafen) or a suitable vehicle.
The administration volume of the test substance is 0.5 ml/mouse. The test substance is administered immediately prior to the test meal (Intralipid labeled with ^{14}C-cholesterol) (cholesterol absorption test).

The feces are collected over a period of 24 h: fecal elimination of ^{14}C-cholesterol and ^{3}H-taurocholic acid (TCA) is determined after 24 hours.

The livers are removed and homogenized, and aliquots are incinerated in an oximate (Model 307, Packard) to determine the amount of ^{14}C-cholesterol which had been taken up/absorbed.

Evaluation:

Feces samples:

The total weight is determined, the sample is made up with water to a defined volume and then homogenized, and an aliquot is evaporated to dryness and incinerated in an oximate (Model 307 from Packard for the incineration of radioactively labeled samples): the amount of radioactive ^{3}H-H2O and ^{14}C-CO2 is extrapolated to the amount of ^{3}H-taurocholic acid and ^{14}C-cholesterol, respectively, that is excreted (dual isotope technique). The ED_{200} values as dose from a dose-effect curve are interpolated as those doses at which the excretion of TCA or cholesterol is doubled, based on a control group treated at the same time.

Liver samples:

The amount of ^{14}C-cholesterol taken up by the liver is based on the administered dose. The ED_{50} values are interpolated from a dose-effect curve as the dose at which the uptake of ^{14}C-cholesterol by the liver is halved (50%), based on a control group.

The ED_{50} values below demonstrate the activity of the compounds of the formula I according to the invention

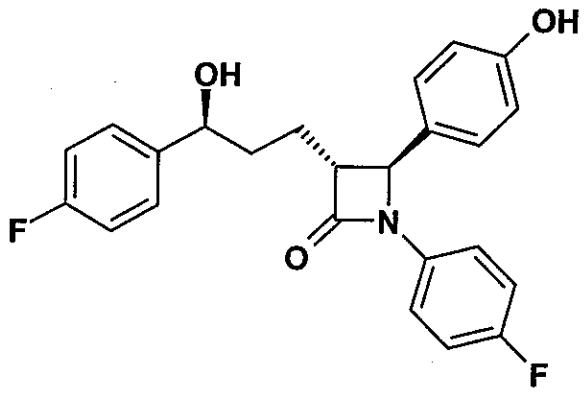
Example No.	ED_{50} (liver) [mg/mouse]
I	1.0
II	> 0.1
IV	0.3
VIII	0.3
IX	< 1.0
X	< 1.0
XIII	< 0.1
XVIII	0.005
XXI	0.1
XXII	0.1
XXV	0.3
XXVIII	0.3

As can be seen from the table, the compounds of the formula I have very good cholesterol-lowering action.

Bioabsorption:

The bioabsorption of the compounds of the formula I was examined using the Caco cell model (A.R. Hilgers et al., Caco-2 cell monolayers as a model for drug transport across the intestinal mucosa, Pharm. Res. 1990, 7, 902).

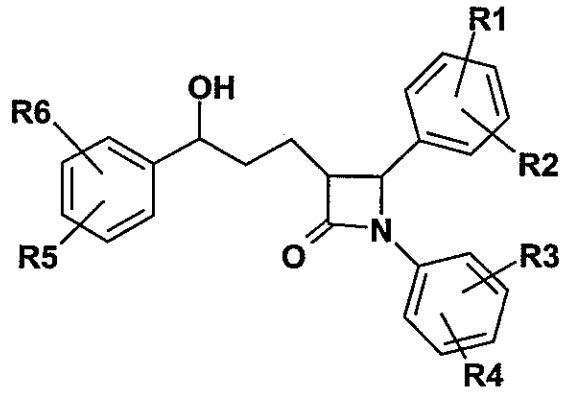
From the measured data, it can be seen that the bioabsorption of the compounds of the formula I according to the invention is considerably lower than that of the compounds described in the prior art (reference structure):



Reference structure:
Ezetimibe

Patent claims:

