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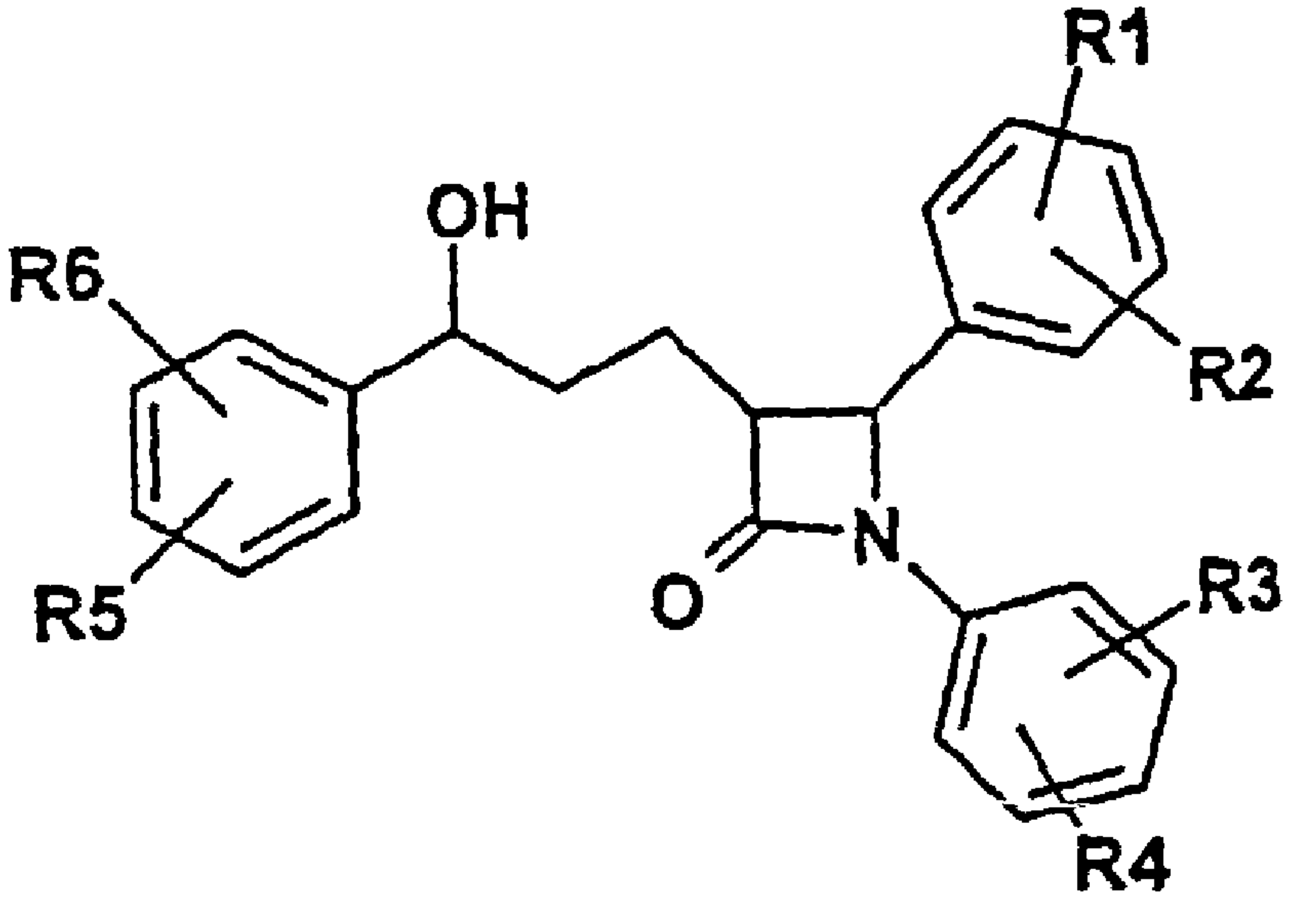
(54) Titre : DIPHENYLAZETIDINONES A NOYAU SUBSTITUE, PROCEDES POUR LES PRODUIRE, MEDICAMENTS CONTENANT CES COMPOSES ET LEUR UTILISATION
(54) Title: RING-SUBSTITUTED DIPHENYL AZETIDINONES, METHOD FOR THE PRODUCTION THEREOF, MEDICAMENTS CONTAINING SAID COMPOUNDS, AND USE THEREOF



(I)

(57) Abrégé/Abstract:
Disclosed are ring-substituted diphenyl azetidinones of formula I, a method for the production thereof, medicaments containing said compounds, and the use thereof for treating hyperlipidemia, arteriosclerosis, and hypercholesterolemia.

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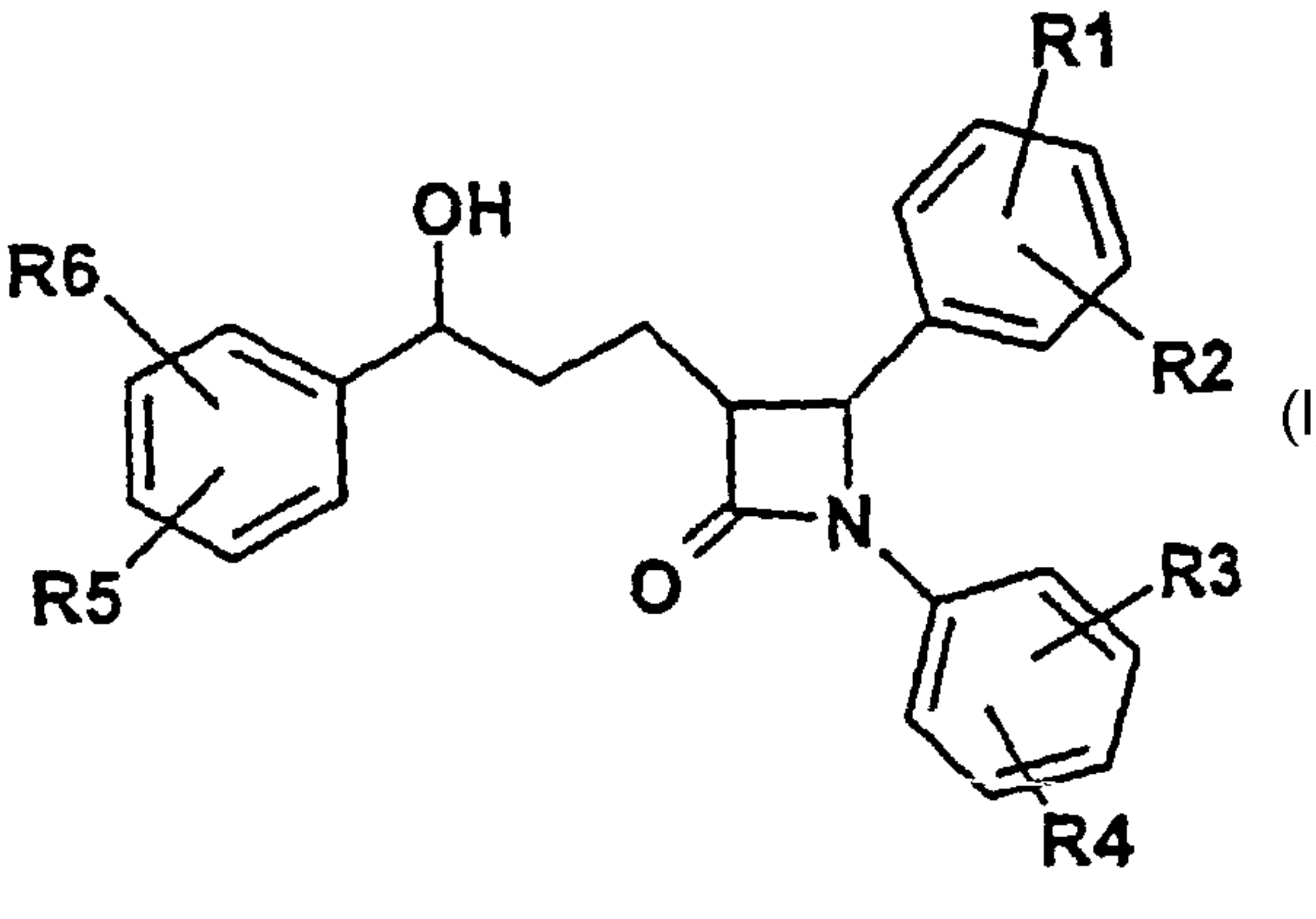
(54) Title: RING-SUBSTITUTED DIPHENYL AZETIDINONES, METHOD FOR THE PRODUCTION THEREOF, MEDICAMENTS CONTAINING SAID COMPOUNDS, AND USE THEREOF

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



(I)

(57) Abstract: Disclosed are ring-substituted diphenyl azetidinones of formula I, a method for the production thereof, medicaments containing said compounds, and the use thereof for treating hyperlipidemia, arteriosclerosis, and hypercholesterolemia.

(57) Zusammenfassung: Ringsubstituierte Diphenylazetidinone der Formel I, Verfahren zu deren Herstellung, diese Verbindungen enthaltende Arzneimittel und deren Verwendung zur Behandlung von Hyperlipidämie sowie Arteriosklerose und Hypercholesterinämie.

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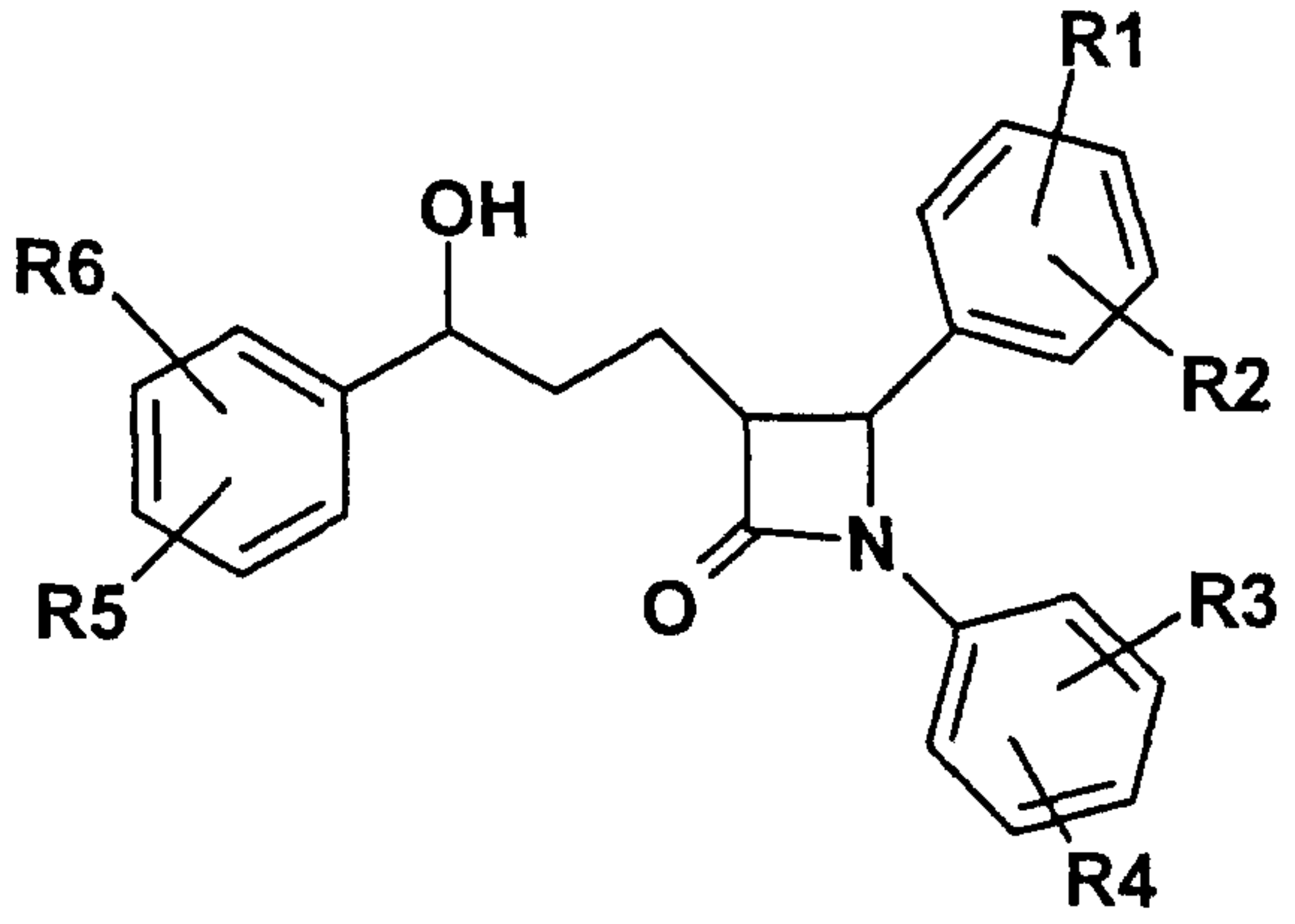
Accordingly, the invention relates to compounds of the formula I



I

in which

R1, R2, R3, R4, R5, R6 independently of one another are $(C_1\text{-}C_{30})$-alkylene-$(LAG)_n$, where n = 1 – 5 and where one or more carbon atoms of the alkylene radical are replaced by aryl or heteroaryl radicals substituted up to three times by R7, or by $(C_3\text{-}C_{10})$-cycloalkyl or heterocycloalkyl radicals substituted up to four times by R7 and 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$[(C_1\text{-}C_6)\text{-alkyl}]_2$, $(C_1\text{-}C_6)$-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;
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 = 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, $CONH_2$;

R7 is 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;
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;
C(NH)(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 sugar residue, disugar residue, trisugar residue, tetrasugar residue; a sugar acid, an amino sugar;
an amino acid residue, an oligopeptide residue comprising 2 to 9 amino acids;
an acyclic, mono-, di- or tricyclic trialkylammonium radical, an acyclic mono-, di- or tricyclic trialkylammoniumalkyl radical, -O-(SO_2)-OH;
-(CH_2)$_{0-10}$-SO_3H; -(CH_2)$_{0-10}$-P(O)(OH)$_2$, -(CH_2)$_{0-10}$-O-P(O)(OH)$_2$,
-(CH_2)$_{0-10}$-COOH, -(CH_2)$_{0-10}$-C(=NH)(NH_2); -(CH_2)$_{0-10}$-C(=NH)(NHOH); -

NR8-C(=NR9)(NR10R11); where n = 1 – 5 and R8, R9, R10 and R11 independently of one another may be H, (C_1-C_6)-alkyl, phenyl, (C_1-C_6)-alkyl-phenyl, (C_3-C_8)-cycloalkyl),

and where in each case at least one of the radicals R1 to R6 must have the meaning (C_1-C_{30})-alkylene-$(LAG)_n$, where n = 1 – 5 and one or more carbon atoms of the alkylene radical are replaced by aryl or heteroaryl radicals substituted up to three times by R7, or by (C_3-C_{10})-cycloalkyl or heterocycloalkyl radicals substituted up to four times by R7 and 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 their physiologically acceptable salts.

Preference is given to compounds of the formula I where at least one of the radicals R1 to R6 the meaning (C_1-C_{30})-alkylene-$(LAG)_n$, where n = 1 – 5 and one or more carbon atoms of the alkylene radical are replaced by aryl or heteroaryl radicals substituted up to three times by R7, or by (C_3-C_{10})-cycloalkyl or heterocycloalkyl radicals substituted up to four times by R7 and 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-.

Particular preference is given to compounds of the formula I where one of the radicals R1 or R3 the meaning (C_1-C_{30})-alkylene-(LAG), where one or more carbon atoms of the alkylene radical are replaced by aryl or heteroaryl radicals substituted up to three times by R7, or by (C_3-C_{10})-cycloalkyl or heterocycloalkyl radicals substituted up to three times by R7 and one or more carbon atoms of the alkylene radical may be replaced by $-S(O)_n-$, where n = 0 – 2, -O-, -(C=O)-, -N(CH_3)-, -N(phenyl)-, -N(CO-$(CH_2)_{1-10}$-COOH)- or –NH-.

Very particular preference is given to compounds of the formula I where at least one of the radicals R1 or R3 the meaning $-(CH_2)_{0-1}-NH-(C=O)_{0-1}-(C_0-C_{25})$-alkylene-$(C=O)_{0-1}-N(R13)_{0-1}$-(LAG) or $-(CH_2)_{0-1}-(C=O)_{0-1}-NH-(C_0-C_{25})$-alkylene-$(C=O)_{0-1}-N(R13)_{0-1}$-(LAG); where one or more carbon atoms of the alkylene radical are replaced by aryl or heteroaryl radicals substituted up to three times by R7, or by (C_3-C_{10})-cycloalkyl or heterocycloalkyl radicals substituted up to three times by R7 and one or more carbon atoms of the alkylene radical may be replaced by oxygen atoms, NH, $N(CH_3)$ or SO_2 , and where R13 may be H or CH_3.

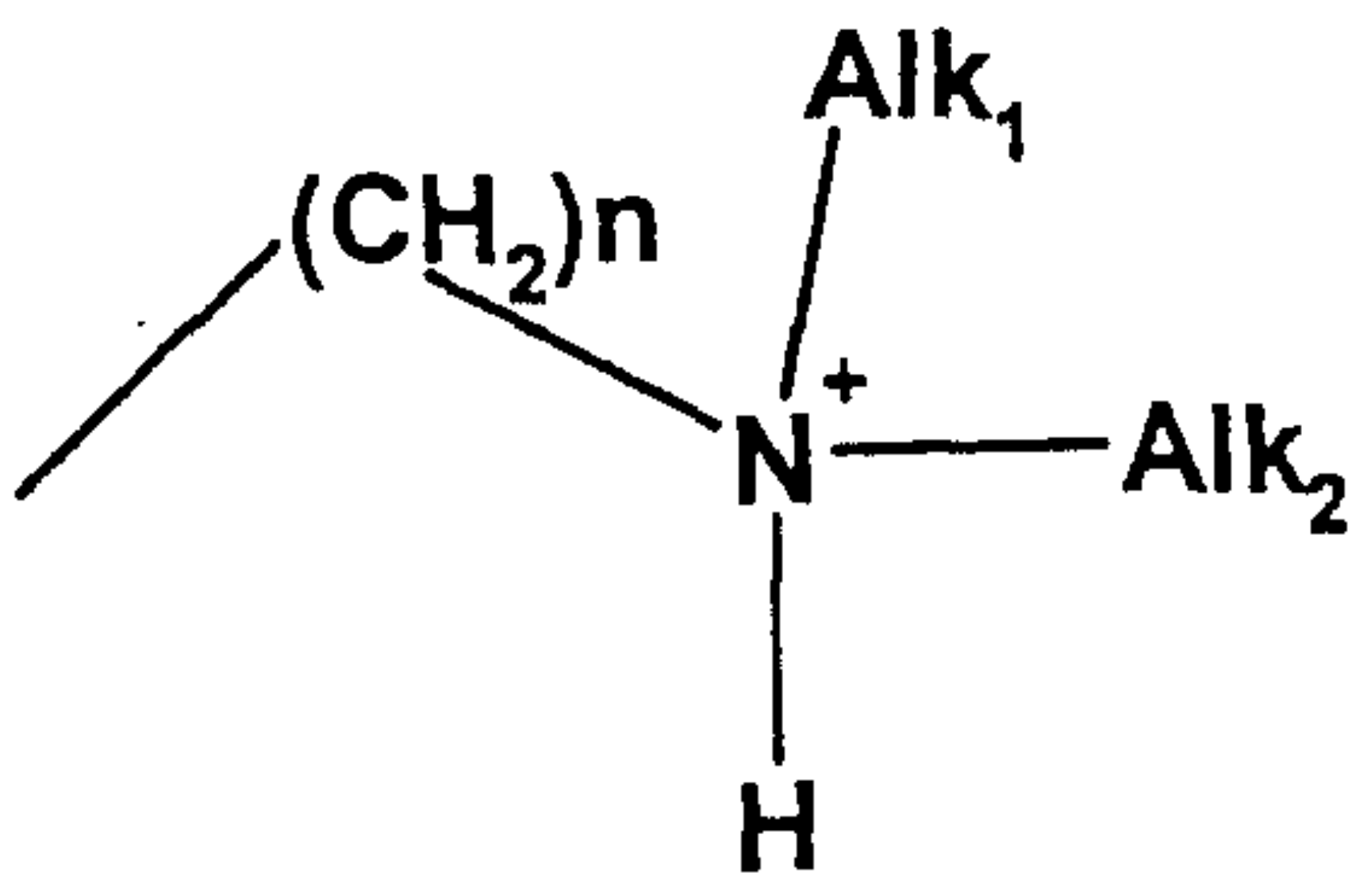
Preference is furthermore given to compounds of the formula I where the group LAG is a monosugar residue, an acyclic mono-, di- or tricyclic trialkylammoniumalkyl radical, a sulfonic acid or a carboxylic acid.

An aryl radical is to be understood as meaning a phenyl, naphthyl, biphenyl, tetrahydronaphthyl, alpha or beta-tetralone, indanyl or indan-1-onyl radical.

A heteroaryl radical is to be understood as meaning a pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyridazin-3-onyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, indolyl, benzimidazolyl, thienyl, furyl, thiazolyl, oxazolyl, isoxazolyl or isothiazolyl radical.

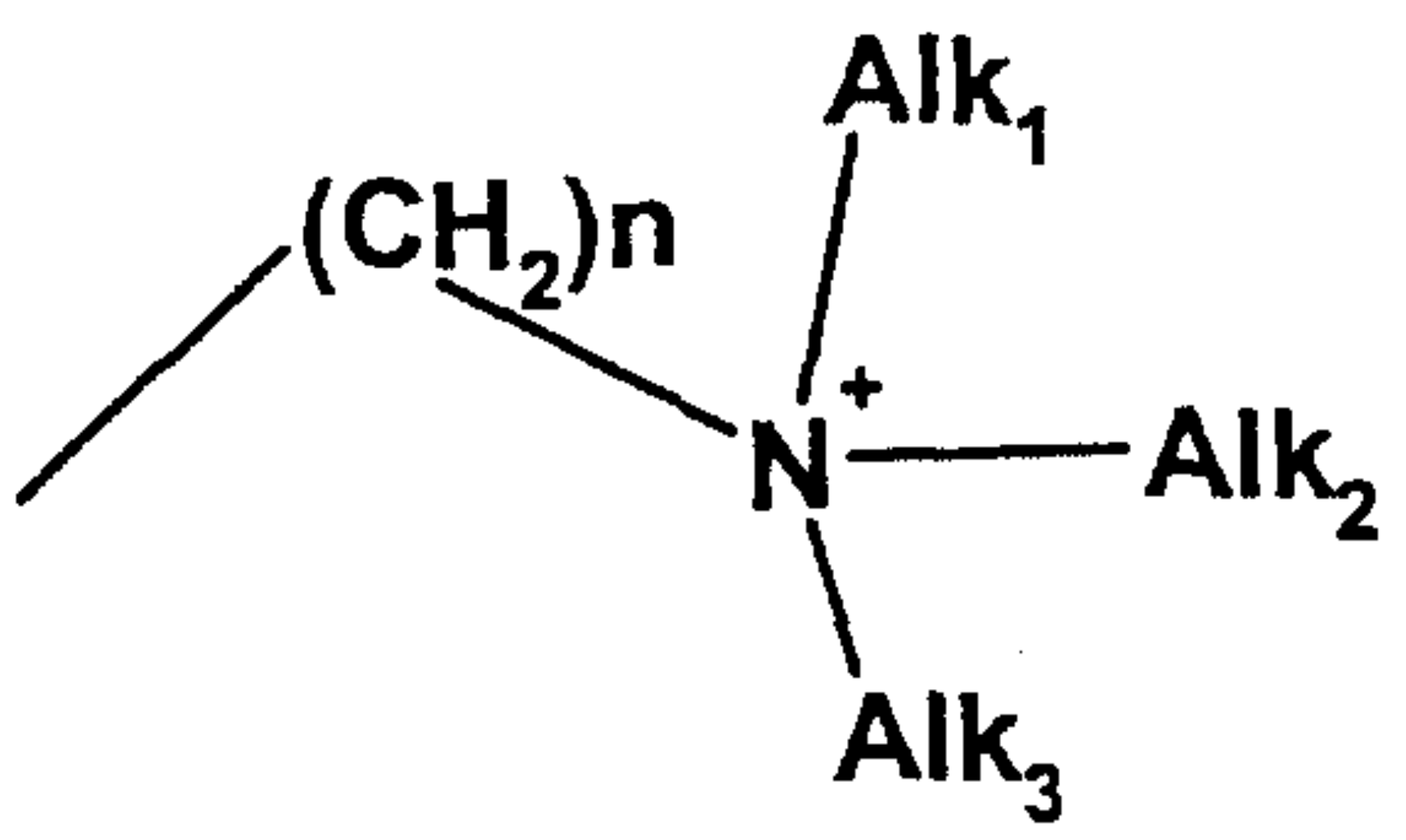
Heterocycloalkyl radicals are to be understood as meaning (C_3-C_{10})-cycloalkyl radicals in which at least one and up to three carbon atoms independently of one another are replaced by NR8, O or $S(O)_n$, where $n = 0 - 2$. Examples are the azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1,4-dioxanyl, tetrahydrofuryl, piperazinyl or thiepanyl radical.

An acyclic trialkylammonium radical is to be understood as meaning the following group



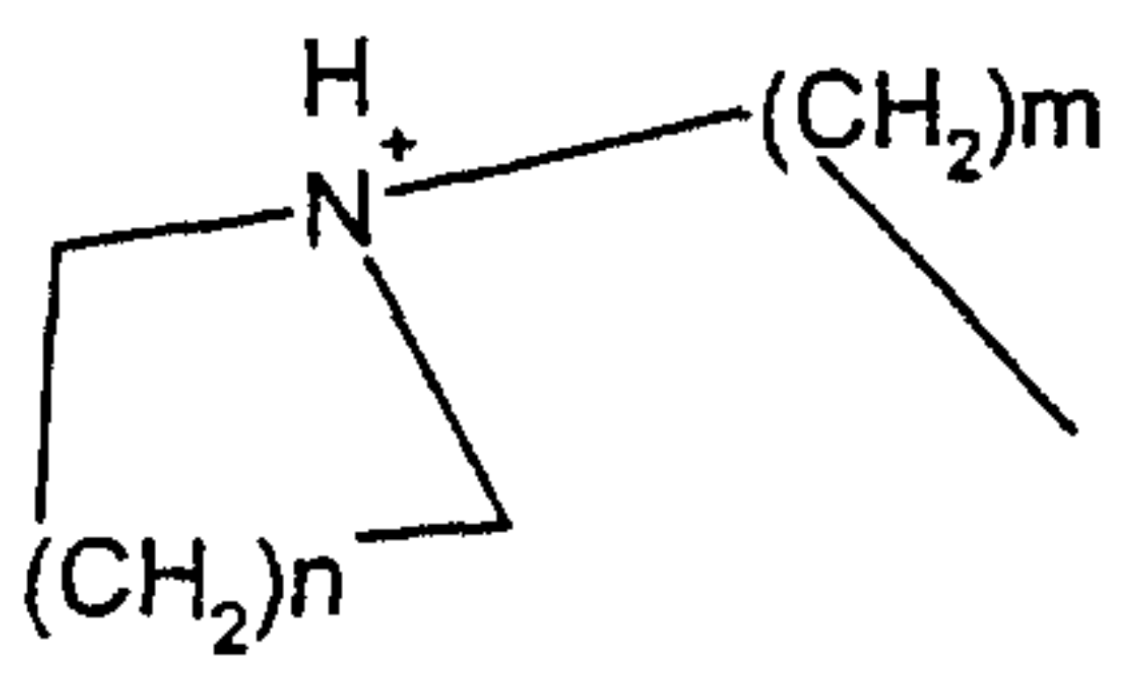
in which n = 0 to 10 and Alk_1 and Alk_2 independently of one another each denote a straight-chain or branched alkyl radical having 1 to 20 carbon atoms.

An acyclic trialkylammoniumalkyl radical is to be understood as meaning the following group



in which n = 0 to 10 and Alk_1, Alk_2, Alk_3 independently of one another each denote a straight-chain or branched alkyl radical having 1 to 20 carbon atoms.

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



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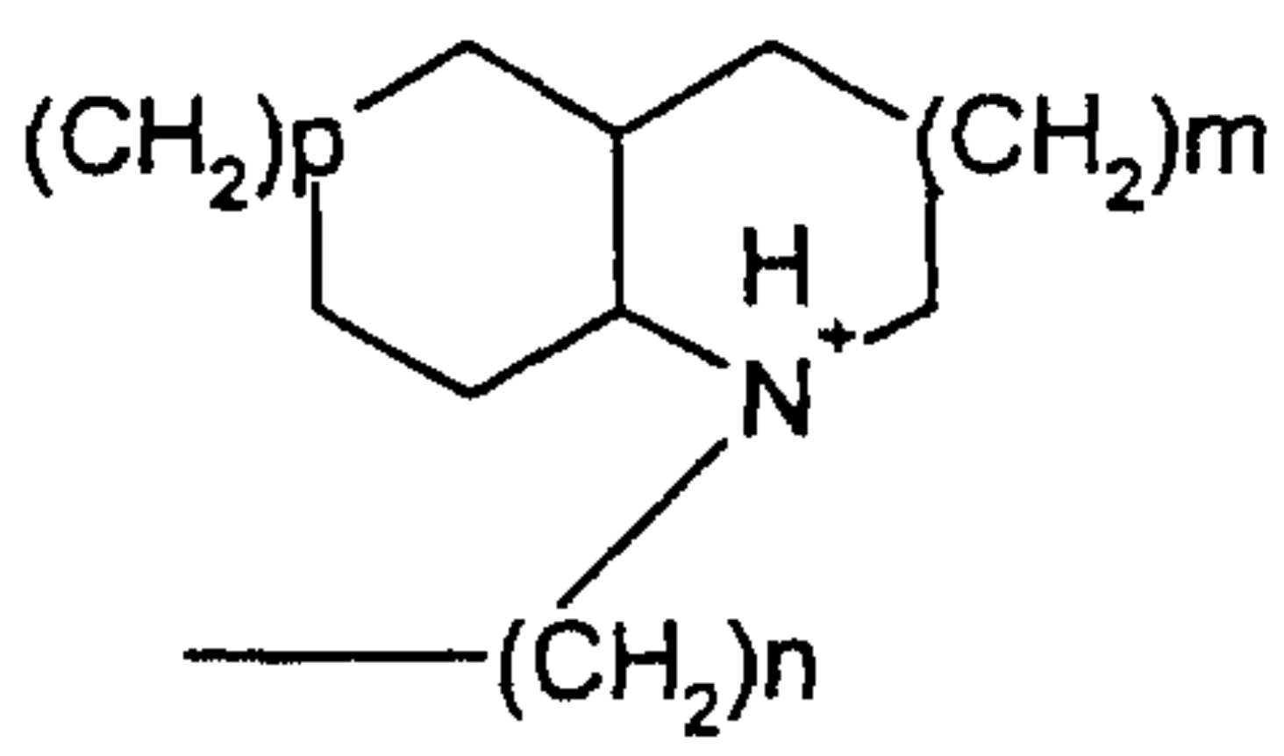

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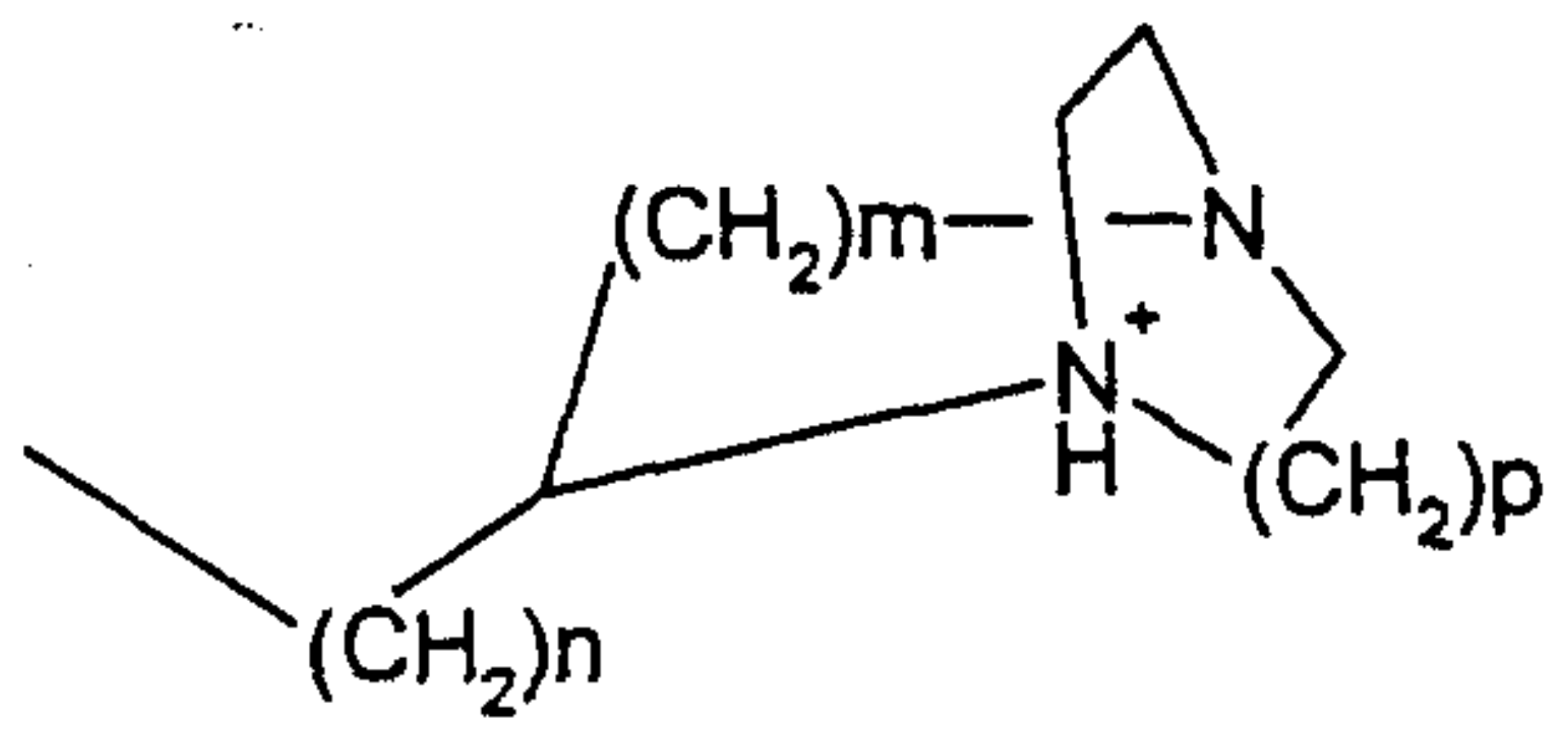
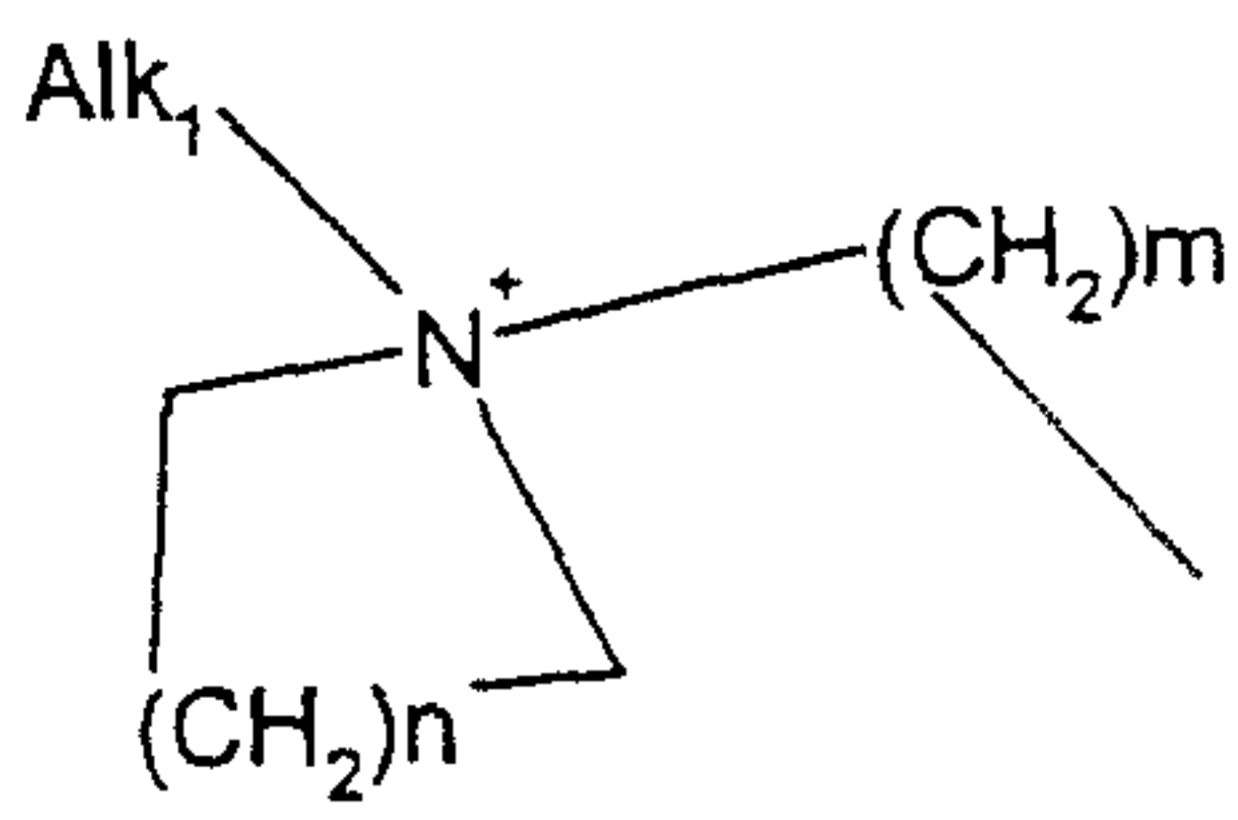


where n, m and p independently of one another can be 0 – 10 and one or more CH_2 groups independently of one another may be replaced by O, $S(O)_n$, where n = 0-2, NH, N-(C_1-C_{10})-alkyl, N-phenyl or N-CH_2-phenyl.

