Description

4-BENZYLAMINOQUINOLINE CONJUGATES WITH BILE ACID AND THEIR HETERO ANALOGS, PROCESS FOR THEIR PREPARATION, PHARMACEUTICALS CONTAINING THESE COMPOUNDS AND USE THEREOF

The invention relates to substituted 4-benzylaminoquinolines and their hetero analogs, and to pharmaceutically acceptable salts and physiologically functional derivatives thereof.

The formation of gallstones is, in addition to a number of factors, essentially determined by the composition of bile, in particular by the concentration and the ratio of cholesterol, phospholipids and bile salts. A precondition for the formation of cholesterol gallstones is the presence of cholesterol-supersaturated bile (ref. Carey, M. C. and Small, D.M. (1978) The physical chemistry of cholesterol solubility in bile. Relationship to gallstone formation and dissolution in man, J. Clin. Invest. 61: 998-1026).

Gallstones have to date been mainly removed surgically so that there is a great therapeutic demand for medical dissolution of gallstones and for the prevention of gallstones forming.

The invention was based on the object of providing compounds which are able to prevent the formation of gallstones by preventing the supersaturation of bile with cholesterol, or by delaying the formation of cholesterol crystals from supersaturated bile.

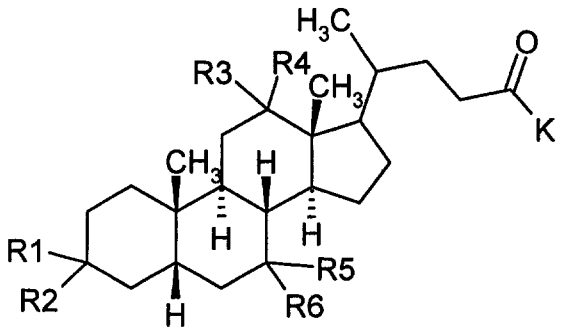
The invention comprises compounds of the formula I

P—L—G

I

in which

G is



G

K is -OR(7), -NR(7)R(8), -HN-CH_2-CH_2-CO_2H, -HN-CH_2-CH_2-SO_3H, -NH-CH_2-CO_2H, -$N(CH_3)CH_2CO_2H$, -HN-CHR(9)CO_2H, -Ocat, where cat is a cation such as, for example, an alkali metal or alkaline earth metal ion or a quaternary ammonium ion;

R(7), R(8) are, independently of one another, hydrogen, (C_1-C_4)-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

R(9) is (C_1-C_4)-alkyl, benzyl, -CH_2-OH, $H_3CSCH_2CH_2$-, HO_2CCH_2-, $HO_2CCH_2CH_2$-;

R(1) to R(6) are, independently of one another, hydrogen, -OR(10), -SR(10), -NR(10)R(13), -OCOR(10), -SCOR(10), -NHCOR(10), -$OPO(OR(10))_2$, -$OSO_2OR(10)$, -R(10), R(1) and R(2), R(3) and R(4), R(5) and R(6) in each case form together the oxygen of a carbonyl group, with always exactly one of the radicals R(1) to R(6) having the meaning of a bond to L;

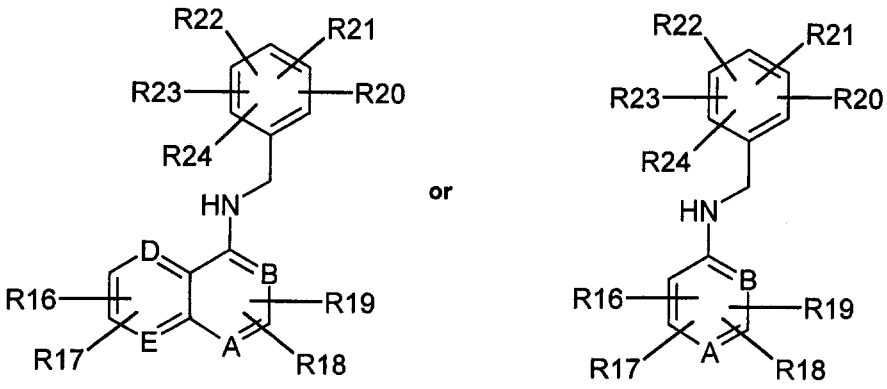
R(10), R(13) are, independently of one another, hydrogen, (C_1-C_4)-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

L is (C_1-C_{15})-alkyl, it being possible for one or more CH_2 units to be replaced by -CH=CH-, -C≡C-, -NR(11)-, -CO-, -O-, $-SO_2-$ or -S-;

R(11) is hydrogen, (C_1-C_8)-alkyl, R(12)-CO-, phenyl, benzyl;

R(12) is hydrogen, (C_1-C_8)-alkyl, phenyl and benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

P is



P P

in which

A is N or CH;
B is N or CH;
D is N or CH;
E is N or CH;

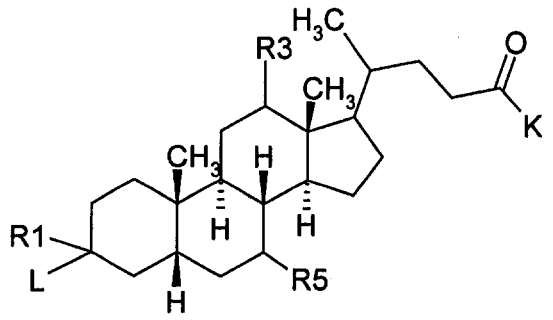
R(16) to R(24) are, independently of one another, hydrogen, F, Cl, Br, I, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine, or are CN, NO_2, NR(25)R(26), OR(25), OCOR(25), COR(25), COOR(25), CONR(25)R(26), $SO_2R(25)$, $SO_2OR(25)$, $SO_2NR(25)R(26)$, with always one of the radicals R(16) to R(24) having the meaning of a bond to L;

R(25), R(26) are, independently of one another, hydrogen, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine, or are phenyl and benzyl;

and the pharmaceutically acceptable salts and physiologically functional derivatives thereof.

Preference is given to compounds of the formula I in which one or more radical(s) have the following meaning

G



G

K -OR(7), -NR(7)R(8), -HN-CH_2-CH_2-CO_2H, -HN-CH_2-CH_2-SO_3H, -NH-CH_2-CO_2H, -N(CH_3)CH_2CO_2H, -HN-CHR(9)CO_2H, -Ocat, where cat is a cation such as, for example, an alkali metal or alkaline earth metal ion or a quaternary ammonium ion;

R(7), R(8) independently of one another hydrogen, (C_1-C_4)-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

R(9) (C_1-C_4)-alkyl, benzyl, -CH_2-OH, $H_3CSCH_2CH_2$-, HO_2CCH_2-, $HO_2CCH_2CH_2$-;

R(1), R(3), R(5) independently of one another hydrogen, -OR(10), NR(10) R(13), -OCOR(10), -NHCOR(10);

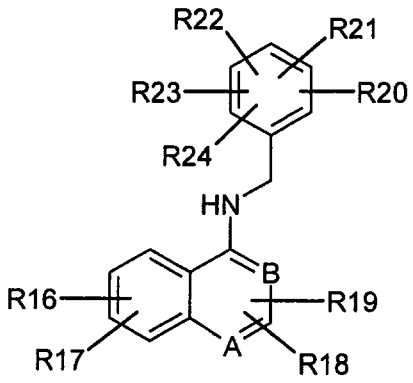
R(10), R(13) independently of one another hydrogen, (C_1-C_4)-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

L (C_1-C_8)-alkyl, it being possible for one or more CH_2 units to be replaced by -CH=CH-, -C≡C-, -NR(11)-, -CO-, -O- or -SO_2-;

R(11) hydrogen, (C_1-C_4)-alkyl, R(12)-CO-, phenyl, benzyl;

R(12) hydrogen, (C_1-C_4)-alkyl, phenyl and benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

P



P

A N or CH;

B N or CH;

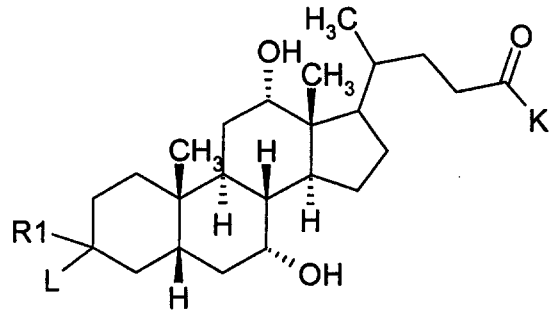
R(16) to R(24) independently of one another hydrogen, F, Cl, Br, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or NR(25)R(26), OR(25), OCOR(25), COR(25), COOR(25), CONR(25)R(26), with always one of the radicals R(16) to R(24) having the meaning of a bond to L;

R(25), R(26) independently of one another hydrogen, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or phenyl, benzyl;

and the pharmaceutically acceptable salts and physiologically functional derivatives thereof.

Particular preference is given to compounds of the formula I in which one or more radical(s) has or have the following meaning

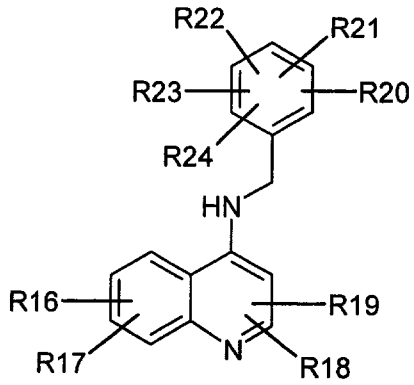
G



G

K	-OR(7), -NR(7) R(8), -HN-CH_2-CH_2-CO_2H, -HN-CH_2-CH_2-SO_3H, -NH-CH_2-CO_2H, -N(CH_3)CH_2CO_2H, -Ocat, where cat is a cation such as, for example, an alkali metal or alkaline earth metal ion or a quaternary ammonium ion;
R(7), R(8)	independently of one another hydrogen, (C_1-C_4)-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;
R(1)	hydrogen, -OH;
L	(C_1-C_5)-alkyl, it being possible for one or more CH_2 units to be replaced by -CH=CH-, -C≡C-, -NR(11)-, -CO-, -O- or -SO_2-;
R(11)	hydrogen, (C_1-C_4)-alkyl, R(12)-CO-, phenyl, benzyl;
R(12)	hydrogen, (C_1-C_4)-alkyl, phenyl and benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

P



P

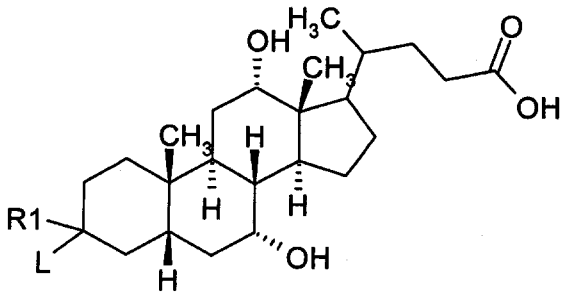
R(16) to R(24) independently of one another hydrogen, F, Cl, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or NR(25)R(26), OR(25), OCOR(25), COR(25), COOR(25), CONR(25)R(26), with always one of the radicals R(16) to R(24) having the meaning of a bond to L;

R(25), R(26) independently of one another hydrogen, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or phenyl and benzyl;

and the pharmaceutically acceptable salts thereof.

Very particular preference is given to compounds of the formula I in which one or more radicals has or have the following meaning

G

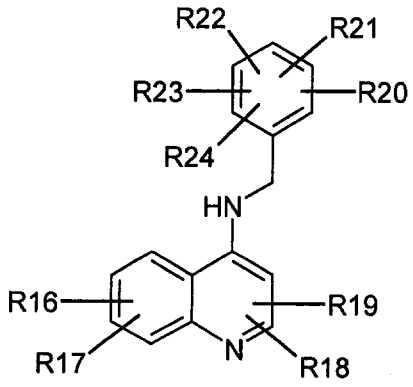


G

R(1) hydrogen, -OH;

L $(C_1\text{-}C_5)$-alkyl, it being possible for one or more CH_2 units to be replaced by -CH=CH-, -C≡C-, -NR(11)-, -CO-, -O- or $-SO_2-$;

P



P

in which

R(16) to R(24) are, independently of one another, hydrogen, F, Cl, $(C_1\text{-}C_4)$-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or NR(25)R(26), OR(25), OCOR(25), COR(25), COOR(25), CONR(25)R(26), with always one of the radicals R(16) to R(24) having the meaning of a bond to L;

R(25), R(26) are, independently of one another, hydrogen , $(C_1\text{-}C_4)$-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or phenyl and benzyl;

and the pharmaceutically acceptable salts thereof.

If the compounds of the formula I contain one or more centers of asymmetry, these may have either the S or the R configuration. The compounds may be in the form of optical isomers, diastereomers, racemates or mixtures thereof.

The expression "it being possible for the alkyl radical to be substituted one or more times by F" also includes perfluorinated alkyl radicals.

The defined alkyl radicals may be either straight-chain or branched.

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

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

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

The physiologically functional derivatives include prodrugs of the novel compounds. Such prodrugs can be metabolized in vivo to a novel compound. These progrugs may or may not themselves have activity.

The novel compounds may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the novel compounds form part of the invention and are a further aspect of the invention.

All references to "compound(s) of formula (I)" hereinafter refer to compound(s) of the formula (I) as described above, and their salts, solvates and physiologically functional derivatives as described herein.

The amount of compound of formula (I) necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient.

The daily dose is generally in the range from 0.1 mg to 100 mg (typically from 0.1 mg to 50 mg) per day and per kilogram body weight, 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 aforementioned weight data relate to the weight of the salt of the compound of the formula I. For prophylaxis or therapy of the abovementioned conditions, the compounds of formula (I) can be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with a compatible carrier. The carrier must, of course, be compatible in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as single dose, for example as tablet which may contain from 0.05% to 95% by weight of the active ingredient. Further pharmaceutically active substances may likewise be present, including further compounds of formula (I). The novel pharmaceutical compositions can be produced by one of the known pharmaceutical methods which consist essentially of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Novel pharmaceutical compositions are those suitable for oral and peroral (for example sublingual) administration although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the particular compound of formula (I) used. The invention also embraces coated formulations and coated slow-release formulations. Formulations resistant to acid and gastric fluid are preferred. Suitable coatings resistant to gastric fluid comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid methyl methacrylate.

