(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International publication date
31 December 2003 (31.12.2003)

PCT

(10) International publication number
WO 2004/000803 A1

(51) International patent classification[7]: C07D 205/08, 487/08, A61K 31/397, A61P 3/06, 9/10 // (C07D 487/08, 241:00, 241:00)

(21) International application number: PCT/EP2003/005814

(22) International filing date: 4 June 2003 (04.06.2003)

(25) Language of filing: German

(26) Language of publication: German

(30) Data relating to the priority:
102 27 507.6 19 June 2002 (19.06.2002) DE

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(81) Designated states *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

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

**Published:**
- *With the International Search Report.*

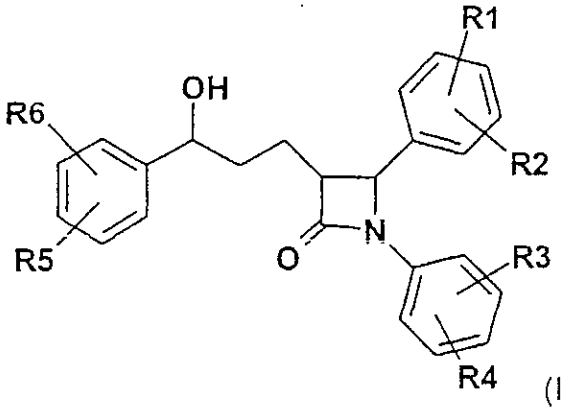
*For an explanation of the two-letter codes and the other abbreviations, reference is made to the explanations ("Guidance Notes on Codes and Abbreviations") at the beginning of each regular edition of the PCT Gazette.*

As printed

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

(54) Bezeichnung: KATIONISCH 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, (I) worin R1, R2, R3, R4, R5 , und R6 die angegebenen Bedeutungen haben, sowie deren physiologisch verträgliche Salze. Die Verbindungen eignen sich z.B. als Hypolipidämika.

Description

# Cationically substituted diphenyl azetidinones, method for their production, medicaments containing said compounds and use thereof

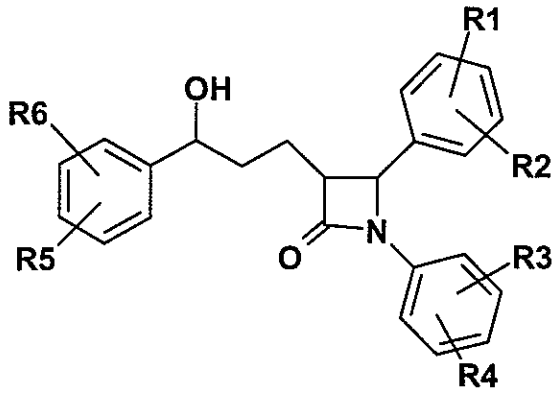
The invention relates to cationically substituted diphenylazetidinones, to their physiologically acceptable salts and to derivatives having physiological functions.

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;
$C(=NH)(NH_2)$, $PO_3H_2$, $SO_3H$, $SO_2\text{-}NH_2$, $SO_2NH(C_1\text{-}C_6)$-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 = 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 = 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-$(C_1\text{-}C_6)$-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, $CONH_2$;

$(LAG)_n$ is a mono-, di- or tricyclic trialkylammonium radical, a mono-, di- or tricyclic trialkylammoniumalkyl radical, $-(CH_2)_{0\text{-}10}\text{-}C(=NH)(NH_2)$; $-(CH_2)_{0\text{-}10}\text{-}C(=NH)(NHOH)$ or -NR7-C(=NR8)(NR9R10) and R7, R8, R9 and R10 independently of one another may be H, $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-phenyl, phenyl, $(C_3\text{-}C_8)$-cycloalkyl) and n may be 1 – 5,

where in each case at least one of the radicals R1 to R6 must have the meaning $(C_0\text{-}C_{30})$-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-, $-N((C_1\text{-}C_6)\text{-alkyl})$-, -N(phenyl)-, $-N((C_1\text{-}C_6)\text{-alkyl-phenyl})$- , $-N(CO\text{-}(CH_2)_{1\text{-}10}\text{-}COOH)$- or -NH-;
and their pharmaceutically acceptable salts.

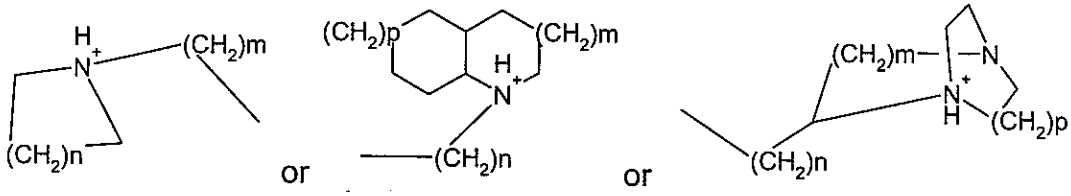
Preference is given to compounds of the formula I where at least one of the radicals R1 to R6 has the meaning $(C_0\text{-}C_{30})$-alkylene-(LAG), where one or more carbon atoms of the alkylene radical may be replaced by -O-, -(C=O)-, $-N((C_1\text{-}C_6)\text{-alkyl})$-, $-N(CO\text{-}(CH_2)_{1\text{-}10}\text{-}COOH)$-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

Particular preference is given to compounds of the formula I where one of the radicals R1 or R3 has the meaning $(C_0\text{-}C_{30})$-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 $-(CH_2)_{0\text{-}1}\text{-Y-W-}(C_0\text{-}C_{25})$-alkylene-Y'-W'-(LAG); where one or more carbon atoms of the alkylene radical may be replaced by 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.