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



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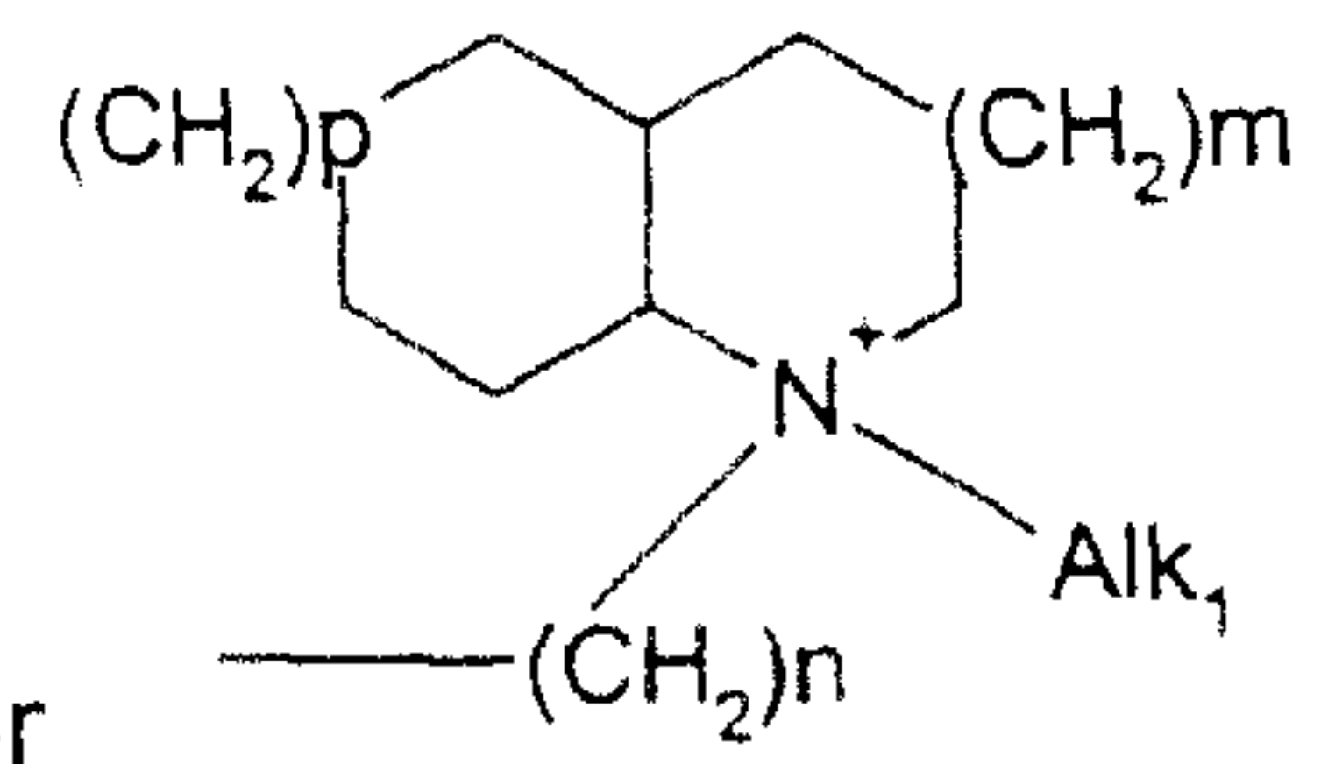

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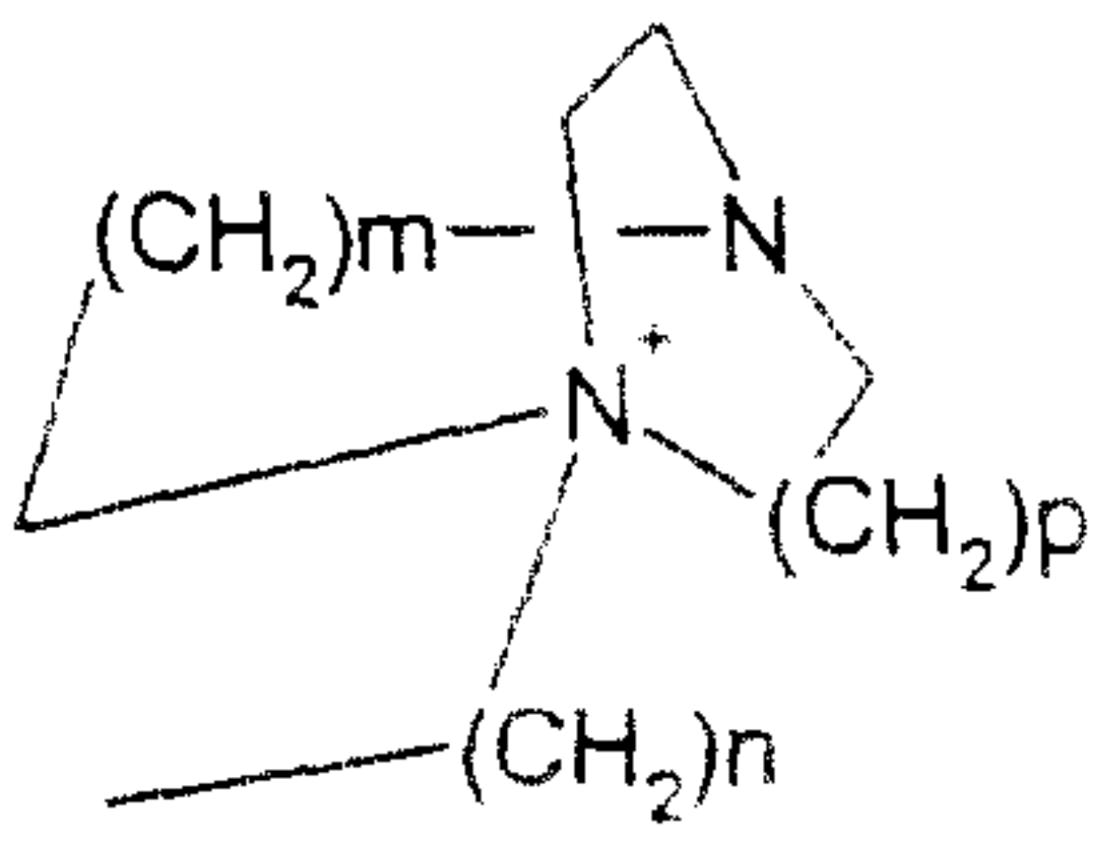

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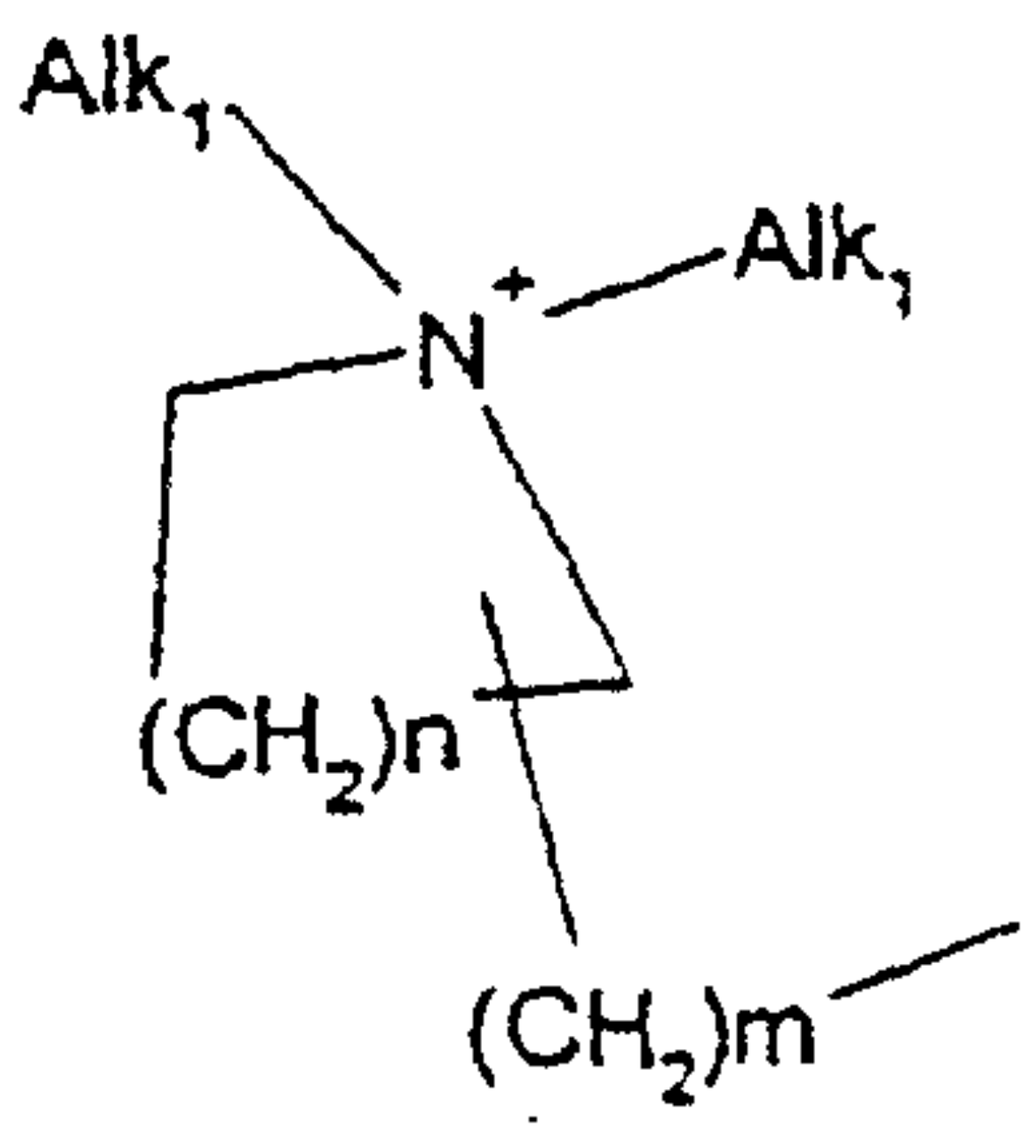

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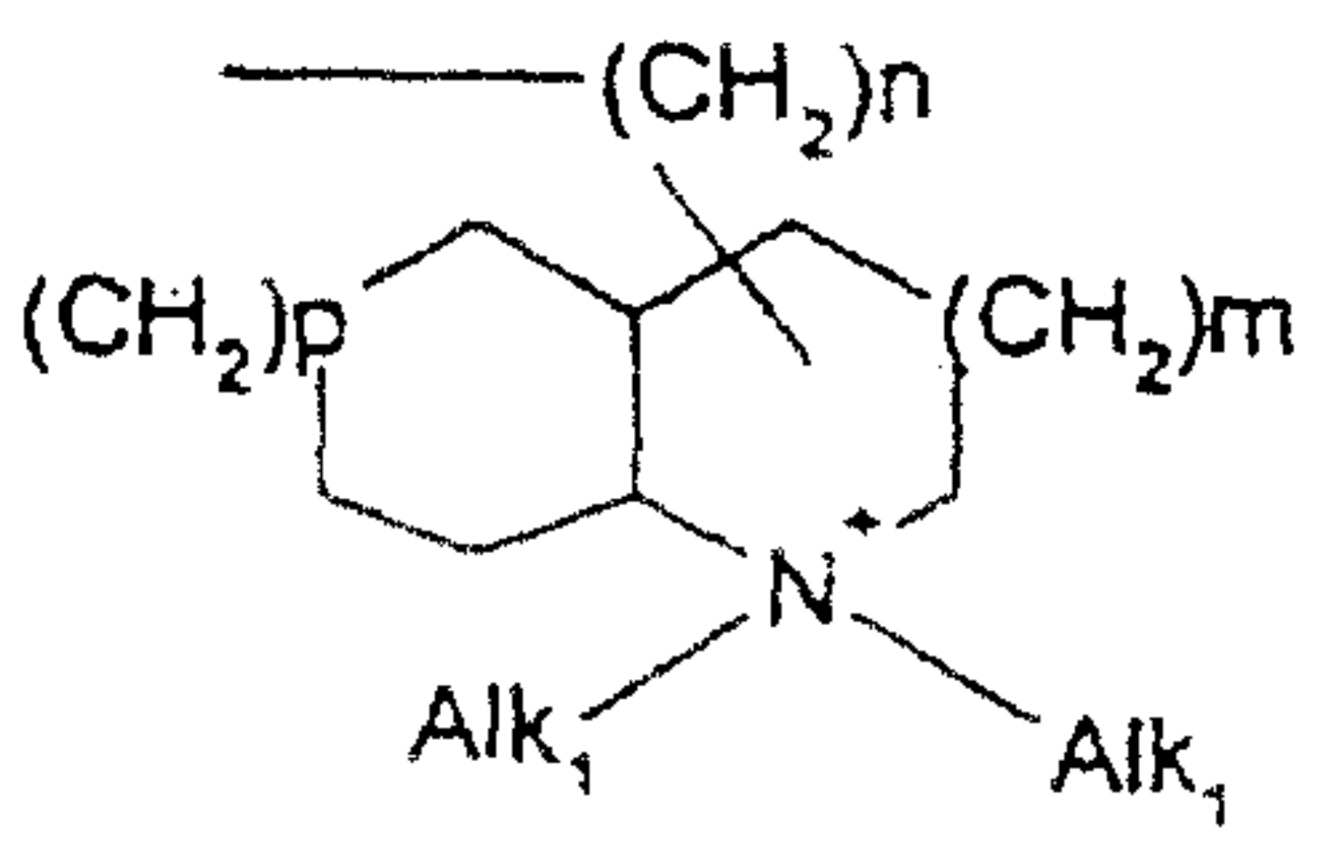

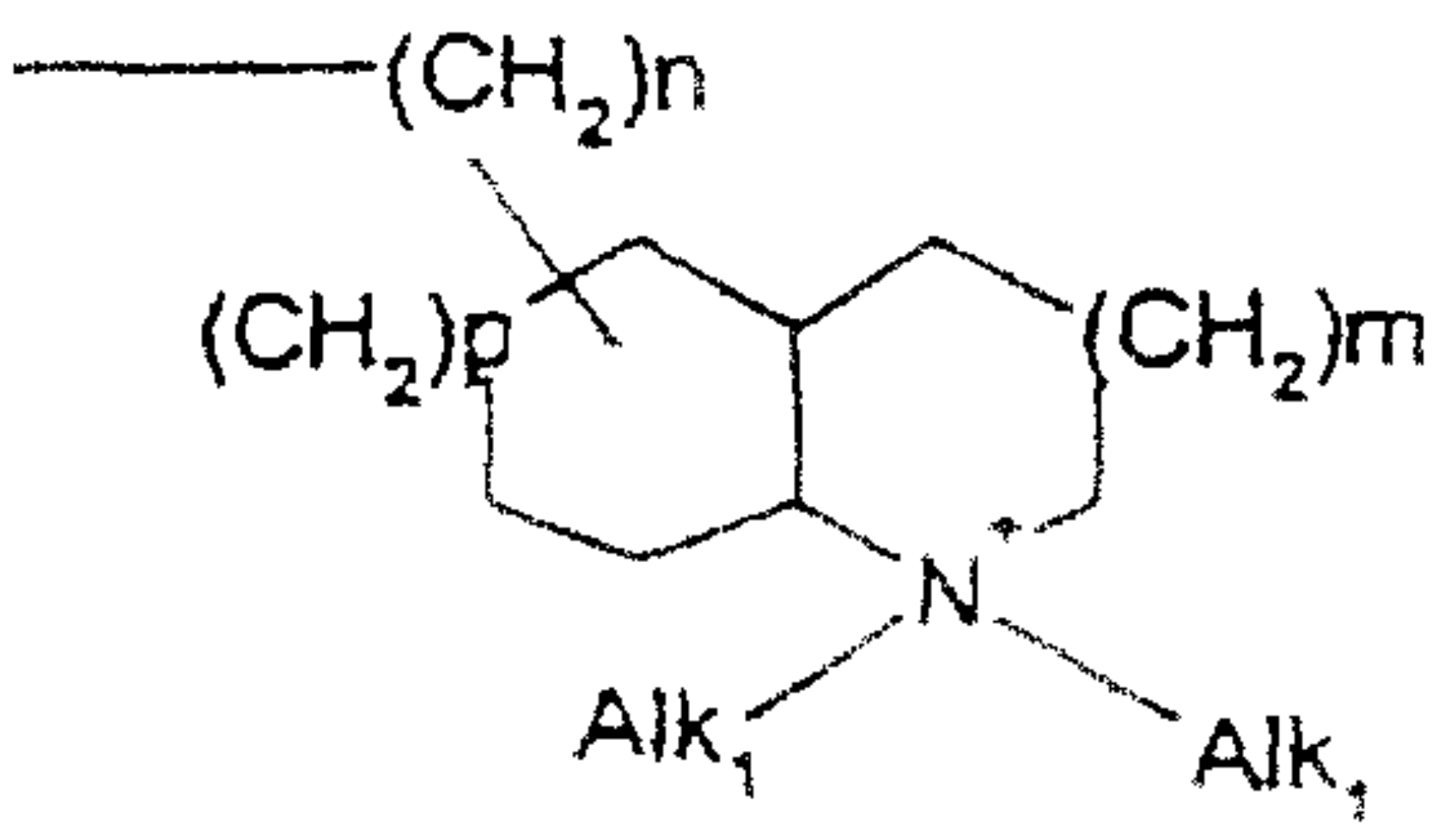

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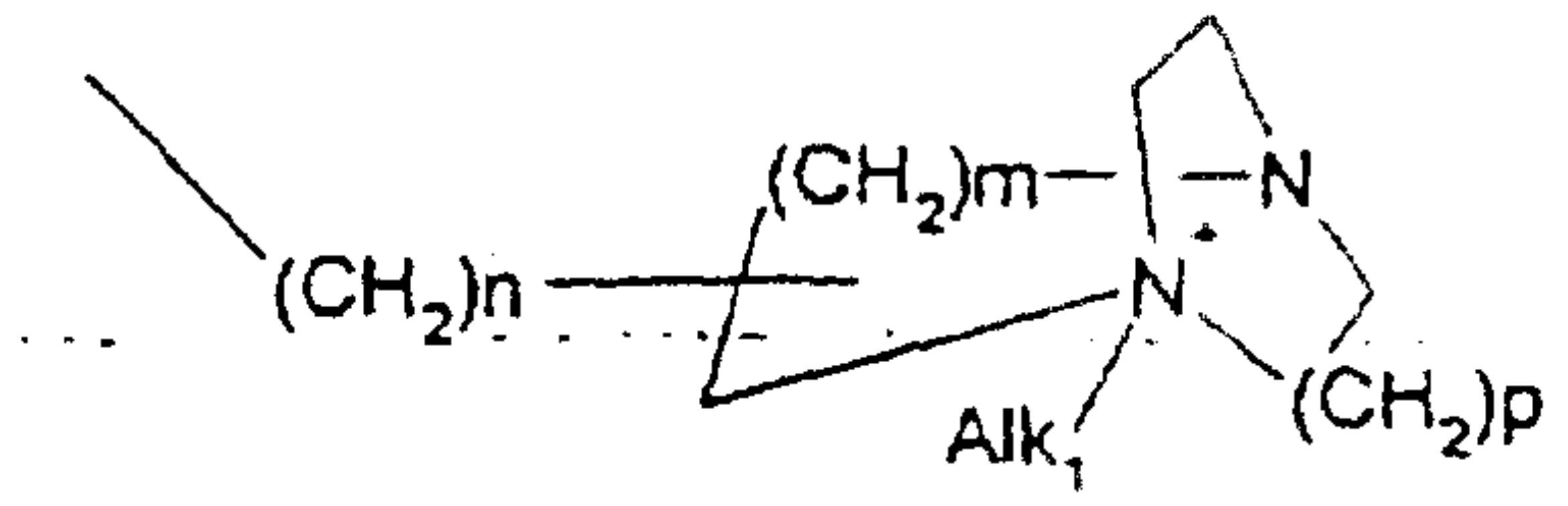


where n, m and p independently of one another can be 0 – 10 and one or more CH_2 groups independently of one another may be replaced by O, $S(O)_n$, where n = 0-2, NH, N-(C_1-C_{10})-alkyl, N-phenyl or N-CH_2-phenyl and Alk_1 is a straight-chain or branched alkyl radical having 1 to 20 carbon atoms.

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 diphenylazetidinone-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-quinazolinylmethoxy]phenyl]methyl]-2,4-thiazolidinedione.

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

In one embodiment, the compounds of the formula I are administered in combination with an active 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.

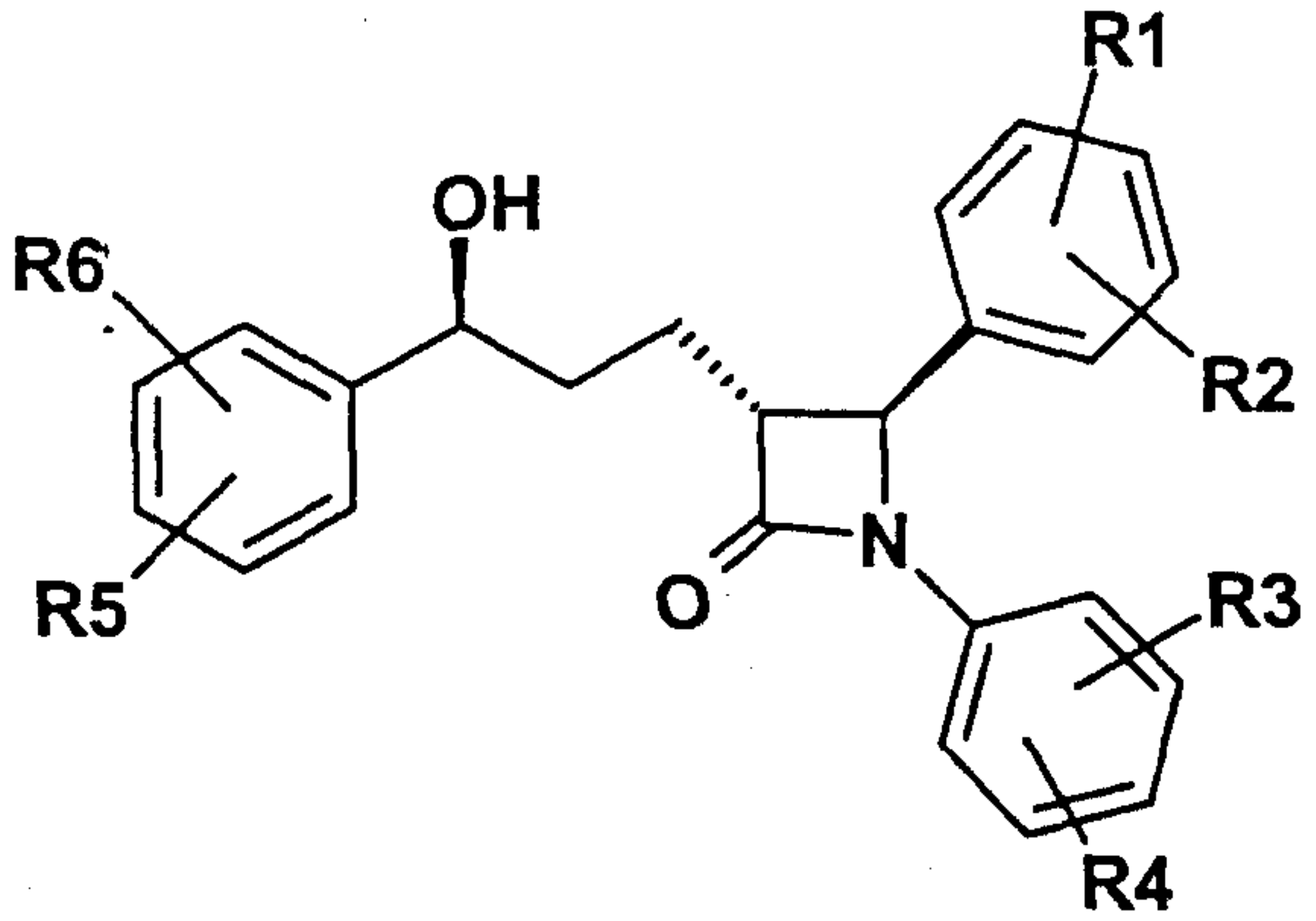
In one embodiment of the invention, the further active compound is leptin.
In one embodiment, the further active compound is dexamphetamine or amphetamine.
In one embodiment, the further active compound is fenfluramine or dexfenfluramine.
In another embodiment, the further active compound is sibutramine.
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:



Sugar residues are to be understood as meaning compounds which are derived from aldoses and ketoses which have 3 to 7 carbon atoms and may belong to the D or the L series; also included are amino sugars, sugar alcohols or sugar acids. Glucose, mannose, fructose, galactose, ribose, erythrose, glycerolaldehyde, sedoheptulose, glucosamine, galactosamine, glucuronic acid, galacturonic acid, gluconic acid, galactonic acid, mannonic acid, glucamine, 3-amino-1,2-propanediol, glucaric acid and galactaric acid may be mentioned by way of example.

Disugars are saccharides composed of two sugar units. Di-, tri- or tetrasaccharides are formed by acetal-like binding of two or more sugars. Here, the bonds may be in the α- or β-form. Lactose, maltose and cellobiose may be mentioned by way of example.

If the sugar is substituted, the substitution is preferably at the hydrogen atom of an OH group of the sugar.

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

The term “amino acids” or “amino acid residues” refers, for example, to the stereoisomeric forms, i.e. the D or L forms, of the following compounds:

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

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

isodesmosine	ornithine
allo-isoleucine	
N-methylglycine	

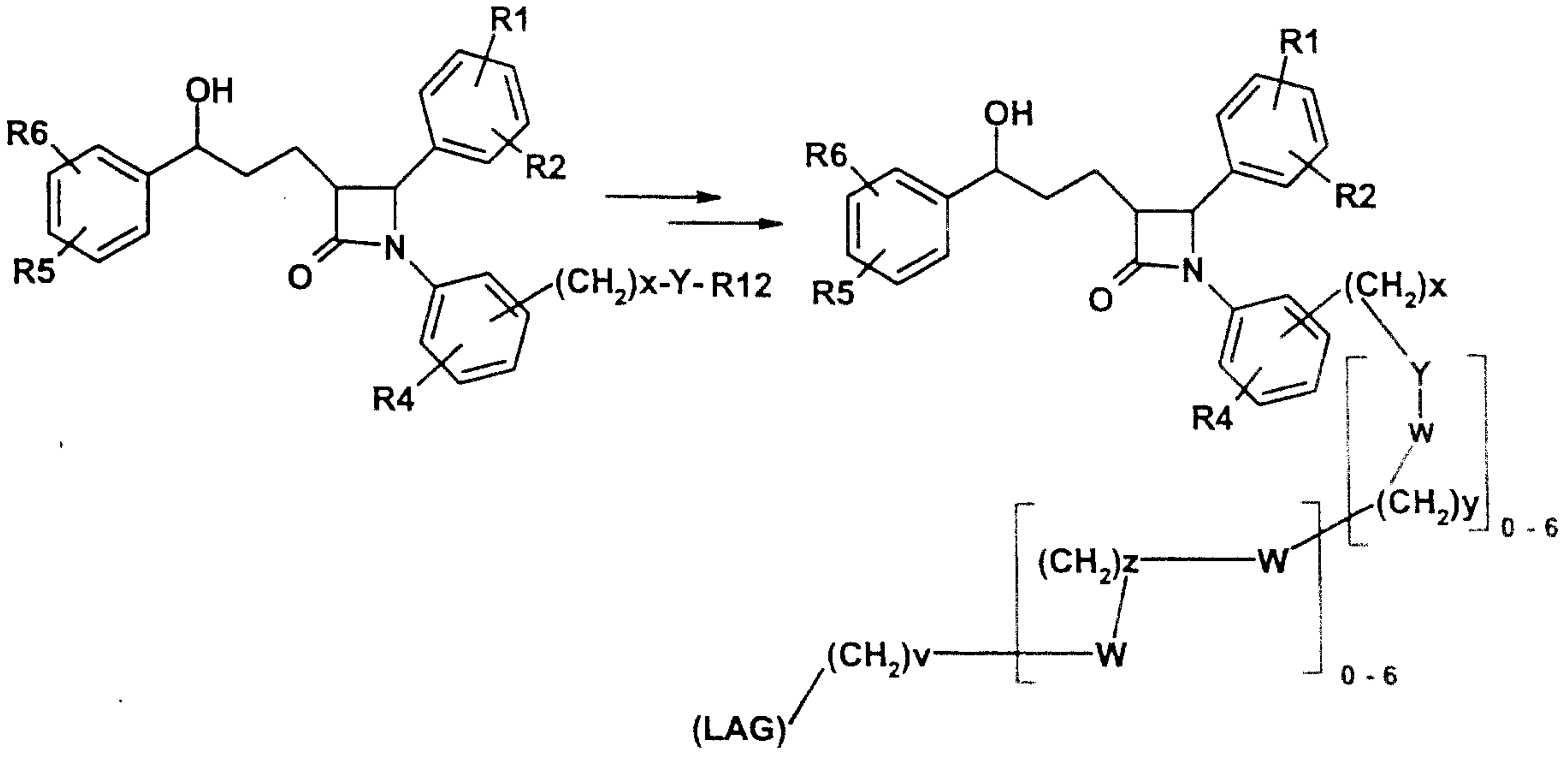
For abbreviating the amino acids, the conventional notation was used (cf. Schröder, Lübke, The Peptides, Volume I, New York 1965, pages XXII-XXIII; Houben-Weyl, Methoden der Organischen Chemie [Methods of organic chemistry], Volume XV/1 and 2, Stuttgart 1974). The amino acid pGlu denotes pyroglutamyl, Nal denotes 3-(2-naphthyl)alanine, azagly-NH_2 denotes a compound of the formula NH_2-NH-$CONH_2$ and D-Asp denotes the D form of aspartic acid. According to their chemical nature, peptides are acid amides, and on hydrolysis they decompose into amino acids.

An oligopeptide is to be understood as meaning a peptide constructed of 2 to 9 of the amino acids mentioned above.

Suitable protective groups (see, for example, T.W. Greene, "Protective Groups in Organic Synthesis") for amino acids are primarily:
Arg(Tos), Arg(Mts), Arg(Mtr), Arg(PMV), Asp(OBzl), Asp(OBut), Cys(4-MeBzl), Cys(Acm), Cys(SBut), Glu(Obzl), Glu(Obut), His(Tos), His(Fmoc), His(Dnp), His(Trt), Lys(Cl-Z), Lys(Boc), Met(O), Ser(Bzl), Ser(But), Thr(Bzl), Thr(But), Trp(Mts), Trp(CHO), Tyr(Br-Z), Tyr(Bzl) or Tyr(But).

Amino protective groups 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;

R12 can be H or, if Y = (C=O) or (C=S), OH;

W can, independently of Y, be an up to trisubstituted aryl or heteroaryl radical or an up to tetrasubstituted (C_3-C_{10})-cycloalkyl or heterocycloalkyl radical or $-S(O)_n-$, 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;

v, x, y and z independently of one another can be 0 to 10.

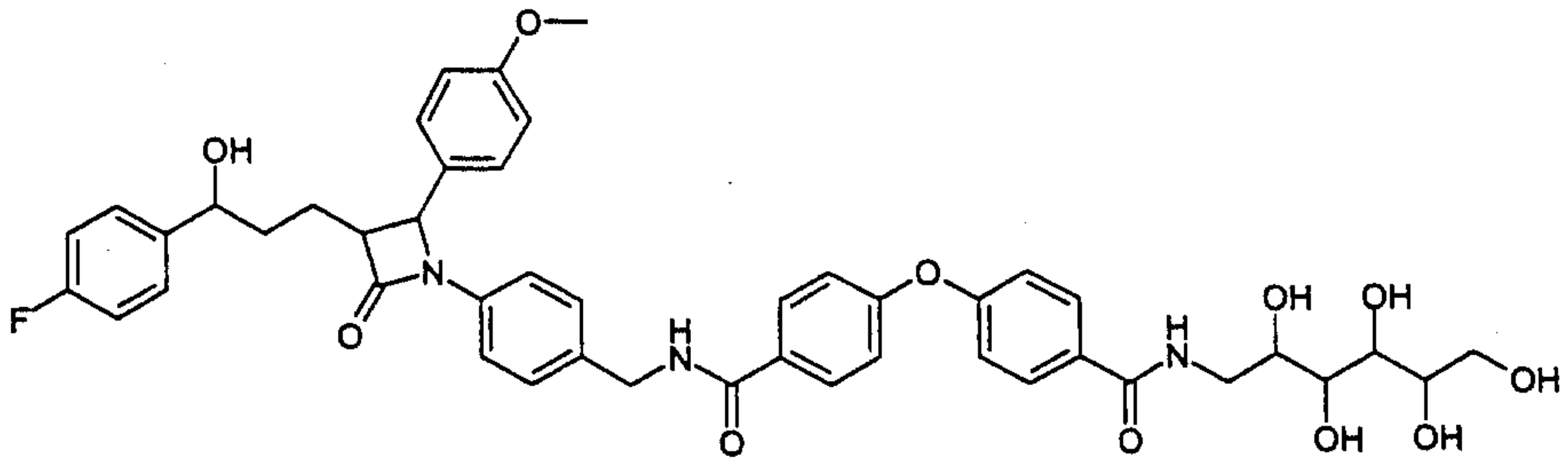
In compound II, -(CH_2)x-Y-R12 can alternatively also be attached to one of the other two phenyl rings.

The process for preparing compounds of the formula I comprises, for example, reacting an amine 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.

