2-AMINO-SUBSTITUTED PYRIDINES WHICH CAN BE USED FOR THE TREATMENT OF ARTERIOSCLEROSIS AND HYPERCLIPOPROTEINAEMIA

The present invention relates to new 2-amino-substituted pyridines, processes for their preparation and their use in medicaments.

The publication US 5 169 857 A2 discloses 7-(polysubstituted pyridyl)-6-heptenoates for the treatment of arteriosclerosis, lipoproteinaemia and hyperlipoproteinaemia. The preparation of 7-(4-aryl-3-pyridyl)-3,5-dihydroxy-6-heptenoates is moreover described in the publication EP 325 130 A2.

The present invention relates to new 2-amino-substituted pyridines of the general formula (I)

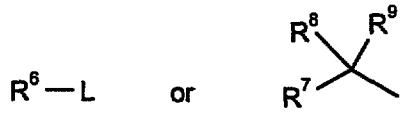
in which

A represents aryl having 6 to 10 carbon atoms, which is optionally identically or differently substituted up to 5 times by halogen, hydroxyl, trifluoromethyl, nitro, trifluoromethoxy or by straight-chain or branched alkyl, acyl, hydroxyalkyl or alkoxy each having up to 7 carbon atoms, or by a group of the formula $-NR^4R^5$,

in which

R^4 and R^5 are identical or different and
denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

D represents aryl having 6 to 10 carbon atoms, which is optionally substituted by nitro, halogen, trifluoromethyl or trifluoromethoxy, or
represents a radical of the formula



in which

R^6 and R^7 are identical or different and

denote cycloalkyl having 3 to 6 carbon atoms, or

denote aryl having 6 to 10 carbon atoms or form a 5- to 7-membered, optionally benzo-fused, saturated or unsaturated, mono-, bi- or tricyclic heterocycle having up to 4 carbon atoms from the group consisting of S, N and/or O,

where the cyclic systems are optionally substituted, in the case of the nitrogen-containing rings also via the N function, identically or differently up to 5 times by halogen, trifluoromethyl, hydroxyl, cyano, carboxyl, trifluoromethoxy, nitro, straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms, by aryl having 6 to 10 carbon atoms or by an optionally benzo-fused, aromatic 5- to 7-membered heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O,

and/or are substituted by a group of the formula $-OR^{10}$, $-SR^{11}$, $-SO_2R^{12}$ or $-NR^{13}R^{14}$,

in which

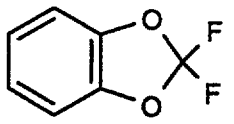
R^{10}, R^{11} and R^{12} are identical or different and

denote aryl having 6 to 10 carbon atoms, which for its part can be identically or differently substituted up to 2 times by phenyl, halogen or by straight-chain or branched alkyl having up to 4 carbon atoms,

R^{13} and R^{14} are identical or different and have the meaning of R^4 and R^5 indicated above,

or

R^6 or R^7 denote a radical of the formula



,

L denotes straight-chain or branched alkyl or alkenyl each having 2 to 10 carbon atoms, each of which is optionally substituted up to 2 times by hydroxyl,

R^8 denotes hydrogen or halogen,

and

R^9 denotes hydrogen, halogen, azido, trifluoromethyl, hydroxyl, trifluoromethoxy, straight-chain or branched alkoxy having up to 5 carbon atoms or a radical of the formula $-NR^{15}R^{16}$,

in which

R^{15} and R^{16} are identical or different and have the meaning of R^4 and R^5 indicated above,

or

R^8 and R^9 together form a radical of the formula =O or $=NR^{17}$,

in which

R^{17} denotes hydrogen or straight-chain or branched alkyl, alkoxy or acyl each having up to 6 carbon atoms,

E represents cycloalkyl having 3 to 8 carbon atoms, or
represents straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 8 carbon atoms or hydroxyl, or
represents phenyl which is optionally substituted by halogen or trifluoromethyl,

R^1 represents straight-chain or branched alkyl having up to 6 carbon atoms, which is substituted by hydroxyl,