1. A compound of the formula I,



I

in which

R1, R2, R3, R4, R5, R6 independently of one another are $(C_0\text{-}C_{30})$-alkylene-$(LAG)_n$, where n may be 1 – 5 and where one or more carbon atoms of the alkylene radical may be replaced by $-S(O)_n$-, where n = 0 – 2, -O-, -(C=O)-, -(C=S)-, -CH=CH-, -C≡C-, -N($(C_1\text{-}C_6)$-alkyl)-, -N(phenyl), -N($(C_1\text{-}C_6)$-alkyl-phenyl)- , -N(CO-$(CH_2)_{1\text{-}10}$-COOH)- or -NH-;

H, F, Cl, Br, I, CF_3, NO_2, N_3, CN, COOH, COO$(C_1\text{-}C_6)$-alkyl, $CONH_2$, CONH$(C_1\text{-}C_6)$-alkyl, CON[$(C_1\text{-}C_6)$-alkyl]$_2$, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, O-$(C_1\text{-}C_6)$-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine;
C(=NH)(NH_2), PO_3H_2, SO_3H, $SO_2\text{-}NH_2$, SO_2NH$(C_1\text{-}C_6)$-alkyl, SO_2N[$(C_1\text{-}C_6)$-alkyl]$_2$, S-$(C_1\text{-}C_6)$-alkyl, S-$(CH_2)_n$-phenyl, SO-$(C_1\text{-}C_6)$-alkyl, SO-$(CH_2)_n$-phenyl, SO_2-$(C_1\text{-}C_6)$-alkyl, SO_2-$(CH_2)_n$-phenyl, where n = 0 – 6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl, NH_2;

NH_2, NH-(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, NH(C_1-C_7)-acyl, phenyl, O-$(CH_2)_n$-phenyl, where n may be 0 – 6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, SO_2-CH_3, COOH, COO-(C_1-C_6)-alkyl, $CONH_2$;

$(LAG)_n$ is -$(CH_2)_{1-10}$-SO_3H, -$(CH_2)_{0-10}$-P(O)(OH)$_2$, -$(CH_2)_{0-10}$-O-P(O)(OH)$_2$, -$(CH_2)_{0-10}$-COOH and n may be 1 - 5;

where in each case at least one of the radicals R1 to R6 must have the meaning (C_0-C_{30})-alkylene-$(LAG)_n$, where n = 1 – 5 and where one or more carbon atoms of the alkylene radical may be replaced by –S(O)$_n$-, where n = 0 – 2, -O-, -(C=O)-, -(C=S)-, -CH=CH-, -C≡C-, -N((C_1-C_6)-alkyl)-, -N(phenyl)-, -N((C_1-C_6)-alkyl-phenyl)- , -N(CO-$(CH_2)_{1-10}$-COOH)- or -NH-,
and its pharmaceutically acceptable salts;

except for the compound 2-{[4-(4-{1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)butyl]methylamino}ethanesulfonic acid and those compounds in which the radicals R1 - R6 have the meaning -O-$(CH_2)_{1-10}$-COOH, (C_1-C_6)-alkylene-COOH or -COOH.

2. A compound of the formula I as claimed in claim 1, wherein

R2, R4, R5, R6 independently of one another are H, F, Cl, Br, I, CF_3, NO_2, N_3, CN, COOH, COO(C_1-C_6)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, O-(C_1-C_6)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine;
C(=NH)(NH_2), PO_3H_2, SO_3H, SO_2-NH_2, SO_2NH(C_1-C_6)-alkyl, SO_2N[(C_1-C_6)-alkyl]$_2$, S-(C_1-C_6)-alkyl, S-$(CH_2)_n$-phenyl, SO-(C_1-C_6)-alkyl, SO-$(CH_2)_n$-phenyl, SO_2-(C_1-C_6)-alkyl, SO_2-$(CH_2)_n$-phenyl, where n may be

0 - 6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2; NH_2, NH-(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, NH(C_1-C_7)-acyl, phenyl, O-$(CH_2)_n$-phenyl, where n may be 0 – 6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, SO_2-CH_3, COOH, COO-(C_1-C_6)-alkyl, $CONH_2$;