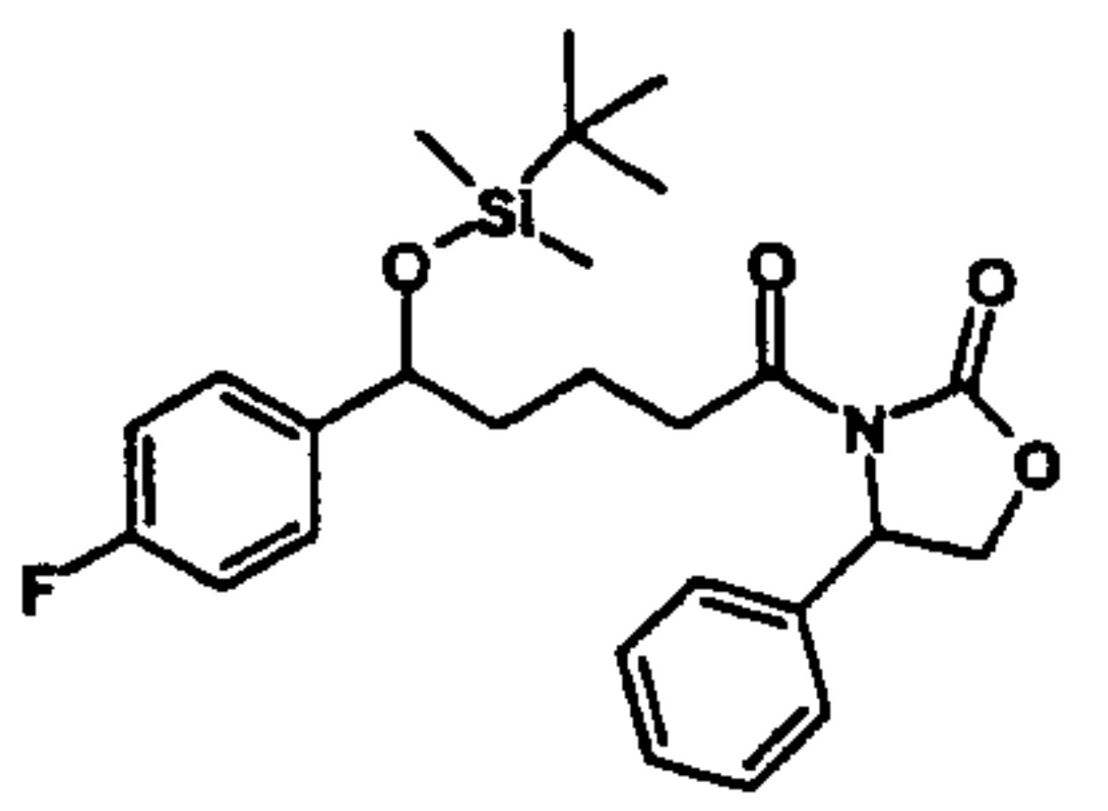
The examples below serve to illustrate the invention in more detail, without limiting the invention to the products and embodiments described in the examples.

Example I

2,3,4,5,6-Pentahydroxyhexylamide of 4-(4-{4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzylcarbamoyl}phenoxy)benzoic acid (7):



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-phenyloxazolidin-2-one (1) 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-fluorophenyl)-1-(4-methoxyphenyl)-2-(2-oxo-4-phenyloxazolidine-3-carbonyl)pentylamino]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 (2) 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 (3) 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 (4) 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) 2,3,4,5,6-Pentahydroxyhexylamide of 4,4'-oxybisbenzoic acid (6):

At room temperature, 0.52 g of 4,4'-oxybisbenzoic acid and 0.36 g of D-glucamine are suspended in 10 ml of dry dimethylformamide, 0.31 g of HOBt and 0.39 g of EDC are added and the mixture is stirred at room temperature for 12 h. The reaction mixture is evaporated to dryness and dried under high vacuum. The residue is thoroughly titrated with water, the resulting suspension is filtered and the residue is titrated with methanol and filtered again. The filtrate is concentrated to half of its volume using a rotary evaporator, and the solution is cooled in an ice bath. The resulting precipitate is filtered off with suction, washed with a little ice-cooled methanol and dried under reduced pressure. This gives the 2,3,4,5,6-pentahydroxyhexylamide of 4,4'-oxybisbenzoic acid (6) of molecular weight 421.40 ($C_{20}H_{23}NO_9$); MS (ESI): 422.28 (MH^+).

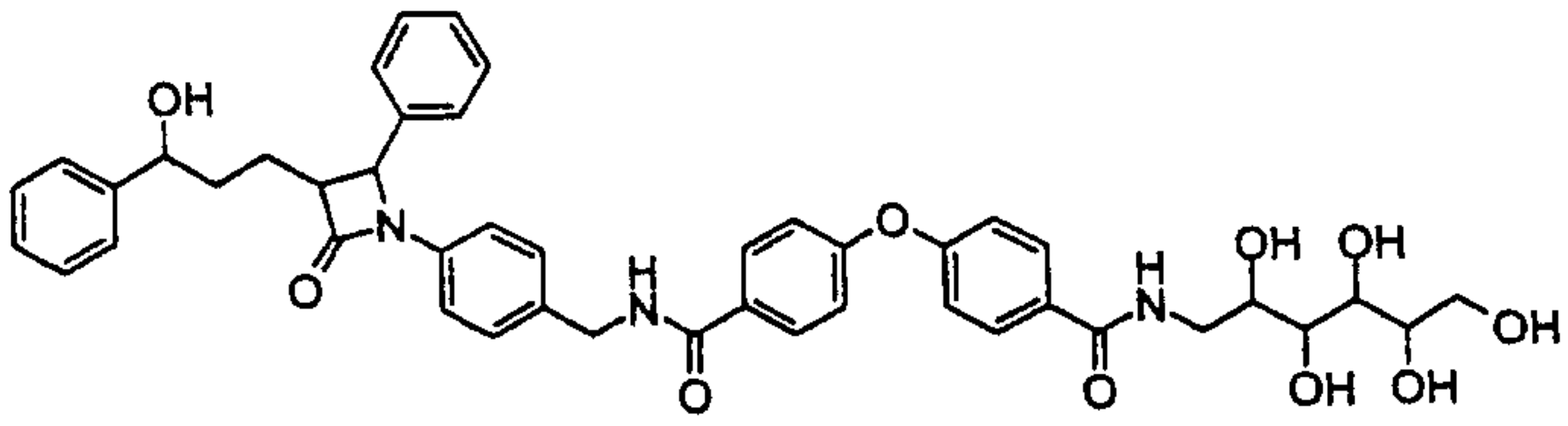
g) 2,3,4,5,6-Pentahydroxyhexylamide of 4-(4-{4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzylcarbamoyl}phenoxy)benzoic acid (7):

87 mg of the compound prepared under e) and 90 mg of the compound prepared under f) are, at room temperature, dissolved in 3 ml of dry dimethylformamide, 31 mg of HOBt and 39 mg of EDC are added and the mixture is stirred at room temperature for 12 h. The reaction mixture is evaporated to dryness under high vacuum and the residue is titrated with dichloromethane, filtered off with suction, washed with dichloromethane and dried under reduced pressure. This gives the 2,3,4,5,6-pentahydroxyhexylamide of 4-(4-{4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-

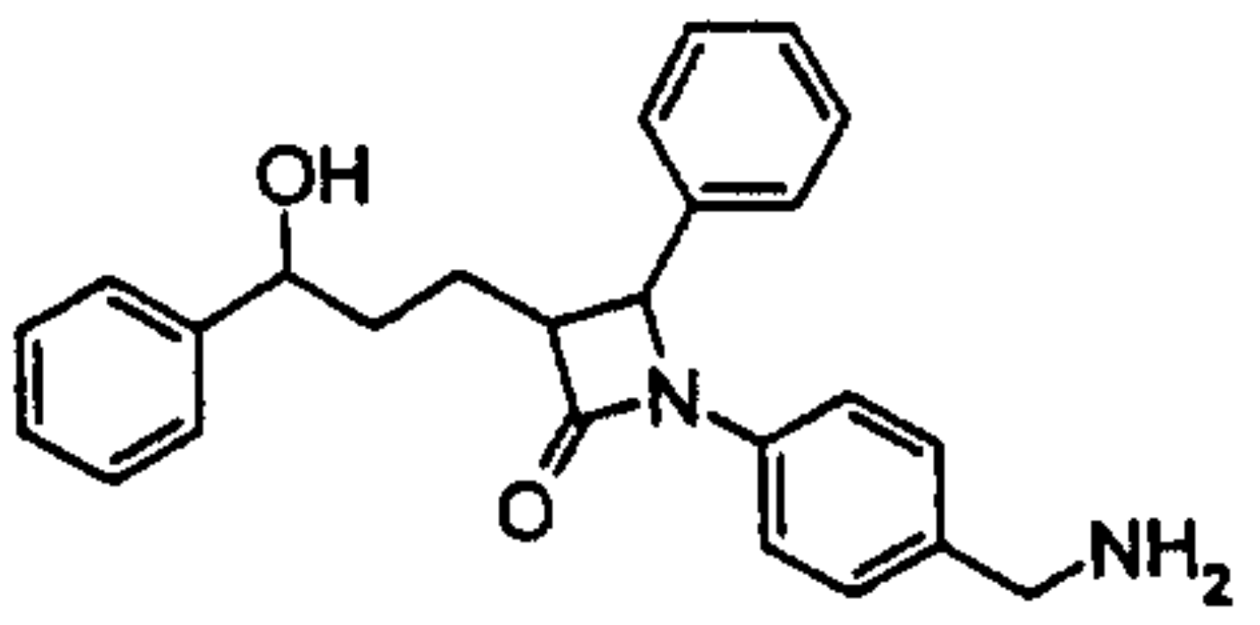
2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzylcarbamoyl}phenoxy)benzoic acid (7) with a molecular weight 837.90 ($C_{46}H_{48}FN_3O_{11}$); MS (ESI): 838,39 (MH^+).

Example II

2,3,4,5,6-Pentahydroxyhexylamide of 4-(4-{4-[3-(3-hydroxy-3-phenylpropyl)-2-oxo-4-phenylazetidin-1-yl]benzylcarbamoyl}phenoxy)benzoic acid (9):



a) 1-(4-Aminomethylphenyl)-3-(3-hydroxy-3-phenylpropyl)-4-phenylazetidin-2-one (8):



This compound is prepared as described above for 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-methoxyphenyl)-azetidin-2-one, except that 3-[5-(tert-butyldimethylsilanyloxy)-5-phenylpentanoyl]-4-phenyloxazolidin-2-one and 4-(benzylideneamino)benzonitrile are used. This gives 1-(4-aminomethylphenyl)-3-(3-hydroxy-3-phenylpropyl)-4-phenylazetidin-2-one (8) of molecular weight 386.50 ($C_{25}H_{26}N_2O_2$); MS (ESI): 370.2 (MH^+-NH_3).

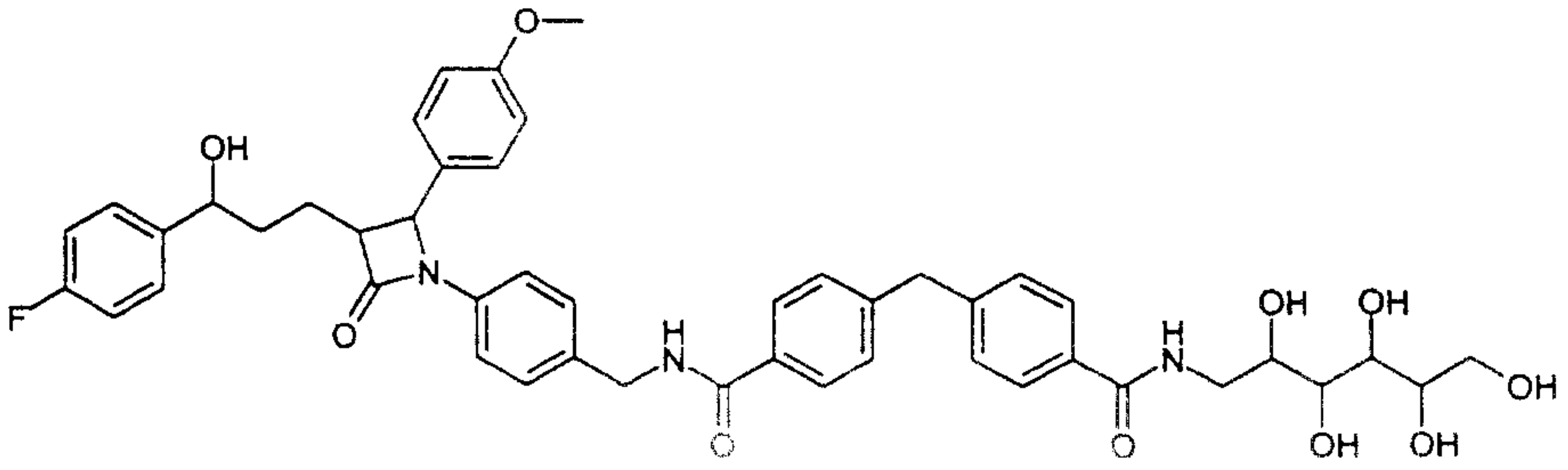
b) 2,3,4,5,6-Pentahydroxyhexylamide of 4-(4-{4-[3-(3-hydroxy-3-phenylpropyl)-2-oxo-4-phenylazetidin-1-yl]benzylcarbamoyl}phenoxy)benzoic acid (9):

The benzylamine from IIa is reacted with the 2,3,4,5,6-pentahydroxyhexylamide of 4,4'-oxybisbenzoic acid from If as described in Example I. This gives the 2,3,4,5,6-

pentahydroxyhexylamide of 4-(4-{4-[3-(3-hydroxy-3-phenylpropyl)-2-oxo-4-phenylazetidin-1-yl]benzylcarbamoyl}phenoxy)benzoic acid (9) of molecular weight 789.89 ($C_{45}H_{47}N_3O_{10}$); MS (ESI): 790.26 (MH^+).

Example III

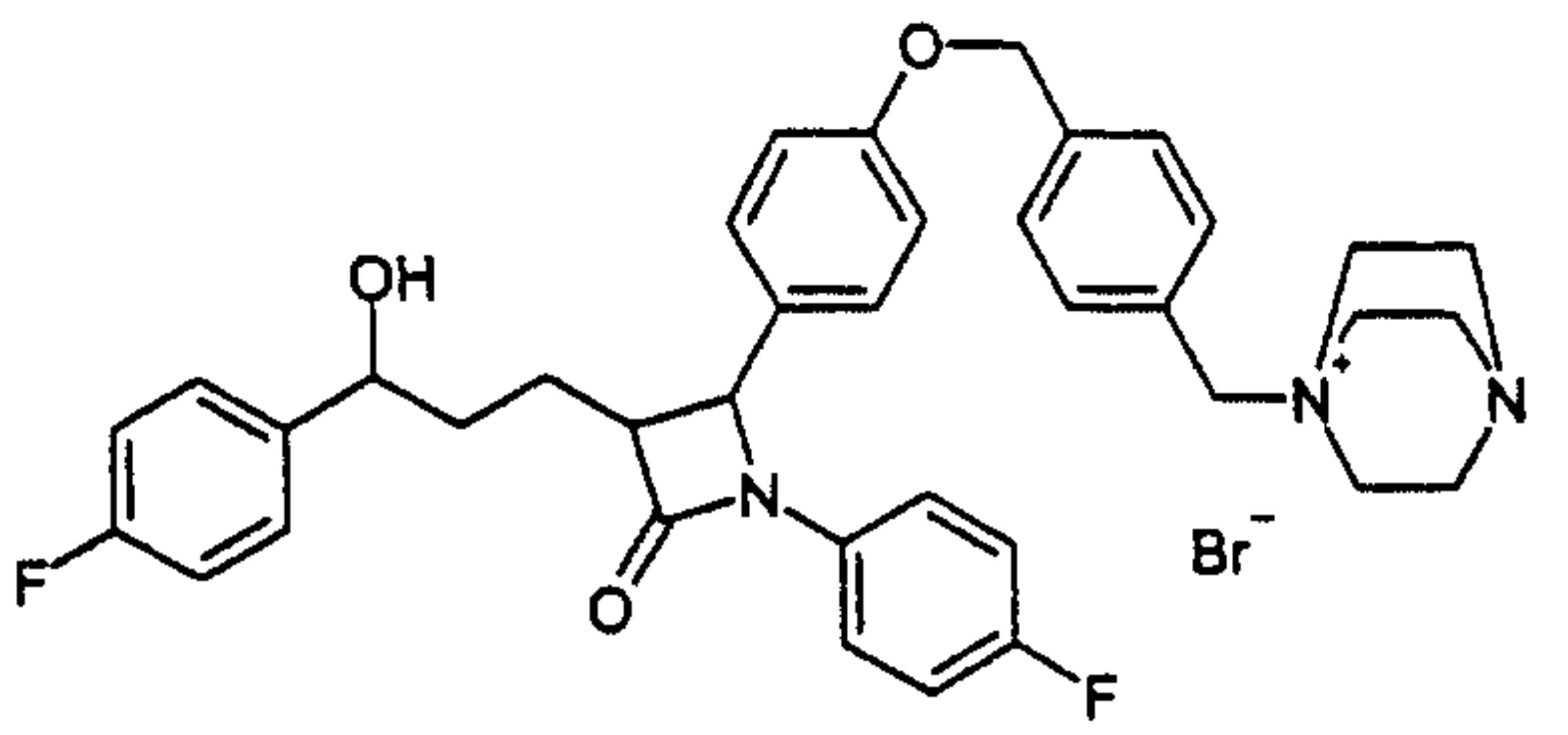
2,3,4,5,6-Pentahydroxyhexylamide of 4-(4-{4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-benzylcarbamoyl}-benzyl)-benzoic acid (10):



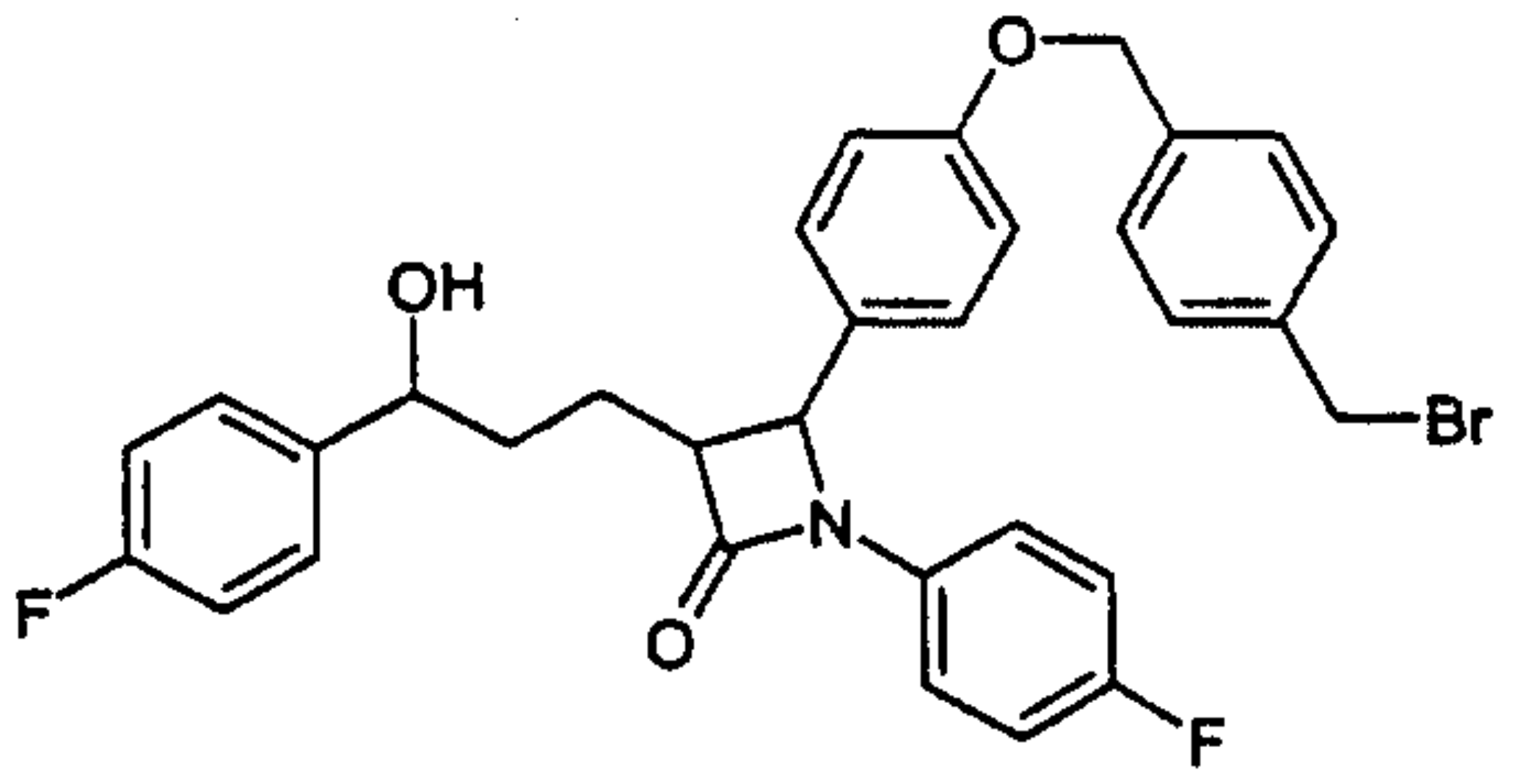
The compound of Example III is obtained analogously to the procedure of Example I, except that the 2,3,4,5,6-pentahydroxyhexylamide of diphenylmethane-4,4'-dicarboxylic acid is used. This gives the 2,3,4,5,6-pentahydroxyhexylamide of 4-(4-{4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-benzylcarbamoyl}benzyl)benzoic acid (10) of molecular weight 835.93 ($C_{47}H_{50}FN_3O_{10}$); MS (ESI): 836.18 (MH^+).

Example IV

1-[4-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxymethyl)benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (13):



a) 4-[4-(4-Bromomethylbenzyloxy)phenyl]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3- hydroxypropyl]azetidin-2-one (12):



3.0 g of 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)- azetidin-2-one (11) 7.0 g of 1,4-bisbromomethylbenzene and 5.0 g of potassium carbonate are dissolved in 100 ml of dimethylformamide and stirred at room temperature 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. The residue is purified by flash chromatography (n-heptane/ethyl acetate). Yield 3.2 g of colorless crystals (12) of molecular weight 592.49 ($C_{32}H_{28}BrF_2NO_3$); MS (ESI): 592.2 (MH^+).

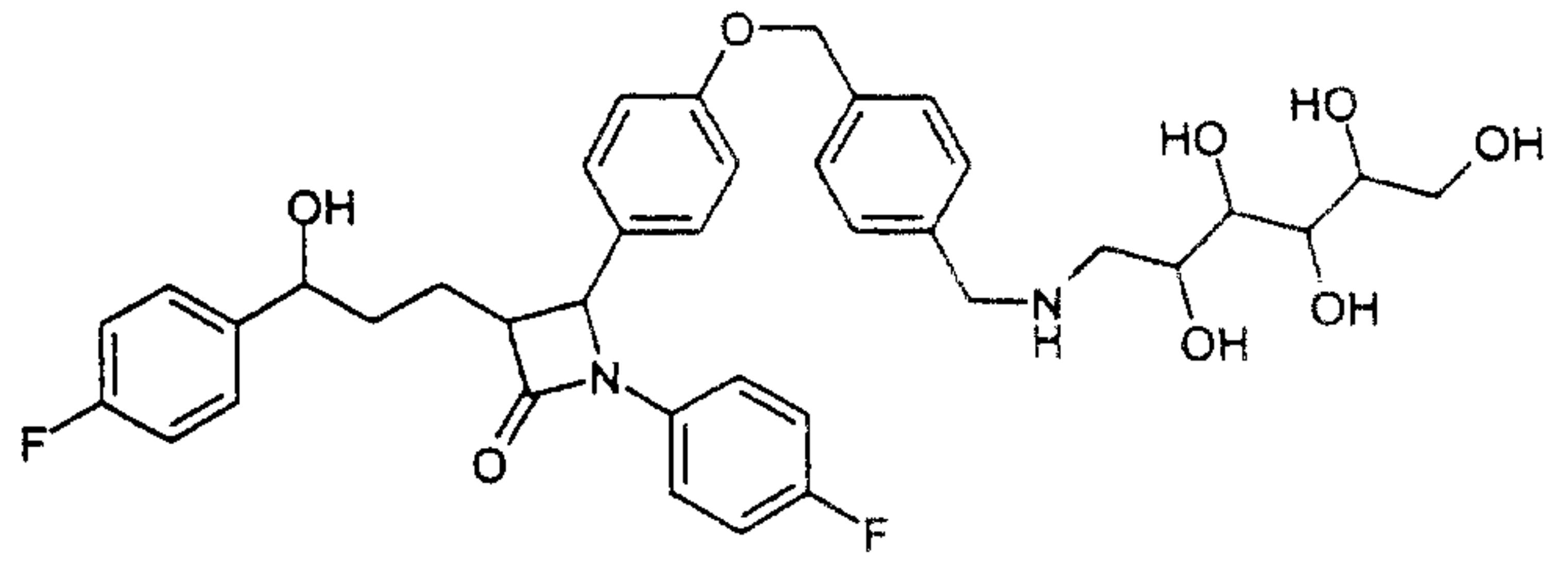
b) 1-[4-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2- yl}phenoxymethyl)benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (13):

180 mg of (12) and 300 mg of 1,4-diazabicyclo[2.2.2]octane (DABCO) are dissolved in 5ml of toluene and stirred at 80°C for 90 min. After the reaction has ended, the mixture is allowed to cool and the colorless solid is filtered off with suction. This gives

195 mg of product (13) of molecular weight 704.66 ($C_{38}H_{40}BrF_2N_3O_3$); MS (ESI): 624.30 (MH^+).

Example V

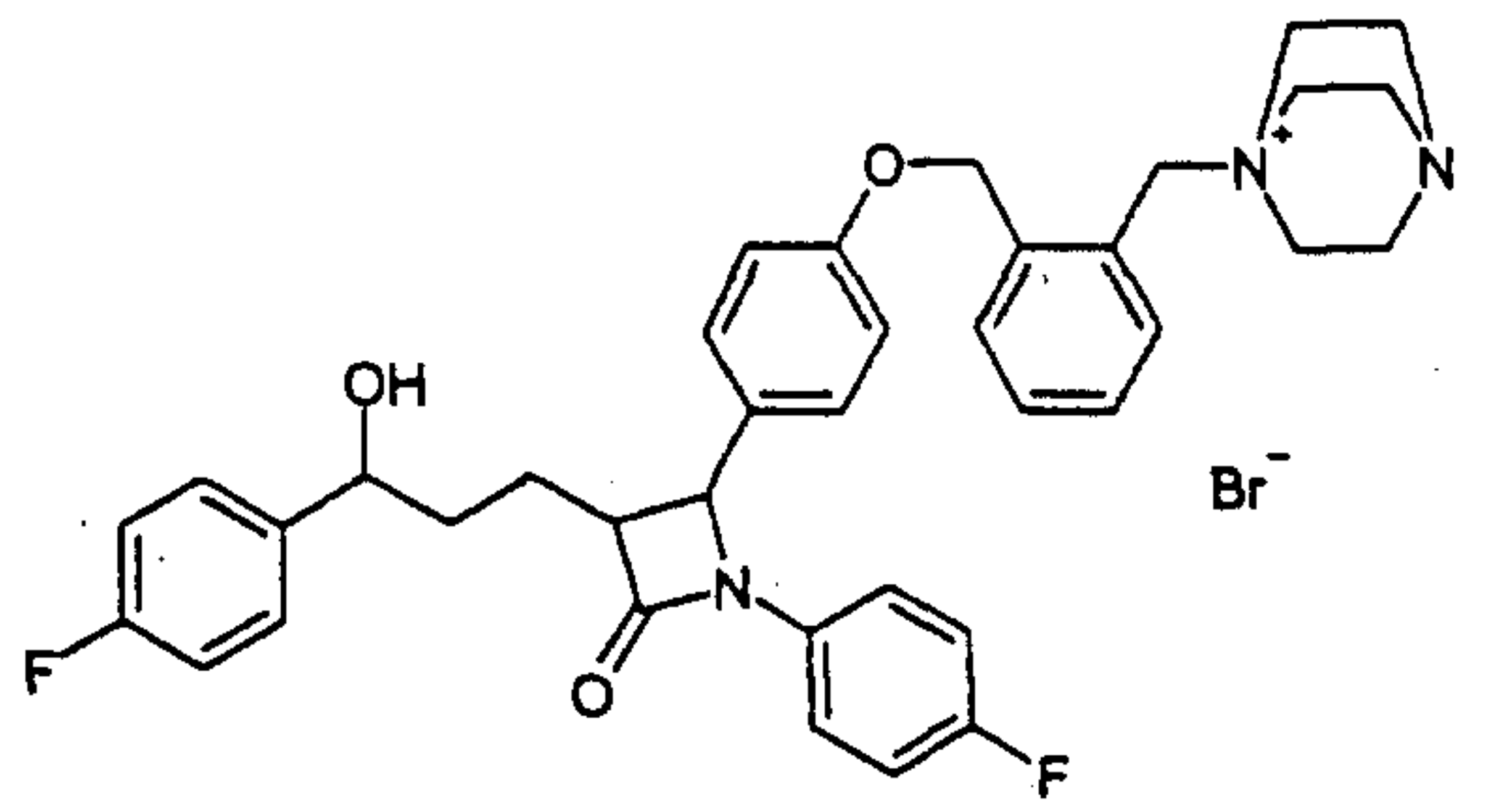
1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{4-[(2,3,4,5,6-pentahydroxyhexylamine)methyl]benzyloxy}phenyl)azetidin-2-one (14)



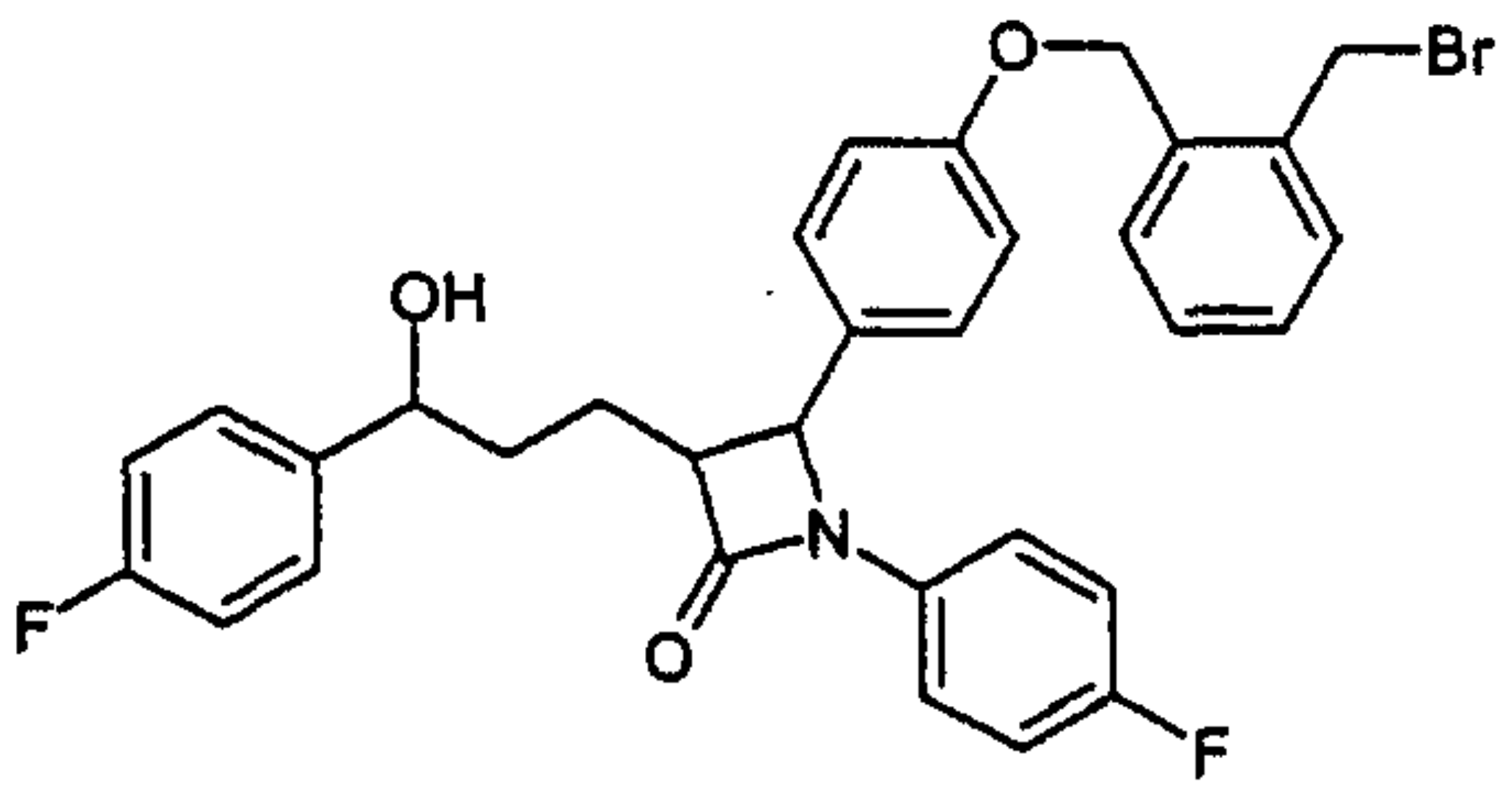
60 mg of (12) and 150 mg of glucamine are dissolved in 5ml of dimethylformamide and stirred at 80°C for 90 min. After the reaction has ended the mixture is dissolved in ethyl acetate and extracted two times with water. The organic phase is dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (methylene chloride/methanol/conc. ammonia 30/10/3). Yield 33 mg of a colorless solid (14) of molecular weight 692.76 ($C_{38}H_{42}F_2N_2O_8$); MS (ESI): 693.5 (MH^+).

Example VI

1-[2-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxymethyl)benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (16):



a) 4-[4-(2-Bromomethylbenzyloxy)phenyl]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one (15):



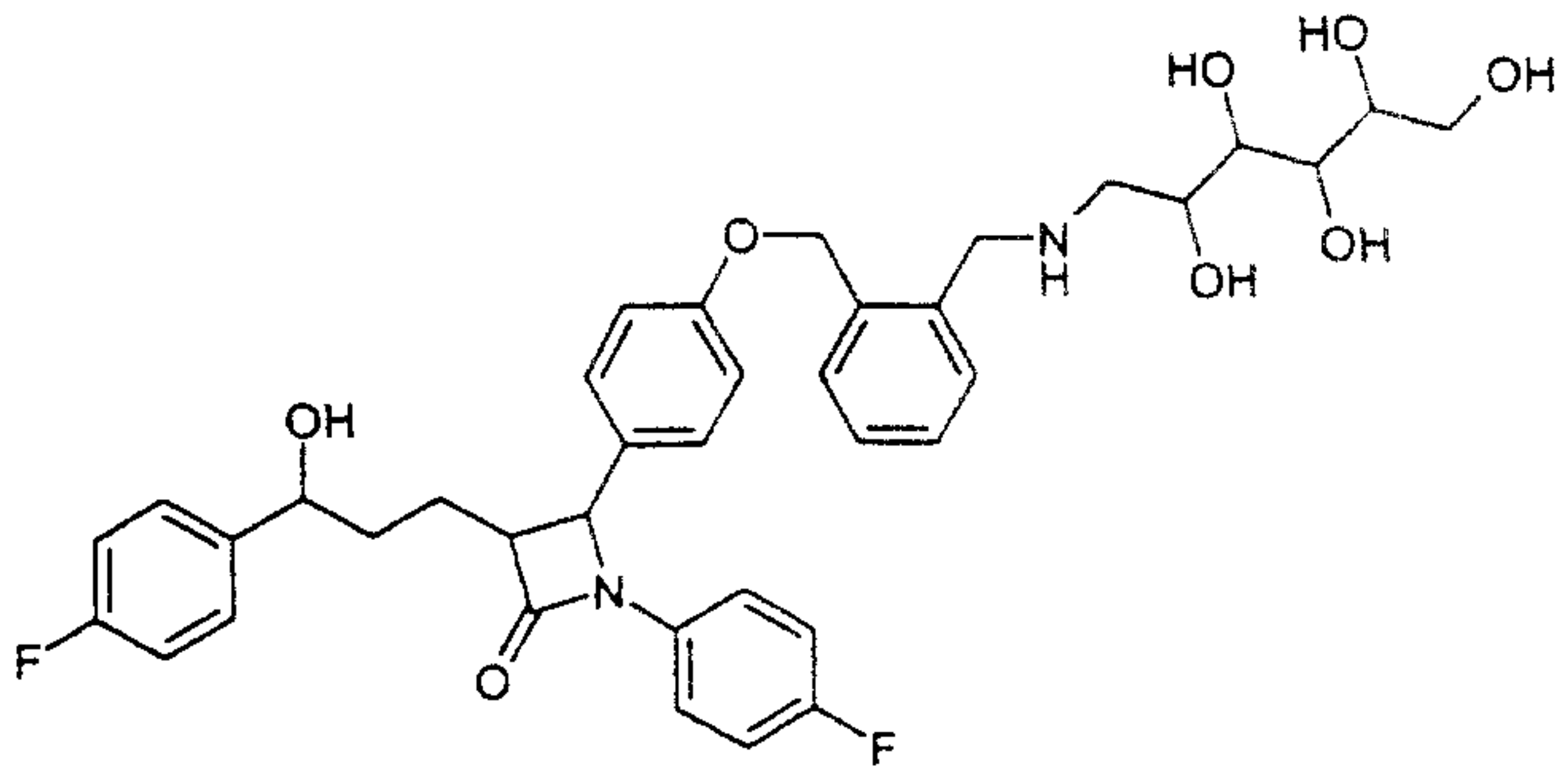
1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-azetidin-2-one (11) is reacted with 1,2-bisbromomethylbenzene and potassium carbonate analogously to Example IV, giving a colorless solid (15) of molecular weight 592.49 ($C_{32}H_{28}BrF_2NO_3$); MS (ESI): 592.2 (MH^+).

b) 1-[4-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2- yl}phenoxymethyl)benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (16):

(15) and DABCO are dissolved in toluene and reacted analogously to Example IV, giving the product (16) as a colorless solid of molecular weight 704.66 ($C_{38}H_{40}BrF_2N_3O_3$); MS (ESI): 624.30 (MH^+).