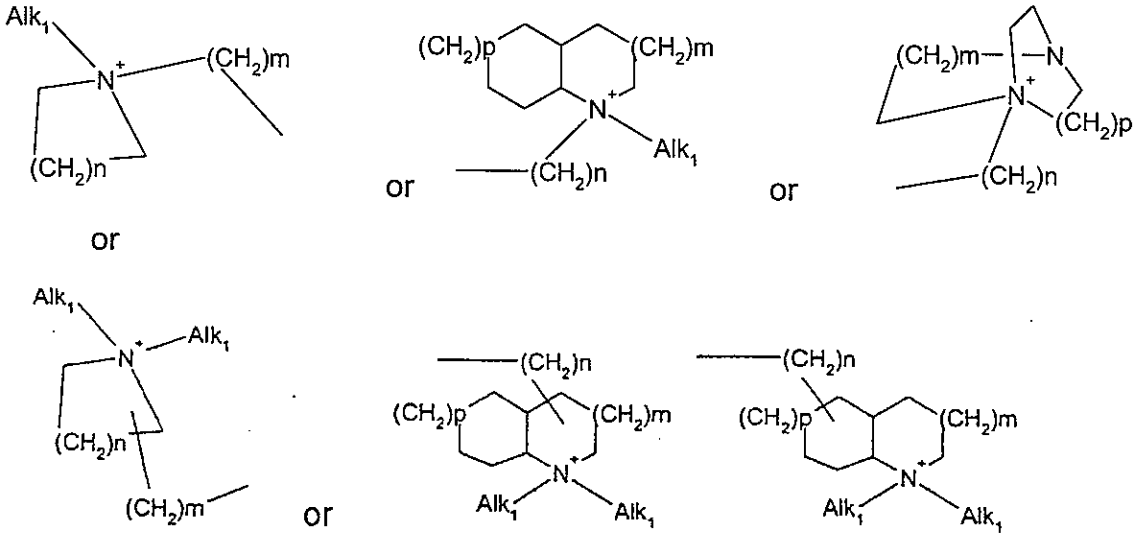
Preference is furthermore given to compounds of the formula I where the group LAG is a dicyclic trialkylammoniumalkyl radical.

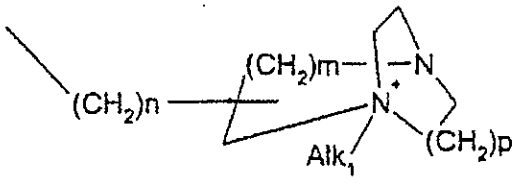
A mono- or di- or tricyclic trialkylammonium radical is to be understood as meaning, for example, radicals such as



where n, m and p independently of one another can be 0 – 10 and one or more $CH_2$ groups independently of one another may be replaced by O, $S(O)_n$, where n may be 0 – 2, NH, N-($C_1$-$C_{10}$)-alkyl, N-phenyl or N-$CH_2$-phenyl.

A mono- or dicyclic trialkylammoniumalkyl radical is to be understood as meaning, for example, radicals such as






where n, m and p independently of one another can be 0 – 10 and one or more $CH_2$ groups independently of one another may be replaced by O, $S(O)_n$, where n may be 0 – 2, NH, N-($C_1$-$C_{10}$)-alkyl, N-phenyl or N-$CH_2$-phenyl and $Alk_1$ is a straight-chain or branched alkyl radical having 1 to 20 carbon atoms.

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 or 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.

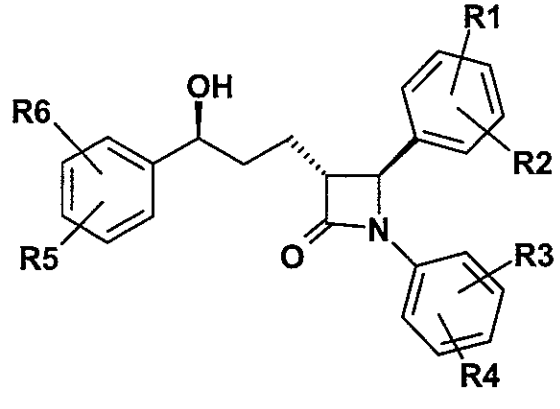
In one embodiment, the further active compound is mazindol or phentermine.

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.

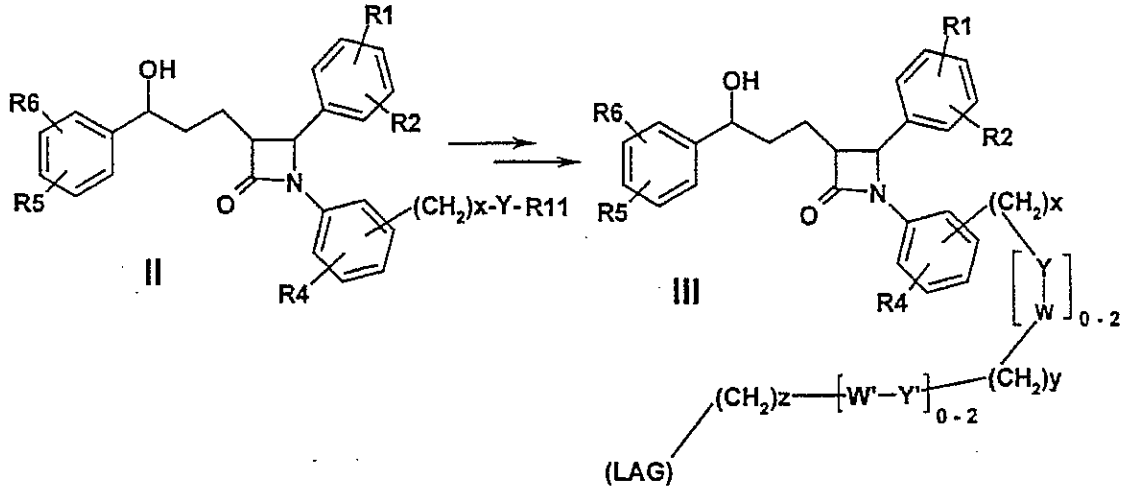
The invention furthermore provides both stereoisomer mixtures of the formula I and the pure stereoisomers of the formula I, and diastereomer mixtures of the formula I and the pure diastereomers. The mixtures are separated by chromatographic means.