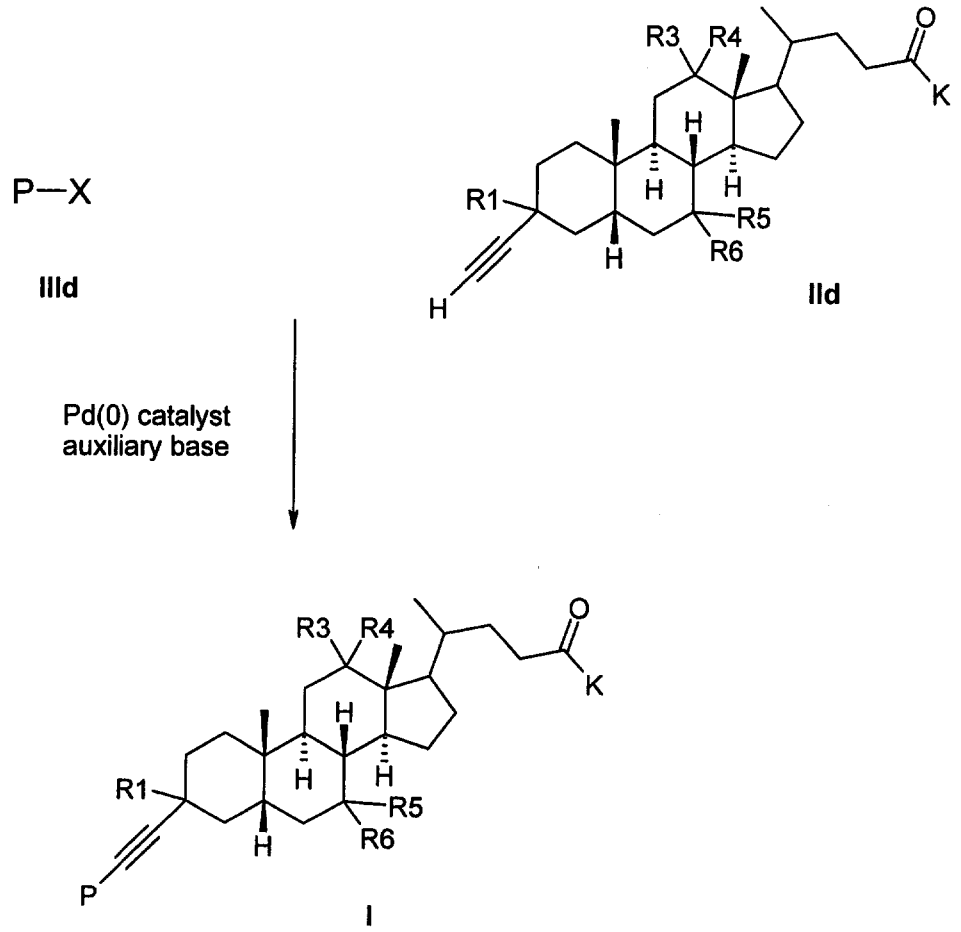
Suitable pharmaceutical compounds for oral administration may be in the form of separate units such as, for example, capsules, cachets, pastilles or

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

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

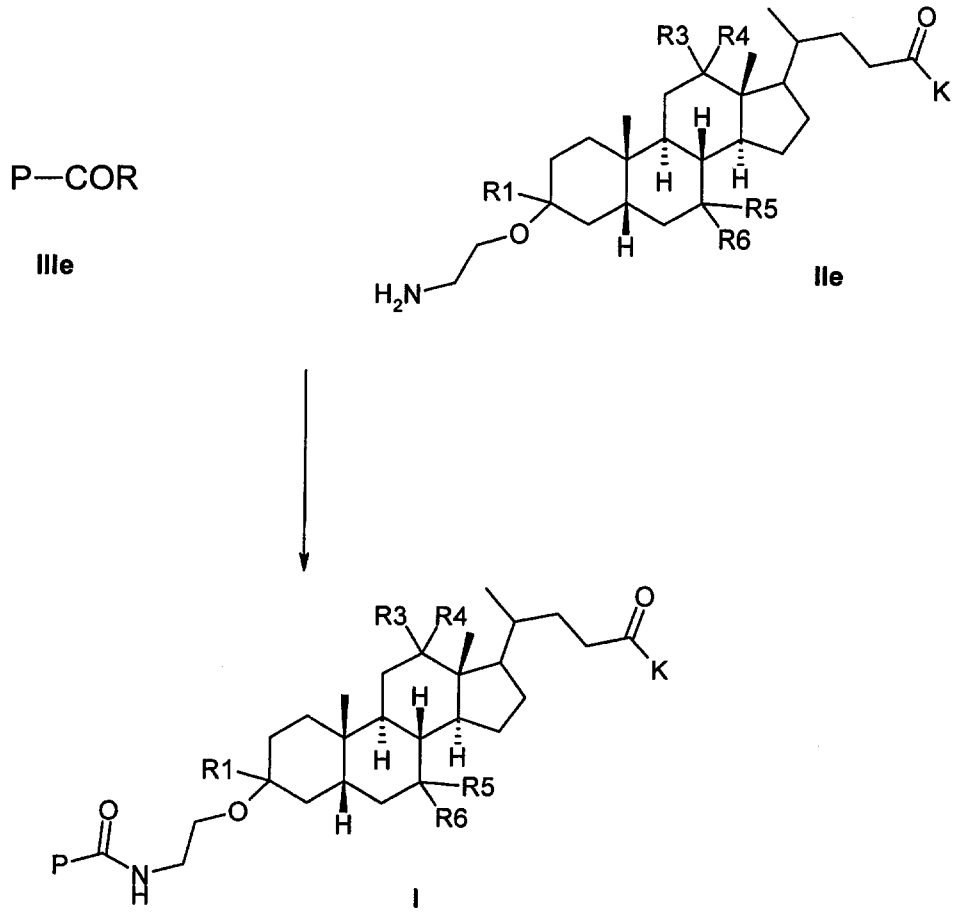
The invention further relates to two processes for preparing the compounds of the formula I.

Process A) This entails a compound of the formula IIId where X is, for example, Br or I being reacted with IId in a Pd(0)-catalyzed coupling reaction. The HX liberated thereby is trapped by an auxiliary base (such as, for example, triethylamine or pyridine).



R1, R2, R3, R4, R5, K and P have the abovementioned meaning. The acetylene-bile acid derivatives of the formula IId are prepared from suitable bile acid ketones. For this purpose, lithium acetylide is added onto keto-bile acids in analogy to known processes (US 5,641,767).

Process B) Carboxylic acids of the formula IIIe (R = OH) are reacted with compounds of the formula IIe in a known manner in the presence of suitable coupling reagents such as, for example, TOTU (Chemiker Zeitung, 98 (1974), 817), DCC/HOBt (J. Am. Chem. Soc., 77 (1955), 1067) or CMC/HOBt (J. Org. Chem., 21 (1956), 439), (see abbreviations) by which means an amide linkage is formed. It is likewise possible to prepare the carboxamides I shown by reacting activated carboxylic acid derivatives IIIe with compounds of the formula IIe in the presence of an auxiliary base (for example triethylamine or pyridine) in a manner known to the skilled worker. Activated carboxylic acid derivatives which should be mentioned in this connection are, for example, the corresponding chlorides (R = Cl), imidazolides (R = 1-imidazolyl; Angew. Chem. Int. Ed. Engl.,1 (1962), 351) or the mixed anhydrides with Cl-COOEt or tosyl chloride.



R1, R2, R3, R4, R5, K and P have the abovementioned meaning. The 3-ethanolamine-bile acid building blocks of the formula IIe are moreover prepared by known processes (Tetrahedron Lett., 34 (1993), 817).

The compounds of the formula I and their pharmaceutically acceptable salts and physiologically functional derivatives are distinguished by having a beneficial effect on the composition of bile and prevent the formation of gallstones by preventing supersaturation of the bile with cholesterol, or by delaying the formation of cholesterol crystals from supersaturated bile. The compounds can be employed alone or in combination with lipid-lowering active ingredients (see Rote Liste, chapter 58). The compounds are particularly suitable for the prophylaxis and for the treatment of gallstones.

The novel compounds of the formula (I) enter the hepatobiliary system and therefore act in these tissues. Thus, the absorption of water from the gall bladder is inhibited through inhibition of the apical NHE antiport of subtype 3 of the gall bladder epithelium, which results in a diluted bile.

Biological testing of the novel compounds took place by measuring the inhibition of the sodium / proton exchanger subtype 3.

1. Test description

The remaining activity of the human NHE-3 protein (expressed in the LAP1 cell line) was determined by measuring the recovery in the intracellular pH (pH_i) after an acidification, which starts when the NHE is capable of functioning, even under bicarbonate-free conditions. For this purpose, the pH_i was determined using the pH-sensitive fluorescent dye BCECF (Calbiochem, the precursor BCECF-AM is employed). The cells were initially loaded with BCECF. The BCECF fluorescence was determined in a "ratio fluorescence spectrometer" (Photon Technology International, South Brunswick, N.J., USA) with excitation wavelengths of 505 and 440 nm and an emission wavelength of 535 nm, and was converted into the pH_i using calibration plots. The cells were incubated in NH_4Cl buffer (pH 7.4) (NH_4Cl buffer: 115 mm NaCl, 20 mm NH_4Cl, 5 mm KCl, 1 mm $CaCl_2$, 1 mm $mgSO_4$, 20 mm Hepes, 5 mm glucose, 1 mg/ml BSA; a pH of 7.4 is adjusted with 1 M NaOH) even during the BCECF loading. The intracellular acidification was induced by addition of 975 µl of an NH_4Cl-free buffer (see below) to 25 µl aliquots of the cells incubated in NH_4Cl buffer. The subsequent rate of pH recovery was recorded for 3 minutes. To calculate the inhibitory power of the tested substances, the cells were initially investigated in buffers in which complete or absolutely no pH recovery took place. For complete pH recovery (100%), the cells were incubated in Na^+-containing buffer (133.8 mm NaCl, 4.7 mm KCl, 1.25 mm $CaCl_2$, 1.25 mm $mgCl_2$, 0.97 mm Na_2HPO_4, 0.23 mm NaH_2PO_4, 5 mm Hepes, 5 mm glucose, a pH of 7.0 is adjusted with 1 M NaOH). To determine the 0% value, the cells were incubated in an Na^+-free buffer (133.8 mm choline chloride, 4.7 mm KCl, 1.25 mm $CaCl_2$, 1.25 mm $mgCl_2$, 0.97 mm K_2HPO_4, 0.23 mm KH_2PO_4, 5 mm Hepes, 5 mm glucose, a pH of 7.0 is adjusted with 1 M NaOH). The substances to be tested were made up in the Na^+-containing buffer. Recovery of the intracellular pH at the tested concentration of a substances was expressed as a percentage of the maximum recovery.

Results:

Example 1:	remaining activity of hNHE3 at 30 µM = 26 %
Example 2:	remaining activity of hNHE3 at 30 µM = 33 %
Example 3:	remaining activity of hNHE3 at 30 µM = 22 %
Example 6:	remaining activity of hNHE3 at 30 µM = 39 %
Example 11:	remaining activity of hNHE3 at 30 µM = 61 %
Example 13:	remaining activity of hNHE3 at 30 µM = 40 %
Example 14:	remaining activity of hNHE3 at 30 µM = 52 %
Example 15:	remaining activity of hNHE3 at 30 µM = 65 %
Example 16:	remaining activity of hNHE3 at 30 µM = 27 %
Example 17:	remaining activity of hNHE3 at 30 µM = 36 %
Example 18:	remaining activity of hNHE3 at 30 µM = 36 %
Example 20:	remaining activity of hNHE3 at 30 µM = 56 %
Example 23:	remaining activity of hNHE3 at 30 µM = 16 %
Example 24:	remaining activity of hNHE3 at 30 µM = 29 %
Example 25:	remaining activity of hNHE3 at 30 µM = 18 %
Example 26:	remaining activity of hNHE3 at 30 µM = 52 %
Example 27:	remaining activity of hNHE3 at 30 µM = 54 %
Example 28:	remaining activity of hNHE3 at 30 µM = 69 %
Example 29:	remaining activity of hNHE3 at 30 µM = 61 %
Example 30:	remaining activity of hNHE3 at 30 µM = 48 %
Example 31:	remaining activity of hNHE3 at 30 µM = 69 %

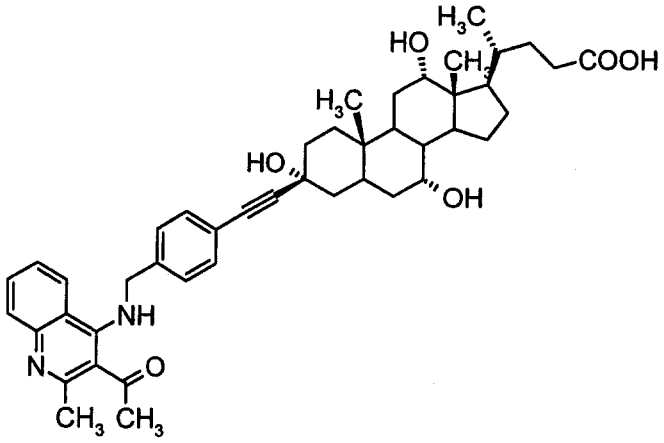
List of abbreviations:

Me	methyl
LAH	lithium aluminum hydride
DMF	N,N-dimethylformamide
EI	electron impact
CI	chemical ionization
RT	room temperature
EA	ethyl acetate
mp	melting point
HEP	n-heptane
DME	dimethoxyethane
ES	electron spray
FAB	fast atom bombardment
THF	tetrahydrofuran
eq.	equivalent
TOTU	O-[(ethoxycarbonyl)cyanomethyleneamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate
HOBt	1-hydroxybenzotriazole
CMC	N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide methyl-p-toluenesulfonate
DCC	dicyclohexylcarbodiimide

The following examples serve to illustrate the invention in detail without restricting the latter to products and embodiments described in the examples.