Example VII

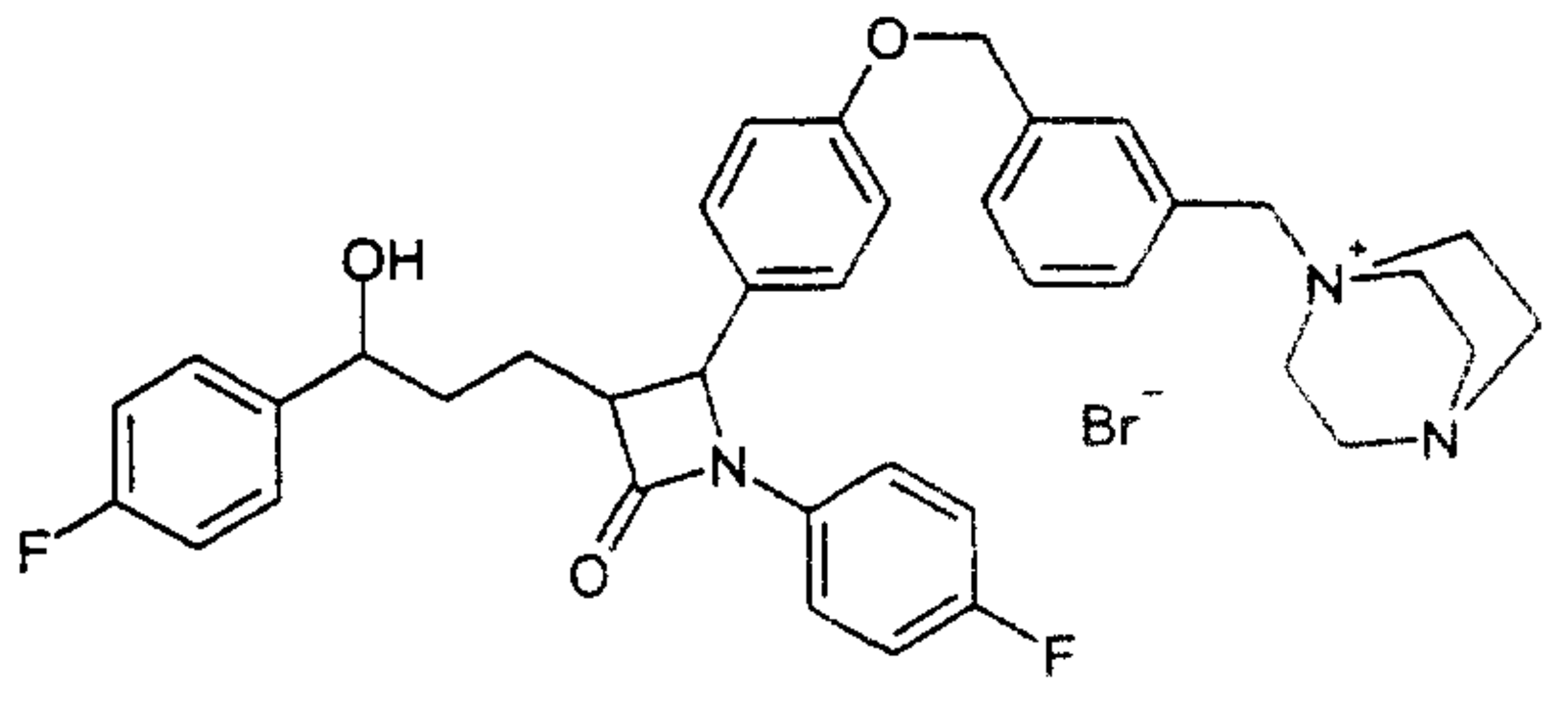
1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{2-[(2,3,4,5,6-pentahydroxyhexylamine)methyl]benzyloxy}phenyl)azetidin-2-one (17):



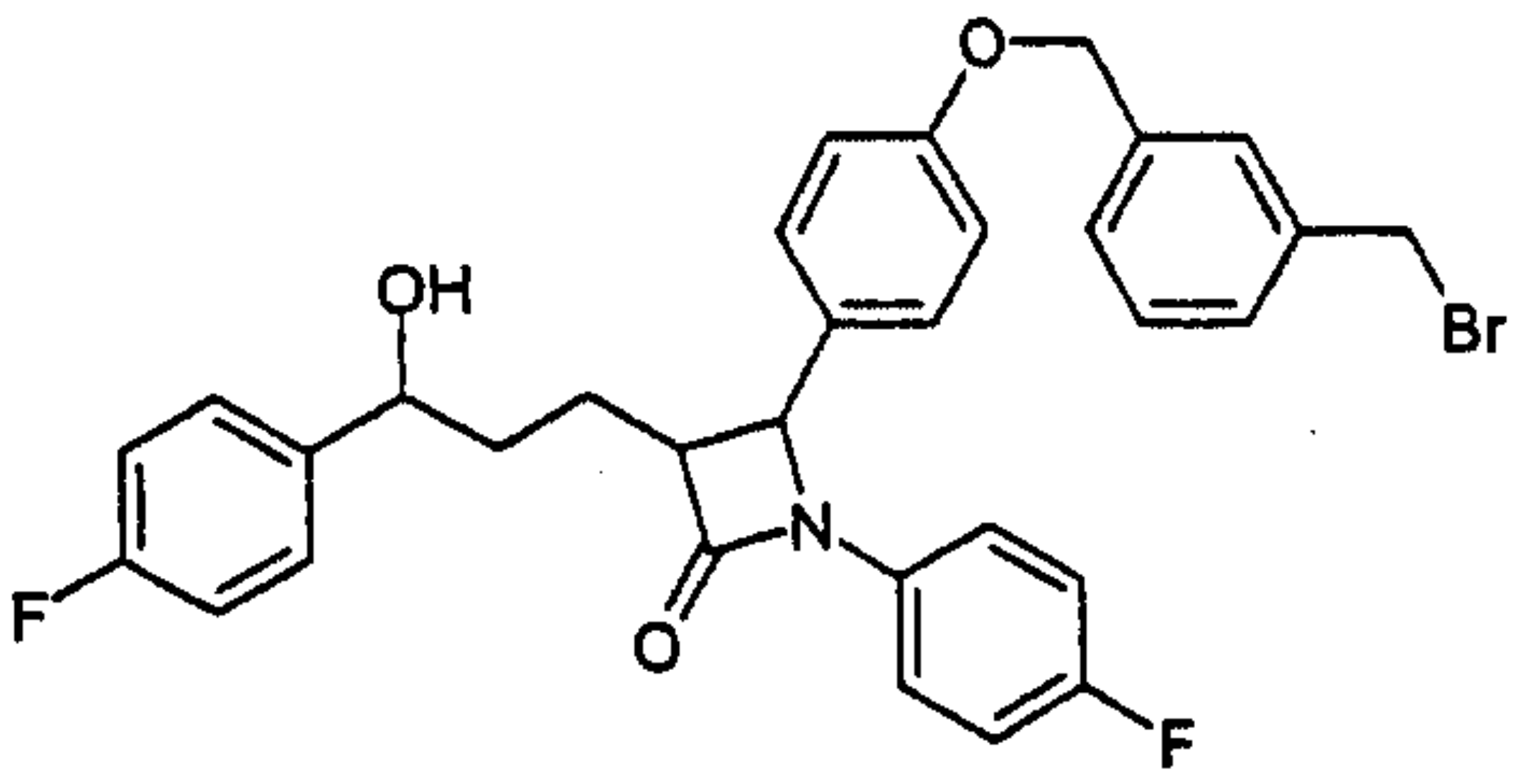
(15) and glucamine are dissolved in dimethylformamide and reacted analogously to Example V, giving the product (17) as a colorless solid of molecular weight 692.76 ($C_{38}H_{42}F_2N_2O_8$); MS (ESI): 693.5 (MH^+).

Example VIII

1-[3-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxymethyl)benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (19):



a) 4-[4-(3-Bromomethylbenzyloxy)phenyl]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3- hydroxypropyl]azetidin-2-one (18):



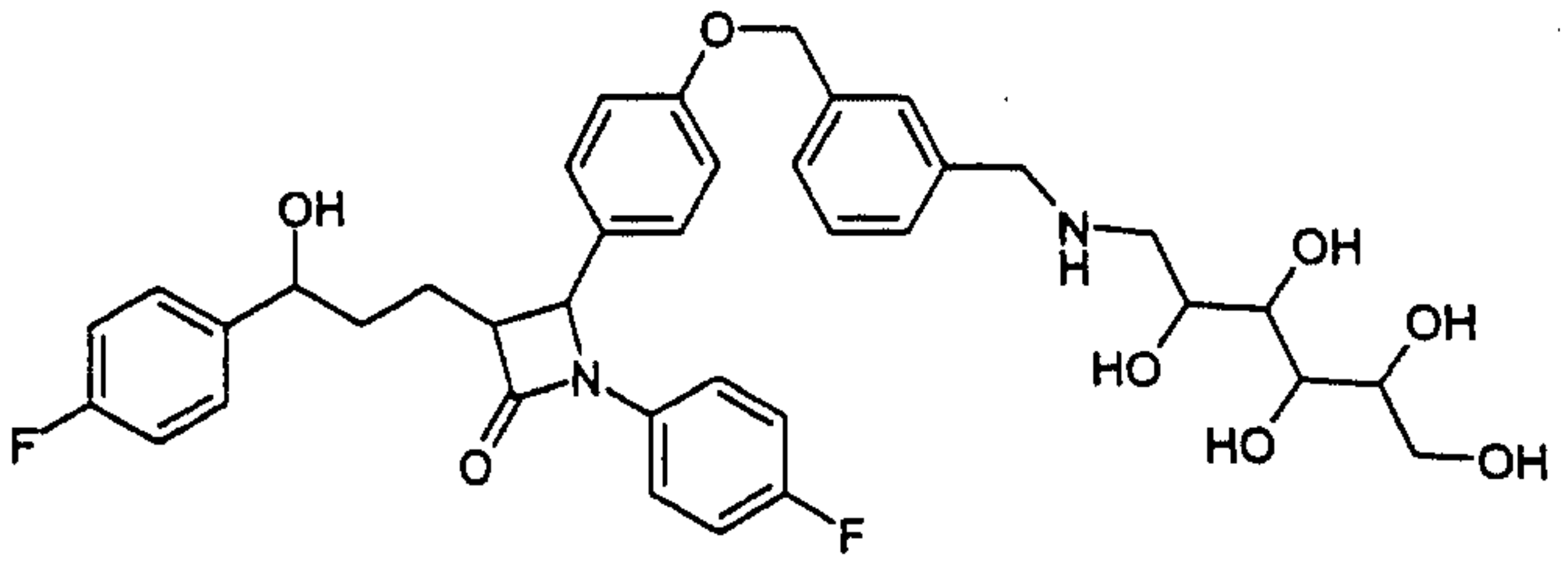
1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one (11) is reacted with 1,3-bisbromomethylbenzene and potassium carbonate analogously to Example IV, giving a colorless solid (18) of molecular weight 592.49 ($C_{32}H_{28}BrF_2NO_3$); MS (ESI): 592.2 (MH^+).

b) 1-[3-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2- yl}phenoxymethyl)benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (19):

(18) and DABCO are dissolved in toluene and reacted analogously to Example IV, giving the product (19) as a colorless solid of molecular weight 704.66 ($C_{38}H_{40}BrF_2N_3O_3$); MS (ESI): 624.30 (MH^+).

Example IX

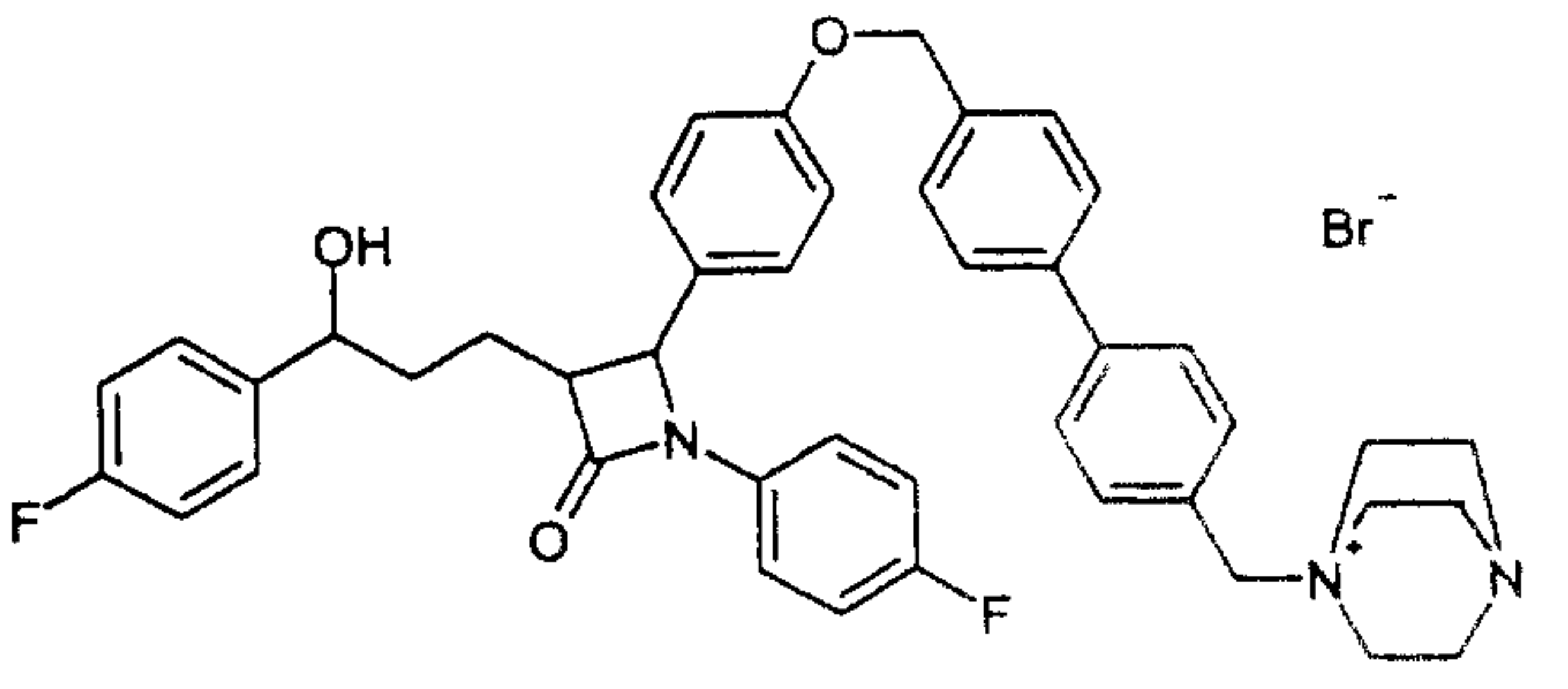
1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{3-[(2,3,4,5,6-pentahydroxyhexylamine)methyl]benzyloxy}phenyl)azetidin-2-one (20):



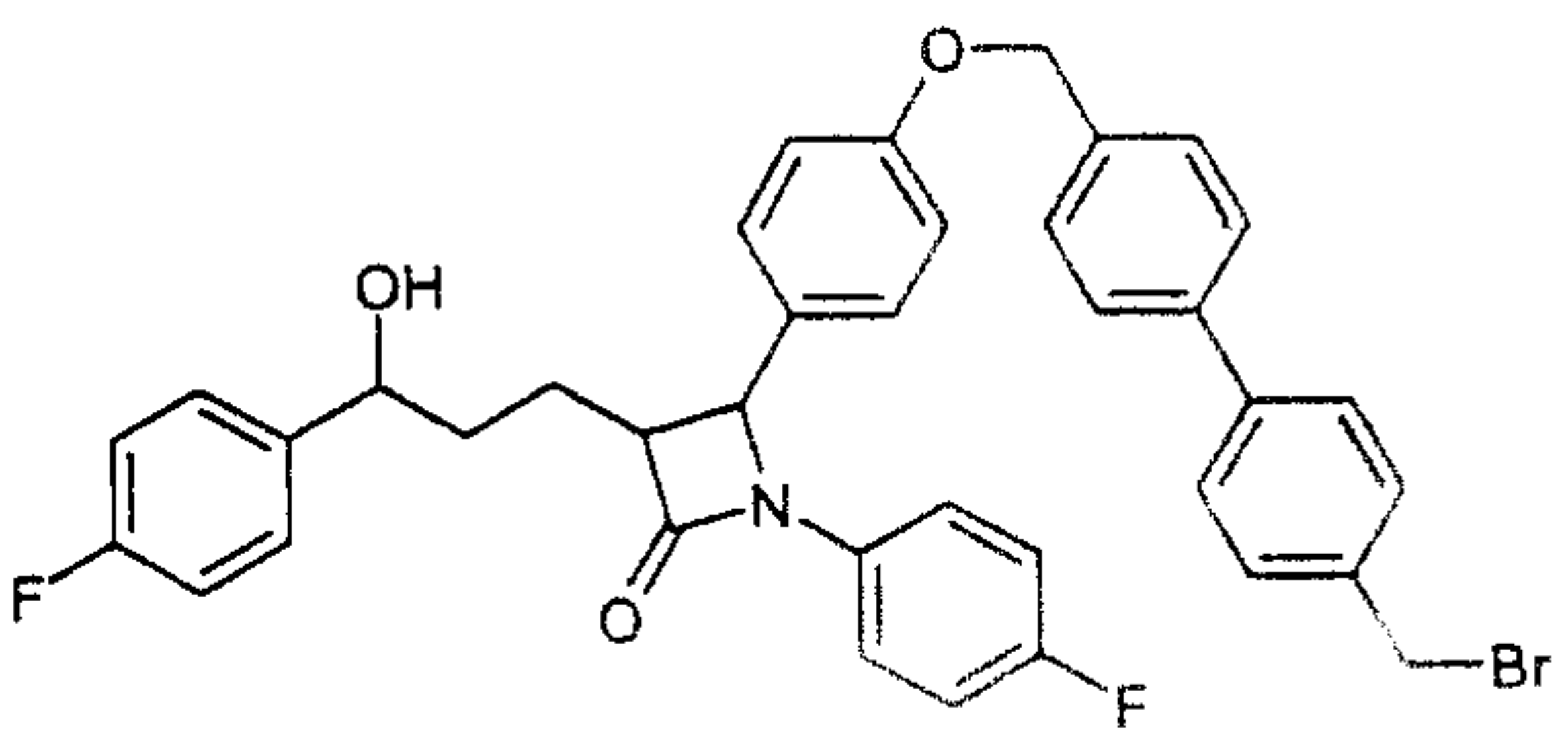
(18) and glucamine are dissolved in dimethylformamide and reacted analogously to Example V, giving the product (20) as a colorless solid of molecular weight 692.76 ($C_{38}H_{42}F_2N_2O_8$); MS (ESI): 693.5 (MH^+).

Example X

1-[4'-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenoxymethyl)biphenyl-4-ylmethyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (22):



a) 4-[4-(4'-Bromomethylbiphenyl-4-ylmethoxy)phenyl]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (21):



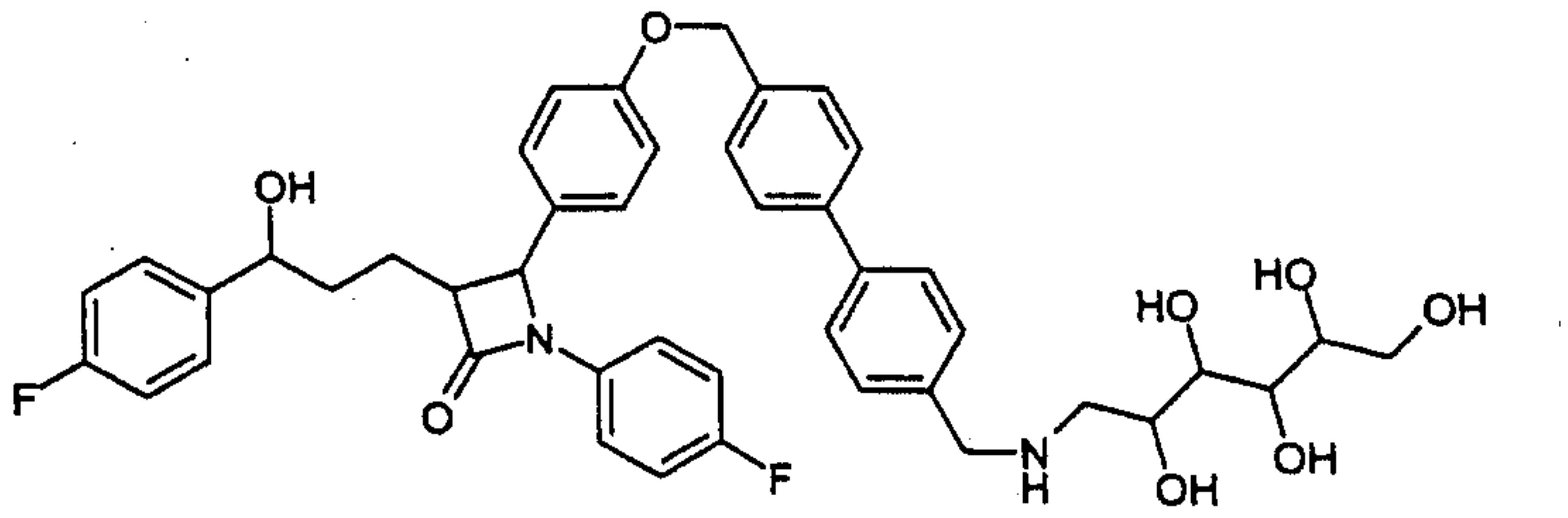
1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-azetidin-2-one (11) is reacted with 4,4'-bisbromomethylbiphenyl and potassium carbonate analogously to Example IV, giving a colorless solid (21) of molecular weight 668.54 ($C_{38}H_{32}BrF_2NO_3$); MS (ESI): 668.1 (MH^+).

b) 1-[4'-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2- yl}phenoxymethyl)biphenyl-4-ylmethyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (22):

(21) and DABCO are dissolved in toluene and reacted analogously to Example IV, giving the product (22) as a colorless solid of molecular weight 780.76 ($C_{44}H_{44}BrF_2N_3O_3$); MS (ESI): 700.3 (MH^+).

Example XI

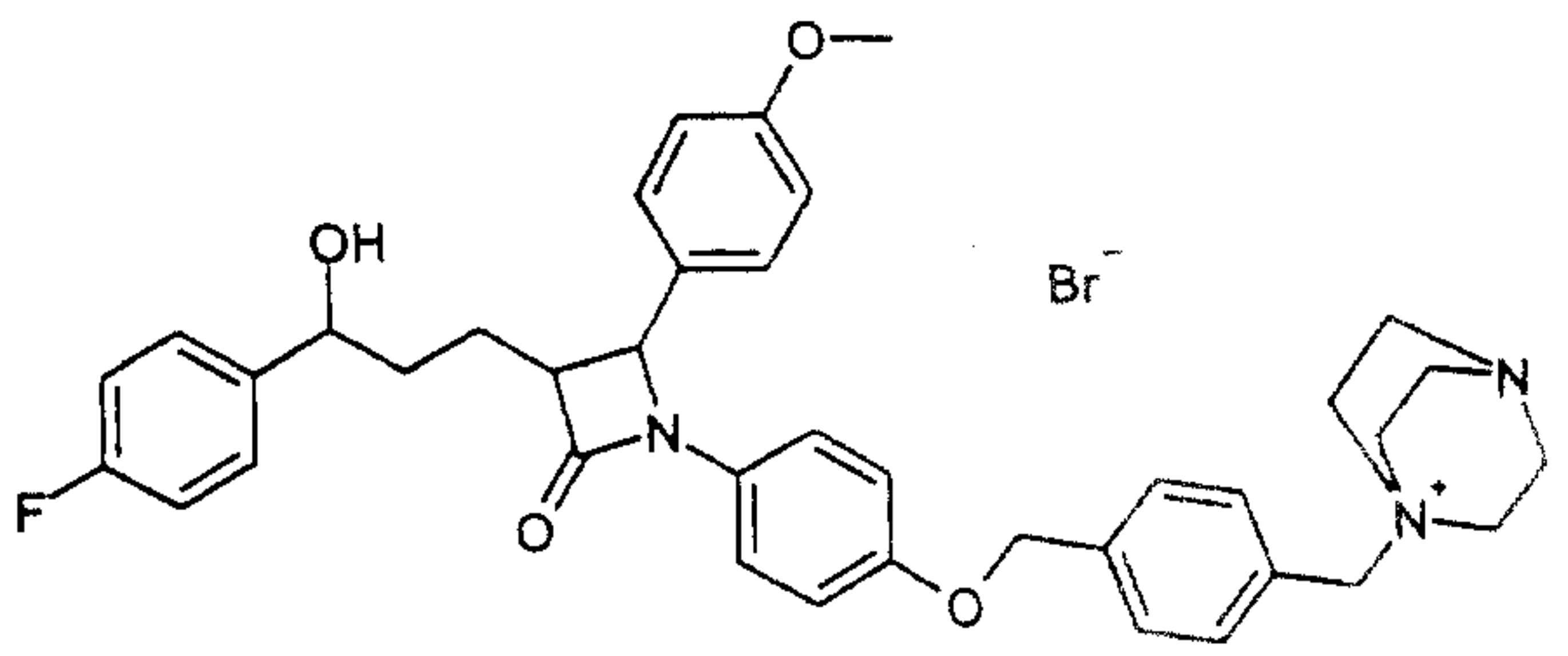
1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{4'-[(2,3,4,5,6-pentahydroxyhexylamine)-methyl]-biphenyl-4-ylmethoxy}-phenyl)-azetidin-2-one (23):



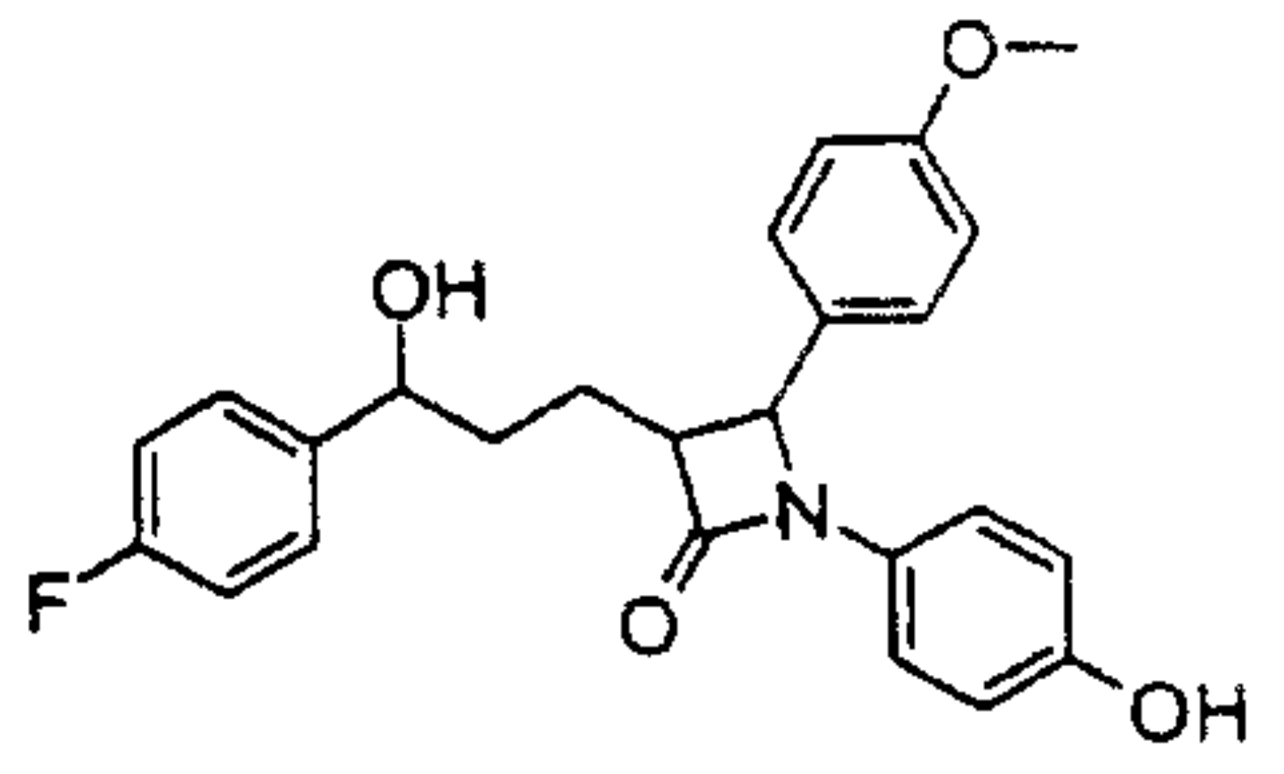
(21) and glucamine are dissolved in dimethylformamide and reacted analogously to Example V giving the product (23) as a colorless solid of molecular weight 768.86 ($C_{44}H_{46}F_2N_2O_8$); MS (ESI): 769.3 (MH^+).

Example XII

1-(4-{4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-phenoxymethyl}-benzyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide (26):

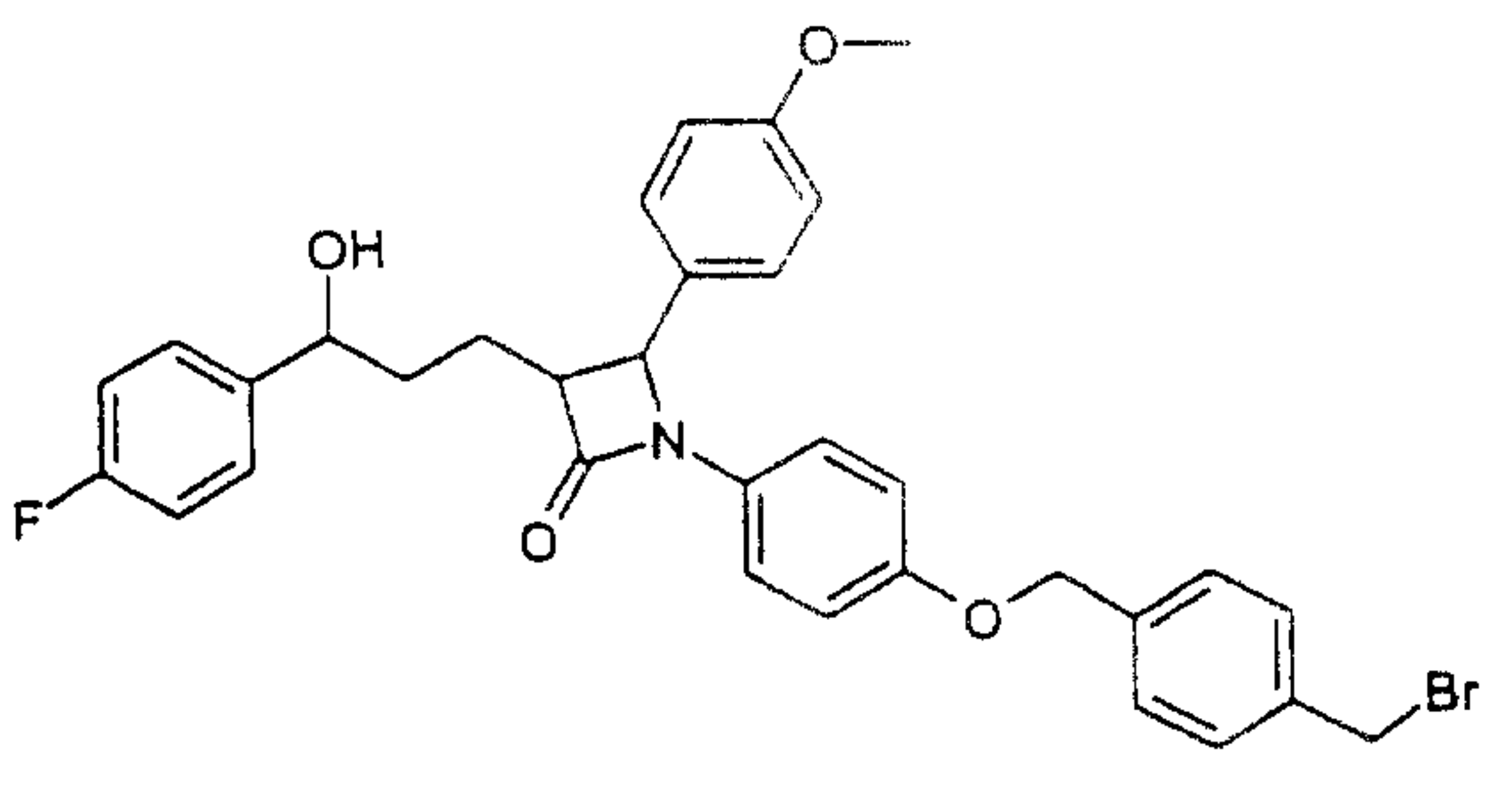


a) 3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-1-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-azetidin-2-one (24):



This compound is prepared as described above for 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-methoxyphenyl)-azetidin-2-one (steps a, b, c, and d), except that 4-[(4-methoxybenzylidene)-amino]-phenol is used. This gives 3-[3-(4-fluorophenyl)-3-hydroxypropyl]-1-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-azetidin-2-one (24) of molecular weight 421.47 ($C_{25}H_{24}FNO_4$); MS (ESI): 422.2 (MH^+).

b) 1-[4-(4-bromomethylbenzyloxy)-phenyl]-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-methoxyphenyl)-azetidin-2-one (25):



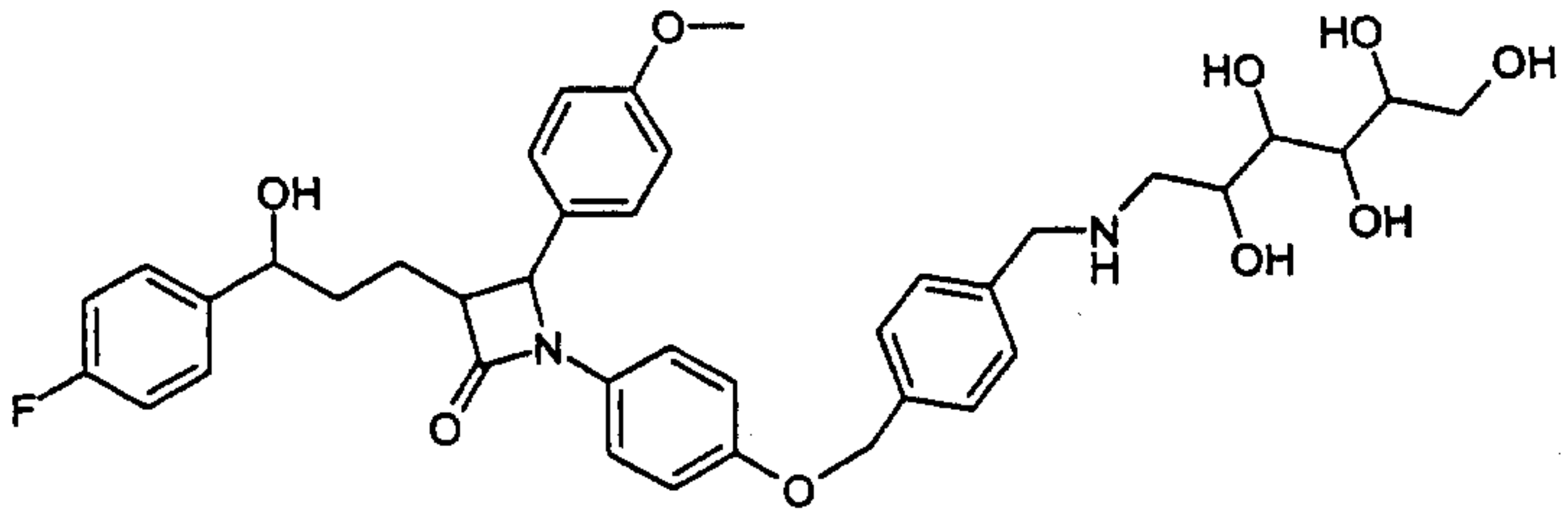
3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-1-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-azetidin-2-one is reacted with 1,4-bisbromomethylbenzene and potassium carbonate analogously to Example IV, giving a colorless solid (25) of molecular weight 604.52 ($C_{33}H_{31}BrFNO_4$); MS (ESI): 605.2 (MH^+).

c) 1-(4-{4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-phenoxymethyl}-benzyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide (26):

(25) and DABCO are dissolved in toluene and reacted analogously to Example IV, giving the product (26) as a colorless solid of molecular weight 716.70 ($C_{39}H_{43}BrFN_3O_4$); MS (ESI): 636.3 (MH^+).