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' und 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.

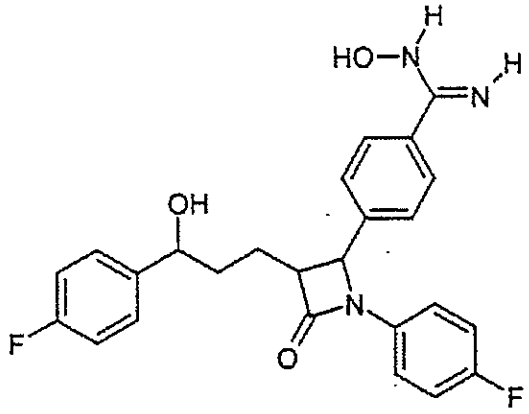
In compound II, -$(CH_2)$x-Y-R11 can alternatively also be attached to one of the other two phenyl rings.

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-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-N-hydroxybenzamidine (3):




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

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 such 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 is then added slowly. The dark mixture is stirred at from –25°C to –30°C over night and then decomposed using 35 ml of a 7% strength solution of tartaric acid, and the mixture is stirred for another hour at room temperature. 15 ml of a 20% strength sodium bicarbonate solution are then added,

and the mixture is again stirred for 1 hour. After phase separation, the organic phase is washed with 30 ml of water, dried over magnesium sulfate and concentrated to about 10 ml. 2 ml of bistrimethylsilylacetamide are added, and the mixture is then heated to reflux for 30 min and then concentrated under reduced pressure. The residue is cristallized 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 (2):

2 g of 4-[5-(4-fluorophenyl)-1-(4-fluorophenylamino)-5-hydroxy-2-(2-oxo-4-phenyloxazolidin-3-carbonyl)pentyl]benzonitrile (1) are dissolved in 20 ml of methyl tert-butyl ether and, together with 100 mg of tetrabutylammonium fluoride trihydrate and 1.3 ml of bistrimethylsilylacetamide, heated at 40°C for about 1 h. The reaction is monitored by thin-layer chromatography. After the reaction has ended, initially 0.2 ml of glacial acetic acid is added and the mixture is stirred for 30 min and 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. A spatula tip of solid sodium bicarbonate is added and the mixture is then again concentrated under reduced pressure, the residue is taken up in ethyl acetate, the organic phase is washed with water and dried and, after removal of the solvent, the residue is 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 ($M+H^+$).

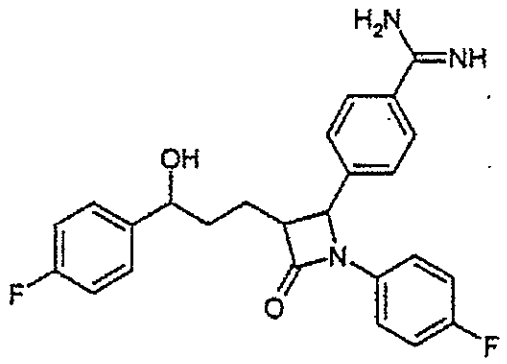
c) 4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-N-hydroxybenzamidine (3):

199 mg of hydroxylammonium hydrochloride are added to a solution of 200 mg of {1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-

yl}benzonitrile and 0.45 ml of triethylamine in 15 ml of isopropanol, and the mixture is stirred at room temperature for 12 h. The reaction solution is extracted twice with ethyl acetate/water. The organic phases are dried over magnesium sulfate and concentrated. This gives the product of molecular weight 451.48 ($C_{25}H_{23}F_2N_3O_3$); MS (ESI): 452.10 ($M+H^+$).

Example II

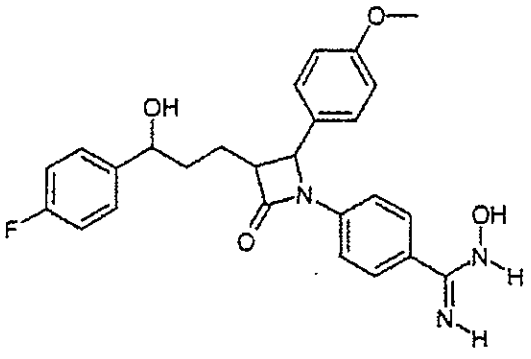
4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}benzamidine (4):



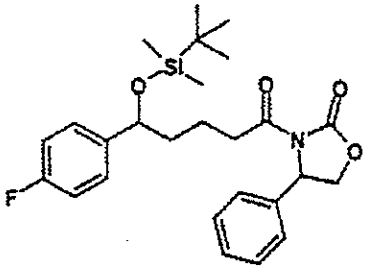

100 mg of 4-{1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-N-hydroxybenzamidine (3) are dissolved in 100 ml of tetrahydrofuran and, with 2 ml of conc. ammonia, hydrogenated over Raney nickel at a hydrogen pressure of 75 bar and 25°C for 30 hours. After addition of magnesium sulfate, the reaction solution is filtered. The filtrate 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 435.48 ($C_{25}H_{23}F_2N_3O_2$); MS (ESI): 436.18 ($M + H^+$).