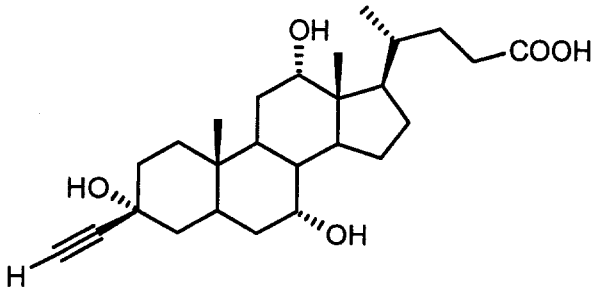
Example 1

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]-benzyl}aminoquinoline



Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



Synthetic route:

a) Methyl 3,7,12-triacetylcholate

90 g of methyl cholate and 3.0 g of dimethylaminopyridine were dissolved in 500 ml of pyridine and, after addition of 500 ml of acetic anhydride, stirred at room temperature overnight. The mixture was poured into ice-water and extracted with ethyl acetate (3x). Drying ($MgSO_4$) and evaporation of the organic phase afforded 92 g of methyl 3,7,12-triacetylcholate, MS(FAB): M^++Li = 555.

b) Methyl 7,12-diacetylcholate

At 5°C, 150 ml of acetic anhydride were slowly added dropwise to 1.5 l of methanol. After 15 minutes, 92 g of methyl 3,7,12-triacetylcholate were added, and the mixture was stirred at room temperature for 1 h. It was poured into ice-water and extracted with ethyl acetate (3x). The organic phase was washed with 1N Na_2CO_3 solution, dried with $mgSO_4$ and evaporated. 85 g of crude product were obtained, MS(FAB): M^++Li = 513.

c) Methyl 3-keto-7,12-diacetylcholate

85 g (168 mmol) of methyl 7,12-diacetylcholate, 183.7 g of pyridinium chlorochromate and 175 g of molecular sieves were stirred in 2.5 l of

dichloromethane at room temperature for 2 h. The mixture was poured into 7 l of diethyl ether, and the solids were filtered off. The solvent was evaporated and the residue was dissolved in ethyl acetate. Chromatography on a Florisil column resulted in 59.6 g of product, MS(FAB): M^++Li = 511.

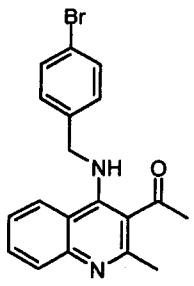
d) Methyl 3β-acetylene-7,12-diacetylcholate

Acetylene was passed into 750 ml of abs. tetrahydrofuran at –55°C under argon for 25 min. 145 ml of 15% n-butyllithium in hexane were added dropwise to this solution, followed by stirring for 10 min. Then 45 g (89 mmol) of methyl 3-keto-7,12-diacetylcholate were added and the mixture was stirred at –40°C for 1.5 h. For workup, 500 ml of saturated aqueous ammonium chloride solution were added and, after extraction with ethyl acetate (3x) , the organic phase was dried over $mgSO_4$ and evaporated. The residue was chromatographed on silica gel (n-heptane/ethyl acetate 1:1). 35.3 g of product were obtained, MS(FAB): M^++Li = 537.

e) 3β-Acetylenecholic acid

35.2 g (66 mmol) of the product from d) were dissolved in 1 l of methanol and, after addition of 300 ml of 2N sodium hydroxide solution, heated under reflux for 25 h. The solvent was evaporated, and the residue was dissolved in water and acidified to pH 2 with 2N hydrochloric acid. The precipitate was filtered off and washed with water to neutrality. Drying of the residue afforded 14.6 g of product, MS(FAB): M^++Li = 439.

Intermediate 2: 2-Methyl-3-(aceto-1-yl)-4-(4-bromobenzyl)aminoquinoline



Synthetic route

a) 2-(1-Methyl-3-oxobut-1-enylamino)benzonitrile prepared by standard methods from 2-aminobenzonitrile (Eur. Pat. Appl., C07D 215/42; J.

Med. Chem., 31 (1988), 1278); yellow solid, melting point: 100°C; MS(CI): M^++H = 201.

b) 1-(4-Amino-2-methylquinolin-3-yl)ethanone can be prepared starting from 2-(1-methyl-3-oxobut-1-enylamino)benzonitrile by cyclization with CuCl and K_2CO_3 (J. Med. Chem., 31 (1988), 1278) or NaOMe-promoted (Eur. Pat. Appl., C07D 215/42) by a known process; yellow solid; MS(CI): M^++H = 201.

c) 1-(4-(4-Bromobenzylamino-2-methylquinolin-3-yl)ethanone
In a two-phase system consisting of 75 ml of CH_2Cl_2 and 55 ml of 50% strength NaOH, 1.8 g of 1-(4-amino-2-methylquinolin-3-yl)ethanone are mixed with 0.15 eq of tetrabutylammonium hydrogen sulfate and vigorously stirred at room temperature for 30 min. Then 1.1 eq of 4-bromobenzyl bromide are added and the mixture is vigorously stirred at room temperature for 4 to 5 h. For workup, the two phases are separated, the aqueous is then extracted 2 x with CH_2Cl_2, and the combined organic phases are then washed 2 x with H_2O and dried with $mgSO_4$. The solvent is distilled off and the residue is purified on silica gel (300 g; CH_2Cl_2 / MeOH 98:2), resulting in the title compound as a colorless glassy solid. MS(ES+): M^++H = 369.

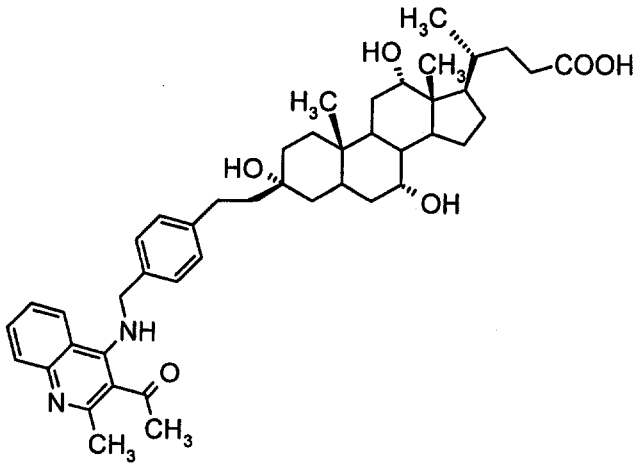
General method for the Pd(0)-catalyzed coupling reaction
The bromoaryl compound (1.0 eq) and the bile acid-acetylene building block (1.5 eq) are introduced into DMF / triethylamine (2:1) and the solution is degassed. After flushing with argon, 0.1 eq each of $Pd(PPh_3)_2Cl_2$ and 0.1 eq of CuI are added and the reaction solution is heated to 80°C. Depending on the progress of the reaction it is worthwhile to add further catalyst or raise the temperature further, possibly up to 100°C. For workup, the solvent is removed and the crude product obtained in this way is purified on silica gel with a CH_2Cl_2/MeOH mixture.

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12 α-trihydroxy-10β,13 β-dimethyl-17β–(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]benzyl}aminoquinoline

Carrying out the reaction by the general method affords after 21 h at 100°C a yellow-orange solid, melting point: 178°C (decomposition), MS(ES+): M^++H = 772.

Example 2:

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)eth-2-yl]benzyl}aminoquinoline

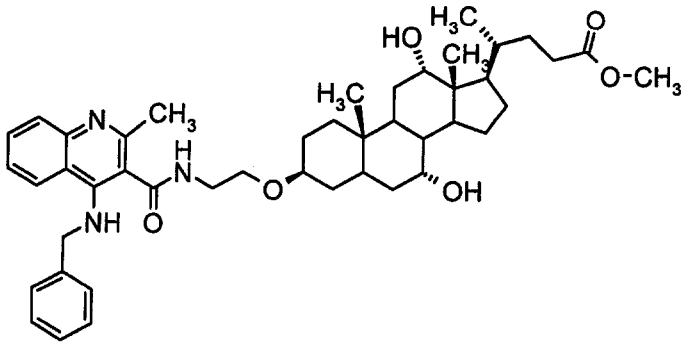


The product obtained above from Example 1 is dissolved in 1:1 ethanol/methanol and, after addition of Pd/C (10%), shaken under an H_2 atmosphere until the conversion is complete. Removal of the Pd catalyst by filtration and of the solvent by distillation provides the hydrogenated product as a yellowish crystalline solid.

Melting point: 172°C (decomposition); MS(ES+): M^++H = 726.

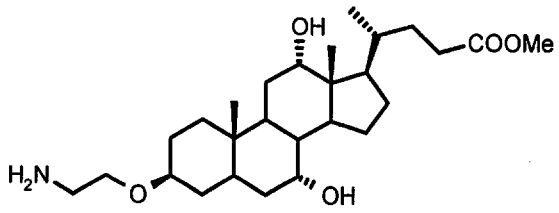
Example 3:

2-Methyl-4-aminobenzylquinoline-3-carboxylic acid N-{2-O-[7α,12α-dihydroxy-10β,13β-dimethyl-17β-(methyl pentanoate-4-yl)hexadecahydrocyclopenta[a]phenanthren-3β-yl]}ethylamide



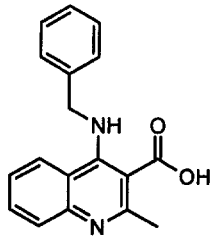
Preparation of the intermediates:

Intermediate 1: Methyl 3β-O-(1-aminoet-2-yl)cholate



The title compound can be prepared in a manner known from the literature starting from cholic acid in six steps (Tetrahedron Lett., 33 (1992), 195; Tetrahedron Lett., 34 (1993), 817).

Intermediate 2: 4-Benzylamino-2-methylquinoline-3-carboxylic acid



Synthetic route:

a) Methyl 4-amino-2-methylquinoline-3-carboxylate is prepared by a method known to the skilled worker (Tetrahedron, 51 (1995), 12277). MS(CI): M^++H = 217.

b) Methyl 4-benzylamino-2-methylquinoline-3-carboxylate is synthesized by the same method as described for 1-(4-(4-bromobenzylamino-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from methyl 4-amino-2-methylquinoline-3-carboxylate and benzyl bromide. MS(ES+): M^++H = 307.

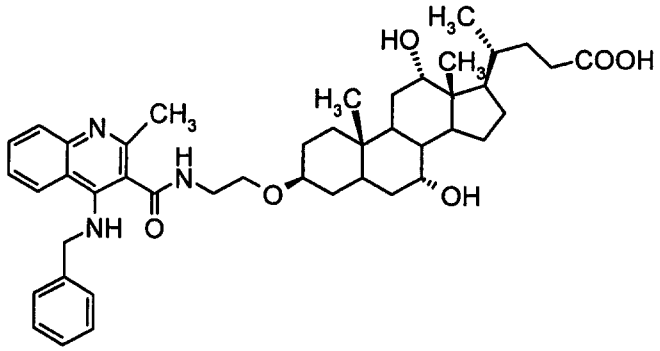
c) 4-Benzylamino-2-methylquinoline-3-carboxylic acid is prepared by hydrolyzing the methyl ester with KOH (5 eq) in ethanolic solution. After conversion is complete, the solvent is removed and the crude product is taken up in 2N NaOH. The aqueous solution is extracted with CH_2Cl_2, the phases are separated and the aqueous phase is neutralized with 2N HCl, whereupon the title compound precipitates. Filtering off and drying provides a colorless solid. Melting point: 190°C; MS(CI): M^++H = 293, M^+-CO_2 = 249.

2-Methyl-4-aminobenzylquinoline-3-carboxylic acid N-{2-O-[7α,12α-dihydroxy-10β,13β-dimethyl-17β-(methyl pentanoate-4-yl)hexadecahydrocyclopenta[a]phenanthren-3β-yl]}ethylamide as trifluoroacetate.

Intermediate 1 (1.0 eq) and intermediate 2 (1.0 eq) are introduced into DMF and, after addition of 1.0 eq of HOBt, at 0°C a solution of 1.1 eq of CMC in DMF is added. If necessary, additional CMC is added and/or the temperature is increased, possibly up to 60°C. For workup, the solvent is removed, and the residue is taken up in ethyl acetate and washed 2 x with saturated $NaHCO_3$. The $NaHCO_3$ phases are extracted once more with ethyl acetate, and the combined organic extracts are washed 2 x with H_2O, dried with $mgSO_4$ and evaporated. The crude product obtained in this way was purified by preparative HPLC, resulting in the title compound as a pale yellowish solid. Melting point: 102°C; MS(ES+): M^++H = 741.

Example 4:

2-Methyl-4-aminobenzyl quinoline-3-carboxylicacid N-{2-O-[7α,12α-dihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3β-yl]}-ethylamide

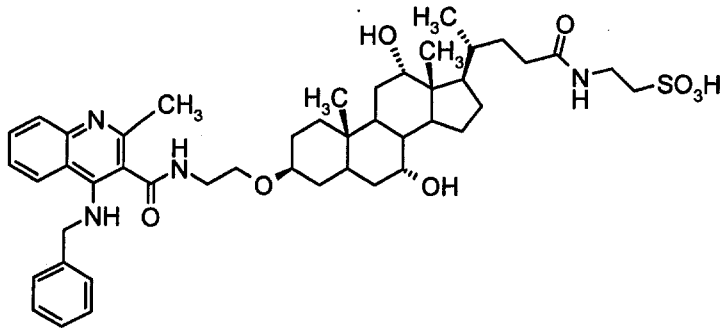


The product from Example 3 is mixed with 5.0 eq of KOH in a methanol/H_2O mixture and stirred at a temperature between room temperature and 50°C. If necessary, additional KOH is added until complete conversion is reached. The solvent is then removed, and the residue is taken up in H_2O and neutralized with 1N HCl. The resulting precipitate is filtered off then dried, resulting in the product as a colorless solid. Melting point: 143°C; MS(ES+): M^++H = 727.