Example XIII

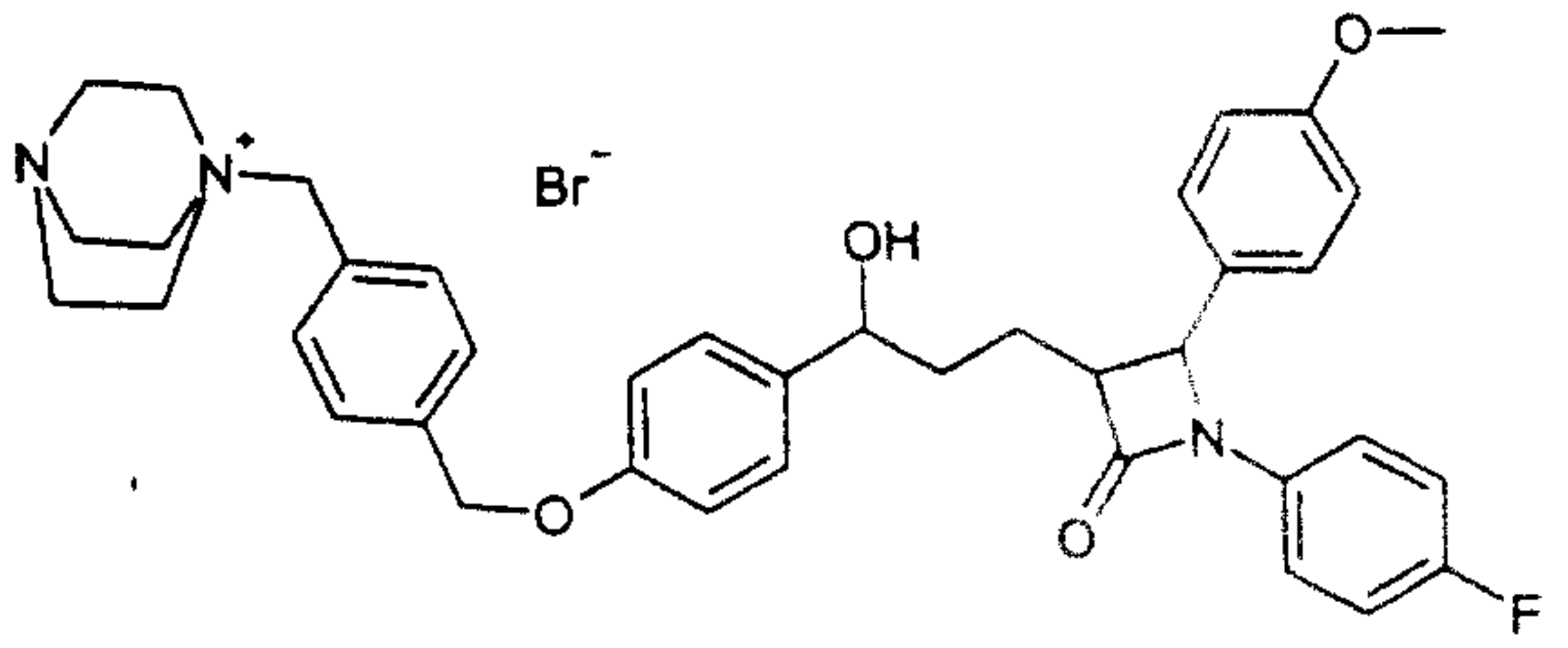
3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-4-(4-methoxyphenyl)-1-(4-{4-[(2,3,4,5,6-pentahydroxyhexylamine)-methyl]-benzyloxy}-phenyl)-azetidin-2-one (27):



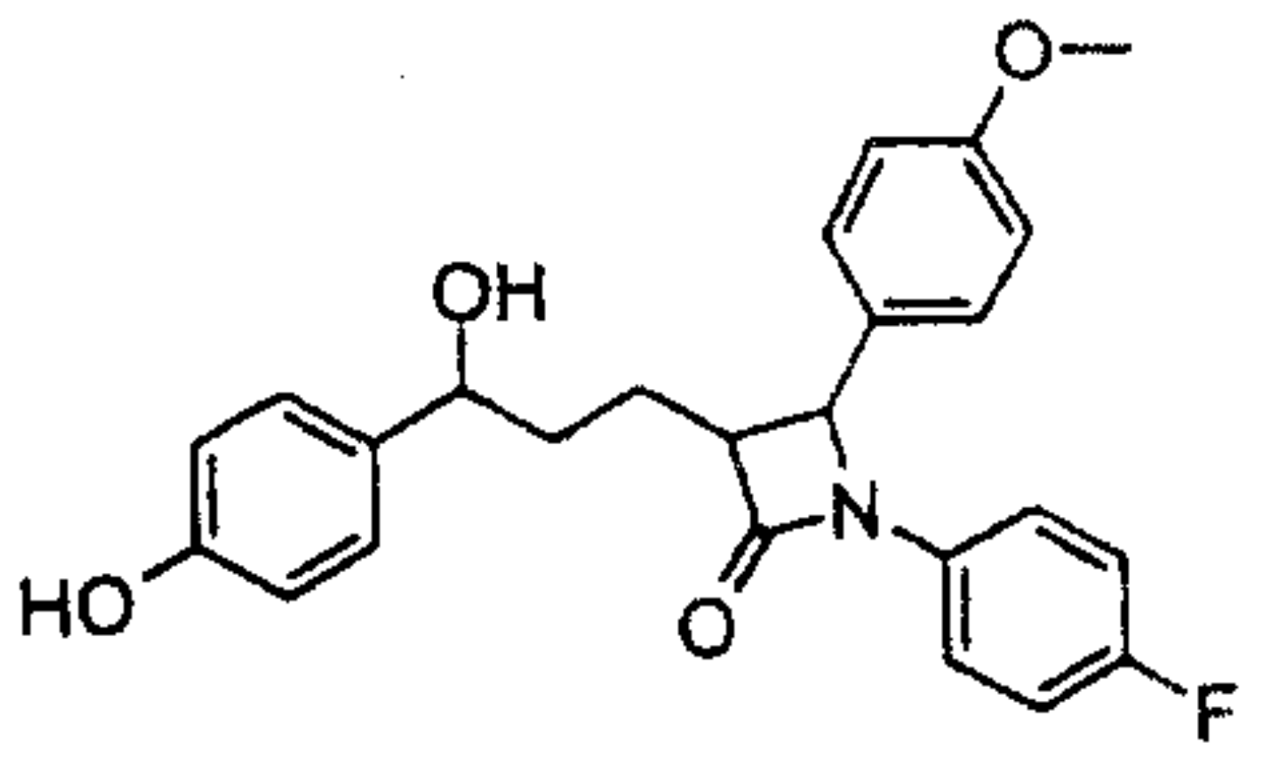
(25) and glucamine are dissolved in dimethylformamide and reacted analogously to Example V, giving the product (27) as a colorless solid of molecular weight 704.80 ($C_{39}H_{45}FN_2O_9$); MS (ESI): 705.31 (MH^+).

Example XIV

1-[4-(4-{3-[1-(4-Fluorophenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl]-1-hydroxypropyl}-phenoxymethyl)-benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (30):

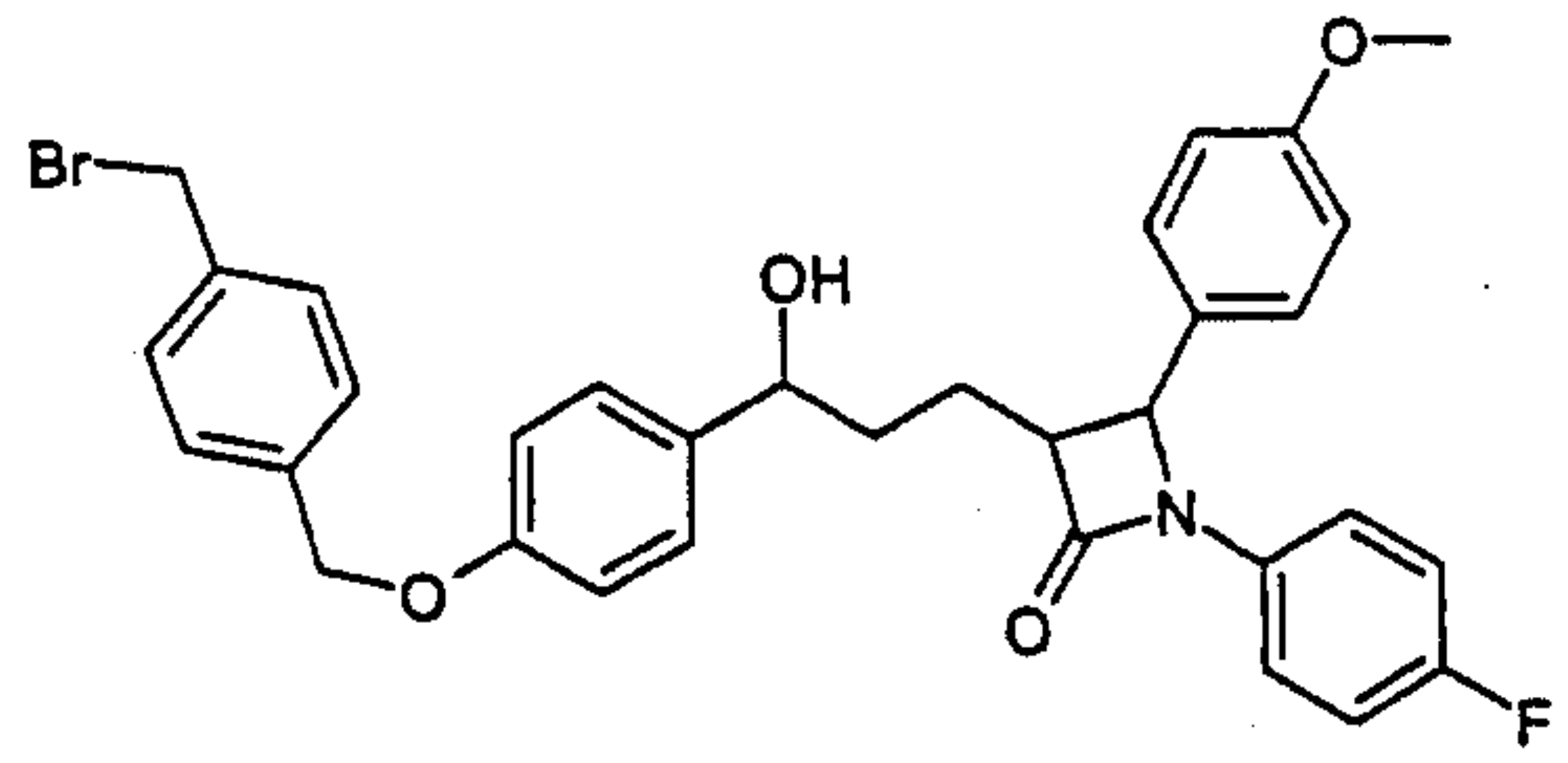


a) 1-(4-Fluorophenyl)-3-[3-hydroxy-3-(4-hydroxyphenyl)-propyl]-4-(4-methoxyphenyl)-azetidin-2-one (28):



This compound is prepared as described above for 1-(4-aminomethylphenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-methoxyphenyl)-azetidin-2-one, except that 3-[5-(4-hydroxyphenyl)-5-hydroxypentanoyl]-4-phenyloxazolidin-2-one and (4-fluorophenyl)-(4-methoxybenzylidene)-amine are used. This gives 1-(4-fluorophenyl)-3-[3-hydroxy-3-(4-hydroxyphenyl)-propyl]-4-(4-methoxyphenyl)-azetidin-2-one (28) of molecular weight 421.47 ($C_{25}H_{24}FNO_4$); MS (ESI): 422.2 (MH^+).

b) 3-{3-[4-(4-Bromomethylbenzyloxy)-phenyl]-3-hydroxypropyl}-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-azetidin-2-one (29):



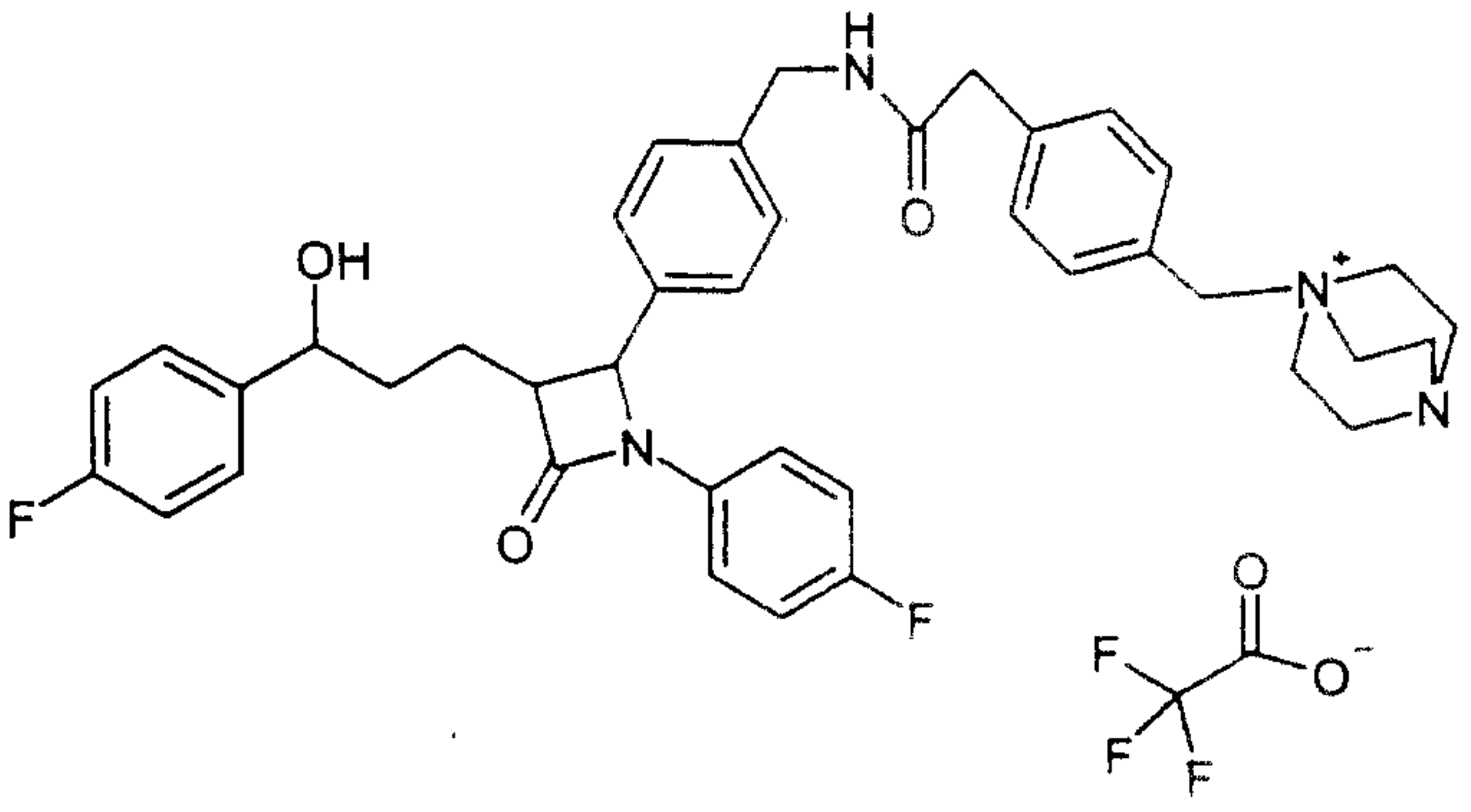
1-(4-Fluorophenyl)-3-[3-hydroxy-3-(4-hydroxyphenyl)-propyl]-4-(4-methoxyphenyl)-azetidin-2-one is reacted with 1,4-bisbromomethylbenzene and potassium carbonate analogously to Example IV, giving a colorless solid (29) of molecular weight 604.52 ($C_{33}H_{31}BrFNO_4$); MS (ESI): 605.2 (MH^+).

c) 1-[4-(4-{3-[1-(4-Fluorophenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl]-1-hydroxypropyl}-phenoxymethyl)-benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane bromide (30):

(29) and DABCO are dissolved in toluene and reacted analogously to Example IV, giving the product (30) as a colorless solid of molecular weight 716.70 ($C_{39}H_{43}BrFN_3O_4$); MS (ESI): 636.3 (MH^+).

Example XV

1-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (35):



a) 1-(4-Carboxymethylbenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide (31):

At 70°C, 1.0 g of (3-bromomethylphenyl) acetic acid in 5 ml of dimethyl sulfoxide are added to a solution of 1.5 g of 1,4-diazabicyclo[2.2.2]octane in 10 ml of dimethyl sulfoxide. 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 261.35 (cation: $C_{15}H_{21}N_2O_2^+$); MS (ESI) 261.1 (M^+).

b) 4-[5-(4-Fluorophenyl)-1-(4-fluorophenylamino)-5-hydroxy-2-(2-oxo-4-phenyloxazolidine-3-carbonyl)-pentyl]-benzonitrile (32):

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 ($M+H^+-Si(CH_3)_3$).

c) {1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzonitrile (33):

2 g of 4-[5-(4-Fluorophenyl)-1-(4-fluorophenylamino)-5-hydroxy-2-(2-oxo-4-phenyl-oxazolidine-3-carbonyl)-pentyl]-benzonitrile 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 ($M+H^+$).

d) 4-(4-Aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one (34):

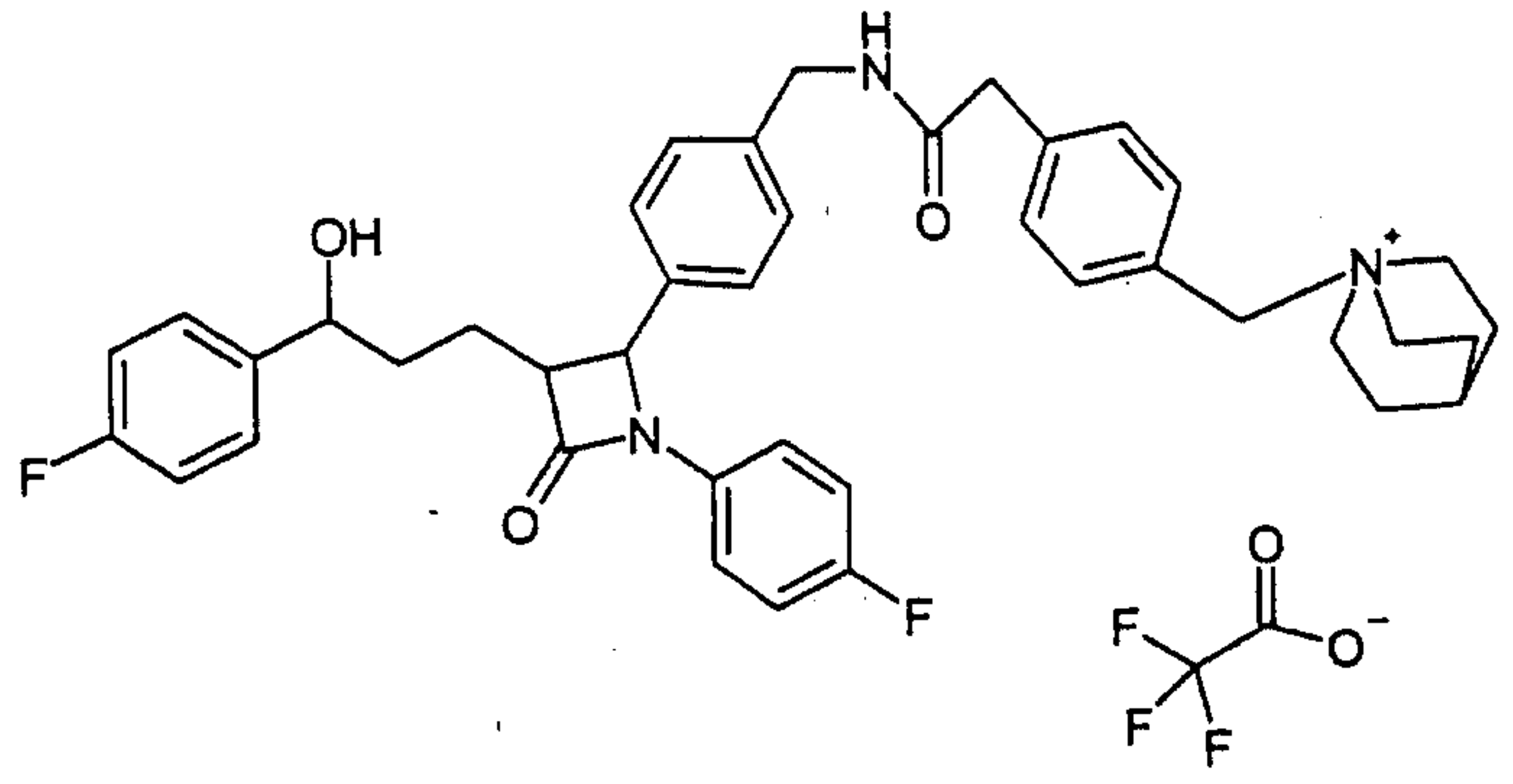
200 mg of {1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzonitrile are dissolved in 20 ml of ethanol and, with 0.5 ml of conc. ammonia, hydrogenated over Raney nickel at a hydrogen pressure of 75 bar and at 25°C for 30 hours. The catalyst is filtered off with suction, 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 ($M+H^+ - H_2O$).

e) 1-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-4-aza-1-azonia-bicyclo[2.2.2]octane; trifluoroacetate (35):

A solution of 70 mg 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 84 mg of 1-(4-carboxymethylbenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide, 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 665.81 (cation: $C_{40}H_{43}F_2N_4O_3$); MS (ESI) 665.33 (M^+).

Example XVI

1-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-1-azoniabicyclo[2.2.2]octane trifluoroacetate (37):



a) 1-(4-Carboxymethylbenzyl)-1-azoniabicyclo[2.2.2]octane bromide (36):

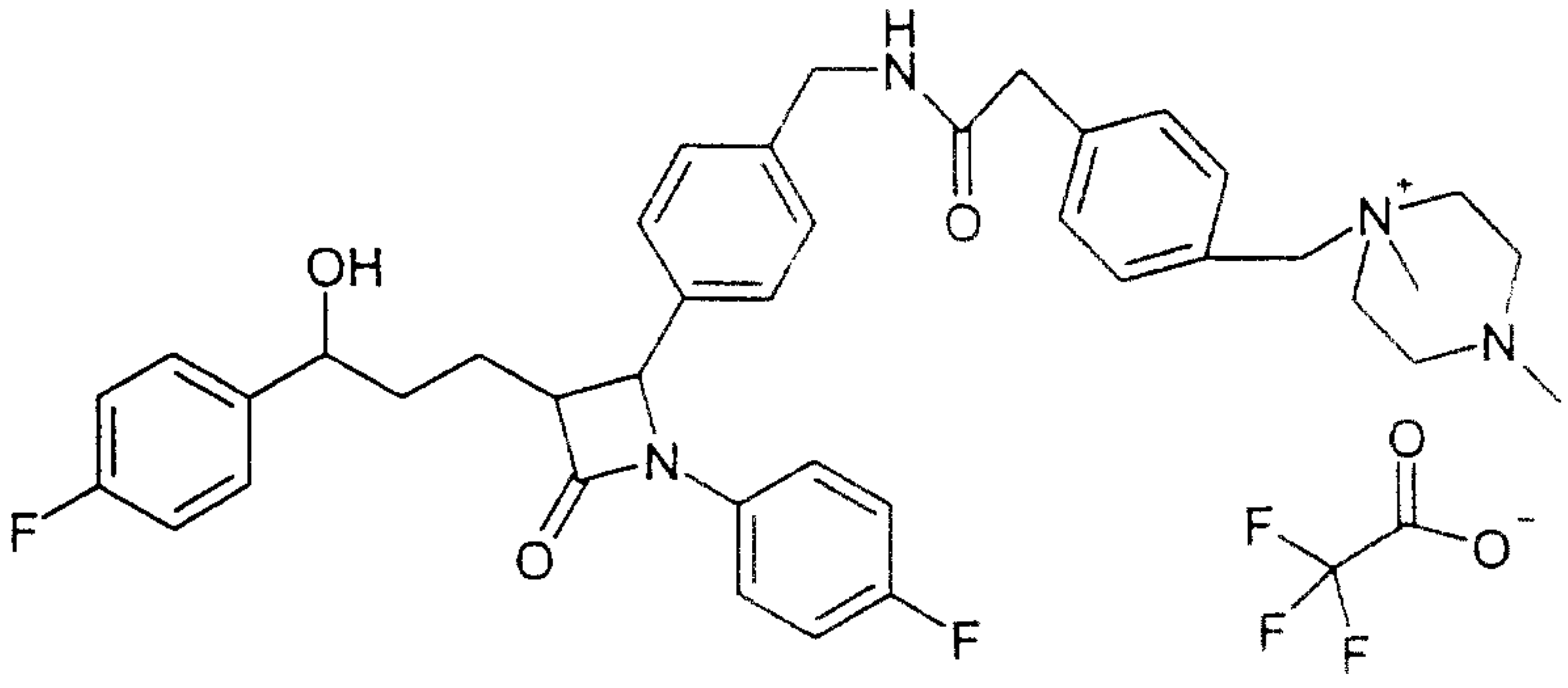
The synthesis is carried out analogously to Example XVa) starting with 1.67 g of 1-azabicyclo[2.2.2]octane. This gives the product of molecular weight 260.36 (cation: $C_{16}H_{22}N_1O_2^+$); MS (ESI) 260.1 (M^+).

b) 1-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-1-azoniabicyclo[2.2.2]octane trifluoroacetate (37):

The synthesis is carried out analogously to Example XVe) starting with 70 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one and 85 mg of 1-(4-carboxymethylbenzyl)-1-azoniabicyclo[2.2.2]octane bromide. This gives the product of molecular weight 664.82 (cation: $C_{41}H_{44}F_2N_3O_3^+$); MS (ESI) 664.33 (M^+).

Example XVII

1-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-1,4-dimethylpiperazin-1-ium trifluoroacetate (39):



a) 1-(4-Carboxymethylbenzyl)-1,4-dimethylpiperazin-1-ium bromide (38):

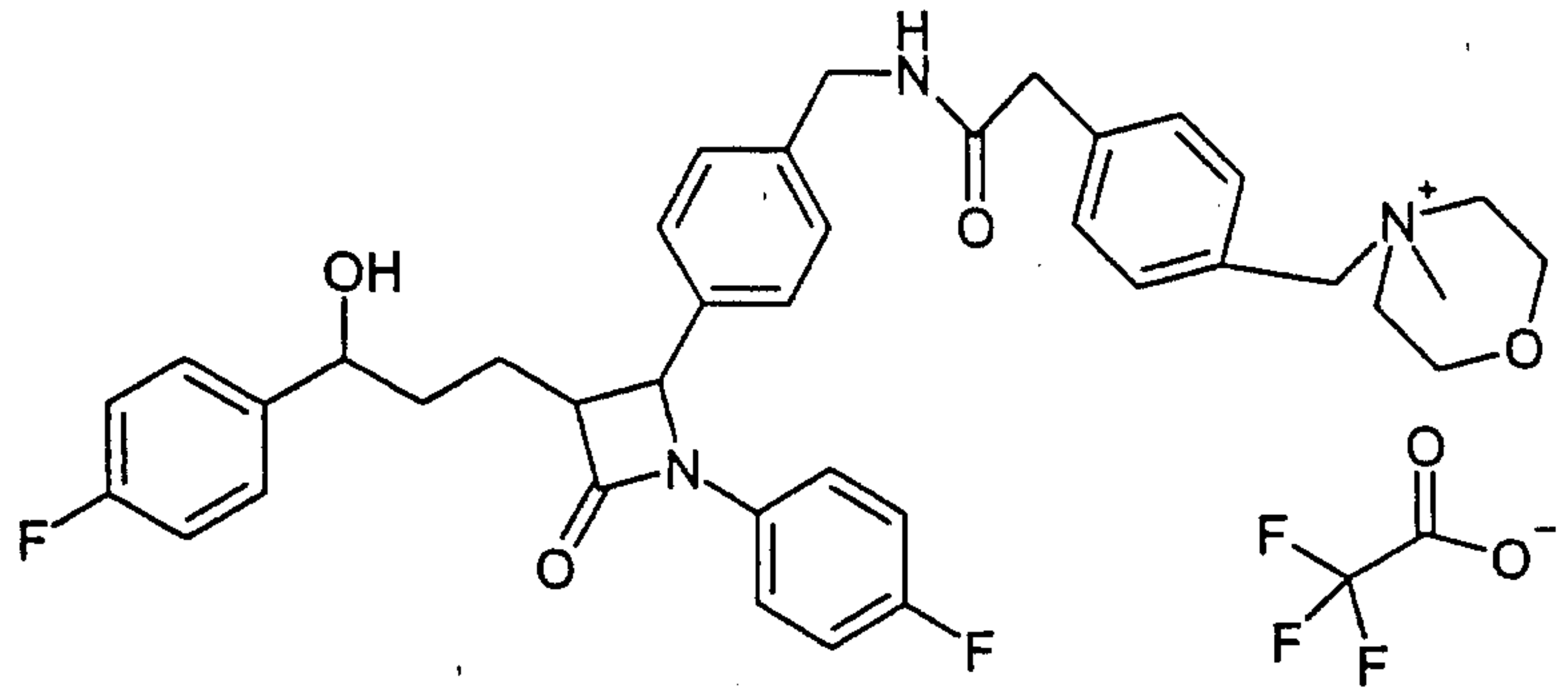
The synthesis is carried out analogously to Example XVa) starting with 1.02 ml of 1,4-dimethylpiperazine. This gives the product of molecular weight 263.36 (cation: $C_{15}H_{23}N_2O_2^+$); MS (ESI) 263.1 (M^+).

b) 1-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-1,4-dimethyl-piperazin-1-ium trifluoroacetate (39):

The synthesis is carried out analogously to Example XVe) starting with 70 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one and 86 mg of 1-(4-carboxymethylbenzyl)-1,4-dimethylpiperazin-1-ium bromide. This gives the product of molecular weight 667.82 (cation: $C_{40}H_{45}F_2N_4O_3^+$); MS (ESI) 667.34 (M^+).

Example XVIII

4-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-4-methylmorpholin-4-ium trifluoroacetate (41):



a) 4-(4-Carboxymethylbenzyl)-4-methylmorpholin-4-ium bromide (40):

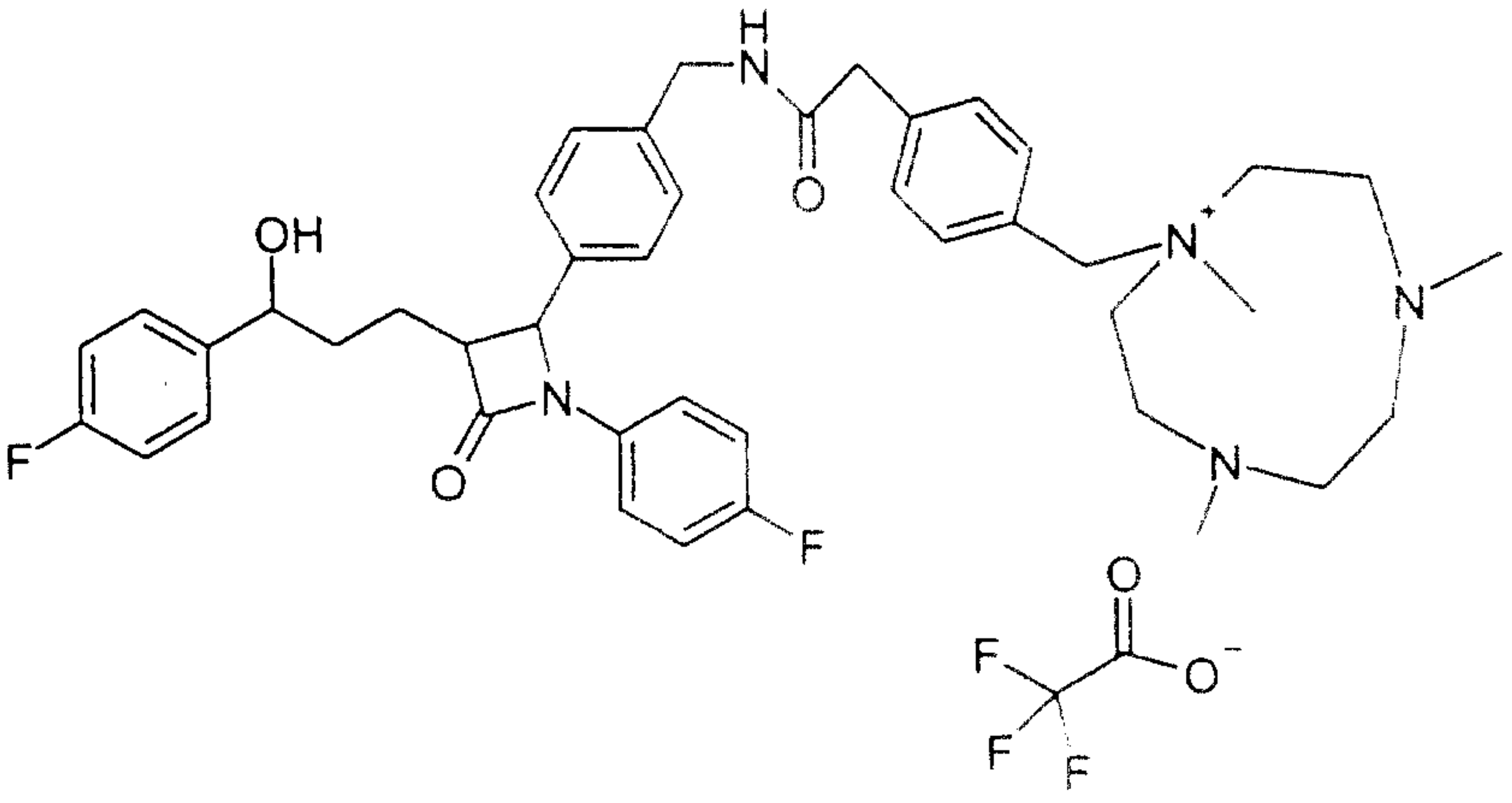
The synthesis is carried out analogously to Example XVa) starting with 1.65 ml of N-methylmorpholine. This gives the product of molecular weight 250.32 (cation: $C_{14}H_{20}N_1O_3^+$); MS (ESI) 250.1 (M^+).

b) 4-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-4-methylmorpholin-4-ium trifluoroacetate (41):

The synthesis is carried out analogously to Example XVe) starting 70 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one and 82 mg of 4-(4-carboxymethylbenzyl)-4-methylmorpholin-4-ium bromide. This gives the product of molecular weight 654.78 (cation: $C_{39}H_{42}F_2N_3O_4^+$); MS (ESI) 654.31 (M^+).