Example III

4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl}-N-hydroxybenzamidine (9):



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



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 twice 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 (5) 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 (6):

16.2 g of 3-[5-(tert-butyldimethylsilanyloxy)-5-(4-fluorophenyl)pentanoyl]-4-phenyloxazolidin-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 to the solution, which is then cooled to –10°C. 8.52 ml of trimethylsilyltriflate are added to the cooled solution, which is then 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 saturated 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-fluorophenyl)-1-(4-methoxyphenyl)-2-(2-oxo-4-phenyloxazolidine-3-carbonyl)pentylamino]benzonitrile (6) 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 (7):

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-butyl ether, 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 (7) 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 (8):

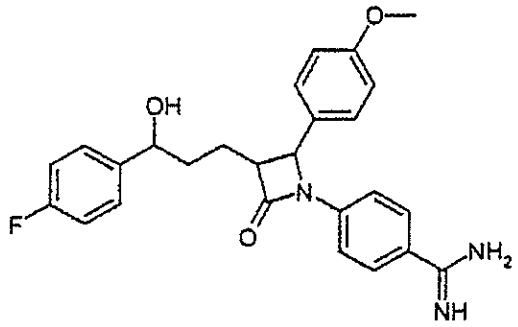
3.5 g of 4-[3-[3-(tert-butyldimethylsilanyloxy)-3-(4-fluorophenyl)propyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzonitrile are dissolved in 65 ml of tetrahydrofuran, 0.74 ml of acetic acid and 8.03 ml of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran are added and the mixture is 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 a further 3 h. The cooled reaction mixture is concentrated under reduced pressure and the residue is purified chromatographically on silica gel using n-heptane/ethyl acetate 2/1. This gives 4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzonitrile (8) of molecular weight 430.48 ($C_{26}H_{23}FN_2O_3$); MS (ESI): 431.24 ($M+H^+$).

e) 4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-N-hydroxybenzamidine (9):

199 mg of hydroxylammonium hydrochloride are added to a solution of 200 mg of 4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzonitrile (8) and 0.45 ml of triethylamin in 15 ml of isopropanol, and the mixture is stirred at room temperature for 12 h. The reaction solution is extracted twice with ethyl acetate/water. The organic phases are dried over magnesium sulfate and concentrated. This gives the product of molecular weight 463.51 ($C_{26}H_{26}F_1N_3O_4$); MS (ESI): 464.19 ($M+H^+$).

Example IV

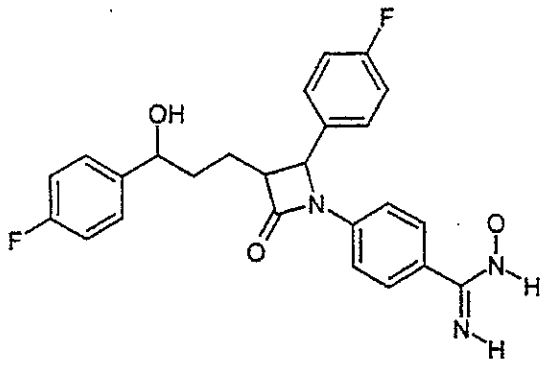
4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzamidine (10):




40 mg of 4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]N-hydroxybenzamidine are dissolved in 10 ml of tetrahydrofuran and, with 1 ml of conc. ammonia, hydrogenated over Raney nickel at 25°C for 6.5 h. Magnesium sulfate is added, and the reaction solution is then filtered. The filtrate 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 447.51 ($C_{26}H_{26}F_1N_3O_3$); MS (ESI): 448.20 ($M + H^+$).

Example V

4-{2-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl}-N-hydroxybenzamidine (12):



a) 4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-fluorophenyl)-4-oxoazetidin-1-yl]benzonitrile (11):

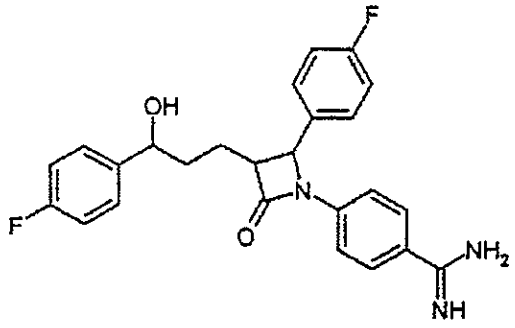
Compound (11) is prepared analogously to the compound of example IIId, the difference being that, instead of 4-[(4-methoxyphenylimino)methyl]benzonitrile, 4-[(4-fluorobenzylidene)amino]benzonitrile is used.

b) 4-{2-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl}-N-hydroxybenzamidine (12):

279 mg of hydroxylammonium hydrochloride are added to a solution of 280 mg of 4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-fluorophenyl)-4-oxoazetidin-1-yl]benzonitrile (11) and 0.65 ml of triethylamine in 15 ml of isopropanol, and the mixture is stirred at room temperature for 12 h. The reaction solution is extracted twice with ethyl acetate/water. The organic phases are dried over magnesium sulfate and concentrated. This gives the product of molecular weight 451.48 ($C_{25}H_{23}F_2N_3O_3$); MS (ESI): 452.10 ($M+H^+$).