Example 5:

2-Methyl-4-aminobenzyl quinoline-3-carboxylicacid N-{2-0-[7α,12α-dihydroxy-10β,13β-dimethyl-17β-(pentanoic acid N-(2-sulfonic

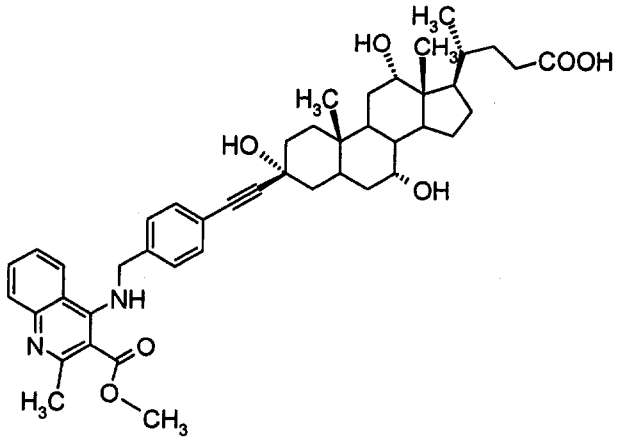
acid)ethylamide-4-yl)hexadecahydrocyclopenta[a]phenanthren-3β-yl]}ethylamide as trifluoroacetate



85 mg of the product acid from Example 3 are dissolved in 5 ml of abs. DMF. At 0°C, a solution of 0.016 ml of NEt_3 in 1 ml of abs. DMF is added, and 1.0 eq of TOTU dissolved in 2 ml of abs. DMF is added dropwise. After stirring at between 0°C and room temperature for 1 h, the resulting solution is added to a mixture of 1.0 eq of taurine, 1 ml of NEt_3, 2 ml of H_2O and 2 ml of DMF and stirring is continued. For workup, the reaction mixture is concentrated and purified by preparative HPLC, resulting in the title compound as a yellowish solid. Melting point: 180°C; MS(ES+): M^++H = 834.

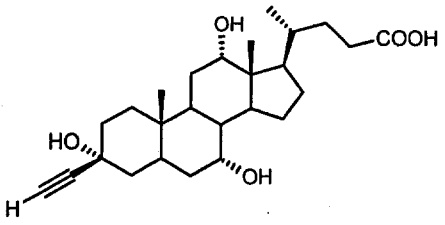
Example 6:

Methyl 2-methyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate



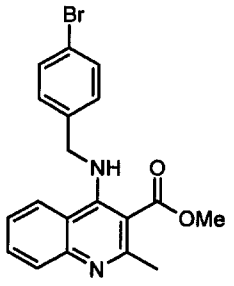
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: Methyl 4-(4-bromobenzylamino)-2-methylquinoline-3-carboxylate



Synthetic route:

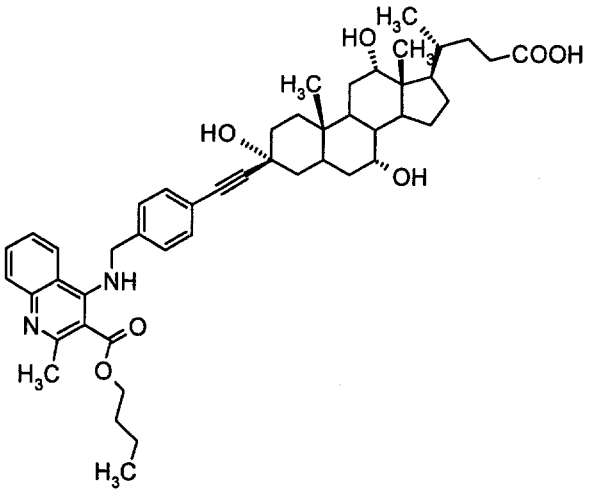
a) Methyl 4-amino-2-methylquinoline-3-carboxylate can be prepared in a manner known to the skilled worker (Tetrahedron 51 (1995), 12277).

b) Methyl 4-(4-bromobenzylamino)-2-methylquinoline-3-carboxylate is synthesized by the same method as described for 1-(4-(4-bromobenzylamino-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from methyl 4-amino-2-methylquinoline-3-carboxylate and 4-bromobenzyl bromide. Melting point: 89°C; MS(ES+): 385/387.

Methyl 2-methyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate is prepared by the general process indicated (see Example 1, p. 18). Melting point: 165°C; MS(FAB): 737.

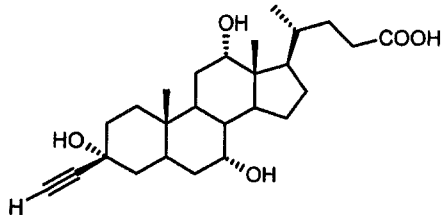
Example 7:

n-Butyl 2-methyl-4-{4-[1-(3α,7α,12α,trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate



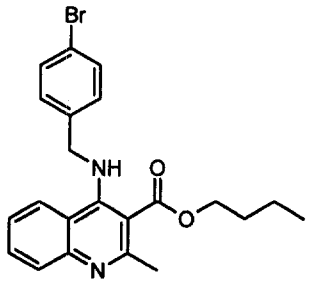
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: n-Butyl 4-(4-bromobenzylamino)-2-methylquinoline-3-carboxylate



Synthetic route:

a) n-Butyl 4-(4-bromobenzylamino)-2-methylquinoline-3-carboxylate

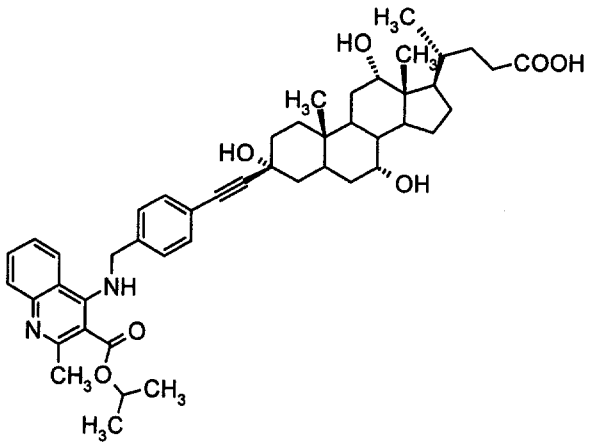
200 mg (1.0 eq) of methyl 4-(4-bromobenzylamino)-2-methylquinoline-3-carboxylate (see Example 5) are dissolved in an n-butanol/THF mixture and, at room temp., 2.5 eq of NaH (55%) are added and the mixture is stirred with exclusion of moisture for 2 h. For workup, the solvent is removed and the residue is taken up in CH_2Cl_2. It is washed [lacuna] H_2O and the aqueous phase is extracted once more with

CH_2Cl_2. The combined organic phases are washed with saturated $NaHCO_3$ solution and dried with $mgSO_4$. Chromatography on silica gel (ethyl acetate/n-heptane 1:1 → 4:1) provides the product ester as a colorless solid. Melting point: 116°C; MS(ES+): 427/429.

n-Butyl 2-methyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate is prepared by the general process indicated (see Example 1). Melting point: 70°C; MS(FAB): 779.

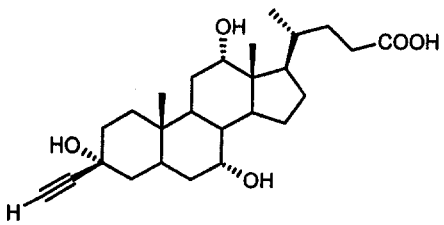
Example 8:

Isopropyl 2-methyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate



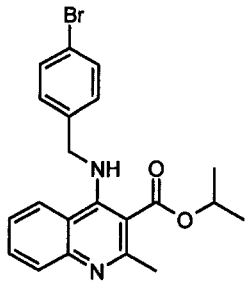
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: Isopropyl 4-(4-bromobenzylamino)-2-methylquinoline-3-carboxylate



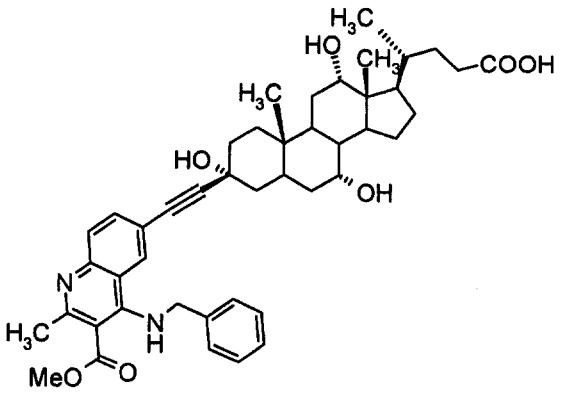
Synthetic route:

a) Isopropyl 4-(4-bromobenzylamino)-2-methylquinoline-3-carboxylate is prepared in analogy to n-butyl 4-(4-bromobenzylamino)-2-methylquinoline-3-carboxylate (see Example 6) by transesterification of the corresponding methyl ester in an isopropanol/THF mixture, resulting in the title compound as a colorless oil. MS(ES+): 413/415.

Isopropyl 2-methyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate is prepared by the general process indicated (see Example 1, p.18). Melting point: 150°C; MS(FAB): 765.

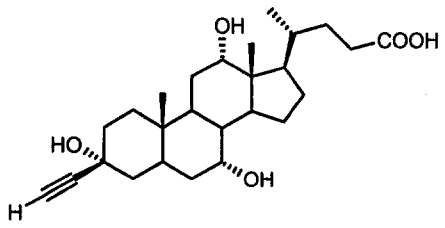
Example 9:

Methyl 2-methyl-4-benzylamino-6-{2-[3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl]ethyn-1-yl}quinoline-3-carboxylate



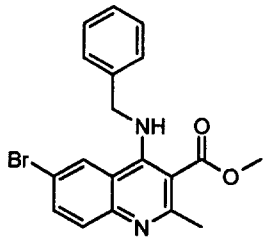
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: Methyl 4-(4-bromobenzylamino)-2-methylquinoline-3-carboxylate



Synthetic route:

a) 5-Bromo-2-aminobenzonitrile can be prepared in a manner known from the literature (Synlett, 1994, 450); MS(CI): 197/199.

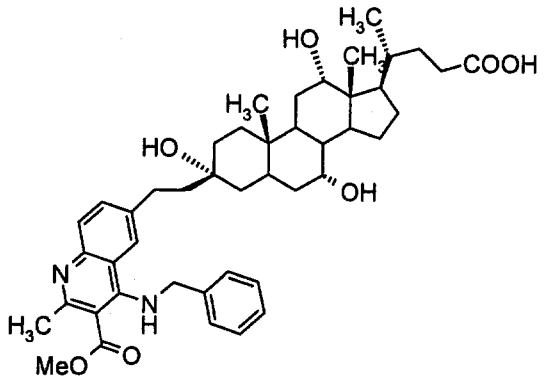
b) Methyl 6-bromo-4-amino-2-methylquinoline-3-carboxylate can be prepared in a manner known to the skilled worker (Tetrahedron 51 (1995), 12277).

c) Methyl 6-bromo-4-benzylamino-2-methylquinoline-3-carboxylate is synthesized by the same process as described for 1-(4-(4-bromobenzylamino)-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from methyl 6-bromo-4-amino-2-methylquinoline-3-carboxylate and 4-bromobenzyl bromide. Melting point: 89°C; MS(ES+): 385/387.

Methyl 2-methyl-4-benzylamino-6-{2-[3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl]ethyn-1-yl}quinoline-3-carboxylate is prepared by the general process indicated (see Example 1). Melting point: 223°C (decomposition); MS(ES+): 737.

Example 10:

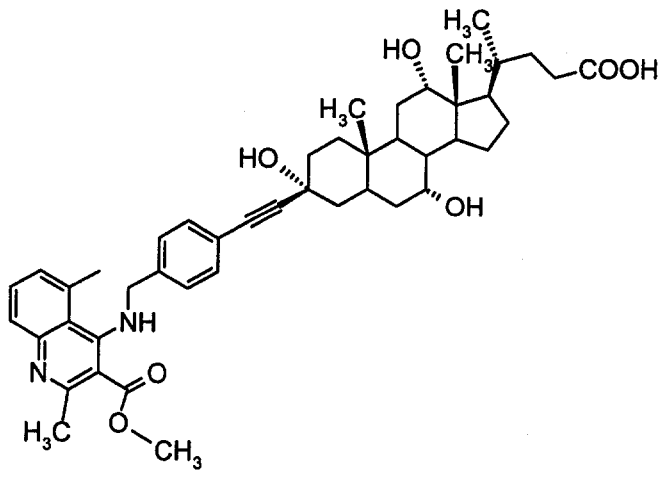
Methyl 2-methyl-4-benzylamino-6-{2-[3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl]eth-1-yl}quinoline-3-carboxylate



The product described in Example 8 is hydrogenated in analogy to the method indicated in Example 2, resulting in the target compound as a pale yellow solid. Melting point: > 185°C (decomposition); MS(FAB): 741.

Example 11

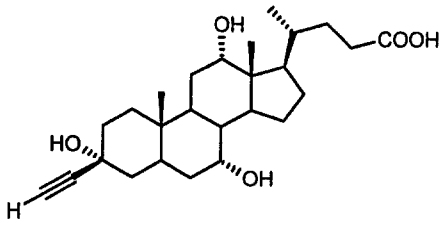
Methyl 2,5-dimethyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate



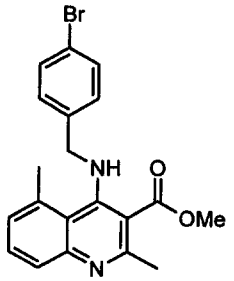
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid

see Example 1



Intermediate 2: Methyl 4-(4-bromobenzylamino)-2,5-dimethylquinoline-3-carboxylate



Synthetic route:

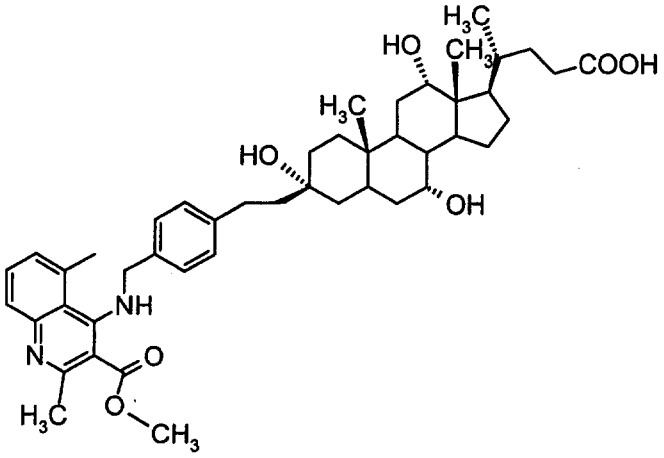
a) Methyl 4-amino-2,5-dimethylquinoline-3-carboxylate can be prepared in analogy to Intermediate 2a, Example 6, in a manner known to the skilled worker (Tetrahedron 51 (1995), 12277).

b) Methyl 4-(4-bromobenzylamino)-2,5-dimethylquinoline-3-carboxylate is synthesized by the same process as described for 1-(4-(4-bromobenzylamino)-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from methyl 4-amino-2,5-dimethylquinoline-3-carboxylate and 4-bromobenzyl bromide. Melting point: 150°C; MS(CI+): 399/401.