Example XIX

1-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-1,4,7-trimethyl-[1,4,7]triazonan-1-ium trifluoroacetate (43):



a) 1,4,7-Trimethyl-1-[4-(2-oxopropyl)-benzyl]-[1,4,7]triazonan-1-ium bromide (42):

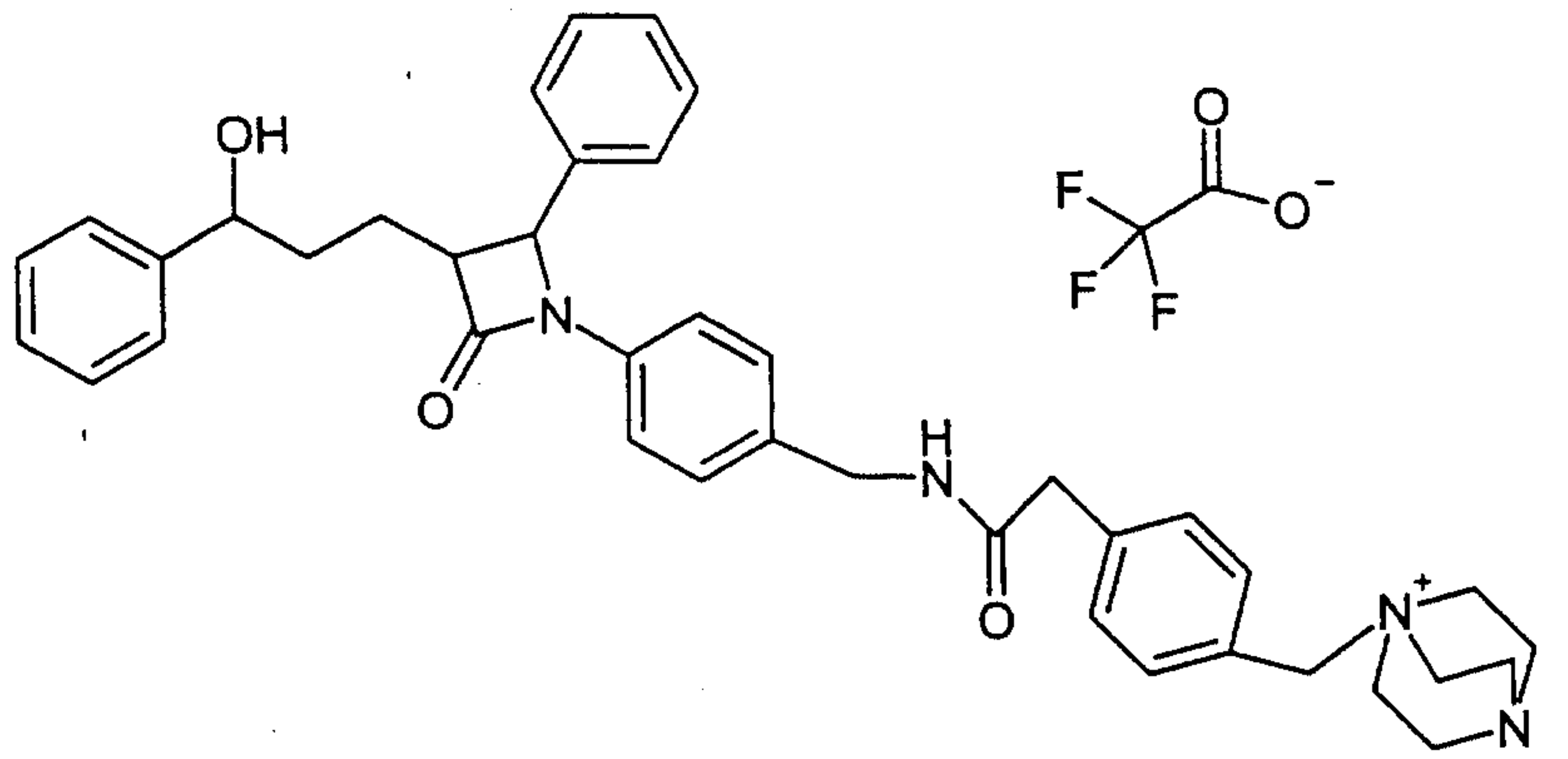
The synthesis is carried out analogously to Example XVa) starting with 500 mg of 1,4,7-trimethyl-[1,4,7]triazonane. This gives the product of molecular weight 321.47 (cation: $C_{18}H_{31}N_3O_2^+$); MS (ESI) 321.2 (M^+).

b) 1-{4-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzylcarbamoyl)-methyl]-benzyl}-1,4,7-trimethyl-[1,4,7]triazonan-1-ium trifluoroacetate (43):

The synthesis is carried out analogously to Example XVe) starting 70 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one and 200 mg of 1,4,7-trimethyl-1-[4-(2-oxopropyl)-benzyl]-[1,4,7]triazonan-1-ium bromide. This gives the product of molecular weight 724.92 (cation: $C_{40}H_{45}F_2N_4O_3^+$); MS (ESI) 724.40 (M^+).

Example XX

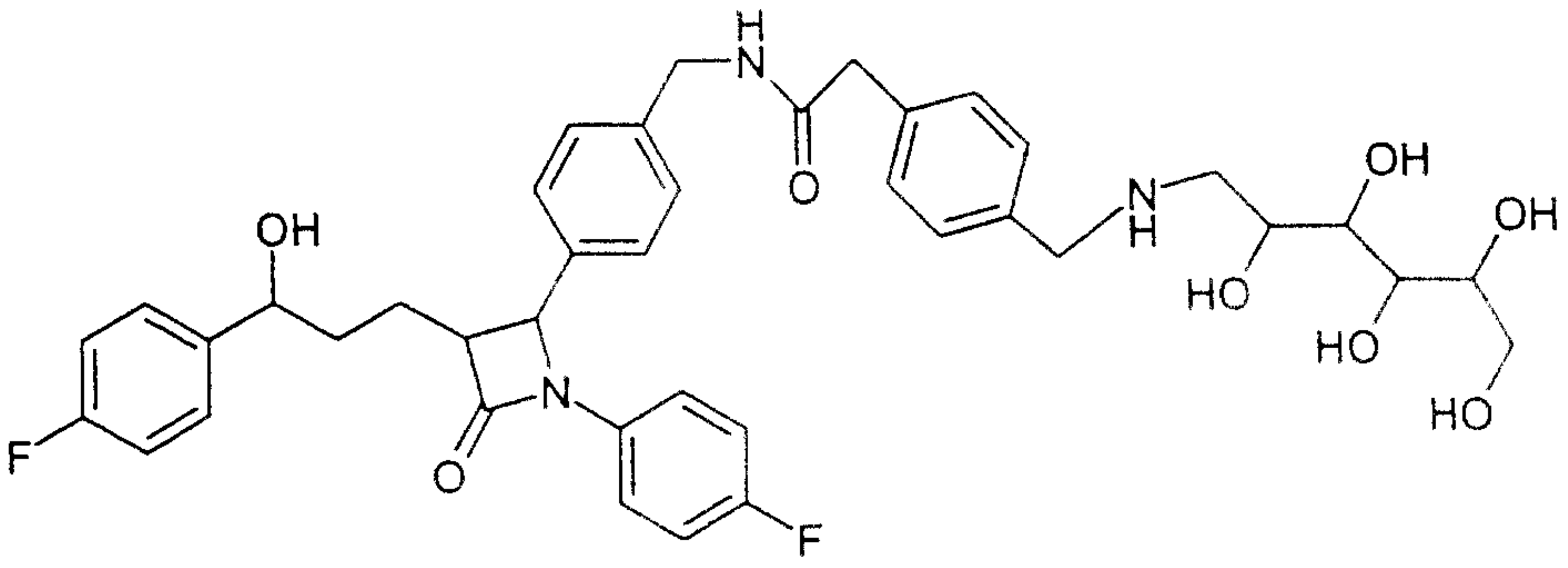
1-[4-({4-[3-(3-Hydroxy-3-phenylpropyl)-2-oxo-4-phenylazetidin-1-yl]-benzylcarbamoyl}-methyl)-benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane trifluoroacetate (44):



The synthesis is carried out analogously to Example XVe) starting 60 mg of 1-(4-aminomethylphenyl)-3-(3-hydroxy-3-phenylpropyl)-4-phenylazetidin-2-one (8) and 82 mg of 1-(4-carboxymethylbenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane bromide. This gives the product of molecular weight 629.83_(cation: $C_{40}H_{45}F_2N_4O_3^+$); MS (ESI) 629.35 (M^+).

Example XXI

N-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzyl)-2-{4-[(2,3,4,5,6-pentahydroxyhexylamino)-methyl]-phenyl}-acetamide (46):



a) {4-[(2,3,4,5,6-Pentahydroxyhexylamino)-methyl]-phenyl}-acetic acid (45):

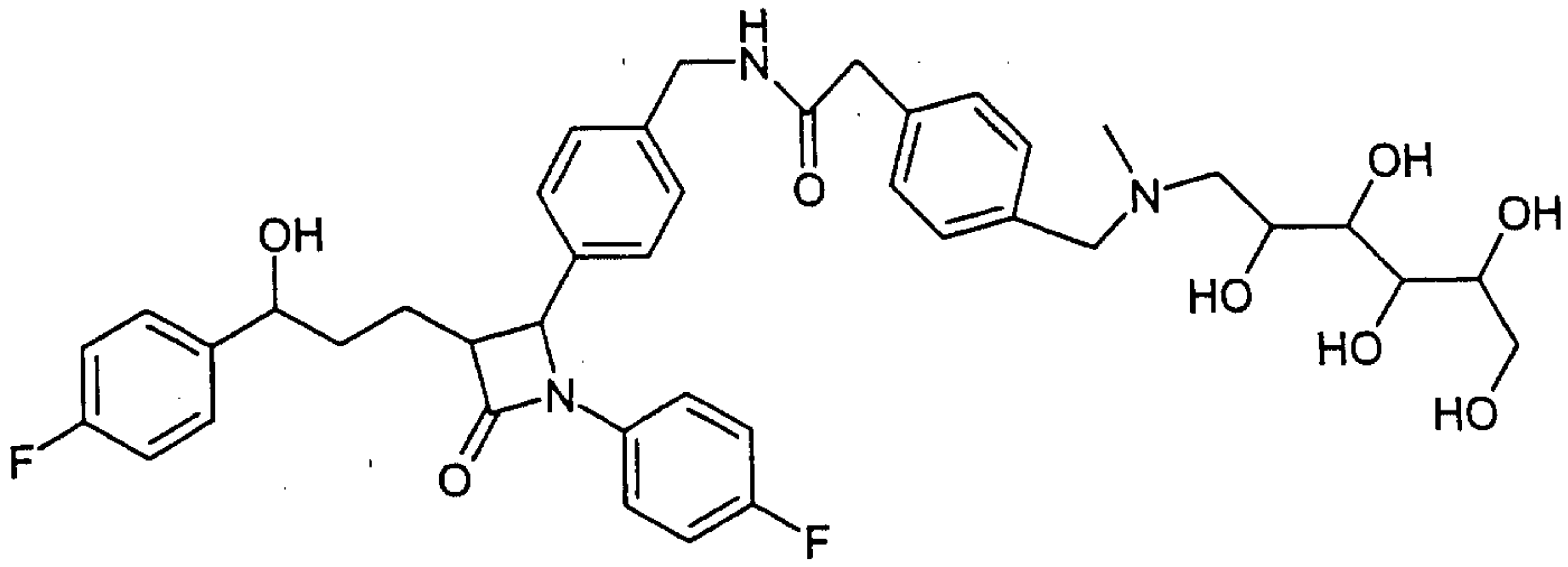
The synthesis is carried out analogously to Example XVa) starting with 989 mg of 6-aminohexane-1,2,3,4,5-pentaol. This gives the product of molecular weight 329.35 ($C_{15}H_{23}N_1O_7$); MS (ESI) 330.2 (M + H^+).

b) N-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzyl)-2-{4-[(2,3,4,5,6-pentahydroxyhexylamino)-methyl]-phenyl}-acetamide (46):

The synthesis is carried out analogously to Example XVe) starting 70 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one and 110 mg of {4-[(2,3,4,5,6-pentahydroxyhexylamino)-methyl]-phenyl}-acetic acid. This gives the product of molecular weight 733.82 ($C_{40}H_{45}F_2N_3O_8^+$); MS (ESI) 734.32 (M + H^+).

Example XXII

N-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzyl)-2-(4-{[methyl-(2,3,4,5,6-pentahydroxyhexyl)-amino]-methyl}-phenyl)-acetamide (48):



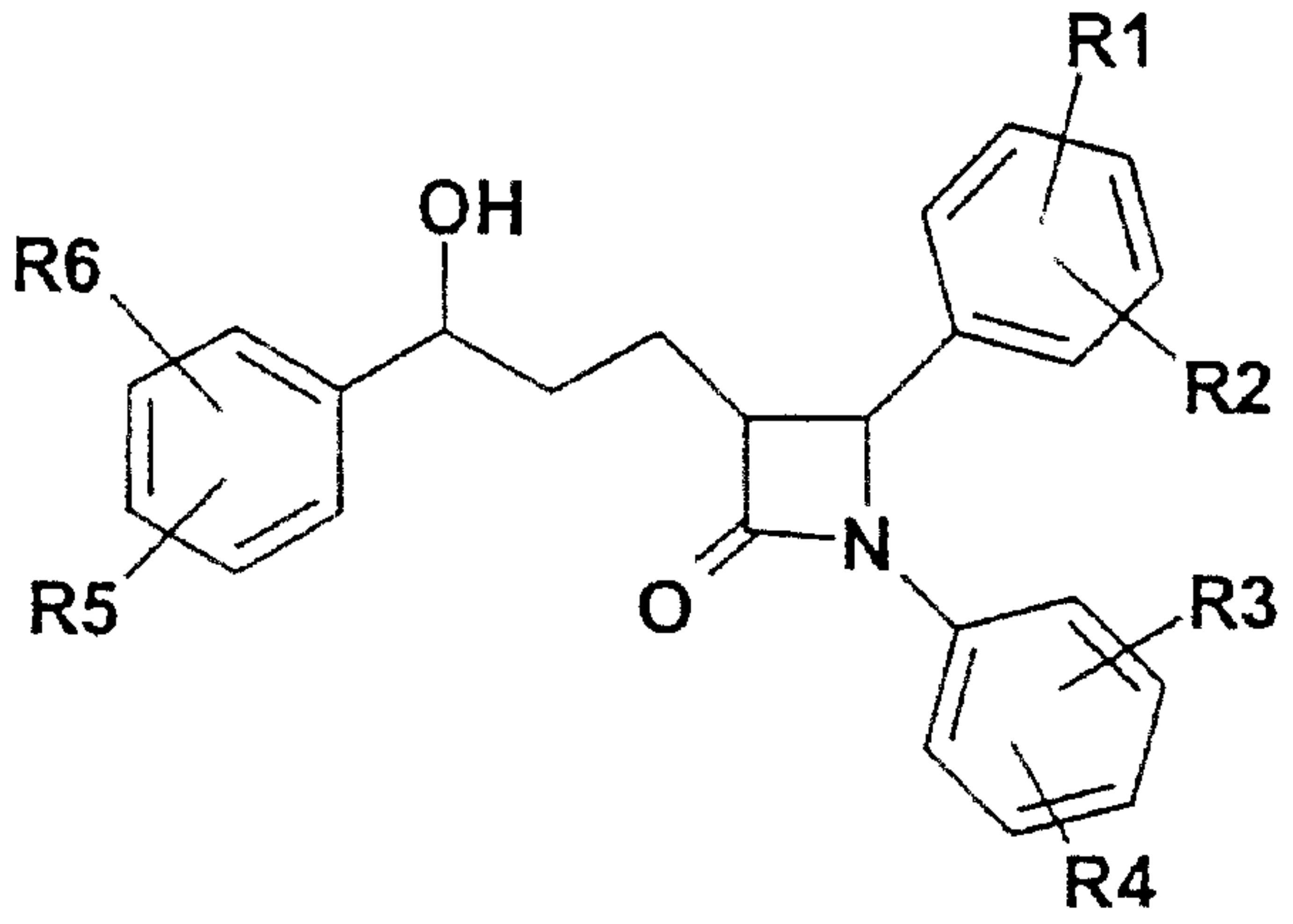
a) (4-{[Methyl-(2,3,4,5,6-pentahydroxyhexyl)-amino]-methyl}-phenyl)-acetic acid (47):

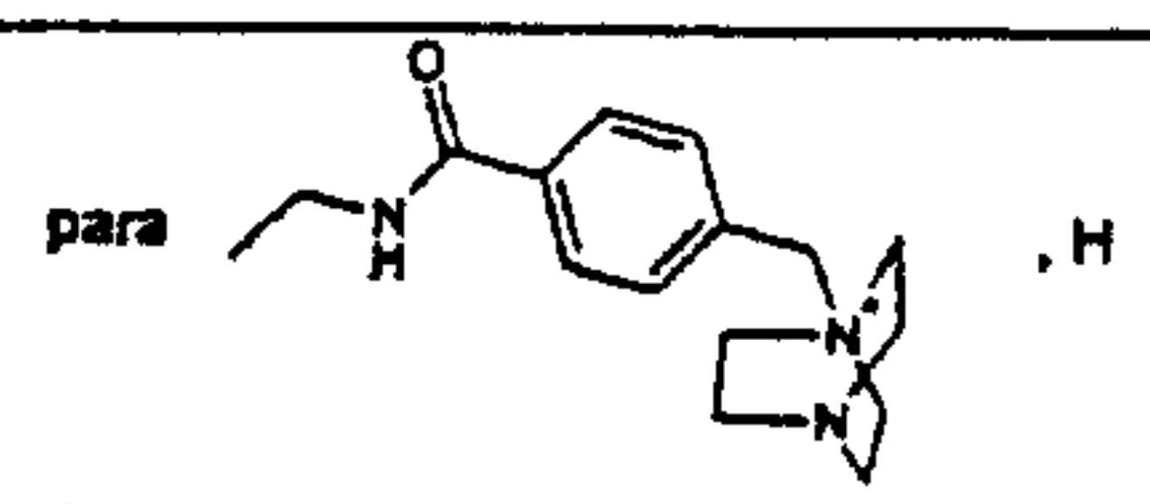
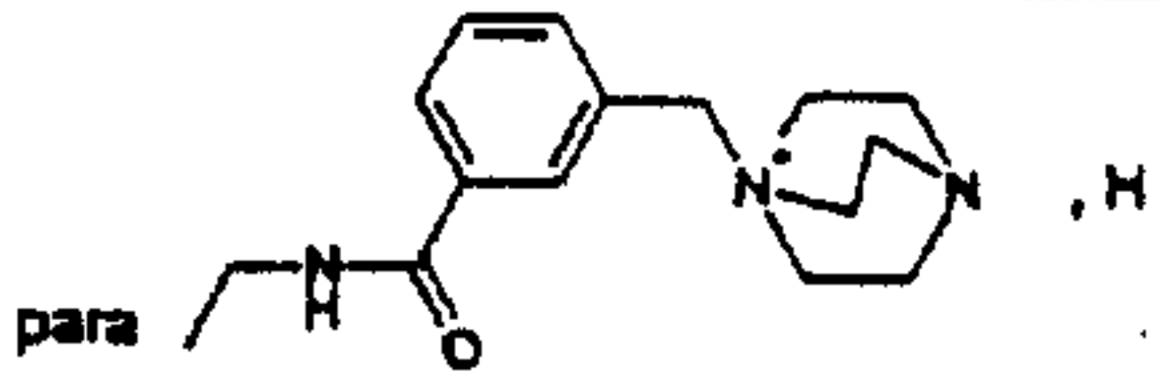
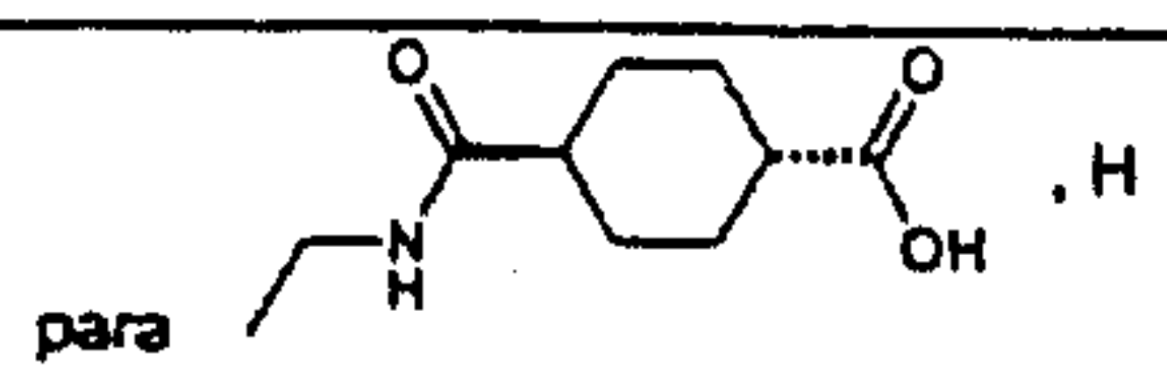
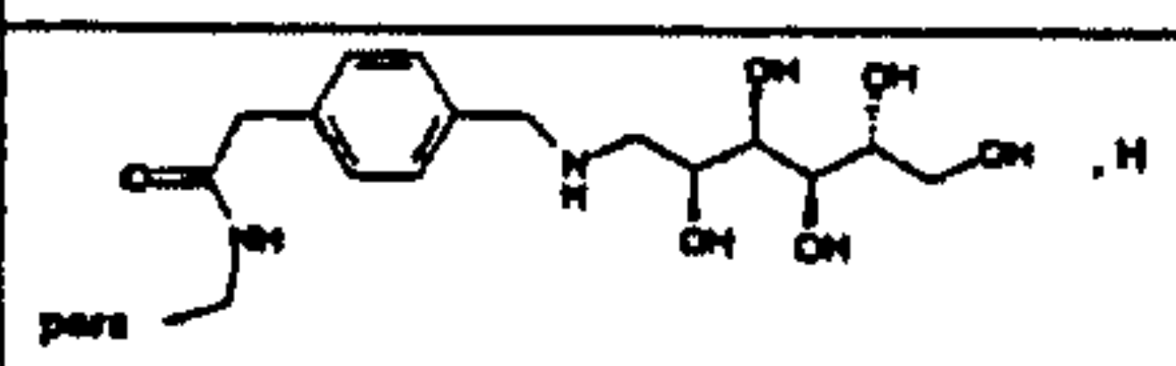
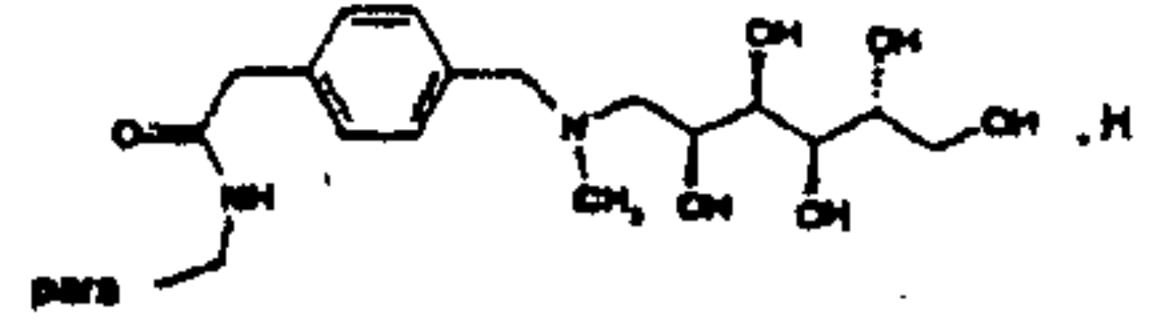
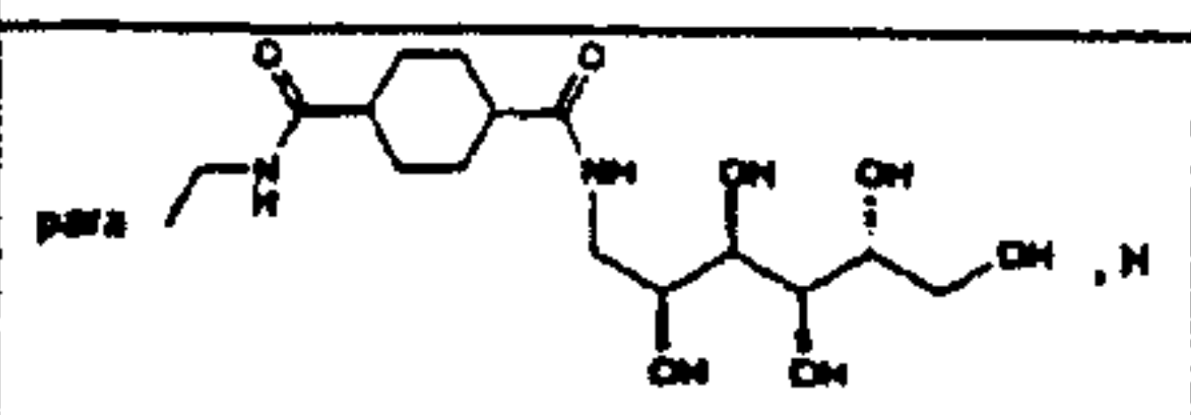
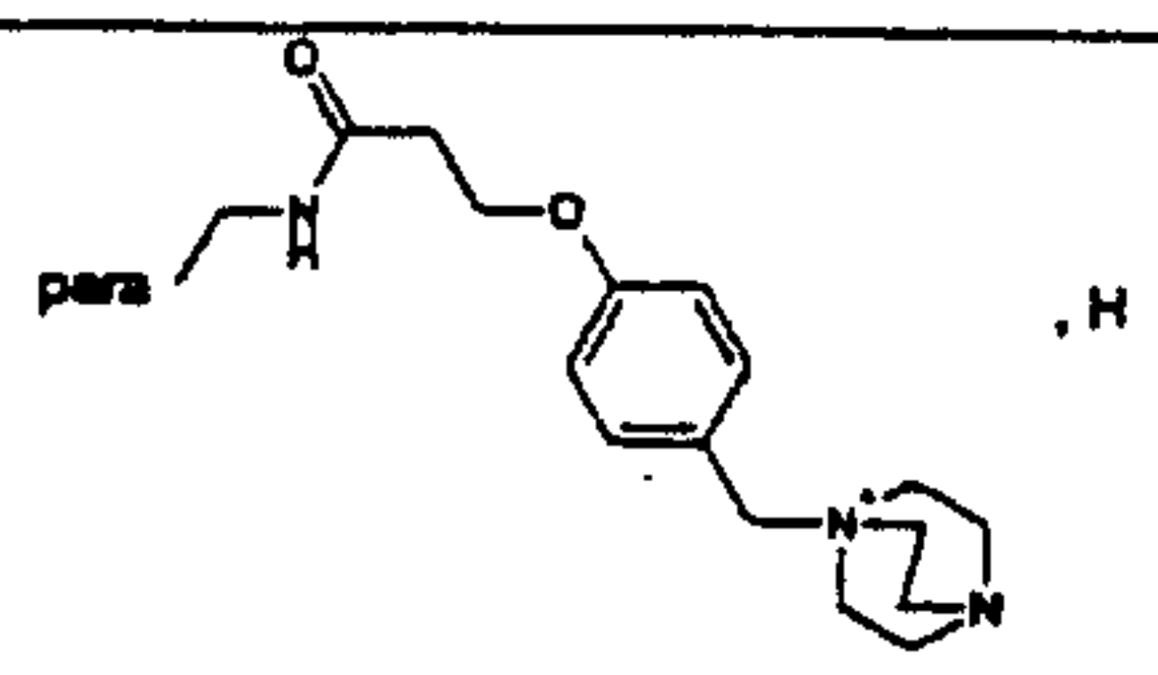
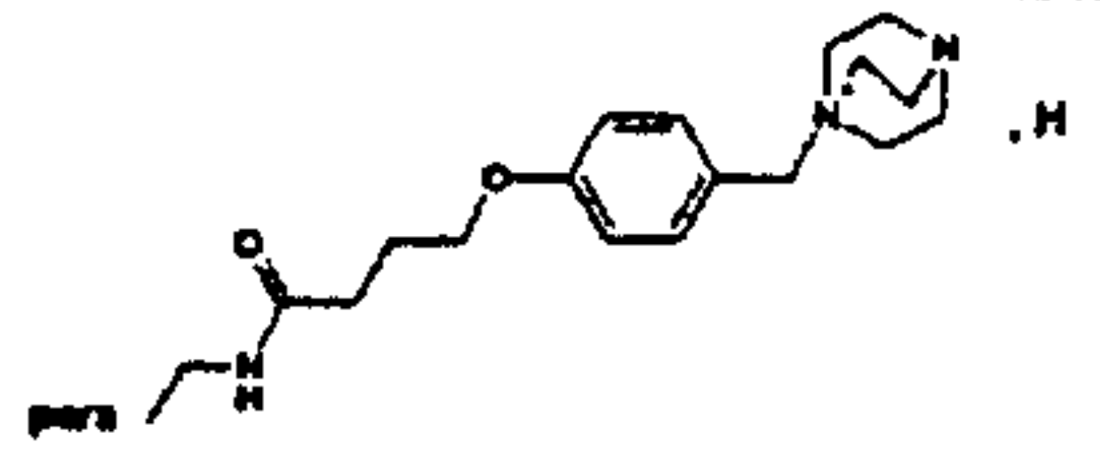
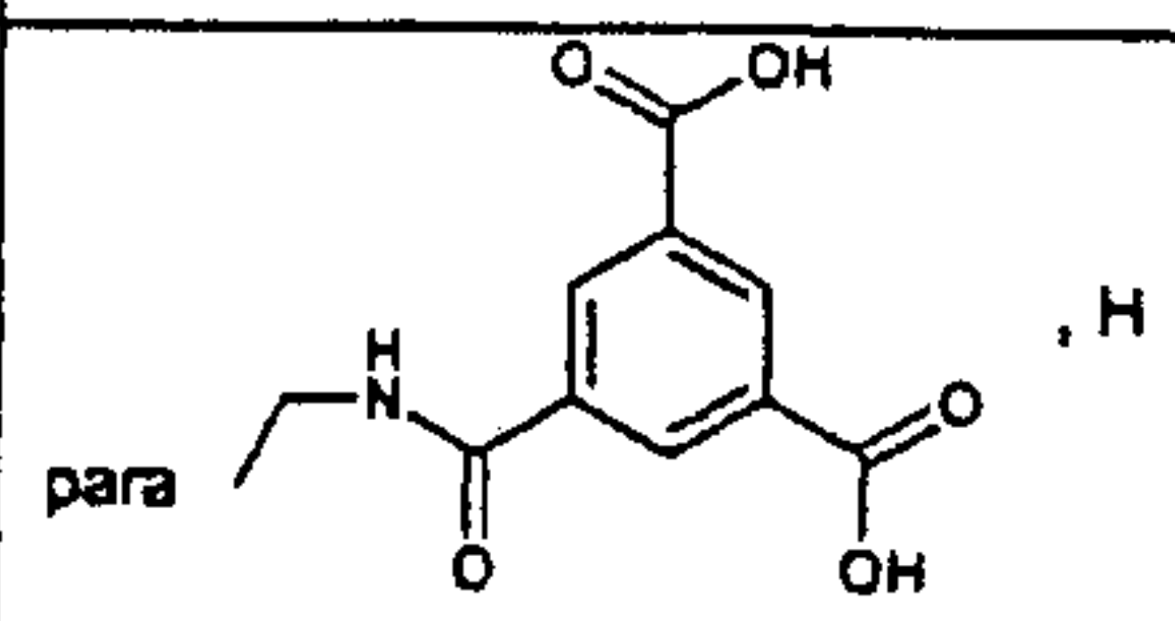
The synthesis is carried out analogously to Example XVa) starting with 1.06 g of 6-methylaminohexane-1,2,3,4,5-pentaol. This gives the product of molecular weight 343.38 ($C_{16}H_{25}N_1O_7$); MS (ESI) 344.2 ($M + H^+$).