Example VI

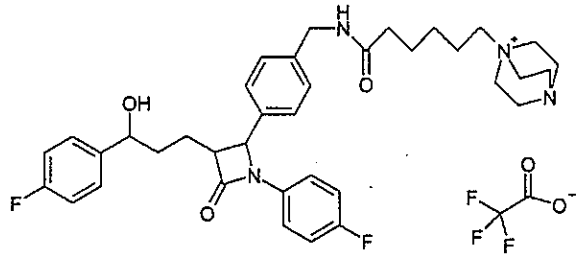
4-{2-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl}-benzamidine (13):



290 mg of 4-{2-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-1-yl}-N-hydroxybenzamidine (12) are dissolved in 15 ml of tetrahydrofuran and, with 1.5 ml of conc. ammonia, hydrogenated over Raney nickel at 25°C for 6.5 h. After addition of magnesium sulfate, the reaction solution is filtered. The filtrate is concentrated. This gives the product of molecular weight 435.48 ($C_{25}H_{23}F_2N_3O_2$); MS (ESI): 436.18 ($M + H^+$).

Example VII

1-[5-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}benzylcarbamoyl)pentyl]-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (15):



a) 1-(5-Carboxypentyl)-4-aza-1-azonia-bicyclo[2.2.2]octane bromide (14):

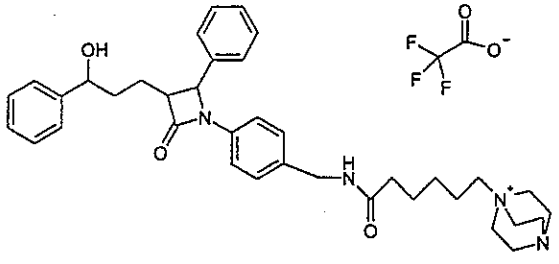
At 70°C, 1.0 g of 6-bromohexanaoic acid in 5 ml of dimethyl sulfoxide is added to a solution of 1.5 g of 1,4-diazabicyclo[2.2.2]octane in 10 ml of dimethylsulfoxide. After 1 h, 100 ml of water are added and the mixture is freeze-dried. The residue is digested with acetone. The residue contains the product of molecular weight 227.33 (cation: $C_{12}H_{23}N_2O_2^+$); MS (ESI) 227.1 ($M^+$).

b) 1-[5-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}benzylcarbamoyl)pentyl]-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (15):

A solution of 70 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one and 23 µl of triethylamine in 0.5 ml of dimethylformamide is added to a solution of 76 mg of 1-(5-carboxypentyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide (14), 64 µl of diisopropylcarbodiimide and 56 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 631.79 (cation: $C_{37}H_{45}F_2N_4O_3$); MS (ESI) 631.34 ($M^+$).

Example VIII

1-[5-(4-{3-[3-Hydroxy-3-phenylpropyl)-2-oxo-4-phenylazetidin-1-yl}benzylcarbamoyl)-pentyl]-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (17):



a) 1-(4-Aminomethylphenyl)-3-[3-hydroxy-3-phenylpropyl]-4-phenylazetidin-2-one (16):

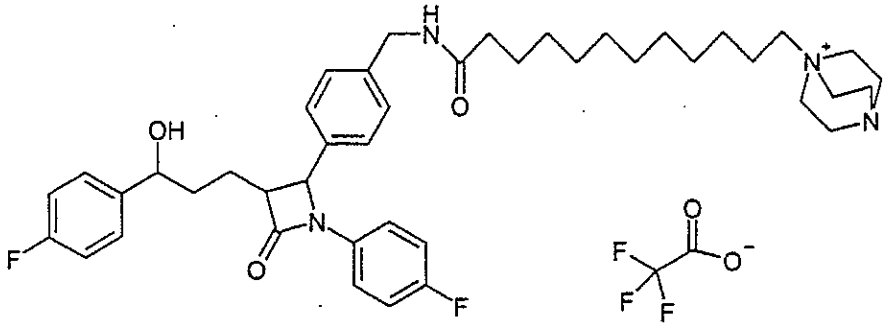
Compound (16) is prepared as described in example IIIa-d, the difference being that, instead of 4-[(4-methoxyphenylimino)methyl]benzonitrile, 4-(benzylidene-amino)benzonitrile is used and, instead of 3-[5-(4-fluorophenyl)-5-hydroxypentanoyl-4-phenyloxazolidin-2-one, 3-[5-(phenyl)-5-hydroxypentanoyl]-4-phenyloxazolidin-2-one is used and that the product IIId is subjected to reduction with Raney nickel.

b) 1-[5-(4-{3-[3-Hydroxy-3-phenylpropyl)-2-oxo-4-phenylazetidin-1-yl}benzyl-carbamoyl)pentyl]-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (17):

The synthesis is carried out analogously to example VIIb starting with 60 mg of 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl-3-hydroxypropyl]-4-phenylazetidin-2-one. This gives the product of molecular weight 595.81 (cation: $C_{37}H_{47}N_4O_3$); MS (ESI) 595.36 ($M^+$).

Example IX

1-[11-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}benzylcarbamoyl)undecyl]-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (19):



a) 1-(11-Carboxyundecyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide (18):

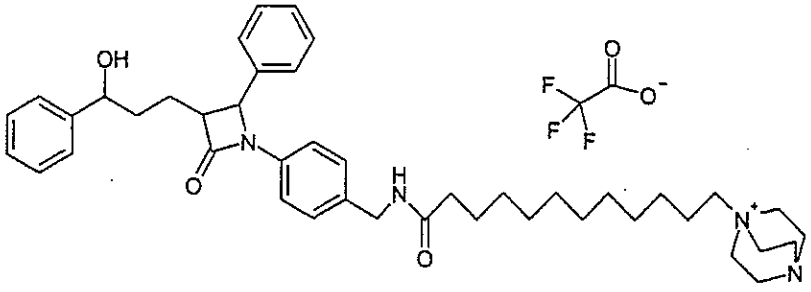
The synthesis is carried out analogously to example VIIa starting with 495 mg of 12-bromododecanoic acid. This gives the product of molecular weight 311.49 (cation: $C_{18}H_{35}N_2O_2^+$); MS (ESI) 311.2 ($M^+$).

b) 1-[11-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-azetidin-2-yl}benzylcarbamoyl)undecyl]-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (19):

The synthesis is carried out analogously to example VIIb. This gives the product of molecular weight 715.96 (cation: $C_{43}H_{57}F_2N_4O_3$); MS (ESI) 715.43 ($M^+$).