Methyl 2,5-dimethyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate is prepared by the general process indicated (see Example 1). Melting point: > 155°C; MS(ES+): M^++H = 751.

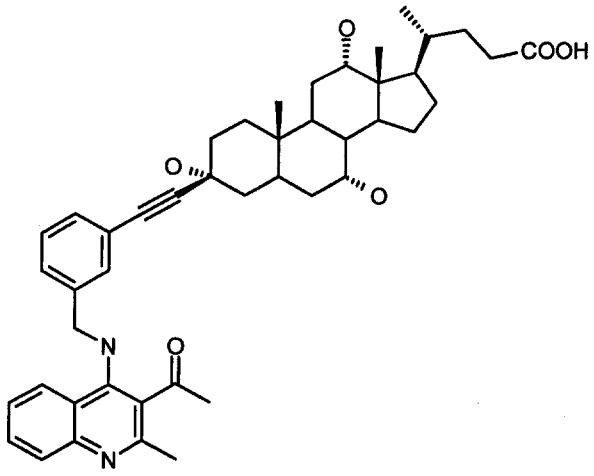
Example 12:

Methyl 2,5-dimethyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)eth-2-yl]benzyl}aminoquinoline-3-carboxylate

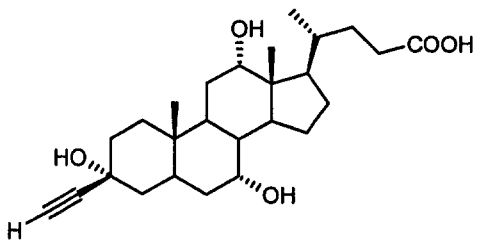


The product described in Example 11 is hydrogenated in analogy to the method indicated in Example 2, resulting in the target compound as a pale yellow solid. Melting point: > 180°C decomposition; MS(ES+): M^++H = 756.

Example 13:
2-Methyl-3-(aceto-1-yl)-4-{3-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]benzyl}aminoquinoline

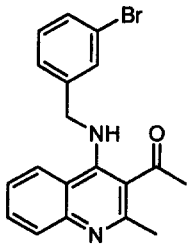


Preparation of the intermediates:
Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: 1-(4-(3-Bromobenzyl)amino-2-methylquinolin-3-yl)ethanone



Synthetic route:

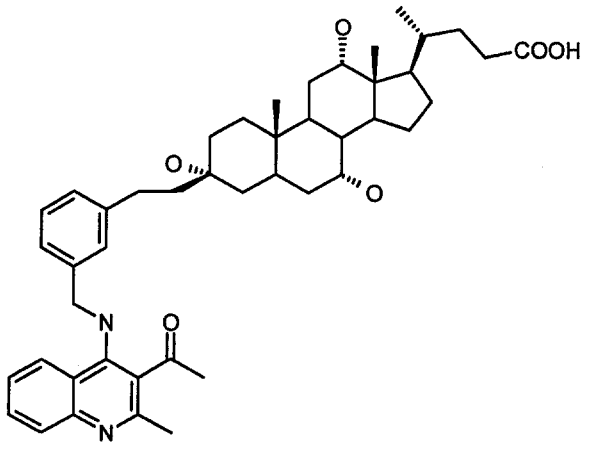
a) 1-(4-Amino-2-methylquinolin-3-yl)ethanone can be prepared in analogy to Intermediate 2a, Example 6, by tin tetrachloride-promoted reaction of 2-aminobenzonitrile and acetyl acetone in a manner known from the literature (Tetrahedron 51 (1995), 12277).

b) 1-(4-(3-Bromobenzyl)amino-2-methylquinolin-3-yl)ethanone is synthesized by the same process as described for 1-(4-(4-bromobenzyl)amino-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from 1-(4-amino-2-methylquinolin-3-yl)ethanone and 3-bromobenzyl bromide. Melting point: 109°C; MS(ES+): 369/371.

2-Methyl-3-(aceto-1-yl)-4-{3-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline is prepared by the general process indicated (see Example 1). Melting point: > 195°C decomposition; MS(ES+): M^++H = 721.

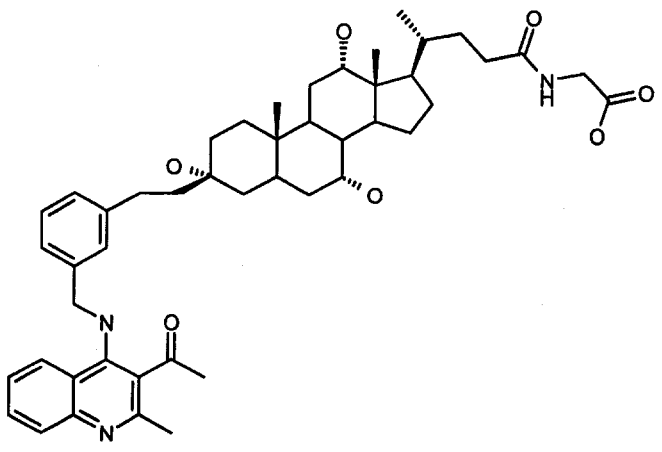
Example 14:

2-Methyl-3-(aceto-1-yl)-4-{3-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethylene-2-yl]benzyl}aminoquinoline



The title compound is obtained by catalytic hydrogenation, as described in Example 2, of the product described in Example 13. Melting point: > 170°C decomposition; MS(FAB+): M^+ = 725.

Example 15:
2-Methyl-3-(aceto-1-yl)-4-{3-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid N-glycylamide-4-yl)hexadecahydrocyclopenta[a]-phenanthren-3-yl)ethylene-2-yl]benzyl}aminoquinoline



Synthetic route:

a) 2-Methyl-3-(aceto-1-yl)-4-{3-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid (N-glycidylethyl ester)amide-4-yl)hexadecahydro-cyclopenta[a]phenanthren-3-yl)ethylene-2-yl]benzyl}aminoquinoline.
55 mg of the product prepared in Example 14 are introduced into 5 ml of abs. DMF and, at 0°C, 1 ml of a solution of 0.1 ml of triethylamine in 10 ml of abs. DMF is added. Addition of 25 mg of TOTU is followed by stirring at 0°C for 20 min and at room temperature for 30 min. This

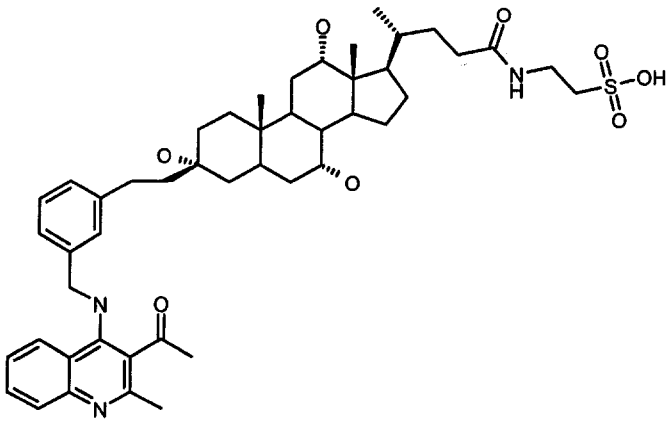
solution is added to a solution consisting of 11 mg of glycine ethyl ester hydrochloride in 2 ml of DMF, 2 ml of H_2O and 1 ml of triethylamine and stirred at room temperature until the conversion is complete. The solvent is distilled off and the residue is chromatographed on silica gel, resulting in 41 mg of the corresponding ethyl ester.

b) 2-Methyl-3-(aceto-1-yl)-4-{3-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid N-glycylamide-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethylene-2-yl]benzyl}aminoquinoline.

41 mg of the prepared ethyl ester are dissolved in 5 ml of methanol and, at room temperature, a solution of 28 mg of KOH in 1.5 ml of H_2O is added dropwise and stirred at room temperature. After 2 hours, the solvent is removed, and the residue is taken up in 5 ml of H_2O and a pH of 5 is adjusted with dilute HCl, whereupon the required product precipitates. The precipitate is filtered off with suction and dried in air. MS(ES+): M^++H: 782.

Example 16:

2-Methyl-3-(aceto-1-yl)-4-{3-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid N-(2-sulfonic acid)ethylamide-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethylene-2-yl]benzyl}aminoquinoline

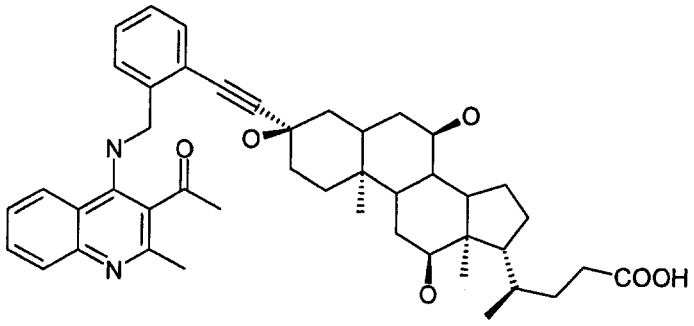


55 mg of the product prepared in Example 14 are introduced into 5 ml of abs. DMF and, at 0°C, 1 ml of a solution of 0.1 ml of triethylamine in 10 ml of abs. DMF is added. Addition of 25 mg of TOTU is followed by stirring at 0°C for 20 min and at room temperature for 30 min. This solution is added to a solution consisting of 10 mg of taurine in 2 ml of DMF, 2 ml of H_2O and 1 ml of triethylamine and stirred at room temperature until conversion is complete. The solvent is removed, and the residue is chromatographed on

silica gel, resulting in 36 mg of the title compound in the form of a pale yellowish solid. MS(ES+): M^++H: 832.

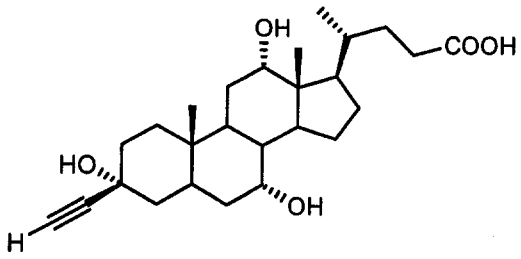
Example 17:

2-Methyl-3-(aceto-1-yl)-4-{2-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]benzyl}aminoquinoline



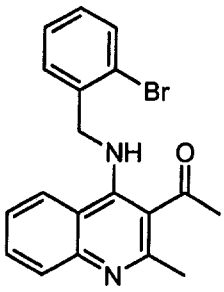
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: 1-(4-(3-Bromobenzyl)amino-2-methylquinolin-3-yl)ethanone



Synthetic route:

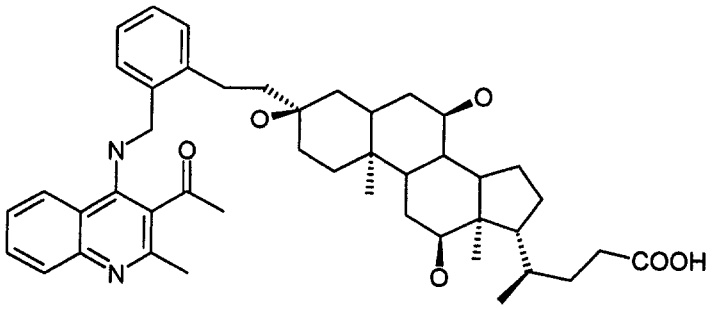
a) 1-4-Amino-2-methylquinolin-3-yl)ethanone: see Example 13 (Tetrahedron 51 (1995), 12277).

b) 4-(2-Bromobenzyl)amino-2-methylquinolin-3-yl)ethanone is synthesized by the same process as described for 1-(4-(4-bromobenzyl)amino-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from 1-(4-amino-2-methylquinolin-3-yl)ethanone and 2-bromobenzyl bromide. Melting point: 134°C; MS(ES+): 369/371.

2-Methyl-3-(aceto-1-yl)-4-{2-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]benzyl}aminoquinoline is prepared by the general process indicated (see Example 1) from the two intermediates. MS(ES+): M^++H = 721.

Example 18:

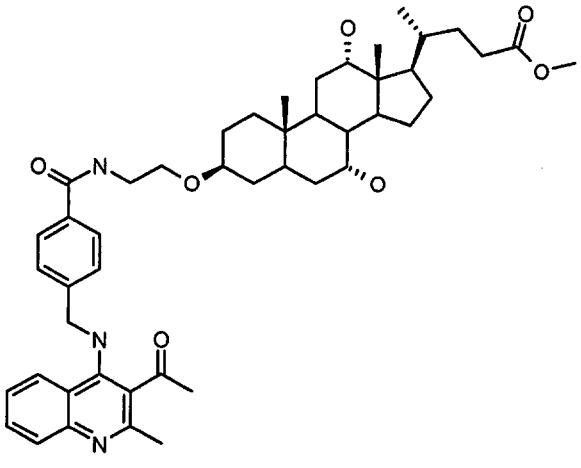
2-Methyl-3-(aceto-1-yl)-4-{2-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethylene-2-yl]benzyl}aminoquinoline



Hydrogenation of the product compound from Example 17 by the method stated in Example 2 provides the required product in the form of a pale yellowish solid. Melting point: > 165°C decomposition; MS(ES+): 725.

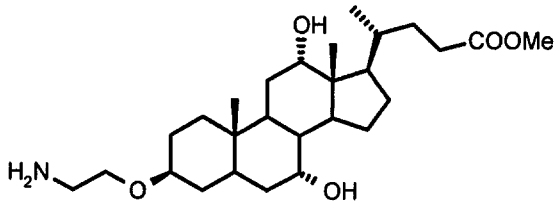
Example 19:

Methyl 4-[3β-(2-{4-[(3-acetyl-2-methylquinolin-4-ylamino)methyl]benzoyl-amino)ethoxy)-7α,12α-dihydroxy-10β,13β-dimethylhexadecahydrocyclo-penta[a]phenanthren-17β-yl]pentanoate



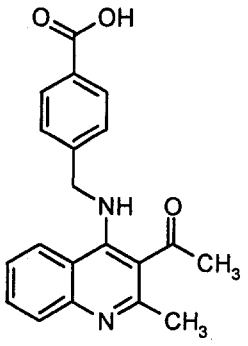
Preparation of the intermediates:

Intermediate 1: Methyl 3β-O-(1-aminoet-2-yl)cholate



see Example 3 (Tetrahedron Lett., 33 (1992), 195; Tetrahedron Lett., 34 (1993), 817).