R^2 and R^3 are identical or different and

represent hydrogen, phenyl, benzyl, cycloalkyl having 3 to 7 carbon atoms or straight-chain or branched alkyl, acyl each having up to 6 carbon atoms, or a group of the formula $-CO-NR^{18}R^{19}$,

in which

R^{18} and R^{19} are identical or different and

denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl having up to 6 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a 5- to 7-membered saturated, partially unsaturated or unsaturated, optionally benzo-fused, mono- or bicyclic heterocycle having up to 4 heteroatoms from the group consisting of S, N and/or O, which can optionally be identically or differently substituted up to three times by nitro, cyano, halogen, trifluoromethyl, hydroxyl, carboxyl, straight-chain or branched alkoxy or alkoxycarbonyl each having up to 5 carbon atoms, phenyl or by straight-chain or branched alkyl having up to 5 carbon atoms, which for its part can be substituted by hydroxyl,
and/or the heterocycle is substituted by a group of the formula $-NR^{20}R^{21}$,

in which

R^{20} and R^{21} have the meaning of R^{18} and R^{19} indicated above and are identical to or different from this,

and their salts.

The new 2-amino-substituted pyridines according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

In the context of the present invention, physiologically acceptable salts are preferred. Physiologically acceptable salts of the compounds according to the invention can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred salts are, for example, those with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

Physiologically acceptable salts can also be metal or ammonium salts of the compounds according to the invention which have a free carboxyl group. Those particularly preferred are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine, ethylenediamine or 2-phenylethylamine.

The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers or their respective mixtures. These mixtures of the enantiomers and diastereomers can be separated into the stereoisomeric uniform constituents in a known manner.

Heterocycle, optionally benzo-fused, in the context of the invention in general represents a saturated or unsaturated 5- to 7-membered, preferably 5- to 6-membered, heterocycle which can contain up to 3 heteroatoms from the group consisting of S, N and/or O. Examples which may be mentioned are: indolyl, isoquinolyl, quinolyl, benzo[b]thiophenyl, benzo[b]furaryl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, morpholinyl or piperidyl. Quinolyl, furyl, pyridyl, thienyl or morpholinyl are preferred.

Preferred compounds of the general formula (I) according to the invention are those

in which

A represents naphthyl or phenyl, each of which is optionally substituted identically or differently up to 3 times by fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, nitro, trifluoromethoxy or by straight-chain or branched alkyl, acyl or alkoxy each having up to 6 carbon atoms, or by a group of the formula $-NR^4R^5$,

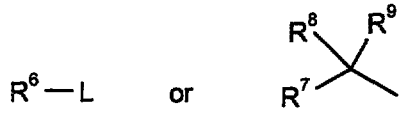
in which

R^4 and R^5 are identical or different and

denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

D represents phenyl which is optionally substituted by nitro, fluorine, chlorine, bromine, trifluoromethyl or trifluoromethoxy, or

represents a radical of the formula



in which

R^6 and R^7 are identical or different and

denote cyclopropyl, cyclopentyl or cyclohexyl, or

denote phenyl, napthyl, pyridyl, tetrazolyl, pyrimidyl, pyrazinyl, pyrrolidinyl, indolyl, morpholinyl, imidazolyl, benzothiazolyl, phenoxathiin-2-yl, benzoxazolyl, furyl, quinolyl or purin-8-yl,

where the cyclic systems are optionally identically or differently substituted up to 3 times, in the case of the nitrogen-containing rings also via the N function, by fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, cyano, carboxyl, trifluoromethoxy, straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms, triazolyl, tetrazolyl, benzoxathiazolyl or phenyl,

and/or are substituted by a group of the formula $-OR^{10}$, $-SR^{11}$ or $-SO_2R^{12}$,

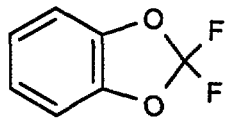
in which

R^{10}, R^{11} and R^{12} are identical or different and

denote phenyl which for its part is identically or differently substituted up to 2 times by phenyl, fluorine or chlorine or by straight-chain or branched alkyl having up to 4 carbon atoms,

or

R^6 or R^7 denote a radical of the formula



,

L denotes straight-chain or branched alkyl or alkenyl each having 2 to 8 carbon atoms, each of which is optionally substituted up to 2 times by hydroxyl,

R^8 denotes hydrogen, fluorine, chlorine or bromine,

and

R^9 denotes hydrogen, fluorine, chlorine, bromine, azido, trifluoromethyl, hydroxyl, trifluoromethoxy, straight-chain or branched alkoxy having up to 4 carbon atoms or a radical of the formula $-NR^{15}R^{16}$,

in which

R^{15} and R^{16} are identical or different and have the meaning of R^4 and R^5 indicated above,

or

R^8 and R^9 together form a radical of the formula =O or $=NR^{17}$,

in which

R^{17} denotes hydrogen or straight-chain or branched alkyl, alkoxy or acyl each having up to 4 carbon atoms,