R1, R3 independently of one another are (C_0-C_{30})-alkylene-(LAG) and where one or more carbon atoms of the alkylene radical may be replaced by -O-, -(C=O)-, -N(CH_3)- or –NH-,

H, F, Cl, Br, I, CF_3, NO_2, N_3, CN, COOH, COO(C_1-C_6)-alkyl, $CONH_2$, CONH(C_1-C_6)-alkyl, CON[(C_1-C_6)-alkyl]$_2$, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, O-(C_1-C_6)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine;
C(=NH)(NH_2), PO_3H_2, SO_3H, SO_2-NH_2, SO_2NH(C_1-C_6)-alkyl, SO_2N[(C_1-C_6)-alkyl]$_2$, S-(C_1-C_6)-alkyl, S-$(CH_2)_n$-phenyl, SO-(C_1-C_6)-alkyl, SO-$(CH_2)_n$-phenyl, SO_2-(C_1-C_6)-alkyl, SO_2-$(CH_2)_n$-phenyl, where n may be 0 - 6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2; NH_2, NH-(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, NH(C_1-C_7)-acyl, phenyl, O-$(CH_2)_n$-phenyl, where n may be 0 – 6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, SO_2-CH_3, COOH, COO-(C_1-C_6)-alkyl, $CONH_2$;

(LAG) is -$(CH_2)_{1\text{-}10}$-SO_3H, -$(CH_2)_{0\text{-}10}$-P(O)$(OH)_2$, -$(CH_2)_{0\text{-}10}$-O-P(O)$(OH)_2$, -$(CH_2)_{0\text{-}10}$-COOH;

where in each case at least one of the radicals R1 or R3 must have the meaning

$(C_0\text{-}C_{30})$-alkylene-(LAG) and where one or more carbon atoms of the alkylene radical may be replaced by -O-, -(C=O)-, $-N(CH_3)-$ or –NH-,
and its pharmaceutically acceptable salts;

except for the compound 2-{[4-(4-{1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)butyl]methylamino}ethanesulfonic acid and those compounds in which the radicals R1 - R6 have the meaning $-O-(CH_2)_{1\text{-}10}$-COOH, $(C_1\text{-}C_6)$-alkylene-COOH or -COOH.

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

R2, R4, R5, R6 independently of one another are H, F, Cl, Br, I, CF_3, NO_2, N_3, CN, COOH, $COO(C_1\text{-}C_6)$-alkyl, $CONH_2$, $CONH(C_1\text{-}C_6)$-alkyl, $CON[(C_1\text{-}C_6)\text{-alkyl}]_2$, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, $O\text{-}(C_1\text{-}C_6)$-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine;
$C(=NH)(NH_2)$, PO_3H_2, SO_3H, $SO_2\text{-}NH_2$, $SO_2NH(C_1\text{-}C_6)$-alkyl, $SO_2N[(C_1\text{-}C_6)\text{-alkyl}]_2$, $S\text{-}(C_1\text{-}C_6)$-alkyl, $S\text{-}(CH_2)_n$-phenyl, $SO\text{-}(C_1\text{-}C_6)$-alkyl, $SO\text{-}(CH_2)_n$-phenyl, $SO_2\text{-}(C_1\text{-}C_6)$-alkyl, $SO_2\text{-}(CH_2)_n$-phenyl, where n may be 0 – 6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, $O\text{-}(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl, NH_2;
NH_2, $NH\text{-}(C_1\text{-}C_6)$-alkyl, $N((C_1\text{-}C_6)\text{-alkyl})_2$, $NH(C_1\text{-}C_7)$-acyl, phenyl, $O\text{-}(CH_2)_n$-phenyl, where n may be 0 – 6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, $O\text{-}(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl, NH_2, $NH(C_1\text{-}C_6)$-alkyl, $N((C_1\text{-}C_6)\text{-alkyl})_2$, $SO_2\text{-}CH_3$, COOH, $COO\text{-}(C_1\text{-}C_6)$-alkyl, $CONH_2$;

R1, R3 independently of one another are $-(CH_2)_{0\text{-}1}\text{-Y-W-}(C_0\text{-}C_{25})$-alkylene-Y'-W'-(LAG), where one or more carbon atoms of the alkylene radical may be replaced by -O-;