Intermediate 2: 4-[(3-Acetyl-2-methylquinolin-4-ylamino)methyl]benzoic acid



Synthetic route:

a) 2-Methyl-3-(aceto-1-yl)-4-(4-bromobenzyl)aminoquinoline is described in Example 1 as Intermediate 2.

b) 4-[(3-Acetyl-2-methylquinolin-4-ylamino)methyl]benzoic acid.

370 mg of 2-methyl-3-(aceto-1-yl)-4-(4-bromobenzyl)aminoquinoline, 79 mg of triphenylhosphine and 78 mg of calcium formate are dissolved in 4 ml of

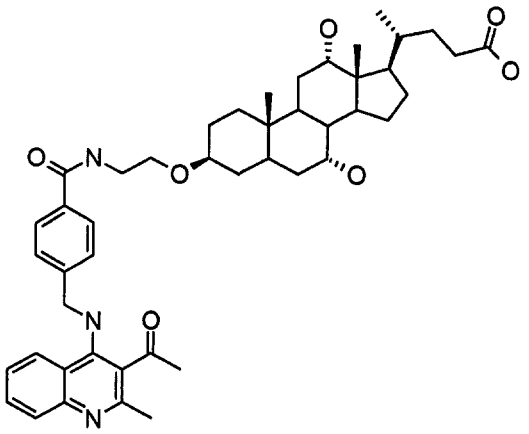
DMF and 4 ml of benzene. Under protective gas, 9 mg of palladium acetate are added and the solution is heated to 120°C under a CO atmosphere. After two hours, 58 mg of tetrakistriphenylphosphine palladium are added and stirring at 120°C is continued. Stirring is continued at the stated temperature until no further increase in conversion can be detected. If necessary, additional palladium catalyst is added. For workup, 2N NaOH is added and the mixture is extracted with dichloromethane. The organic phase is extracted once again with 2N NaOH, and the combined aqueous phases are extracted with dichloromethane. The NaOH extracts are adjusted to a pH of 6 with 6N HCl and concentrated in vacuo. The residue is taken up in a little methanol. Insoluble salts are filtered off. The filtrate is concentrated and taken up in a little H_2O. The product results as a yellow insoluble solid, which is filtered off with suction and dried in air. 81 mg of a yellow solid are obtained. Melting point: > 210°C decomposition; MS(ES+): 335.

Methyl 4-[3β-(2-{4-[(3-acetyl-2-methylquinolin-4-ylamino)methyl]benzoylamino)ethoxy)-7α,12α-dihydroxy-10β,13β-dimethylhexadecahydrocyclopenta[a]phenanthren-17β-yl]-pentanoate

67 mg of Intermediate 2 are dissolved in 5 ml of DMF and, at 0°C, 1 ml of a solution of 0.28 ml of triethylamine in 10 ml of DMF is added. Addition of a solution of 66 mg of TOTU in 2 ml of DMF is followed by stirring at 0°C for 30 min and at room temp. for a further 45 min. This solution is added dropwise to a second solution of 93 mg of Intermediate 1 in 2 ml of DMF and 1 ml of triethylamine and stirred at room temp. until conversion is found to be complete. For workup, the residue after concentration in vacuo is taken up in ethyl acetate. The precipitate is filtered off and the filtrate is washed with $NaHCO_3$ solution and with H_2O. The organic phase is separated off and dried with $mgSO_4$, and the solvent is removed. The residue obtained in this way is chromatographed together with the removed precipitate on silica gel, resulting in 71 mg of the product as a yellow-orange solid. Melting point: > 98°C decomposition; MS(ES+): 782.

Example 20:

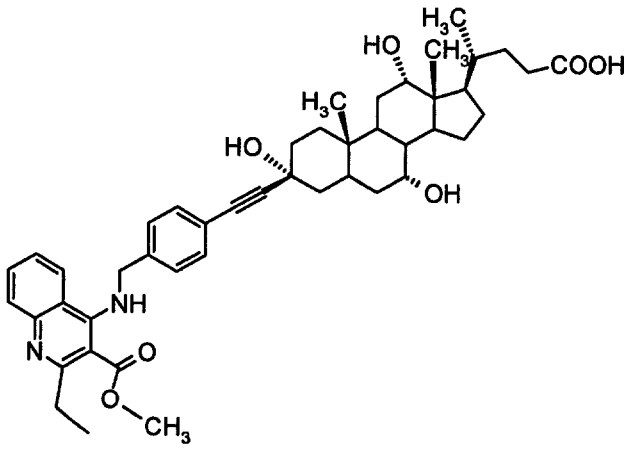
4-[3β-(2-{4-[(3-Acetyl-2-methylquinolin-4-ylamino)methyl]benzoylamino)-ethoxy)-7α,12α-dihydroxy-10β,13β-dimethylhexadecahydrocyclopenta-[a]phenanthren-17β-yl]pentanoic acid.



The ester obtained in Example 19 is reacted in analogy to the hydrolysis described in Example 4, resulting in the required product as a colorless solid. Melting point: > 145°C decomposition; MS(ES+): 768.

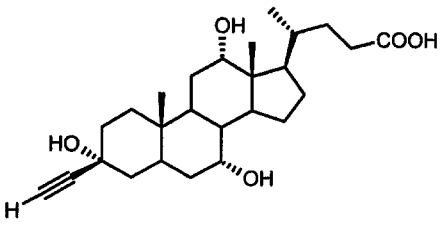
Example 21

Methyl 2-ethyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate



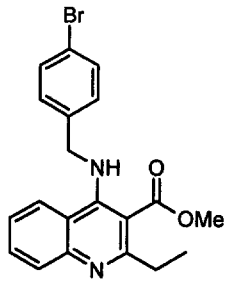
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: Methyl 4-(4-bromobenzylamino)-2-ethylquinoline-3-carboxylate



Synthetic route:

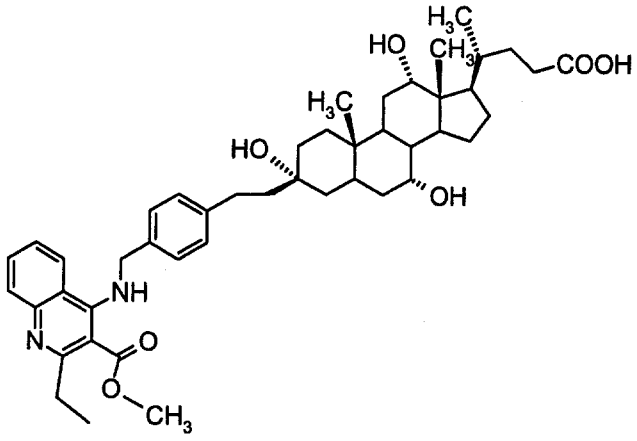
a) Methyl 4-amino-2-ethylquinoline-3-carboxylate can be prepared in a manner known to the skilled worker (Tetrahedron 51 (1995), 12277).

b) Methyl 4-(4-bromobenzylamino)-2-ethylquinoline-3-carboxylate is synthesized by the same process as described for 1-(4-(4-bromobenzyl-amino)-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from methyl 4-amino-2-ethylquinoline-3-carboxylate and 4-bromobenzyl bromide. MS(ES+): 399/401.

Methyl 2-ethyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminoquinoline-3-carboxylate is prepared by the general process indicated (see Example 1). Melting point: > 200°C; MS(FAB): 751.

Example 22:

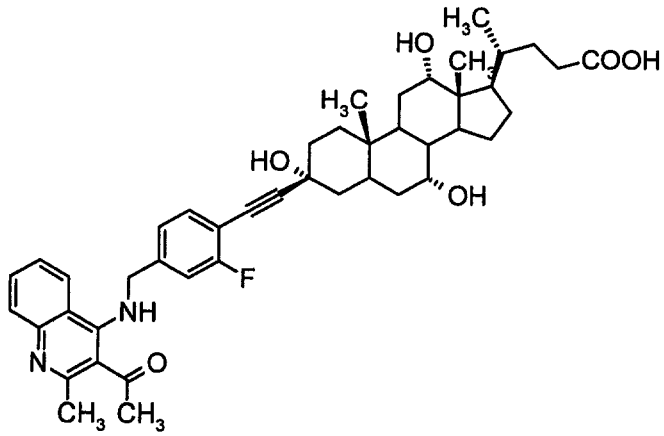
Methyl 2-ethyl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethylene-2-yl]benzyl}aminoquinoline-3-carboxylate



The product described in Example 21 is hydrogenated in analogy to the method indicated in Example 2, resulting in the target compound as a pale yellow solid. Melting point: > 190°C (decomposition); MS(ES+): 755.

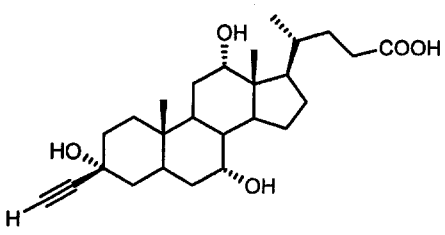
Example 23:

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]-3-fluorobenzyl}aminoquinoline



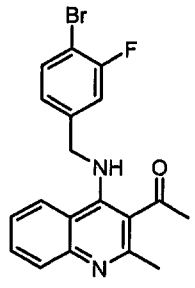
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: 1-(4-(4-Bromo-3-fluorobenzyl)amino-2-methylquinolin-3-yl)ethanone



Synthetic route:

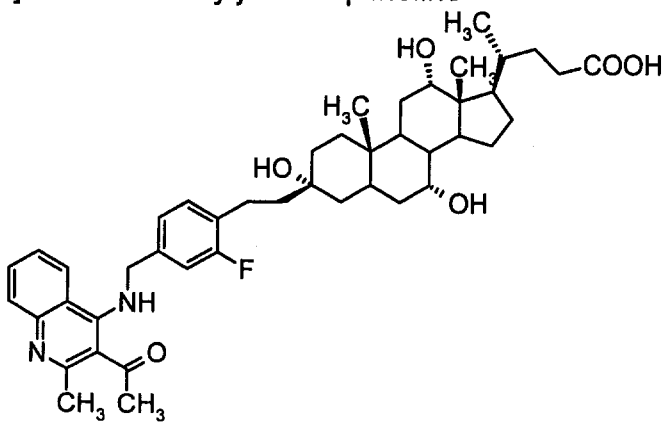
a) 1-(4-Amino-2-methylquinolin-3-yl)ethanone; see Example 13 (Tetrahedron 51 (1995), 12277).

b) 1-(4-(4-Bromo-3-fluorobenzyl)amino-2-methylquinolin-3-yl)ethanone is synthesized by the same process as described for 1-(4-(4-bromobenzyl)amino-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from 1-(4-amino-2-methylquinolin-3-yl)-ethanone and 4-bromo-3-fluorobenzyl bromide. MS(ES+): 387/389.

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]-3-fluorobenzyl}aminoquinoline is prepared by the general process indicated (see Example 1). MS(FAB): 739.

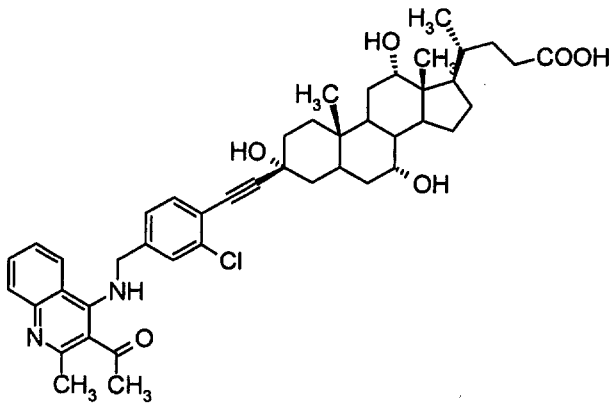
Example 24:

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethylene-2-yl]-3-fluorobenzyl}aminoquinoline

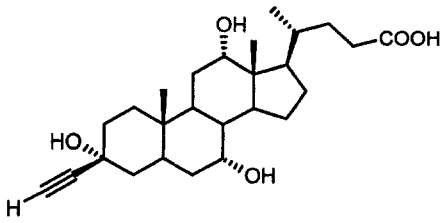


The product described in Example 23 is hydrogenated in analogy to the method indicated in Example 2, resulting in the target compound as a pale yellow solid. MS(ES+): 744.

Example 25:
2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]-3-chlorobenzyl}aminoquinoline

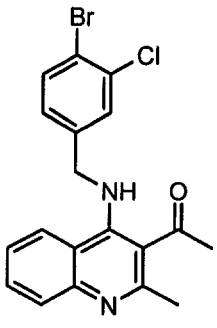


Preparation of the intermediates:
Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: 1-(4-(4-Bromo-3-chlorobenzyl)amino-2-methylquinolin-3-yl)ethanone



Synthetic route:

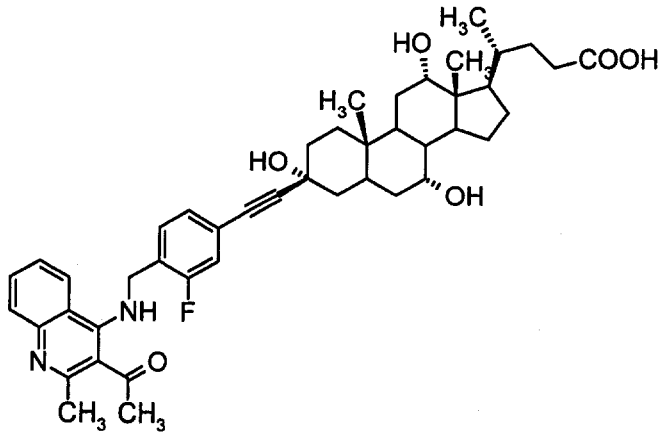
a) 1-(4-Amino-2-methylquinolin-3-yl)ethanone; see Example 13 (Tetrahedron 51 (1995), 12277).

b) 1-(4-(4-Bromo-3-chlorobenzyl)amino-2-methylquinolin-3-yl)ethanone is synthesized by the same process as described for 1-(4-(4-bromo-benzyl)amino-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from 1-(4-amino-2-methylquinolin-3-yl)ethanone and 4-bromo-3-chlorobenzyl bromide. MS(ES+):403/405.