Example X

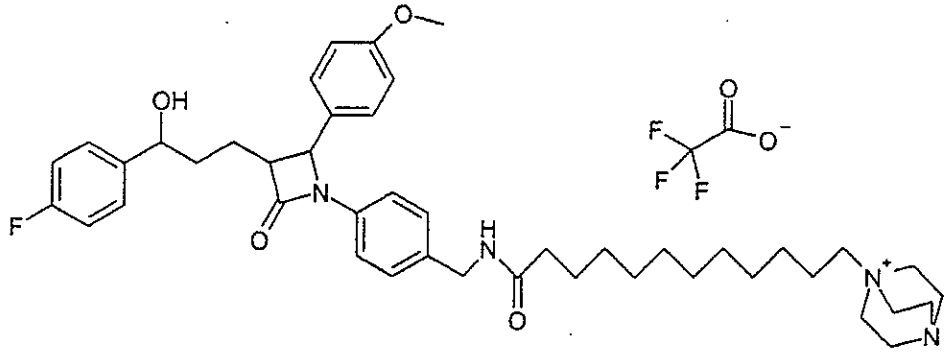
1-[11-{4-[3-(3-Hydroxy-3-phenylpropyl)-2-oxo-4-phenylazetidin-1-yl]benzylcarbamoyl}undecyl)-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (20):



The synthesis is carried out analogously to example IXb starting with 74 mg of 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-phenylazetidin-2-one. This gives the product of molecular weight 679.97 (cation: $C_{43}H_{59}N_4O_3$); MS (ESI) 679.50 ($M^+$).

Example XI

1-[11-{4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzylcarbamoyl}undecyl)-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (21):



a)

A solution of 50 mg of 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxy-propyl]-4-(4-methoxyphenyl)azetidin-2-one and 25 µl of triethylamine in 1 ml of dimethylformamide is added to a solution of 70 mg of 12-bromododecanoic acid, 50 mg of EDC and 40 mg of hydroxybenzotriazole in 3 ml of dimethylformamide, and the mixture is stirred at room temperature for 1 h. The reaction solution is diluted with ethyl acetate and washed three times with aqueous sodium chloride solution. The organic phase is filtered through silica gel, concentrated and separated by flash

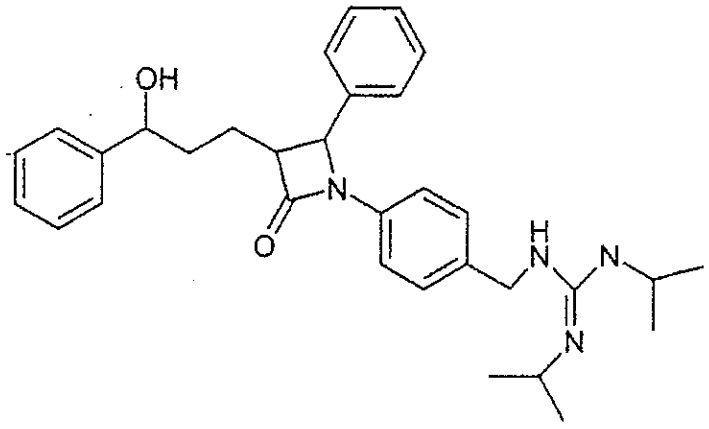
chromatography. This gives the alkyl bromide (72 mg) with molecular weight 695.72 ($C_{38}H_{48}BrFN_2O_4$); MS (ESI) 695.4 ($M + H^+$).

b)

72 mg of the alkyl bromide prepared above are, together with 100 mg of DABCO, stirred in 4 ml of toluene at 100°C for 20 hours. 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 727.99 (cation: $C_{44}H_{60}F_1N_4O_4$); MS (ESI) 727.5 ($M^+$).

Example XII

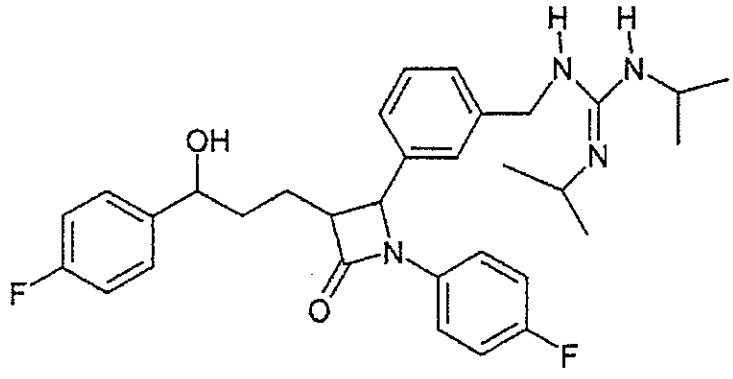
N-{4-[3-(3-Hydroxy-3-phenylpropyl)-2-oxo-4-phenylazetidin-1-yl]benzyl}-N',N"-diisopropylguanidine (22)




A solution of 76 mg of 1-(4-aminomethylphenyl)-3-[3-hydroxy-3-phenylpropyl]-4-phenylazetidin-2-one, 64 µl of diisopropylcarbodiimide, 56 mg of hydroxybenzotriazole and 23 µl triethylamine in 2 ml of dimethylformamide is stirred at room temperature for 22 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 512.70 ($C_{32}H_{40}N_4O_2$); MS (ESI) 513.4 ($M+H^+$).