H, F, Cl, Br, I, CF_3, NO_2, N_3, CN, COOH, $COO(C_1-C_6)$-alkyl, $CONH_2$, $CONH(C_1-C_6)$-alkyl, $CON[(C_1-C_6)\text{-alkyl}]_2$, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, $O-(C_1-C_6)$-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine;

$C(=NH)(NH_2)$, PO_3H_2, SO_3H, SO_2-NH_2, $SO_2NH(C_1-C_6)$-alkyl, $SO_2N[(C_1-C_6)\text{-alkyl}]_2$, $S-(C_1-C_6)$-alkyl, $S-(CH_2)_n$-phenyl, $SO-(C_1-C_6)$-alkyl, $SO-(CH_2)_n$-phenyl, $SO_2-(C_1-C_6)$-alkyl, $SO_2-(CH_2)_n$-phenyl, where n may be 0 – 6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, $O-(C_1-C_6)$-alkyl, (C_1-C_6)-alkyl, NH_2;

NH_2, $NH-(C_1-C_6)$-alkyl, $N((C_1-C_6)\text{-alkyl})_2$, $NH(C_1-C_7)$-acyl, phenyl, $O-(CH_2)_n$-phenyl, where n may be 0 – 6, the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, $O-(C_1-C_6)$-alkyl, (C_1-C_6)-alkyl, NH_2, $NH(C_1-C_6)$-alkyl, $N((C_1-C_6)\text{-alkyl})_2$, SO_2-CH_3, COOH, $COO-(C_1-C_6)$-alkyl, $CONH_2$;

Y, W, Y' W' independently of one another are NH, NCH_3, C=O, O, a bond or $S(O)_n$, where n = 0 – 2;

or Y-W or Y'-W' in each case together are a bond.

(LAG) is $-(CH_2)_{1-10}-SO_3H$, $-(CH_2)_{0-10}-P(O)(OH)_2$, $(CH_2)_{0-10}-O-P(O)(OH)_2$, $-(CH_2)_{0-10}-COOH$;

where in each case at least one of the radicals R1 or R3 must have the meaning $-(CH_2)_{0-1}-Y-W-(C_0-C_{25})$-alkylene-Y'-W'-(LAG), where one or more carbon atoms of the alkylene radical may be replaced by -O-;

and its pharmaceutically acceptable salts;

except for the compound 2-{[4-(4-{1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxy)butyl]methylamino}ethanesulfonic acid and those compounds in which the radicals R1 - R6 have the meaning $-O-(CH_2)_{1-10}-COOH$, (C_1-C_6)-alkylene-COOH or -COOH.

4. A compound of the formula I as claimed in one or more of claims 1 to 3, wherein

(LAG) is a carboxylic acid radical or a sulfonic acid radical,
and its pharmaceutically acceptable salts.

5. A medicament comprising one or more compounds as claimed in one or more of claims 1 to 4.

6. A medicament comprising one or more compounds as claimed in one or more of claims 1 to 4 and at least one further active compound.

7. The medicament as claimed in claim 6, comprising, as further active compound, one or more compounds which normalize lipid metabolism.

8. The medicament as claimed in claim 6 or 7, which comprises, as further active compound, one or more
antidiabetics, hypoglycemically active compounds, HMGCoA 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 adsorbers, 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 compounds which act 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 serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormones, growth hormone-releasing compounds, TRH agonists, decoupling protein 2 or 3 modulators, leptin agonists, DA agonists (bromocriptine, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR

modulators or TR-β-agonists or amphetamines.

9. A compound as claimed in one or more of claims 1 to 4 for use as a medicament for the treatment of impaired lipid metabolism.

10. A process for preparing a medicament comprising one or more of the compounds as claimed in one or more of claims 1 to 4, which comprises mixing the active compound with a pharmaceutically acceptable carrier and bringing this mixture into a form suitable for administration.

11. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for treating hyperlipidemia.

12. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for lowering the serum cholesterol concentration.

13. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for treating arteriosclerotic manifestations.

14. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for treating insulin resistance.