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]-3-chlorobenzyl}aminoquinoline is prepared by the general process indicated (see Example 1). MS(FAB): 755.

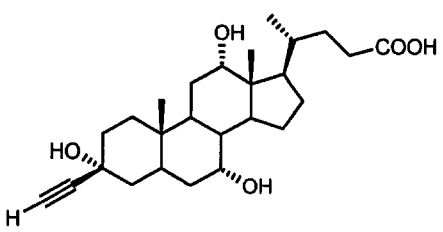
Example 26:

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]-2-fluorobenzyl}aminoquinoline



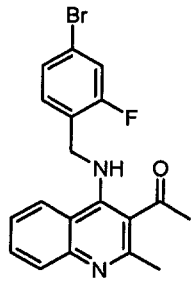
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: 1-(4-(4-Bromo-2-fluorobenzyl)amino-2-methylquinolin-3-yl)ethanone



Synthetic route:

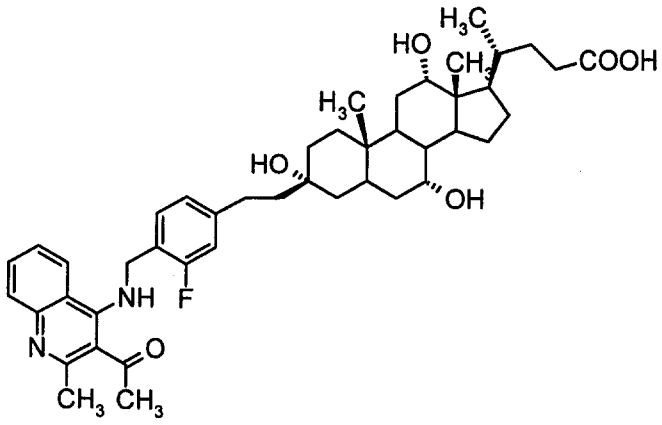
a) 1-(4-Amino-2-methylquinolin-3-yl)ethanone; see Example 13 (Tetrahedron 51 (1995), 12277).

b) 1-(4-(4-Bromo-2-fluorobenzyl)amino-2-methylquinolin-3-yl)ethanone is synthesized by the same process as described for 1-(4-(4-bromo-benzyl)amino-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from 1-(4-amino-2-methylquinolin-3-yl)ethanone and 4-bromo-2-fluorobenzyl bromide. MS(ES+): 387/389.

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]-2-fluorobenzyl}aminoquinoline is prepared by the general process indicated (see Example 1). MS(ES+): 739.

Example 27:

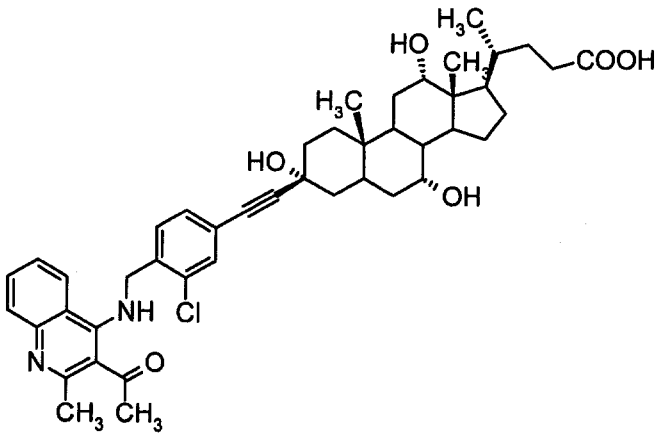
2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethylene-2-yl]-2-fluorobenzyl}aminoquinoline



The product described in Example 26 is hydrogenated in analogy to the method indicated in Example 2, resulting in the target compound as a pale yellow solid. MS(ES+): 744.

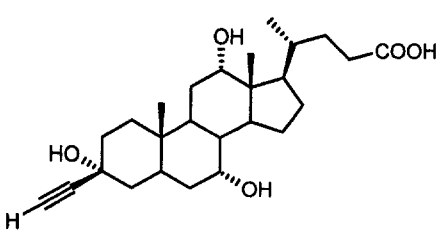
Example 28

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]-2-chlorobenzyl}aminoquinoline



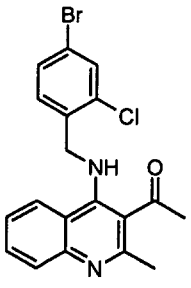
Preparation of the intermediates:

Intermediate 1: 3β-Acetylenecholic acid



see Example 1

Intermediate 2: 1-(4-(4-Bromo-2-chlorobenzyl)amino-2-methylquinolin-3-yl)ethanone



Synthetic route:

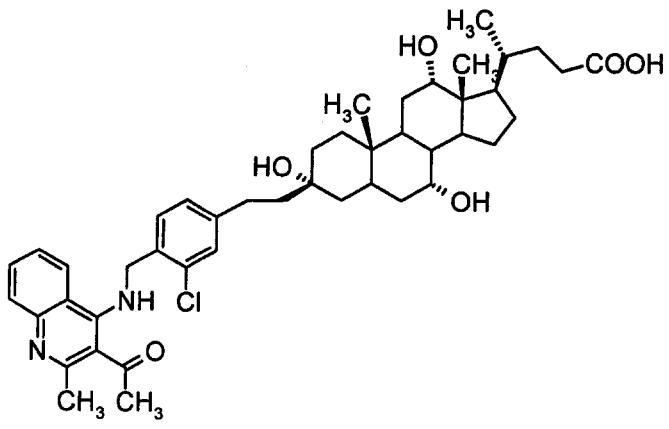
c) 1-(4-Amino-2-methylquinolin-3-yl)ethanone; see Example 13 (Tetrahedron 51 (1995), 12277).

d) 1-(4-(4-Bromo-2-chlorobenzyl)amino-2-methylquinolin-3-yl)ethanone is synthesized by the same process as described for 1-(4-(4-bromobenzyl)amino-2-methylquinolin-3-yl)ethanone (Example 1, Intermediate 2c) starting from 1-(4-amino-2-methylquinolin-3-yl)ethanone and 4-bromo-2-chlorobenzyl bromide. MS(FAB+): 403/405.

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]-2-chlorobenzyl}aminoquinoline is prepared by the general process indicated (see Example 1). MS(FAB+): 756.

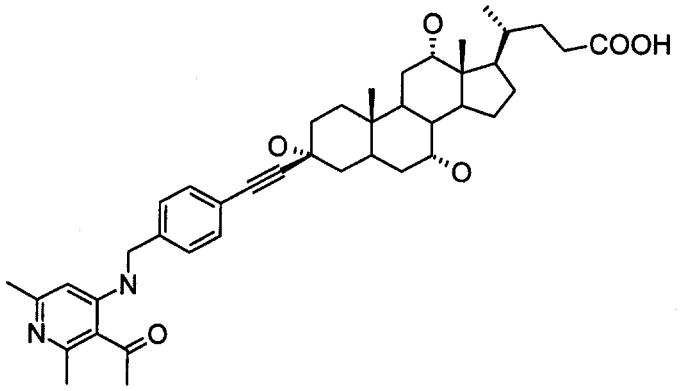
Example 29:

2-Methyl-3-(aceto-1-yl)-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethylene-2-yl]-2-chlorobenzyl}aminoquinoline

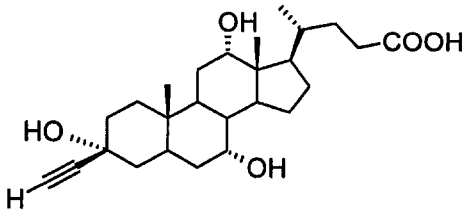


The product described in Example 28 is hydrogenated in analogy to the method indicated in Example 2, resulting in the target compound as a pale yellow solid. MS(ES+): 760.

Example 30:
2,6-Dimethyl-3-acet-1-yl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]benzyl}aminopyridine.

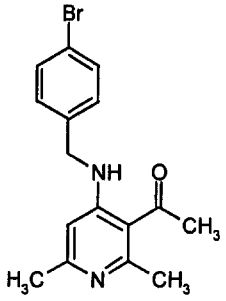


Preparation of the intermediates:
Intermediate 1: 3β-Acetylenecholic acid



see Example 1.

Intermediate 2: 1-[4-(4-Bromobenzylamino)-2,6-dimethylpyridin-3-yl]-ethanone



Synthetic route:

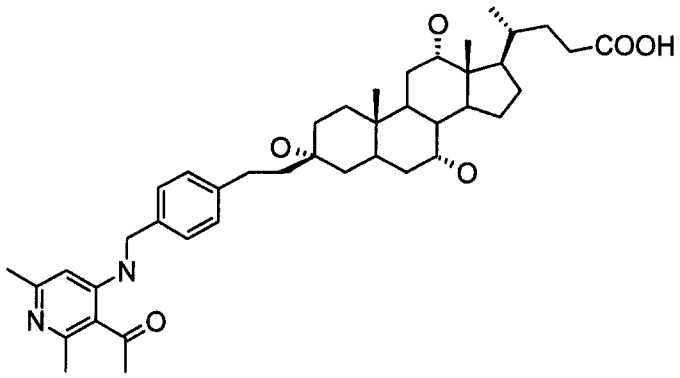
a) 3-Acetyl-2,6-dimethyl-1H-pyridin-4-one can be prepared by a process known from the literature (Chem. Pharm. Bull., 31, 1983, 4303).

b) 1-(4-Chloro-2,6-dimethylpyridin-3-yl)ethanone is synthesized in a manner known to the skilled worker (J. Heterocyclic Chem., 18, 1981, 603).

c) 1-[4-(4-Bromobenzylamino)-2,6-dimethylpyridin-3-yl]ethanone
1.0 g of 1-(4-chloro-2,6-dimethylpyridin-3-yl)ethanone is dissolved in 10 ml of dimethylacetamide, and 1.5 equivalents of 4-bromobenzylamine are added. The solution is heated at 140 to 150°C until no further increase in conversion can be detected. A further equivalent of 4-bromobenzylamine may be added if necessary. For workup, the solvent is distilled off in vacuo, and the residue is chromatographed on silica gel, resulting in the title compound as a yellow oil. MS(ES+): 333/335.

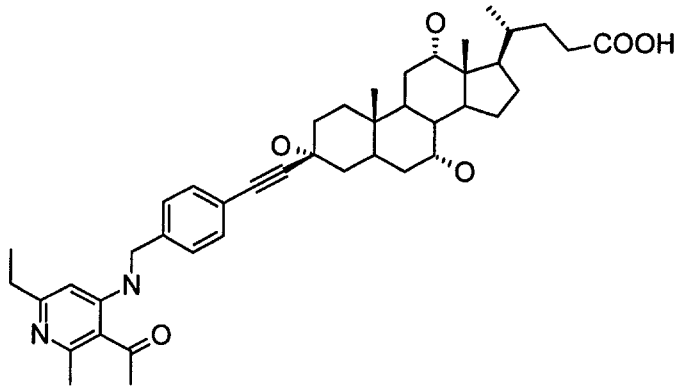
2,6-Dimethyl-3-acet-1-yl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethyn-2-yl]benzyl}aminopyridine is prepared by the general process (see Example 1). MS(ES+): 685.

Example 31:
2,6-Dimethyl-3-acet-1-yl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)-ethylene-2-yl]benzyl}aminopyridine.

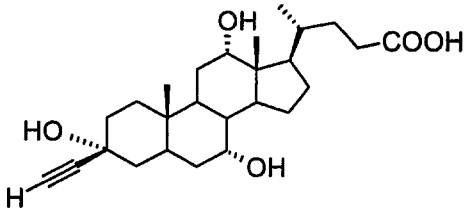


The product obtained in Example 30 is hydrogenated by the process described in Example 2, resulting in the title compound as a pale yellowish solid. MS(ES+): 689.

Example 32:
2-Ethyl-6-methyl-5-acet-1-yl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminopyridine.

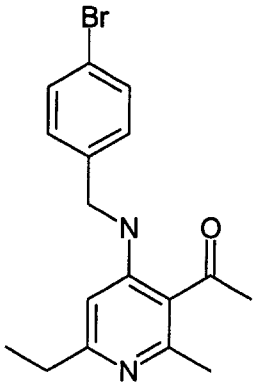


Preparation of the intermediates:
Intermediate 1: 3β-Acetylenecholic acid



see Example 1.

Intermediate 2: 1-[4-(4-Bromobenzylamino)-2-ethyl-6-methylpyridin-5-yl]ethanone



Synthetic route:

a) 2,2-Dimethyl-5-propionyl-[1,3]dioxane-4,6-dione is synthesized in a manner known from the literature (J. Org. Chem., 43, 1978, 2087).

b) 3-Acetyl-6-ethyl-2-methyl-1H-pyridin-4-one is synthesized by a method based on that described in Example 30 (Example 30; Intermediate 2a) (Chem. Pharm. Bull., 31, 1983, 4303).

d) 1-(4-Chloro-6-ethyl-2-methylpyridin-3-yl)ethanone is prepared in analogy to Intermediate 2b, Example 30, by a process known from the literature (J. Heterocyclic Chem., 18, 1981, 603).

e) 1-[4-(4-Bromobenzylamino)-2-ethyl-6-methylpyridin-5-yl]ethanone is prepared by the method described in Example 30 (Intermediate 2c) starting from 4-chloro-2-ethyl-6-methylpyridine and 4-bromobenzylamine. MS(ES+): 347/349.

2-Ethyl-6-methyl-5-acet-1-yl-4-{4-[1-(3α,7α,12α-trihydroxy-10β,13β-dimethyl-17β-(pentanoic acid-4-yl)hexadecahydrocyclopenta[a]phenanthren-3-yl)ethyn-2-yl]benzyl}aminopyridine is prepared by the general process (see Example 1). MS(ES+): 700.