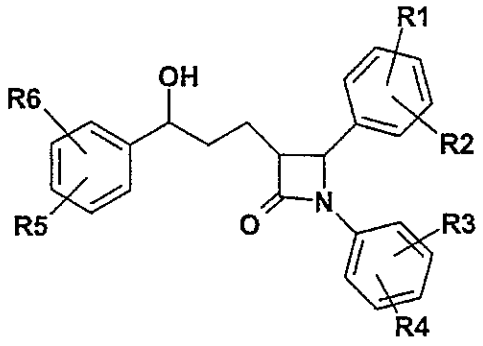
Example XIII

N-(3-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}benzyl)-N',N"-diisopropylguanidine (23)

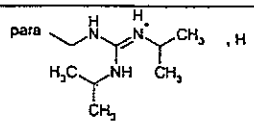
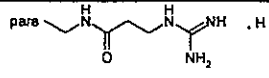
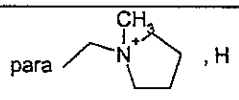
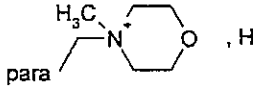
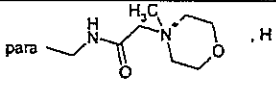
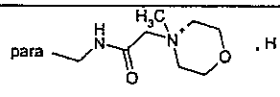
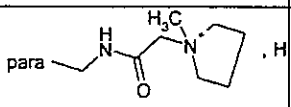
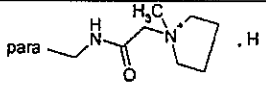


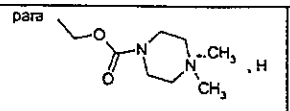
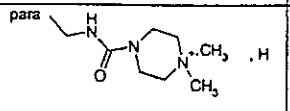
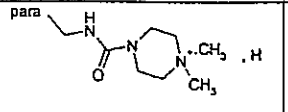
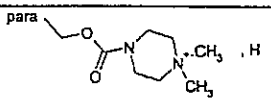
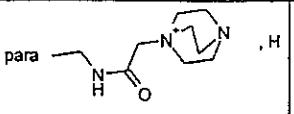
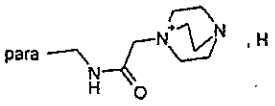
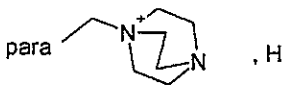
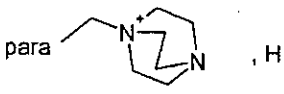
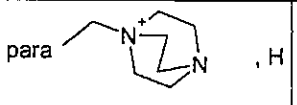
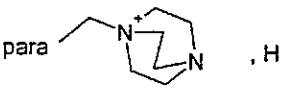
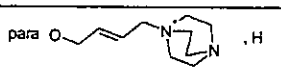
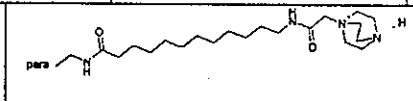

The synthesis is carried out analogously to example XII starting with 60 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one. This gives the product of molecular weight 548.68 ($C_{32}H_{38}F_2N_4O_2$); MS (ESI) 549.4 ($M + H^+$).

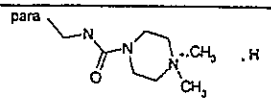
Table 1: Compounds of the formula I




I

| Ex. | R1, R2 | R3, R4 | R5, R6 | Salt | Molecular weight of the free base or acid (calculated) | Molecular weight (found) |
|---|---|---|---|---|---|---|
| XIV | para-O-$CH_3$, H |  | para-F, H | $CF_3COO^-$ | 560.72 | 561.23 ($MH^+$) |
| XV | para-O-$CH_3$, H |  | para-F, H | - | 547.63 | 548.33 ($MH^+$) |
| XVI |  | H, H | para-F, H | $I^-$ | 473.26 | 473.3 ($M^+$) |
| XVII |  | H, H | para-F, H | $I^-$ | 489.26 | 489.3 ($M^+$) |
| XVIII |  | para-F, H | para-F, H | $I^-$ | 564.27 | 564.3 ($M^+$) |
| XIX | para-O-$CH_3$, H |  | para-F, H | $I^-$ | 576.29 | 576.3 ($M^+$) |
| XXI |  | para-F, H | para-F, H | $I^-$ | 548.27 | 548.3 ($M^+$) |
| XXI | para-O-$CH_3$, H |  | para-F, H | $I^-$ | 560.29 | 560.3 ($M^+$) |

| | | | | | | |
|---|---|---|---|---|---|---|
| XXII | para-O-$CH_3$, H |  | para-F, H | $I^-$ | 576.29 | 576.3 ($M^+$) |
| XXIII | para-O-$CH_3$, H |  | para-F, H | $I^-$ | 575.30 | 575.4 ($M^+$) |
| XXIV | H, H |  | H, H | $I^-$ | 527.30 | 527.3 ($M^+$) |
| XXV |  | para-F, H | para-F, H | $I^-$ | 564.27 | 564.3 ($M^+$) |
| XXVI | para-O-$CH_3$, H |  | para-F, H | $I^-$ | 587.30 | 587.4 ($M^+$) |
| XXVII |  | para-F, H | para-F, H | $I^-$ | 575.28 | 575.3 ($M^+$) |
| XXVIII |  | para-F, H | para-F, H | $CF_3COO^-$ | 518.26 | 518.3 ($M^+$) |
| XXIX |  | H, H | para-F, H | $Br^-$ | 500.27 | 500.3 ($M^+$) |
| XXX | para-O-$CH_3$, H |  | para-F, H | $Br^-$ | 530.28 | 530.3 ($M^+$) |
| XXXI |  | para-F, H | H, H | $Br^-$ | 500.27 | 500.3 ($M^+$) |
| XXXII |  | para-F, H | para-F, H | $Br^-$ | 574.29 | 574.3 ($M^+$) |
| XXXIII | para-O-$CH_3$, H |  | para-F, H | $Br^-$ | 784.48 | 784.5 ($M^+$) |