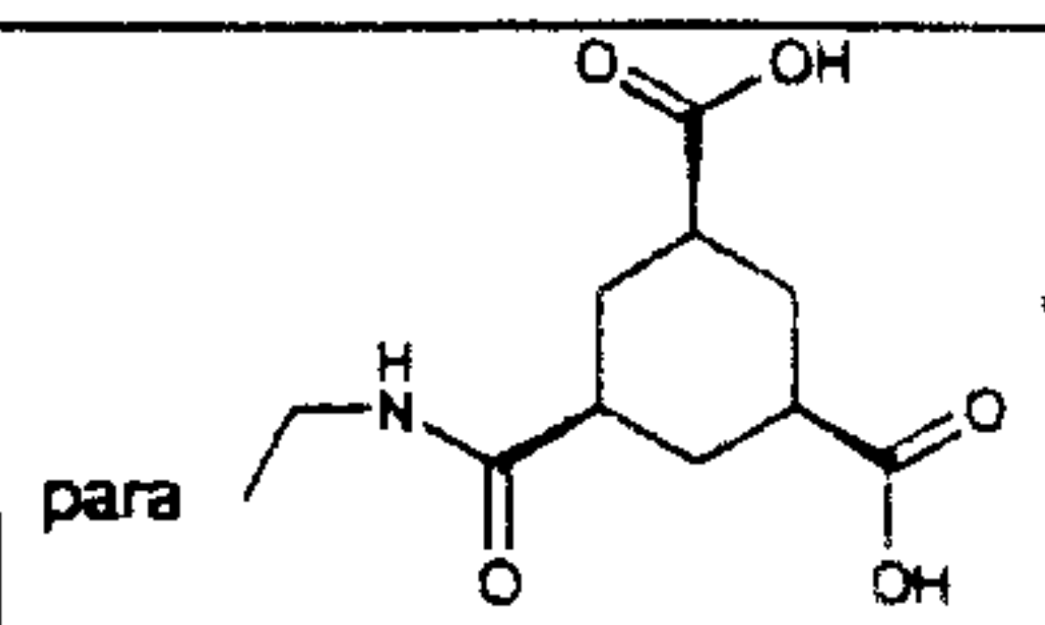
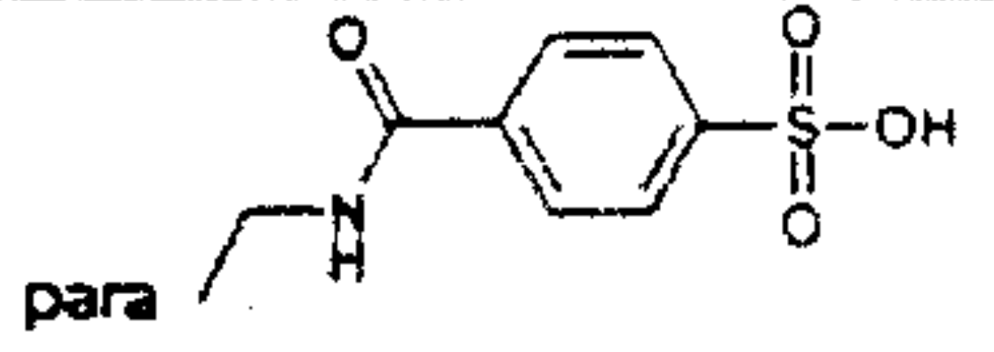
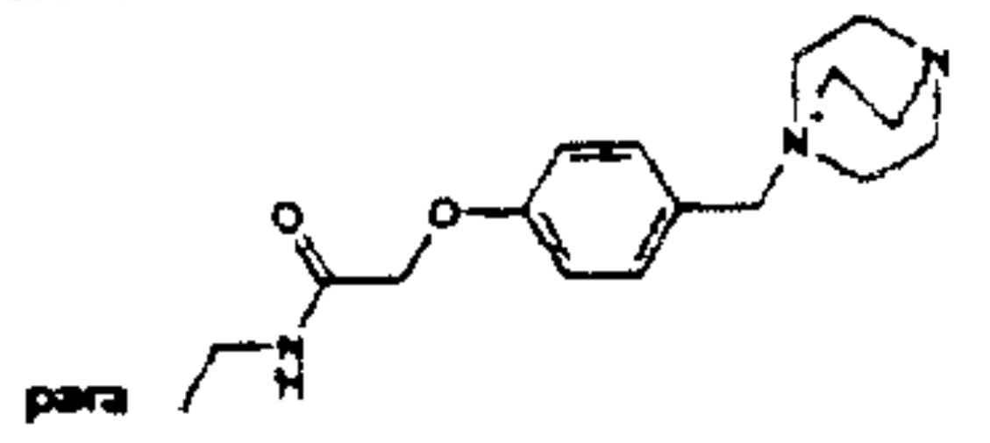
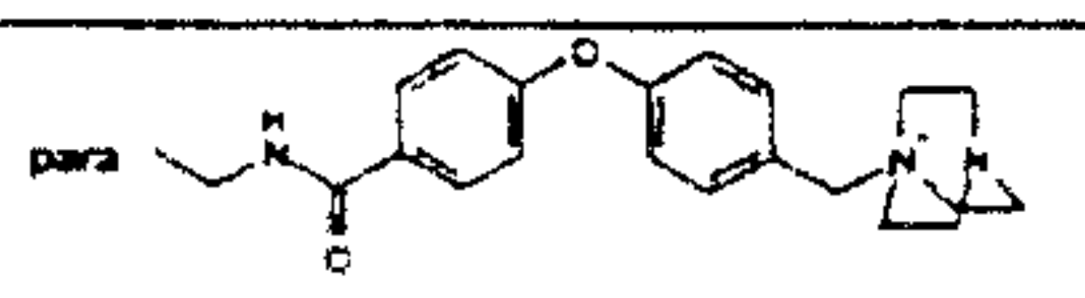
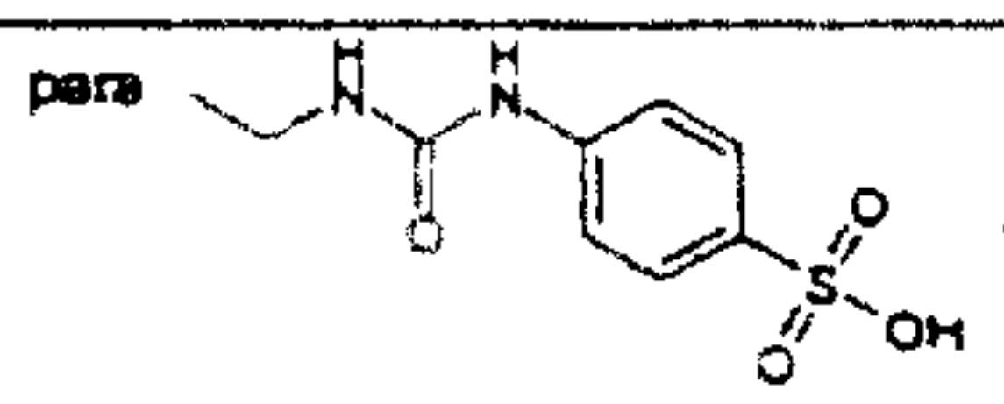
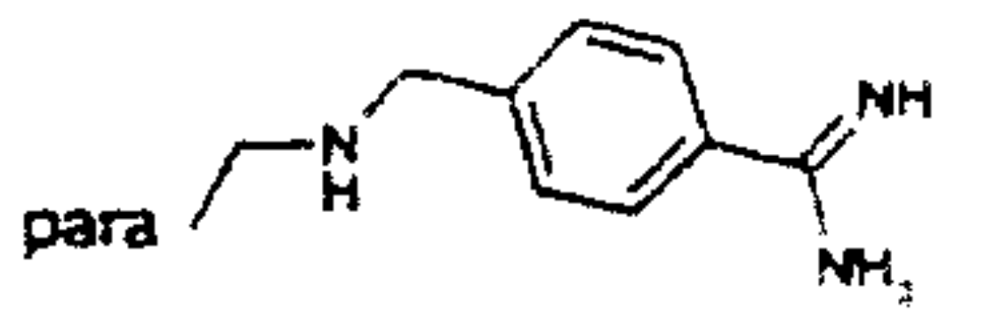
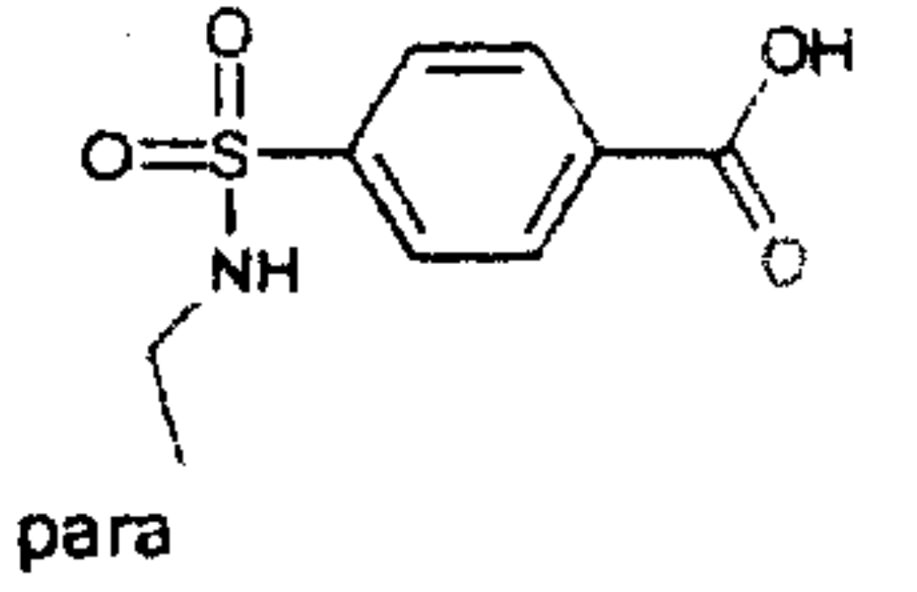
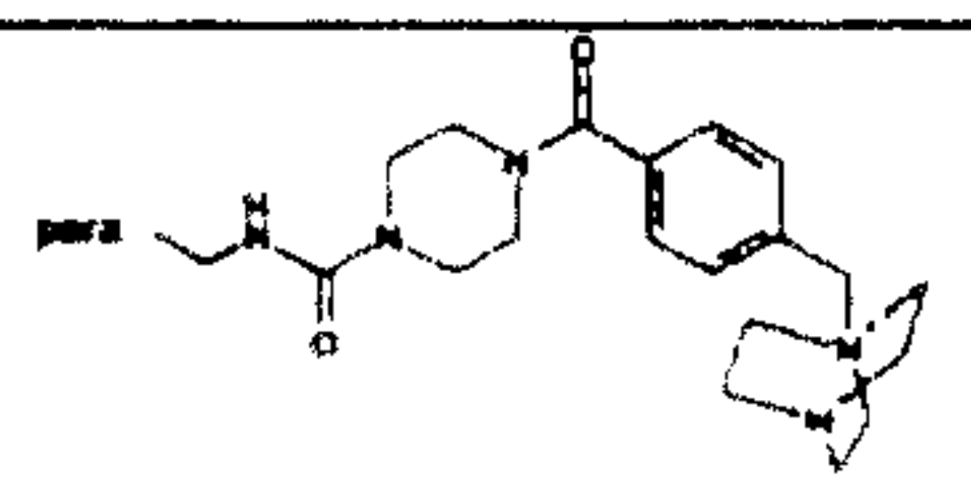
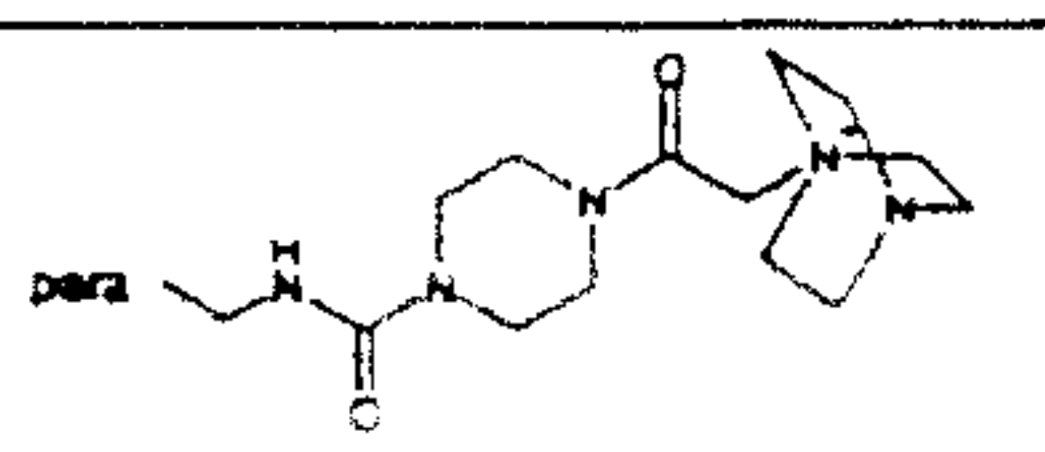
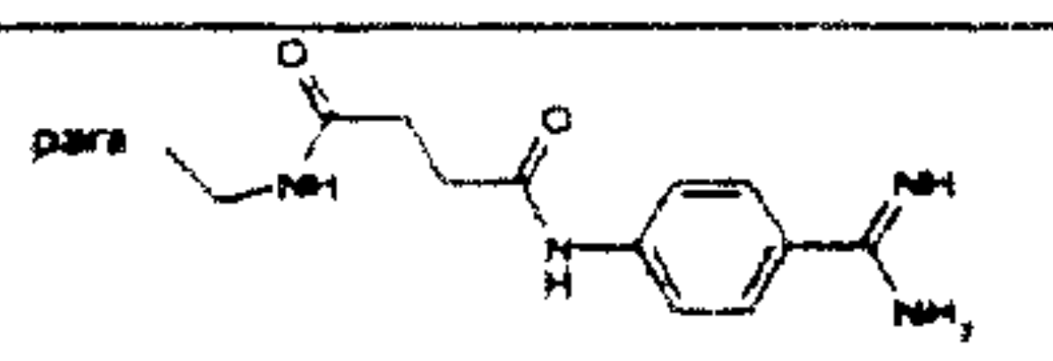
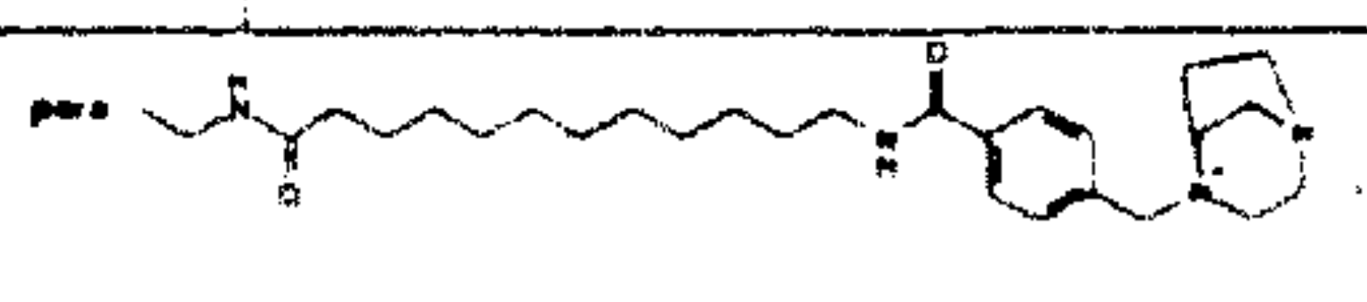
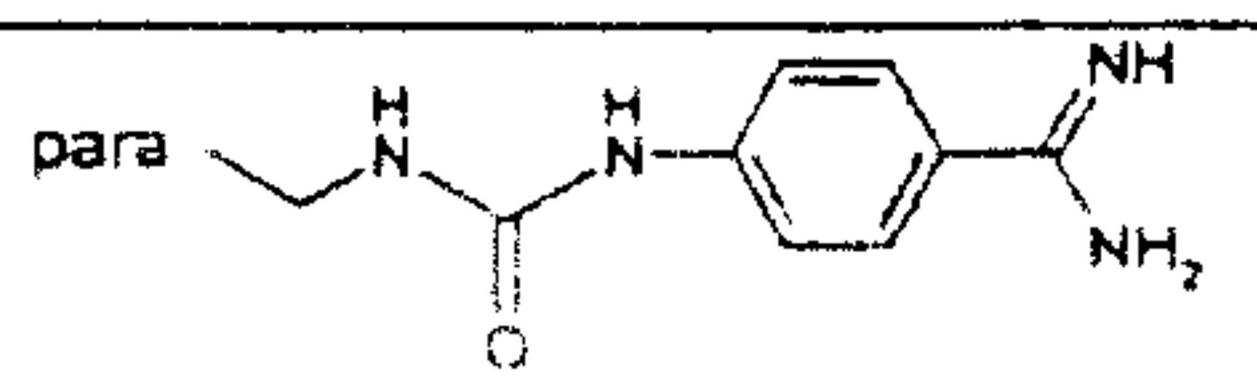
b) N-(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}-benzyl)-2-(4-{[methyl-(2,3,4,5,6-pentahydroxyhexyl)-amino]-methyl}-phenyl)-acetamide (48):

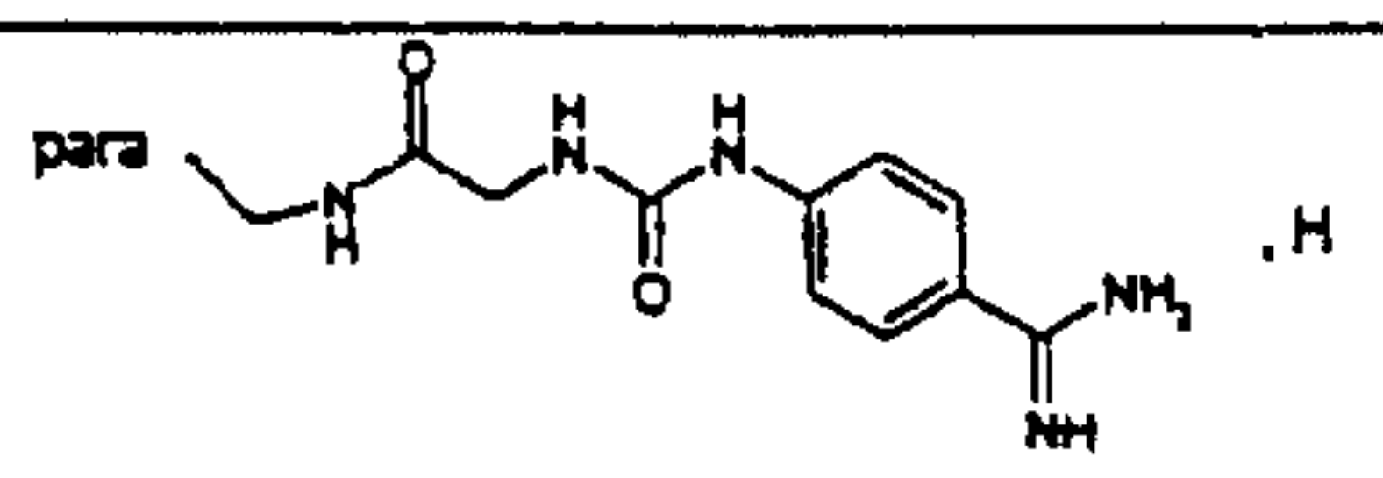
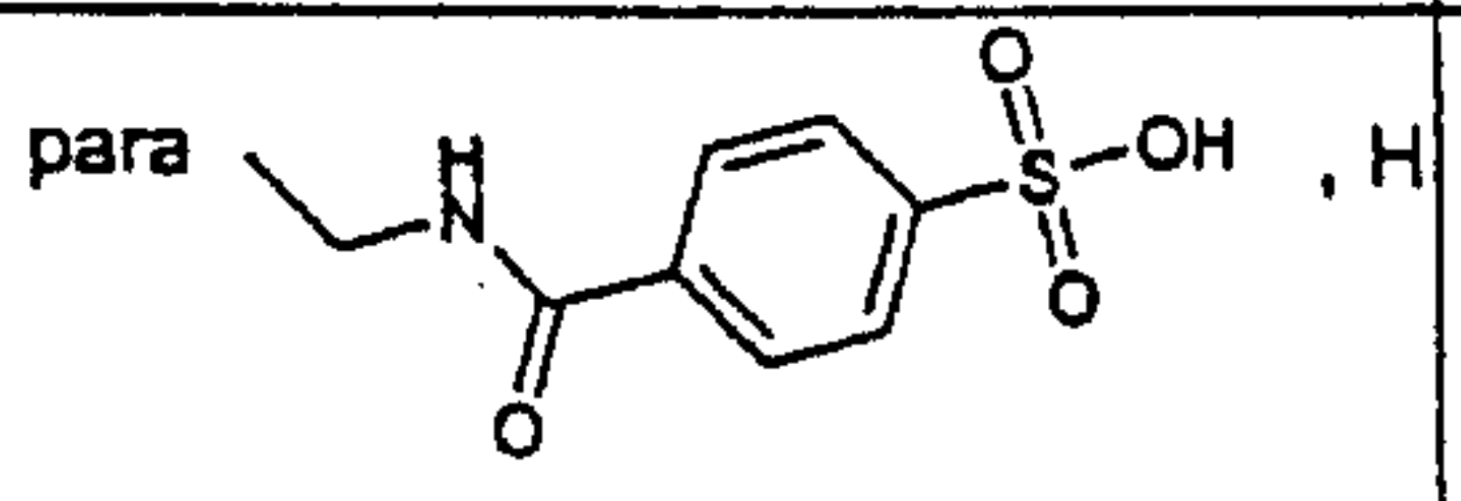
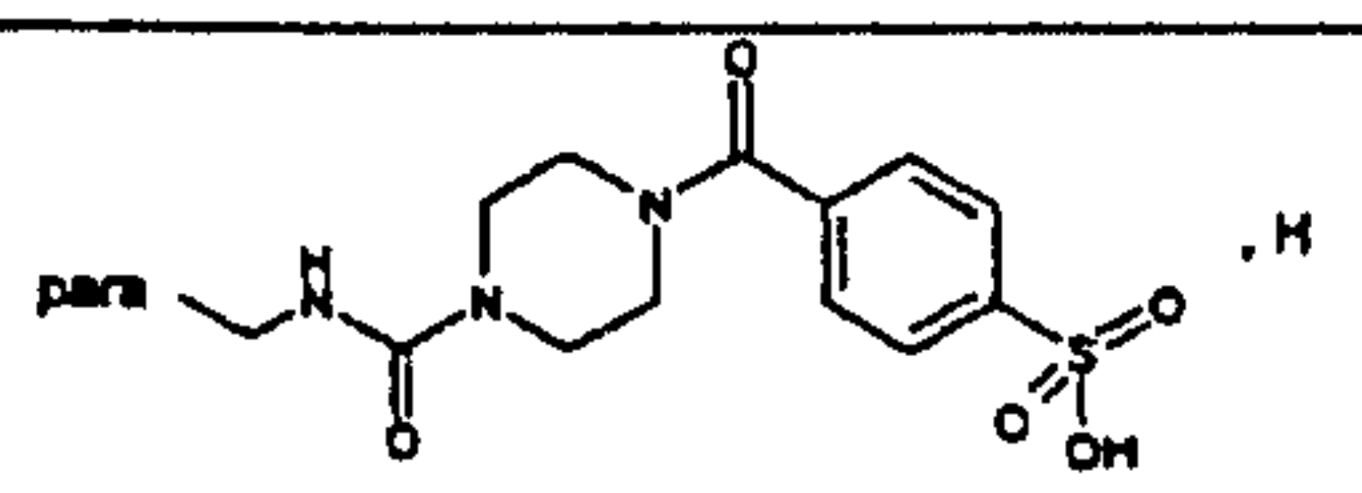
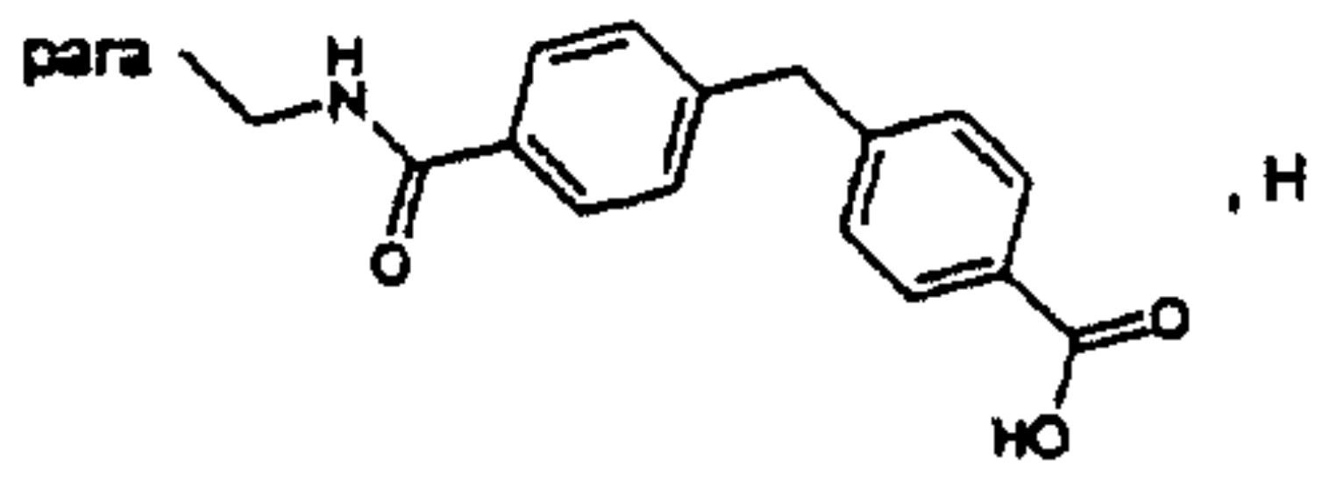
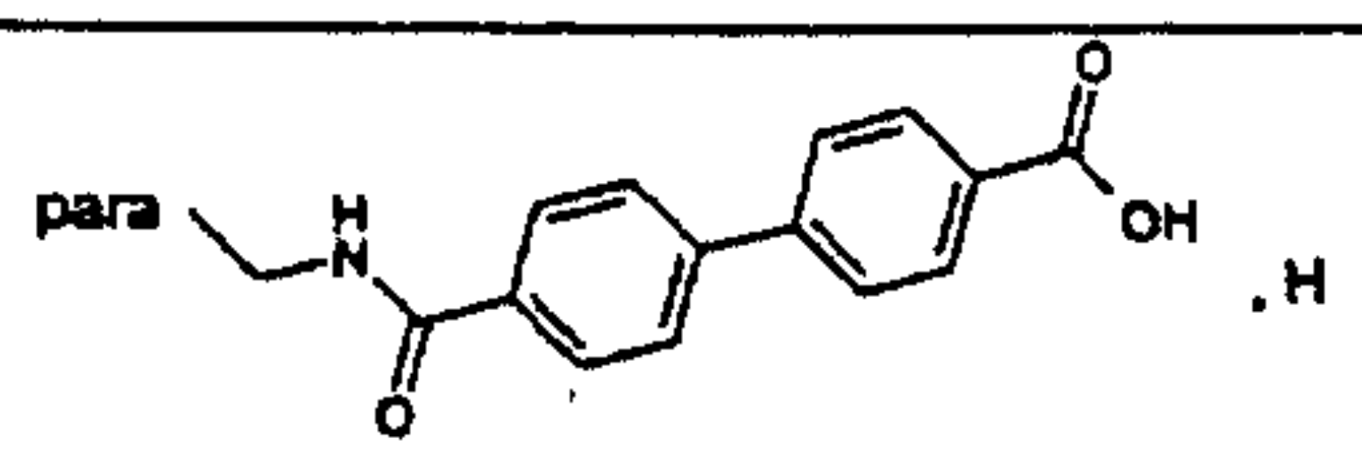
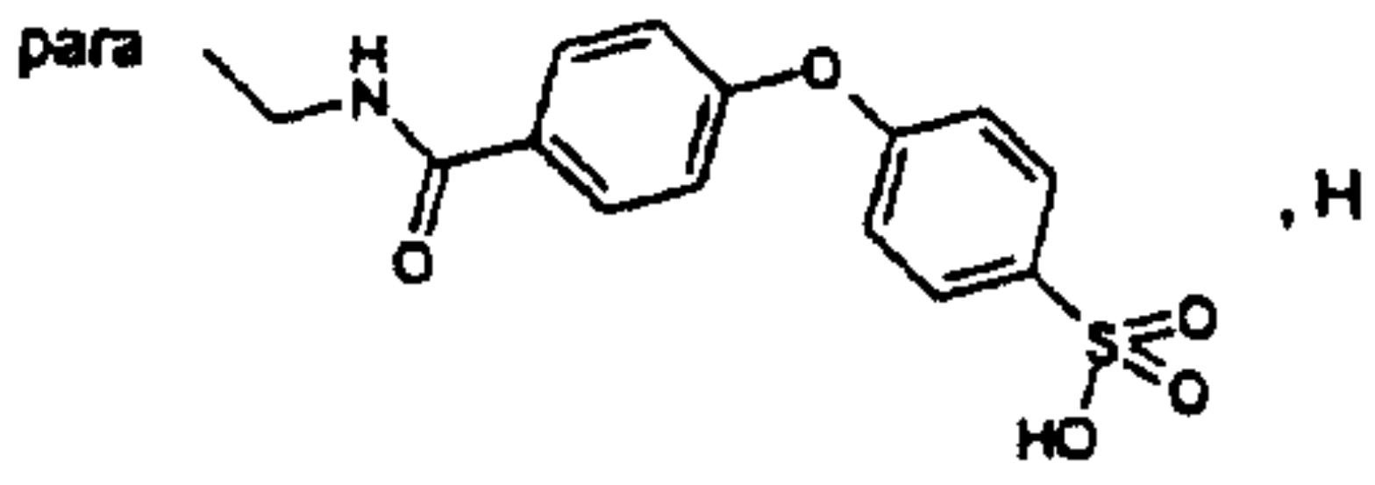
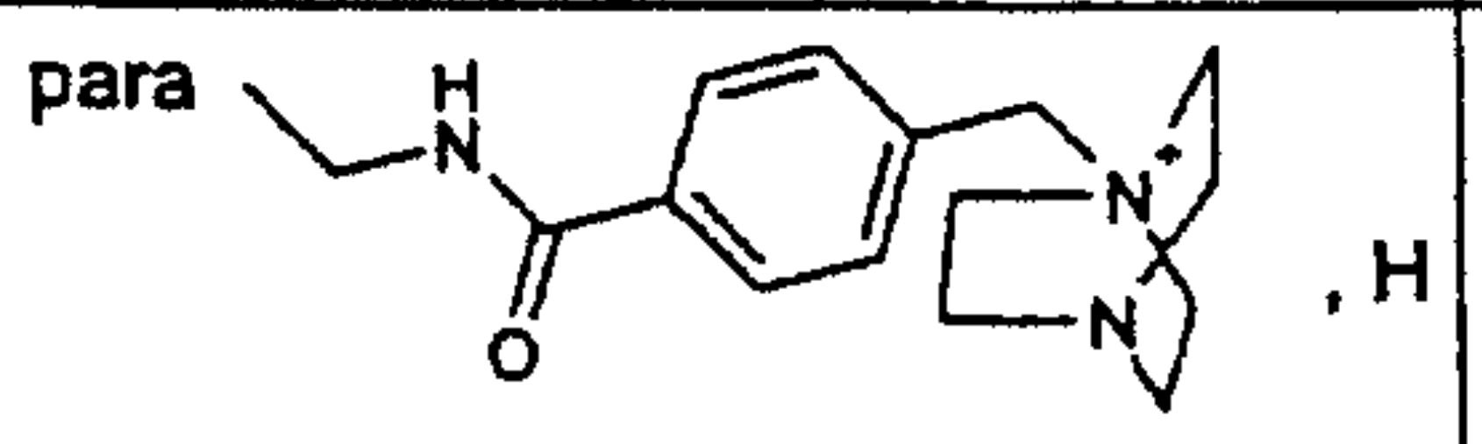
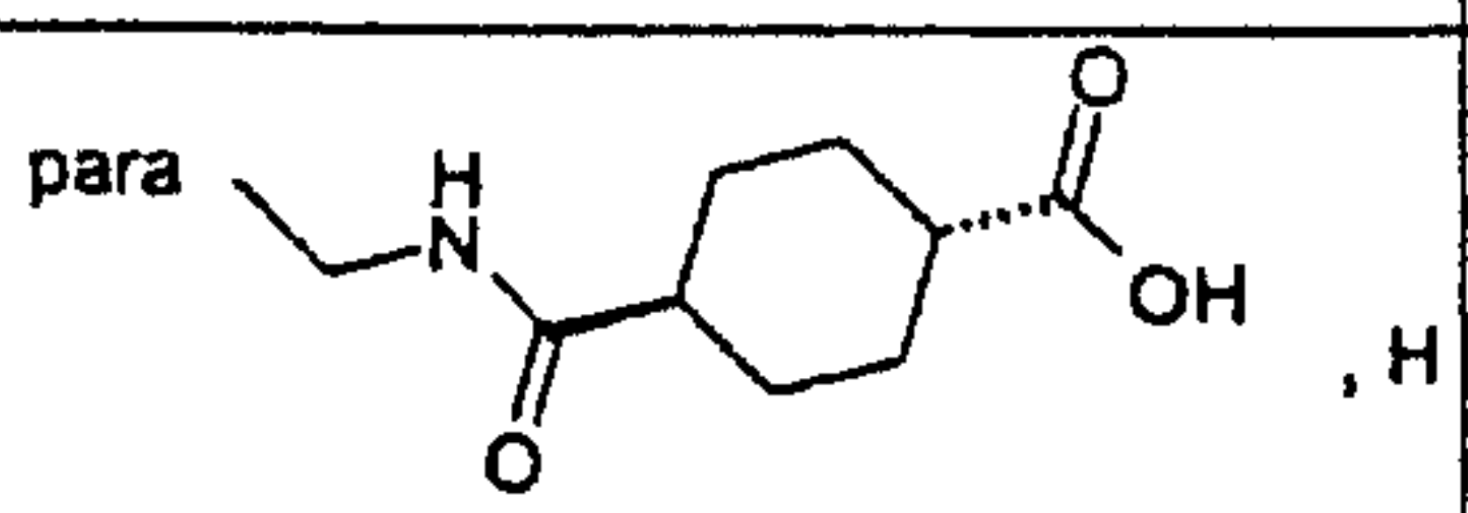
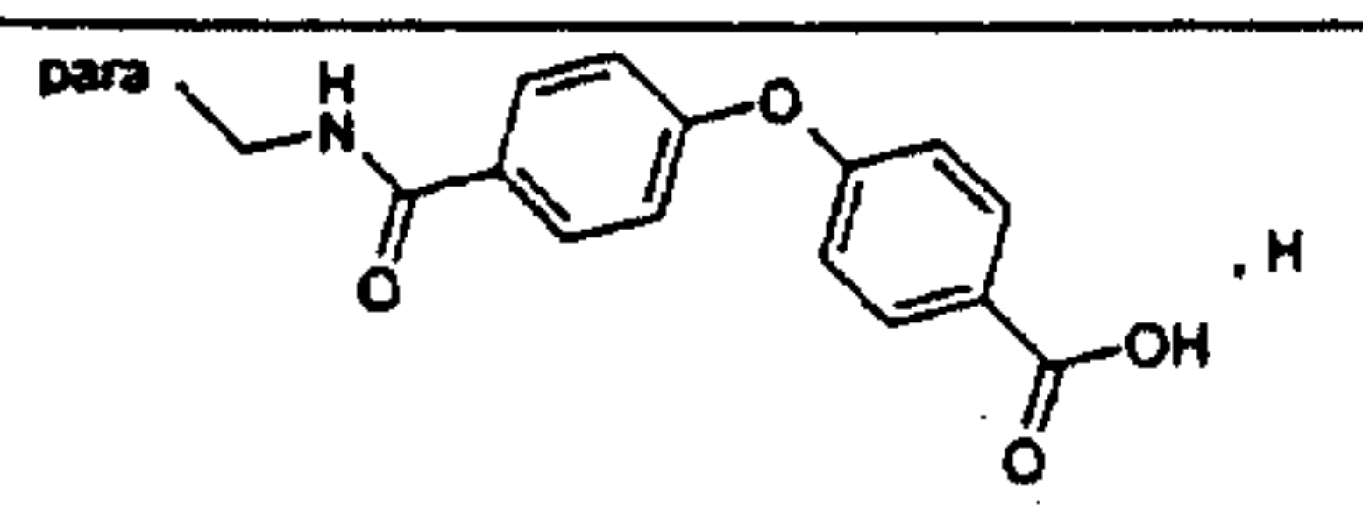
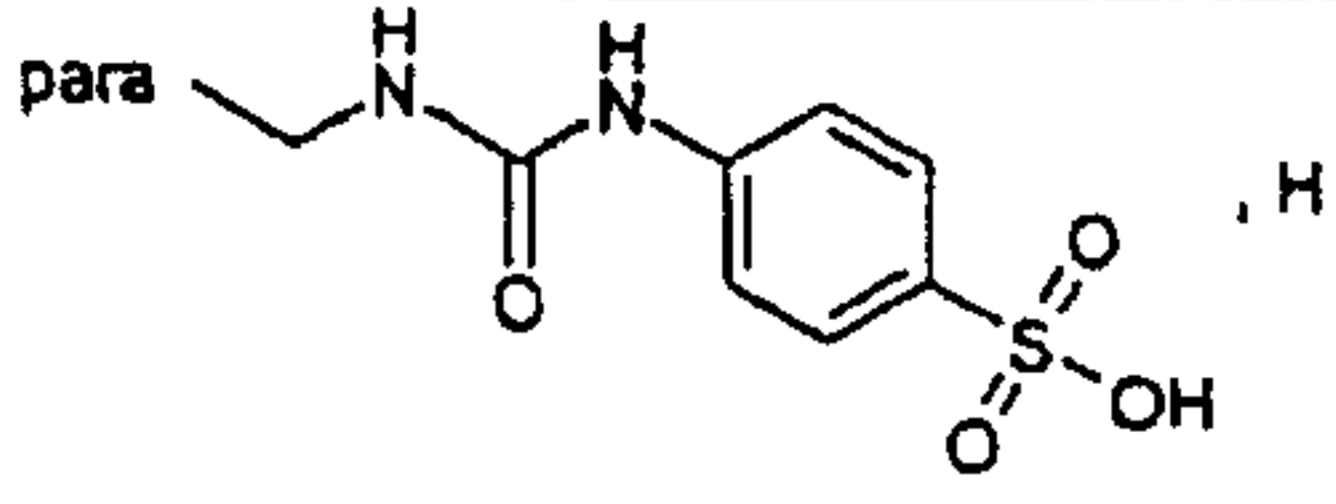
The synthesis is carried out analogously to Example XVe) starting 70 mg of 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-azetidin-2-one and 114 mg of (4-{[methyl-(2,3,4,5,6-pentahydroxyhexyl)-amino]-methyl}-phenyl)-acetic acid. This gives the product of molecular weight 747.84 ($C_{41}H_{47}F_2N_3O_8^+$); MS (ESI) 748.35 ($M + H^+$).