Patent claims:

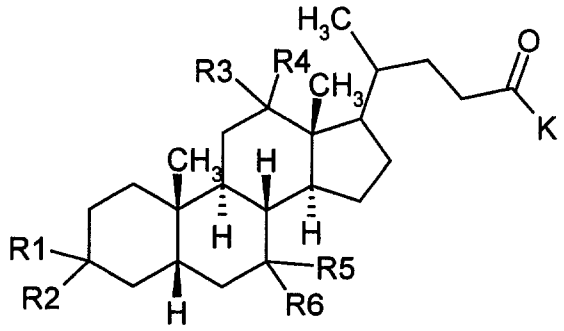
1. A compound of the formula I

P—L—G

I

in which

G is



G

K is -OR(7), -NR(7)R(8), -HN-CH_2-CH_2-CO_2H, -HN-CH_2-CH_2-SO_3H, -NH-CH_2-CO_2H, -N(CH_3)CH_2CO_2H, -HN-CHR(9)CO_2H, -Ocat, where cat is a cation such as, for example, an alkali metal or alkaline earth metal ion or a quaternary ammonium ion;

R(7), R(8) are, independently of one another, hydrogen, (C_1-C_4)-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

R(9) is (C_1-C_4)-alkyl, benzyl, -CH_2-OH, $H_3CSCH_2CH_2$-, HO_2CCH_2-, $HO_2CCH_2CH_2$-;

R(1) to R(6) are, independently of one another, hydrogen, -OR(10), -SR(10), -NR(10)R(13), -OCOR(10), -SCOR(10), -NHCOR(10), -OPO(OR(10))$_2$, -OSO_2OR(10), -R(10), R(1) and R(2), R(3) and R(4), R(5) and R(6) in each case form together the oxygen of a carbonyl group, with always exactly

one of the radicals R(1) to R(6) having the meaning of a bond to L;

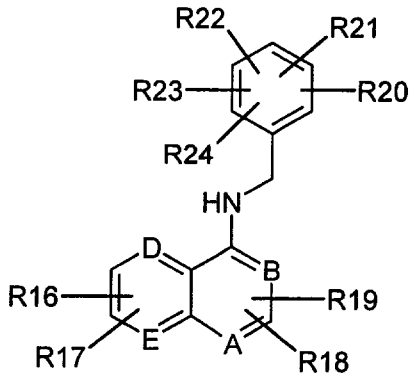
R(10), R(13) are, independently of one another, hydrogen, (C_1-C_4)-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

L is (C_1-C_{15})-alkyl, it being possible for one or more CH_2 units to be replaced by -CH=CH-, -C≡C-, -NR(11)-, -CO-, -O-, $-SO_2-$ or -S-;

R(11) is hydrogen, (C_1-C_8)-alkyl, R(12)-CO-, phenyl, benzyl;

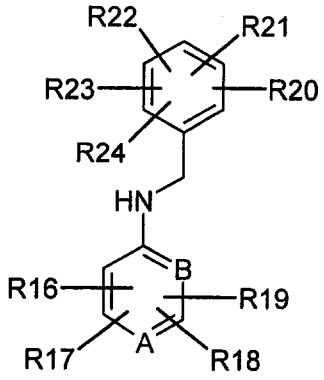
R(12) is hydrogen, (C_1-C_8)-alkyl, phenyl and benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

P is



P

or



P

in which

A is N or CH;
B is N or CH;
D is N or CH;
E is N or CH;

R(16) to R(24) are, independently of one another, hydrogen, F, Cl, Br, I, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine, or are CN, NO_2, NR(25)R(26), OR(25), OCOR(25), COR(25), COOR(25),

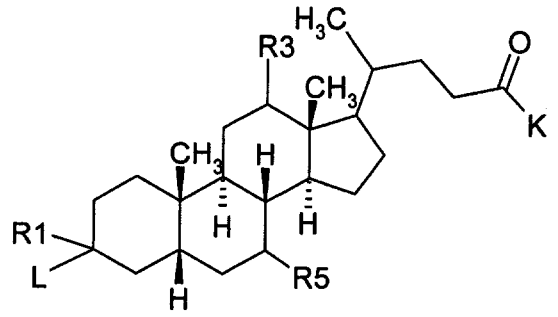
CONR(25)R(26), $SO_2R(25)$, $SO_2OR(25)$, $SO_2NR(25)R(26)$, with always one of the radicals R(16) to R(24) having the meaning of a bond to L;

R(25), R(26) are, independently of one another, hydrogen, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine, or are phenyl and benzyl;

and the pharmaceutically acceptable salts thereof.

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

G



G

K -OR(7), -NR(7)R(8), $-HN-CH_2-CH_2-CO_2H$, $-HN-CH_2-CH_2-SO_3H$, $-NH-CH_2-CO_2H$, $-N(CH_3)CH_2CO_2H$, $-HN-CHR(9)CO_2H$, -Ocat, where cat is a cation such as, for example, an alkali metal or alkaline earth metal ion or a quaternary ammonium ion;

R(7), R(8) independently of one another hydrogen, (C_1-C_4)-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

R(9) (C_1-C_4)-alkyl, benzyl, $-CH_2-OH$, $H_3CSCH_2CH_2-$, HO_2CCH_2-, $HO_2CCH_2CH_2-$;

R(1), R(3), R(5) independently of one another hydrogen, -OR(10), NR(10) R(13), -OCOR(10), -NHCOR(10);

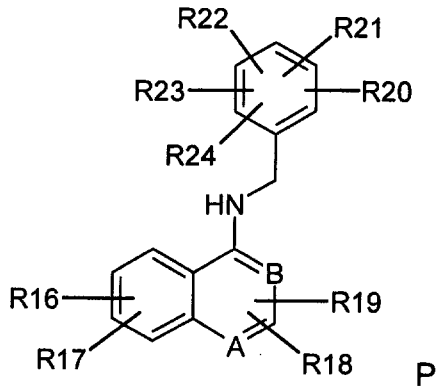
R(10), R(13) independently of one another hydrogen, $(C_1$-$C_4)$-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

L $(C_1$-$C_8)$-alkyl, it being possible for one or more CH_2 units to be replaced by -CH=CH-, -C≡C-, -NR(11)-, -CO-, -O- or $-SO_2$-;

R(11) hydrogen, $(C_1$-$C_4)$-alkyl, R(12)-CO-, phenyl, benzyl;

R(12) hydrogen, $(C_1$-$C_4)$-alkyl, phenyl and benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

P



P

A N or CH;

B N or CH;

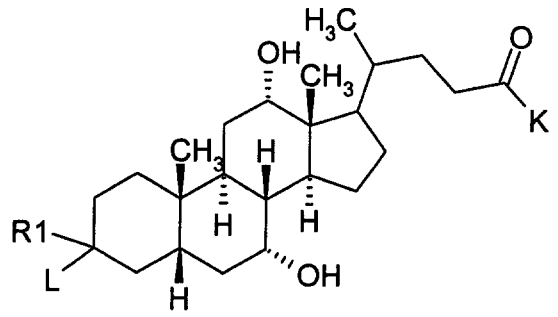
R(16) to R(24) independently of one another hydrogen, F, Cl, Br, $(C_1$-$C_4)$-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or NR(25)R(26), OR(25), OCOR(25), COR(25), COOR(25), CONR(25)R(26), with always one of the radicals R(16) to R(24) having the meaning of a bond to L;

R(25), R(26) independently of one another hydrogen, $(C_1$-$C_4)$-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or phenyl, benzyl;

and the pharmaceutically acceptable salts thereof.

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

G



G

K -OR(7), -NR(7) R(8), -HN-CH_2-CH_2-CO_2H, -HN-CH_2-CH_2-SO_3H, -NH-CH_2-CO_2H, -N(CH_3)CH_2CO_2H, -Ocat, where cat is a cation such as, for example, an alkali metal or alkaline earth metal ion or a quaternary ammonium ion;

R(7), R(8) independently of one another hydrogen, (C_1-C_4)-alkyl, phenyl or benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

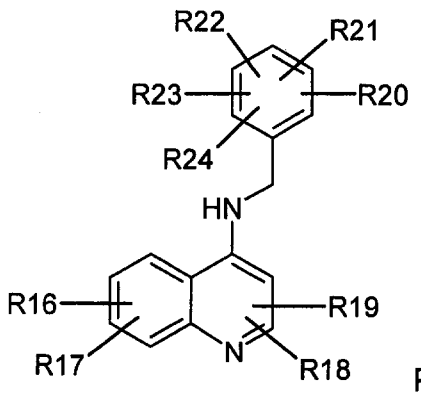
R(1) hydrogen, -OH;

L (C_1-C_5)-alkyl, it being possible for one or more CH_2 units to be replaced by -CH=CH-, -C≡C-, -NR(11)-, -CO-, -O- or -SO_2-;

R(11) hydrogen, (C_1-C_4)-alkyl, R(12)-CO-, phenyl, benzyl;

R(12) hydrogen, (C_1-C_4)-alkyl, phenyl and benzyl, it being possible for the phenyl nucleus to be substituted up to 3 times by F, Cl, CF_3, methyl, methoxy;

P



P

R(16) to R(24) independently of one another hydrogen, F, Cl, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,

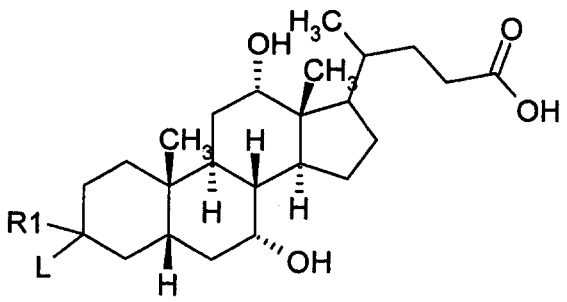
or NR(25)R(26), OR(25), OCOR(25), COR(25), COOR(25), CONR(25)R(26), with always one of the radicals R(16) to R(24) having the meaning of a bond to L;

R(25), R(26) independently of one another hydrogen, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,

or phenyl and benzyl; and the pharmaceutically acceptable salts thereof.

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

G

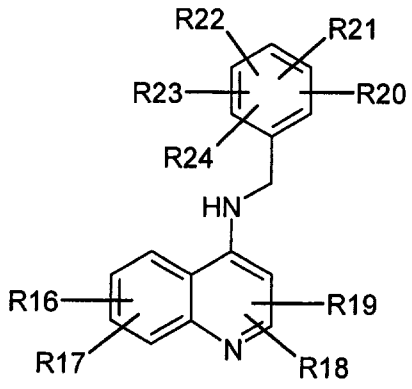


G

R(1) hydrogen, -OH;

L (C_1-C_5)-alkyl, it being possible for one or more CH_2 units to be replaced by -CH=CH-, -C≡C-, -NR(11)-, -CO-, -O- or -SO_2-;

P



P

in which

R(16) to R(24) are, independently of one another, hydrogen, F, Cl, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or NR(25)R(26), OR(25), OCOR(25), COR(25), COOR(25), CONR(25)R(26), with always one of the radicals R(16) to R(24) having the meaning of a bond to L;

R(25), R(26) are, independently of one another, hydrogen, (C_1-C_4)-alkyl, it being possible for the alkyl radicals to be substituted one or more times by fluorine,
or phenyl and benzyl;

and the pharmaceutically acceptable salts thereof.

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

6. A pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 4 and one or more lipid-lowering active ingredients.

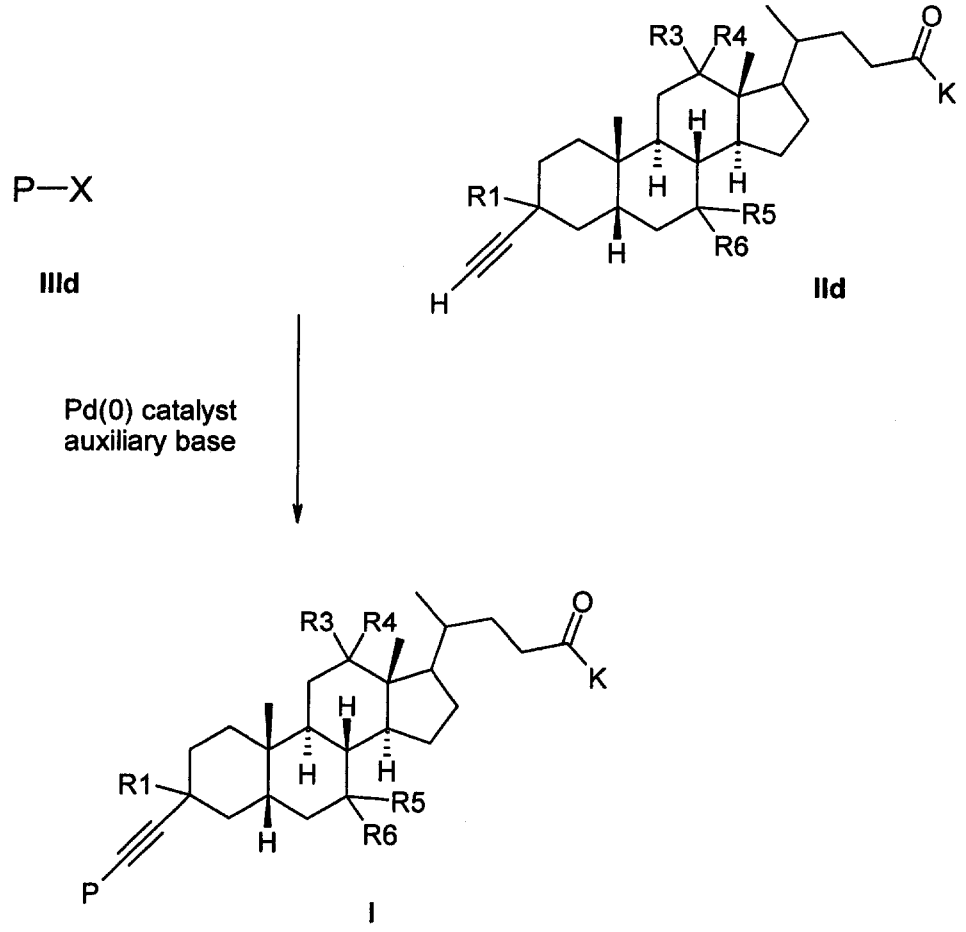
7. A process for the production of a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 4, which

comprises mixing the active ingredient with a pharmaceutically suitable carrier and converting this mixture into a form suitable for administration.

8. The use of the compounds as claimed in one or more of claims 1 to 4 for the production of a medicine.

9. The use of the compounds as claimed in one or more of claims 1 to 4 for the production of a medicine for the prophylaxis or treatment of gallstones.

10. A process for the preparation of the compounds as claimed in one or more of claims 1 to 4, which comprises reacting in accordance with the following formula diagram



a compound of the formula IId, in which K, R(1) and R(3) to R(6) have the meanings indicated for formula I, with a compound P-X of the formula IIId, in which P has the meaning indicated for formula I.