| | | | | | | |
|---|---|---|---|---|---|---|
| XXXIV |  | para-F, H | para-F, H | $I^-$ | 563.28 | 563.3 ($M^+$) |

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] |
|---|---|
| III | 0.1 |
| VII | 0.1 |
| IX | 0.1 |
| X | < 1.0 |
| XI | 0.3 |

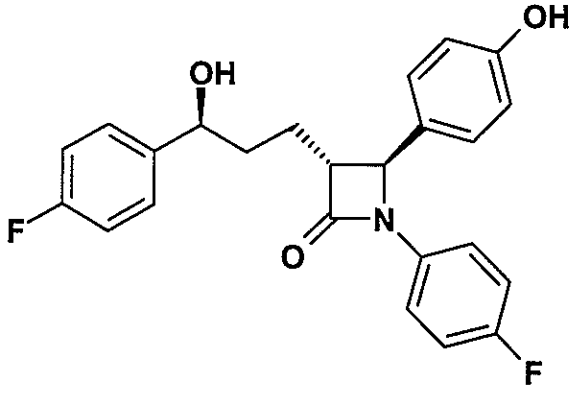
| | |
|---|---|
| XV | 0.3 |
| XVIII | 0.3 |
| XIX | 0.3 |
| XXI | 0.1 |
| XXII | 0.3 |
| XXV | 0.1 |
| XXVI | 0.03 |
| XXXII | 0.3 |
| XXXIV | 0.3 |

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).

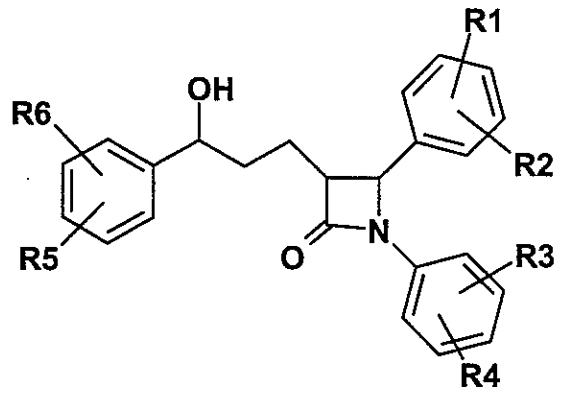
From the measured data, it can be seen that the bioabsorption of the compounds of the formula I according to the invention is considerably lower than that of the compounds described in the prior art (reference structure):




**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)$(NH_2)$, $PO_3H_2$, $SO_3H$, $SO_2$-$NH_2$, $SO_2$NH$(C_1\text{-}C_6)$-alkyl, $SO_2$N[$(C_1\text{-}C_6)$-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-($C_1$-$C_6$)-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 = 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 a mono-, di- or tricyclic trialkylammonium radical, a mono-, di- or tricyclic trialkylammoniumalkyl radical, -$(CH_2)_{0-10}$-C(=NH)($NH_2$), -$(CH_2)_{0-10}$-C(=NH)(NHOH) or -NR7-C(=NR8)(NR9R10);

R7, R8, R9 and R10 independently of one another are H, ($C_1$-$C_6$)-alkyl, ($C_1$-$C_6$)-alkyl-phenyl, phenyl, ($C_3$-$C_8$)-cycloalkyl);

n is 1, 2, 3, 4, 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.

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 = 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 = 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 = 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 = 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 a mono-, di- or tricyclic trialkylammonium radical, a mono-, di- or tricyclic trialkylammoniumalkyl radical, -$(CH_2)_{0-10}$-C(=NH)($NH_2$), -$(CH_2)_{0-10}$-C(=NH)(NHOH) or -NR7-C(=NR8)(NR9R10);

R7, R8, R9 and R10 independently of one another are H, ($C_1$-$C_6$)-alkyl, ($C_1$-$C_6$)-alkyl-phenyl, phenyl, ($C_3$-$C_8$)-cycloalkyl);

where in each case at least one of the radicals R1 or R3 must have 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-;
and its physiologically acceptable salts.

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($C_1$-$C_6$)-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)($NH_2$), $PO_3H_2$, $SO_3H$, $SO_2$-$NH_2$, $SO_2$NH($C_1$-$C_6$)-alkyl, $SO_2$N[($C_1$-$C_6$)-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 = 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 = 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 -$(CH_2)_{0-1}$-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-;

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 = 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 = 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, $N((C_1$-$C_6)$-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' taken together are each a bond.

(LAG) is a mono-, di- or tricyclic trialkylammonium radical, a mono-, di- or tricyclic trialkylammoniumalkyl radical, -$(CH_2)_{0-10}$-C(=NH)$(NH_2)$, -$(CH_2)_{0-10}$-C(=NH)(NHOH) or -NR7-C(=NR8)(NR9R10);

R7, R8, R9 and R10 independently of one another are H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-phenyl, phenyl, $(C_3$-$C_8)$-cycloalkyl);

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.

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

LAG is a tricyclic trialkylammoniumalkyl 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.