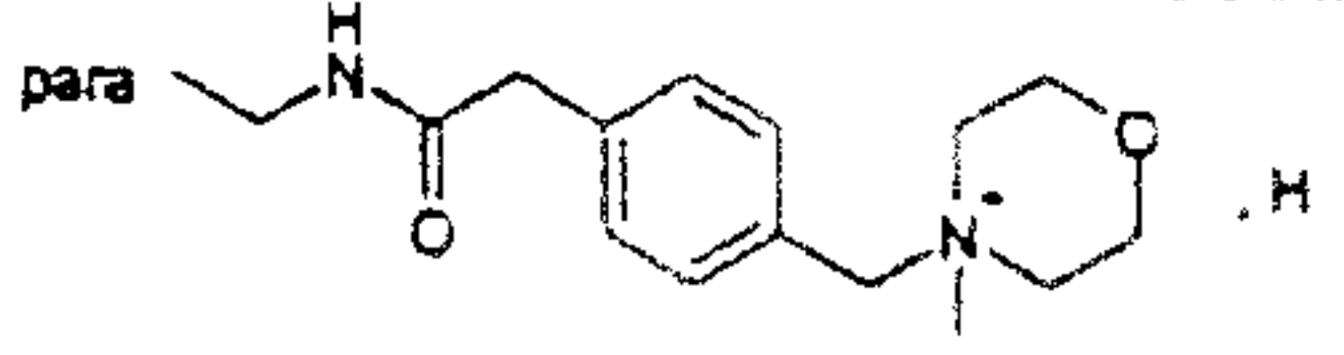
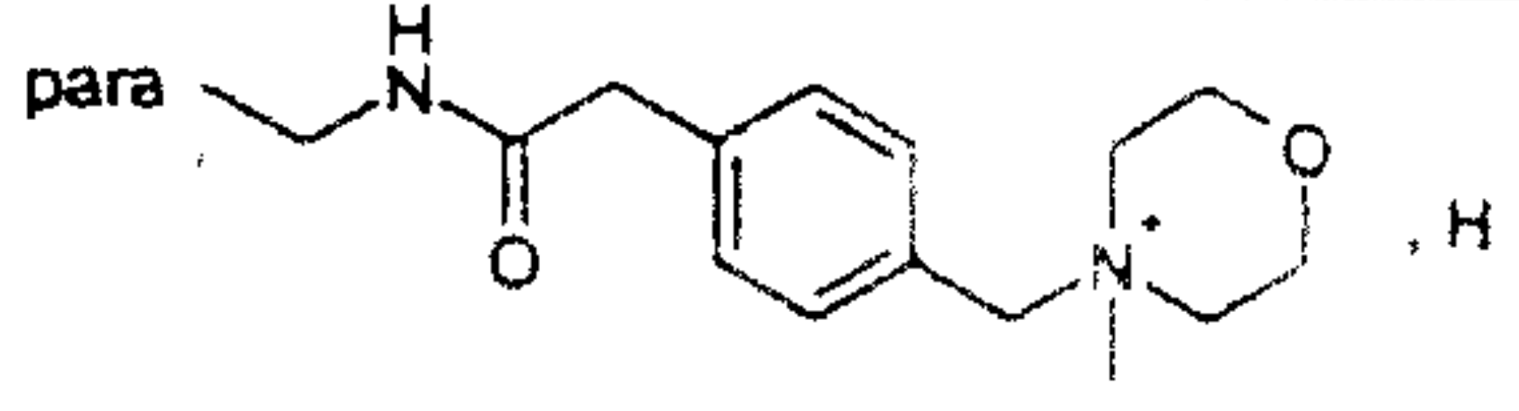
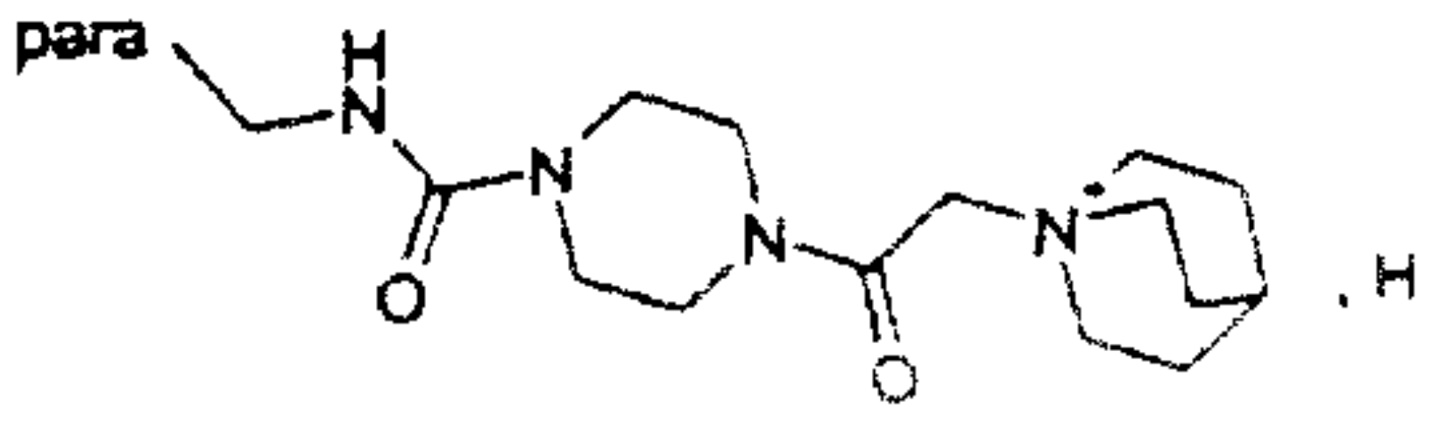
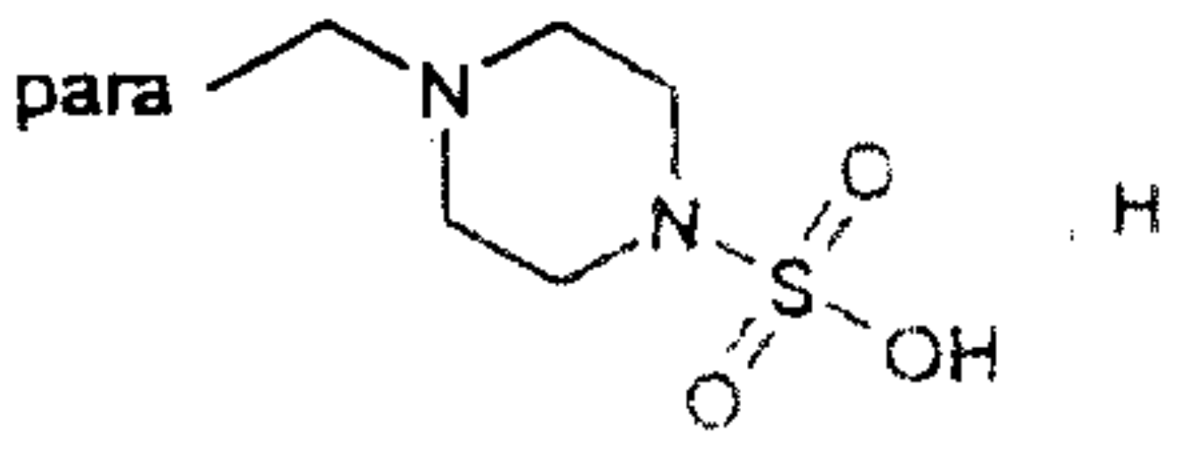
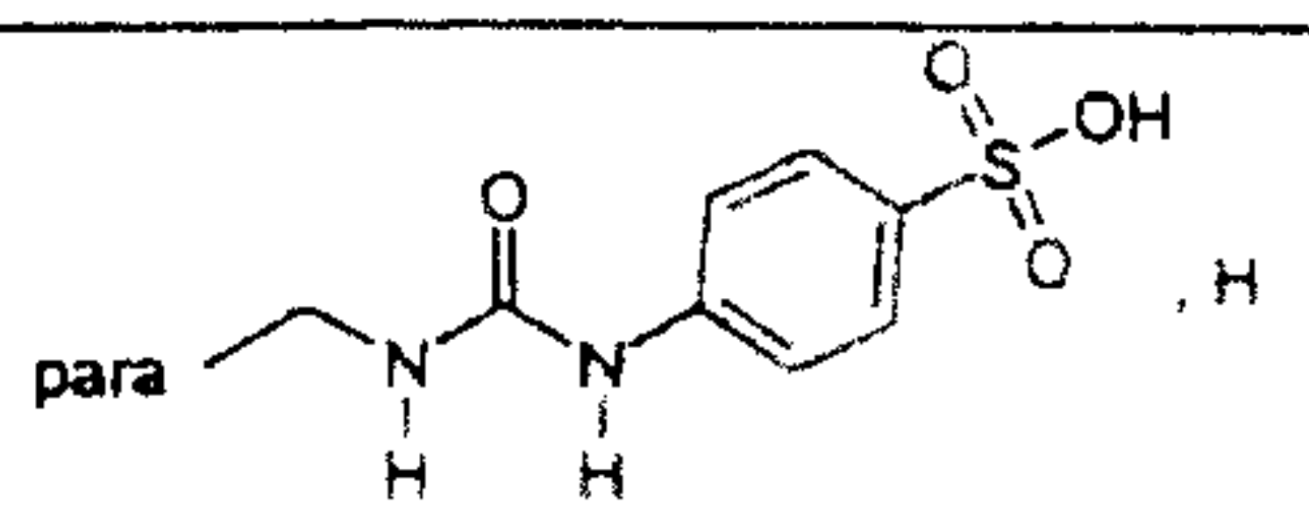
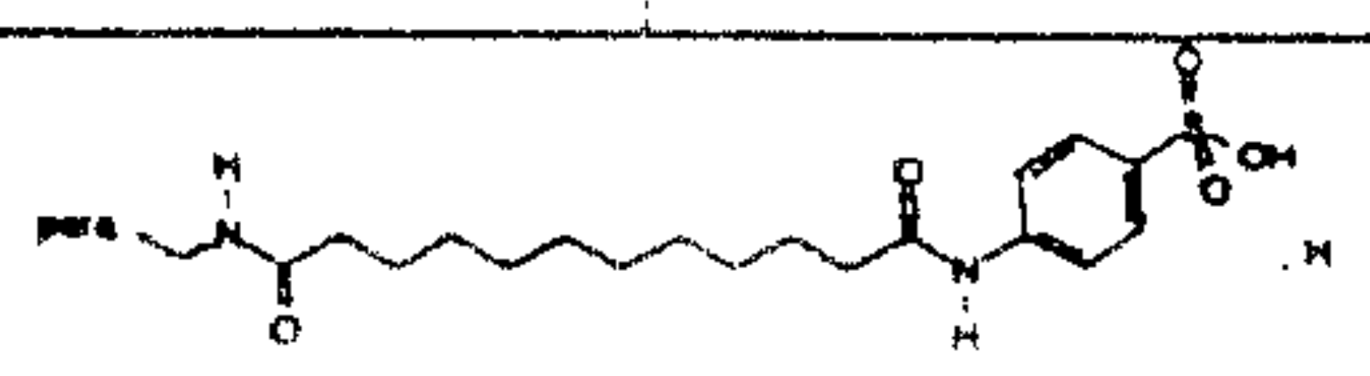
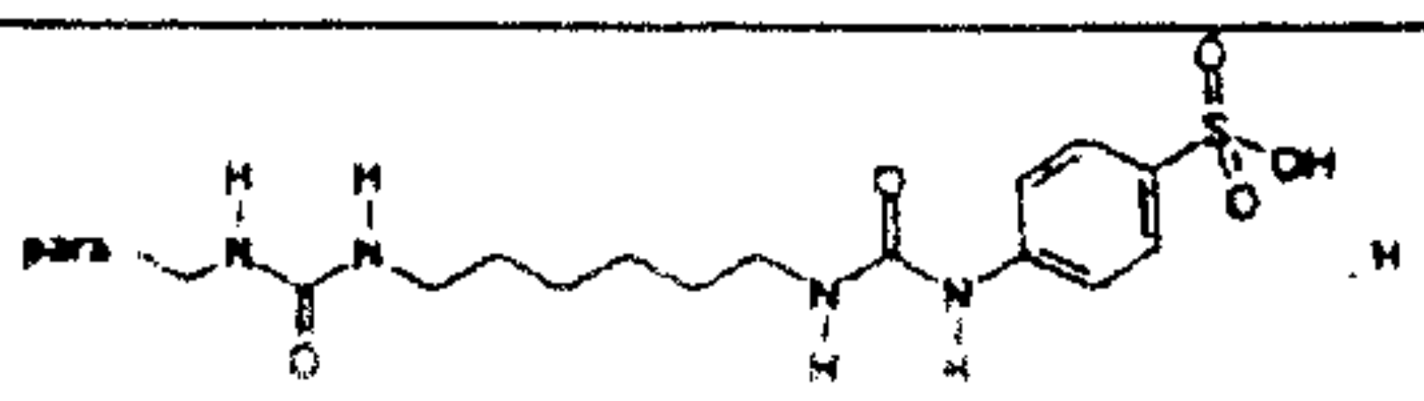
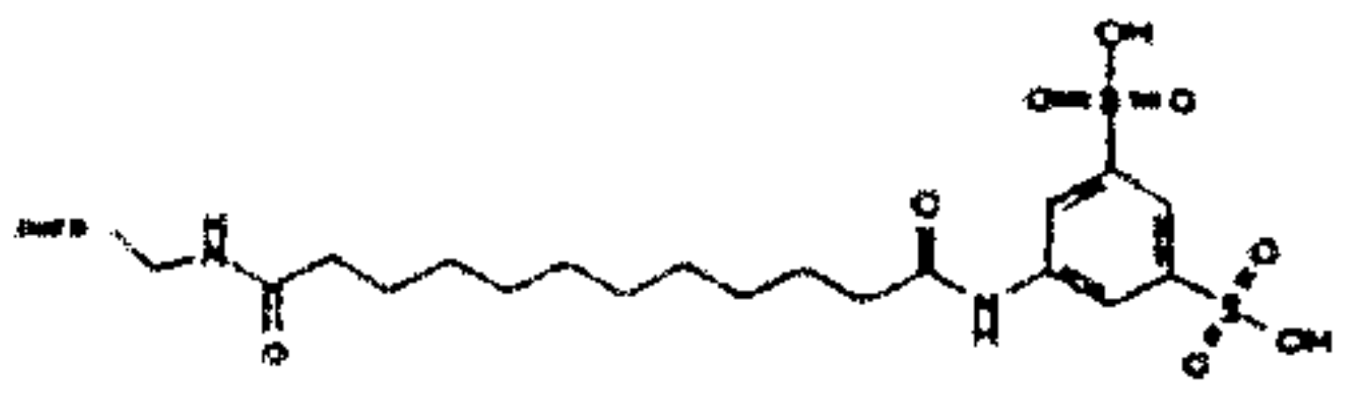
Table 1: Compounds of the formula I



Ex.	R1, R2	R3, R4	R5, R6	Salz	Molecular weight of the free base or acid (calculated)	Molecular weight (found)
XXIII		para-F, H	para-F, H	Cl^-	651.78	651.31 (M^+)
XXIV		para-F, H	para-F, H	CF_3COO^-	651.78	651.31 (M^+)
XXV		para-F, H	para-F, H	-	567.64	577.25 (MH^+)
XXVI		para-F, H	para-F, H	-	662.69	663.22 (MH^+)
XXVII	para-O-CH3, H		para-F, H	CF_3COOH	745.85	746.34 (MH^+)
XXVIII	para-O-CH3, H		para-F, H	CF_3COOH	759.88	760.35 (MH^+)
XXIX		para-F, H	para-F, H	-	739.82	740.33 (MH^+)
XXX		para-F, H	para-F, H	CF_3COO^-	695.84	659.34 (M^+)
XXXI		para-F, H	para-F, H	CF_3COO^-	709.86	709.35 (M^+)
XXXII		para-F, H	para-F, H	-	614.60	597.18 (MH^+-H_2O)

XXXIII	 , H	para-F, H	para-F, H	-	620.65	621.24 (MH^+)
XXXIV	 , H	para-F, H	para-F, H	-	606.65	607.32 (MH^+)
XXXV	 , H	para-F, H	para-F, H	CF_3COO^-	681.33	681.5 (M^+)
XXXVI	para-O-CH_3, H	 , H	para-F, H	Cl^-	755.92	755.36 (M^+)
XXXVII	para-O-CH_3, H	 , H	H, H	-	615.71	616.21 (MH^+)
XXXVIII	 , H	para-F, H	para-F, H	CF_3COOH	554.65	555.20 (MH^+)
XXXIX	 , H	para-F, H	para-F, H	-	606.65	607.39 (MH^+)
XL	para-O-CH_3, H	 , H	para-F, H	Cl^-	775.95	775.40 (M^+)
XLI	para-O-CH_3, H	 , H	para-F, H	Cl^-	699.85	699.33 (M^+)
XLII	para-O-CH_3, H	 , H	para-F, H	HCl	651.74	652.38 (MH^+)
XLIII	para-O-CH_3, H	 , H	para-F, H	Br^-	860.51	860.6 (M^+)
XLIV	para-O-CH_3, H	 , H	para-F, H	-	595.67	596.38 (MH^+)

XLV	para-O-CH_3, H		para-F, H	CF_3COOH	652.73	653.37 (MH^+)
XLVI	para-O-CH_3, H		para-F, H	-	618.68	617.33 ($M-H^+$; measured in negative mode
XLVII	para-O-CH_3, H		para-F, H	-	730.81	731.41 (MH^+)
XLVIII	para-O-CH_3, H		para-F, H	-	672.76	655.28 (MH^+-H_2O)
IL	para-O-CH_3, H		para-F, H	-	658.73	659.27 (MH^+)
L	para-O-CH_3, H		para-F, H	-	710.78	693.25 (MH^+-H_2O)
LI	para-O-CH_3, H		para-F, H	Cl^-	663.82	663.28 (M^+)
LII	para-O-CH_3, H		para-F, H	-	588.68	589.34 (MH^+)
LIII	para-O-CH_3, H		para-F, H	-	674.73	657.35 (MH^+-H_20)
LIV	para-O-CH_3, H		para-F, H	-	633.70	615.70 (M^+-H_2O)

LV	para-O-CH$_3$, H		para-F, H	Br	666.72	666.33 (M$^+$)
LVI		para-F, H	para-F, H	Br	654.68	654.31 (M$^+$)
LVII		para-F, H	para-F, H	I$^-$	687.35	687.4 (M$^+$)
LVIII		para-F, H	para-F, H	-	571.65	572.4 (MH$^+$)
LIX		para-F, H	para-F, H	-	621.66	622.33 (MH$^+$)
LX	para-O-CH$_3$, H		para-F, H	-	801.98	784.21 (M$^+$ - H$_2$O)
LXI	para-O-CH$_3$, H		para-F, H	-	775.90	758.18 (M$^+$ - H$_2$O)
LXII	para-O-CH3, H		para-F, H	-	882.04	883.49 (MH+)

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	< 0.1
II	< 1.0
IV	< 0.1
V	< 0.1
VI	0.3
VII	< 1.0
VIII	< 1.0
IX	< 0.1

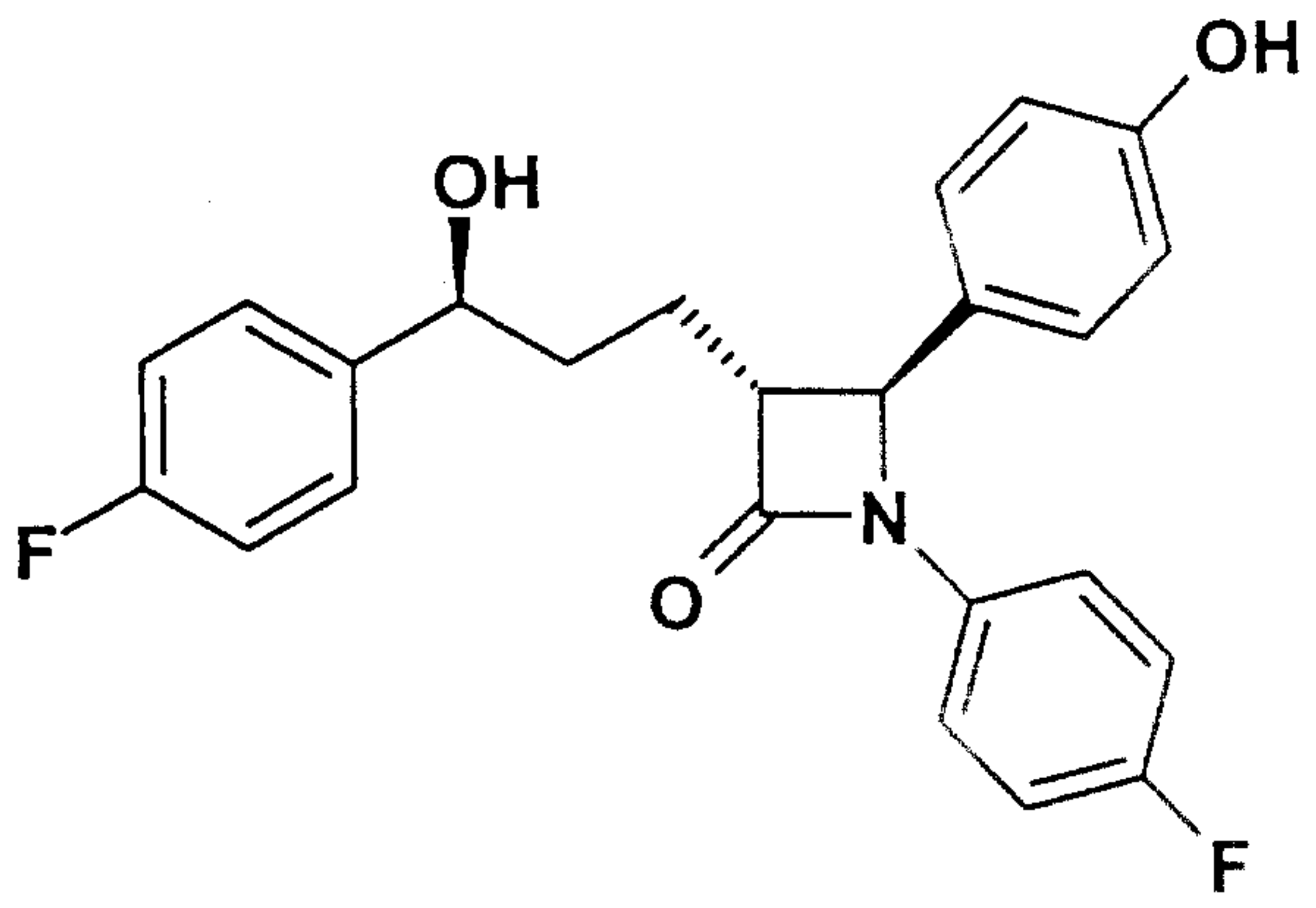
XV	< 1.0
XXIII	0.3
XXV	0.3
XXVI	0.1
XXVII	0.3
XXIX	0.3
XXXI	0.3
XXXVI	0.03
XXXVII	0.1
XXXVIII	0.1
XLI	0.03
XLIII	0.3
XLIV	0.3
XLVI	0.3
XLVIII	0.03
L	0.1
LII	0.3
LIII	0.03

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).

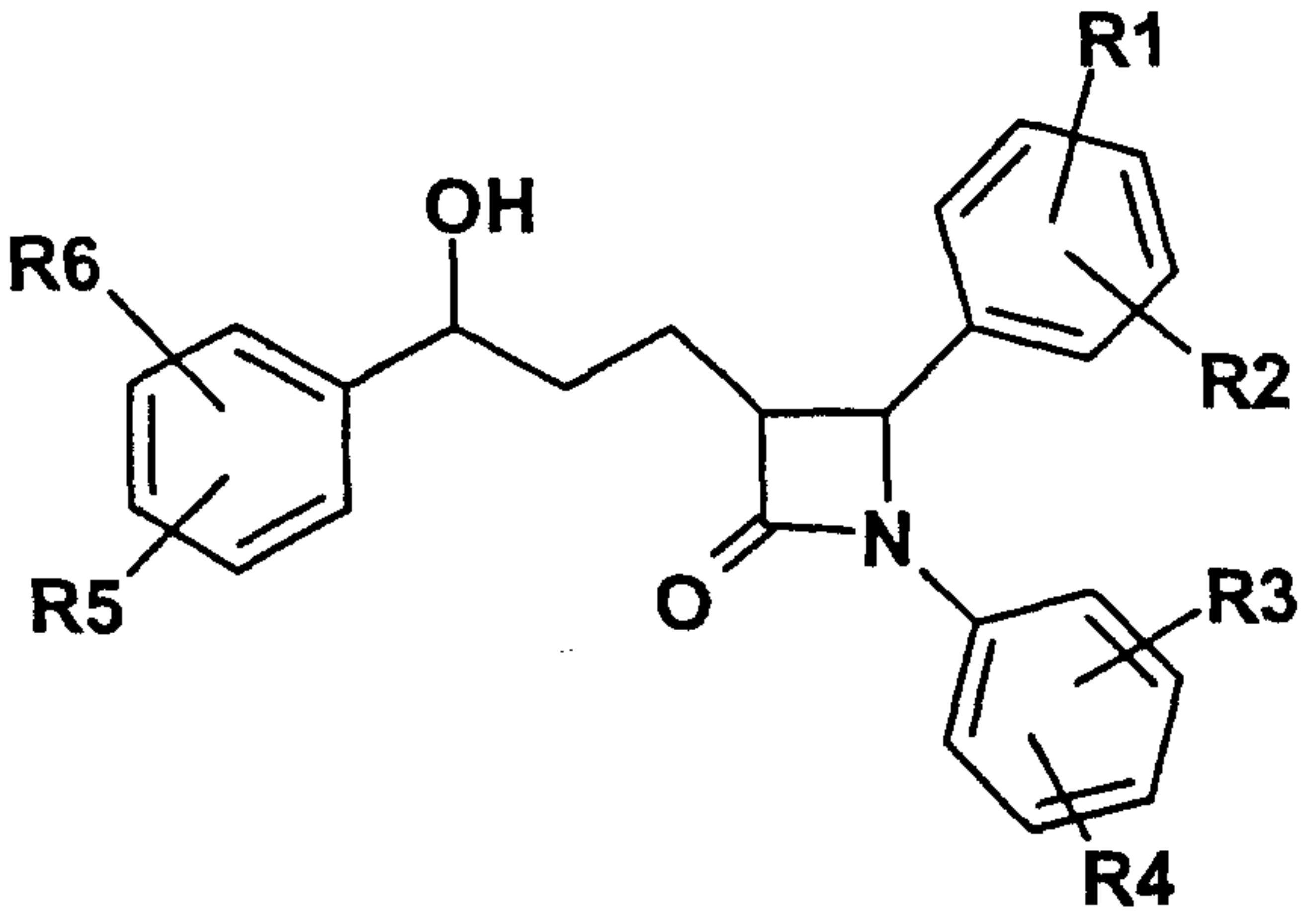
From the measured data, it can be seen that the bioabsorption of the compounds of the formula I according to the invention is considerably lower than that of the compounds described in the prior art (reference structure):



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_1-C_{30})-alkylene-$(LAG)_n$, where n = 1 – 5 and where one or more carbon atoms of the alkylene radical are replaced by aryl or heteroaryl radicals substituted up to three times by R7, or by (C_3-C_{10})-cycloalkyl or heterocycloalkyl radicals substituted up to four times by R7 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-;

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;
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, $CONH_2$;

R7 is 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;
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;
C(NH)(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 sugar residue, disugar residue, trisugar residue, tetrasugar residue; a sugar acid, an amino sugar;

an amino acid residue, an oligopeptide residue comprising 2 to 9 amino acids;

an acyclic, mono-, di- or tricyclic trialkylammonium radical, an acyclic mono-, di- or tricyclic trialkylammoniumalkyl radical, -O-(SO_2)-OH; -(CH_2)$_{0-10}$-SO_3H; -(CH_2)$_{0-10}$-P(O)(OH)$_2$, -(CH_2)$_{0-10}$-O-P(O)(OH)$_2$, -(CH_2)$_{0-10}$-COOH, -(CH_2)$_{0-10}$-C(=NH)(NH_2); -(CH_2)$_{0-10}$-C(=NH)(NHOH); -NR8-C(=NR9)(NR10R11); where n = 1 – 5 and R8, R9, R10 and R11 independently of one another may be H, (C_1-C_6)-alkyl, phenyl, (C_1-C_6)-alkyl-phenyl, (C_3-C_8)-cycloalkyl),

and where in each case at least one of the radicals R1 to R6 must have the meaning (C_1-C_{30})-alkylene-(LAG)$_n$, where n = 1 – 5 and one or more carbon atoms of the alkylene radical are replaced by up to trisubstituted aryl or heteroaryl radicals or by up to tetrasubstituted (C_3-C_{10})-cycloalkyl or heterocycloalkyl radicals and may additionally 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;

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_1-C_{30})-alkylene-(LAG), where one or more carbon atoms of the alkylene radical are replaced by aryl or heteroaryl radicals substituted up to three times by R7, or by (C_3-C_{10})-cycloalkyl or heterocycloalkyl radicals substituted up to three times by R7 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)-, -N(CH_3)-, -N(phenyl)-, -N(CO-(CH_2)$_{1-10}$-COOH)- 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;
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, $CONH_2$;

R7 is 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;

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 where 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;

C(NH)(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 sugar residue, disugar residue, trisugar residue, tetrasugar residue; a sugar acid, an amino sugar;

an amino acid residue, an oligopeptide residue comprising 2 to 9 amino acids;

an acyclic, mono-, di- or tricyclic trialkylammonium radical, an acyclic mono-, di- or tricyclic trialkylammoniumalkyl radical, -O-(SO_2)-OH; -(CH_2)$_{0-10}$-SO_3H; -(CH_2)$_{0-10}$-P(O)(OH)$_2$, -(CH_2)$_{0-10}$-O-P(O)(OH)$_2$, -(CH_2)$_{0-10}$-COOH, -(CH_2)$_{0-10}$-C(=NH)(NH_2); -(CH_2)$_{0-10}$-C(=NH)(NHOH); -NR8-C(=NR9)(NR10R11); where n = 1 – 5 and R8, R9, R10 and R11 independently of one another may be H, (C_1-C_6)-alkyl, phenyl, (C_1-C_6)-alkyl-phenyl, (C_3-C_8)-cycloalkyl),

and where in each case at least one of the radicals R1 or R3 must have the meaning (C_1-C_{30})-alkylene-(LAG), where one or more carbon atoms of the alkylene radical are replaced by up to trisubstituted aryl or heteroaryl radicals or by up to trisubstituted (C_3-C_{10})-cycloalkyl or heterocycloalkyl radicals and may additionally be replaced by

-S(O)$_n$-, where n = 0 – 2, -O-, -(C=O)-, -N(CH$_3$)-, -N(phenyl)-, -N(CO-(CH$_2$)$_{1-10}$-COOH)- 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;

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$_2$)$_{0-1}$-NH-(C=O)$_{0-1}$-(C$_0$-C$_{25}$)-alkylene-(C=O)$_{0-1}$-N(R13)$_{0-1}$-(LAG) or -(CH$_2$)$_{0-1}$-(C=O)$_{0-1}$-NH-(C$_0$-C$_{25}$)-alkylene-(C=O)$_{0-1}$-N(R13)$_{0-1}$-(LAG); where one or more carbon atoms of the alkylene radical are replaced by aryl or heteroaryl radicals substituted up to three times by R7, or by (C$_3$-C$_{10}$)-cycloalkyl or heterocycloalkyl radicals substituted up to three times by R7 and where one or more carbon atoms of the alkylene radical may be replaced by oxygen atoms;

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;

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, $CONH_2$;

R7 is 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;

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;

C(NH)(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 sugar residue, disugar residue, trisugar residue, tetrasugar residue; a sugar acid, an amino sugar; an amino acid residue, an oligopeptide residue comprising 2 to 9 amino acids; an acyclic, mono-, di- or tricyclic trialkylammonium radical, an acyclic mono-, di- or tricyclic trialkylammoniumalkyl radical, $-O-(SO_2)-OH$; $-(CH_2)_{0-10}-SO_3H$; $-(CH_2)_{0-10}-P(O)(OH)_2$, $-(CH_2)_{0-10}-O-P(O)(OH)_2$, $-(CH_2)_{0-10}-COOH$, $-(CH_2)_{0-10}-C(=NH)(NH_2)$; $-(CH_2)_{0-10}-C(=NH)(NHOH)$; -NR8-C(=NR9)(NR10R11); where n = 1 – 5 and R8, R9, R10 and R11 independently of one another may be H, (C_1-C_6)-alkyl, phenyl, (C_1-C_6)-alkyl-phenyl, (C_3-C_8)-cycloalkyl),
R13	is H or CH_3;

and where in each case at least one of the radicals R1 or R3 must have the meaning $-(CH_2)_{0-1}-NH-(C=O)_{0-1}-(C_0-C_{25})$-alkylene-$(C=O)_{0-1}-N(R13)_{0-1}$-(LAG) or $-(CH_2)_{0-1}-(C=O)_{0-1}-NH-(C_0-C_{25})$-alkylene-$(C=O)_{0-1}-N(R13)_{0-1}$-(LAG) and one or more carbon atoms of the alkylene radical are replaced by up to trisubstituted aryl or heteroaryl radicals or by up to trisubstituted (C_3-C_{10})-cycloalkyl or heterocycloalkyl radicals and may additionally be replaced by $-S(O)_n-$, where n = 0 – 2, -O-, -(C=O)-, $-N(CH_3)-$, -N(phenyl)- or –NH-;
and its physiologically acceptable salts.

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

LAG	is a monosugar residue, an acyclic mono-, di- or tricyclic trialkylammoniumalkyl radical, a sulfonic acid or a carboxylic acid,

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

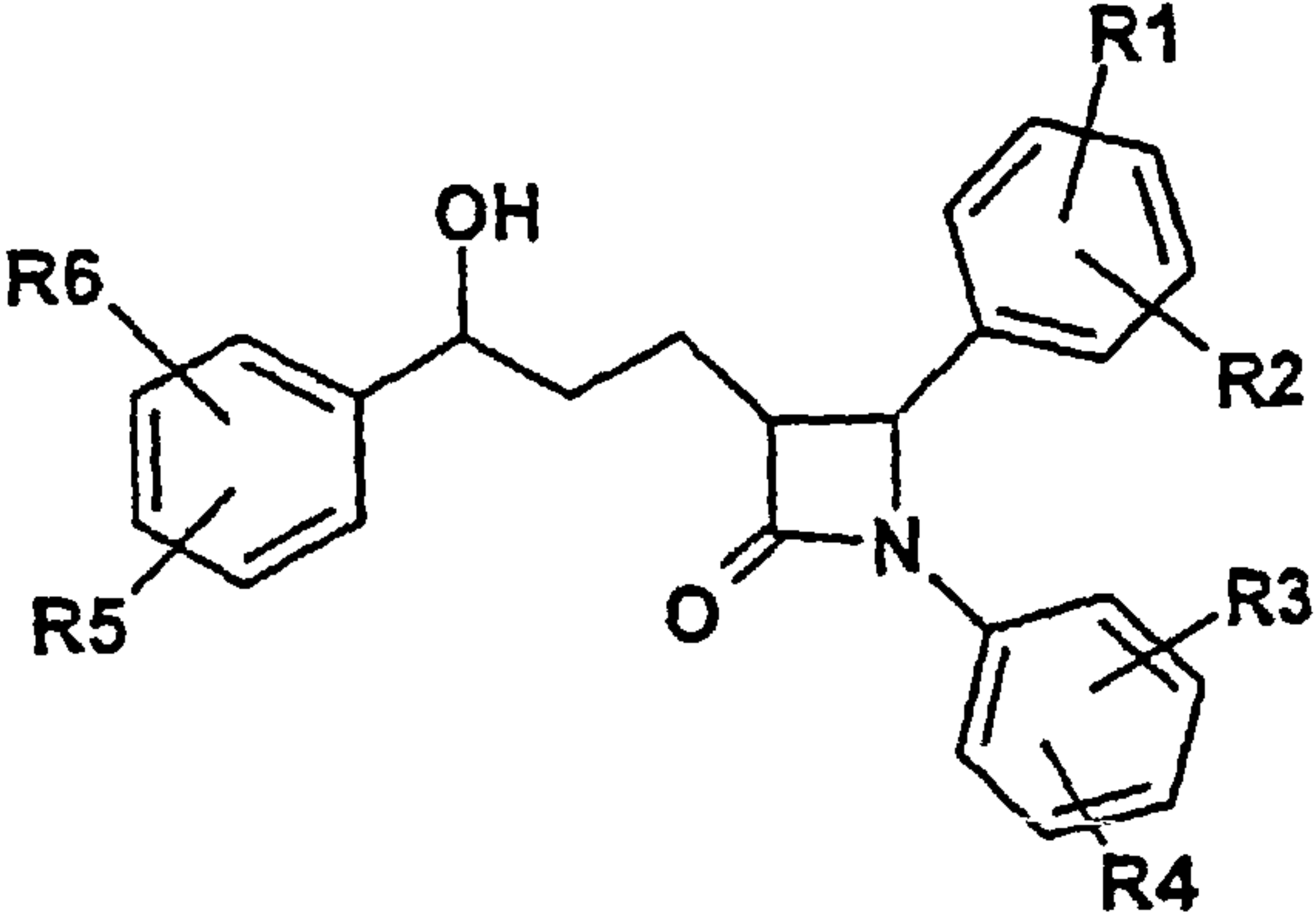
compounds as claimed in one or more of claims 1 to 4, which comprises mixing the active compound with a pharmaceutically acceptable carrier and bringing this mixture into a form suitable for administration.

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.



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