E represents cyclopropyl, -butyl, -pentyl, -hexyl or -heptyl, or represents straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by cyclopropyl, -butyl, -hexyl, -pentyl, -heptyl or by hydroxyl, or represents phenyl which is optionally substituted by fluorine, chlorine or trifluoromethyl,

R^1 represents straight-chain or branched alkyl having up to 5 carbon atoms, which is substituted by hydroxyl,

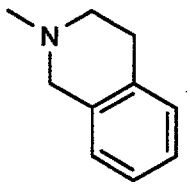
R^2 and R^3 are identical or different and
represent hydrogen, phenyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl or represent straight-chain or branched alkyl, acyl each having up to 5 carbon atoms, or a group of the formula $-CO-NR^{18}R^{19}$,

in which

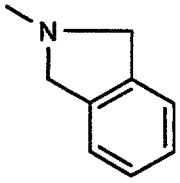
R^{18} and R^{19} are identical or different and
denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl having up to 5 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a pyrryl, imidazolyl, pyrrolidinyl, morpholin, piperidinyl or piperazinyl ring or a radical of the formula



or



,

where the heterocycles are optionally substituted by hydroxyl, trifluoromethyl, fluorine, chlorine, bromine, hydroxyl, carboxyl, methylhydroxyl or straight-chain the branched alkxoy or alkoxy-carbonyl each having up to 4 carbon atoms,

and their salts.

Particularly preferred compounds of the general formula (I) according to the invention are those

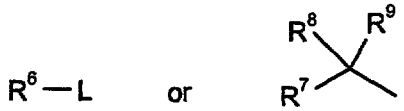
in which

A represents naphthyl or phenyl, each of which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, nitro, trifluoromethoxy or by straight-chain or branched alkyl, acyl or alkoxy each having up to 5 carbon atoms, or by a group of the formula $-NR^4R^5$,

in which

R^4 and R^5 are identical or different and
denote hydrogen, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

D represents phenyl which is optionally substituted by nitro, fluorine, chlorine or bromine, or
represents a radical of the formula



in which

R^6 and R^7 are identical or different and
denotes cyclopropyl, cyclopentyl or cyclohexyl, or
denotes phenyl, naphthyl, pyridyl, tetrazolyl, pyrimidyl, pyrazinyl, phenoxathiin-2-yl, indolyl, imidazolyl, pyrrolidinyl, morpholinyl, benzothiazolyl, benzoxazolyl, furyl, quinolyl or purin-8-yl,
where the cyclic systems are optionally identically or differently substituted up to 3 times, in the case of the nitrogen-containing rings also via the N function, by fluorine, chlorine, trifluoromethyl, hydroxyl, cyano, carboxyl, trifluoromethoxy, straight-chain or

branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms, triazolyl, tetrazolyl, benzothiazolyl or phenyl,

and/or are substituted by a group of the formula $-OR^{10}$, $-SR^{11}$ or $-SO_2R^{12}$,

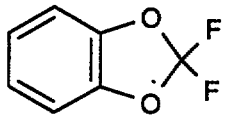
in which

R^{10}, R^{11} and R^{12} are identical or different and

denote phenyl which for its part is identically or differently substituted up to 2 times by phenyl, fluorine, chlorine or by straight-chain or branched alkyl having up to 3 carbon atoms,

or

R^6 or R^7 denote a radical of the formula



,

L denotes straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms, each of which is optionally substituted up to 2 times by hydroxyl,

R^8 denotes hydrogen or fluorine,

and

R^9 denotes hydrogen, fluorine, chlorine, bromine, azido, trifluoromethyl, hydroxyl, trifluoromethoxy, methoxy or a radical of the formula $-NR^{15}R^{16}$,

in which

R^{15} and R^{16} are identical or different and have the meaning of R^4 and R^5 indicated above,

or

R^8 and R^9 together form a radical of the formula =O or $=NR^{17}$,

in which

R^{17} denotes hydrogen or straight-chain or branched alkyl, alkoxy or acyl each having up to 3 carbon atoms,

E represents cyclopropyl, cyclopentyl or cyclohexyl, or phenyl which is optionally substituted by fluorine or trifluoromethyl, or
represents straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,

R^1 represents straight-chain or branched alkyl having up to 4 carbon atoms, which is substituted by hydroxyl,

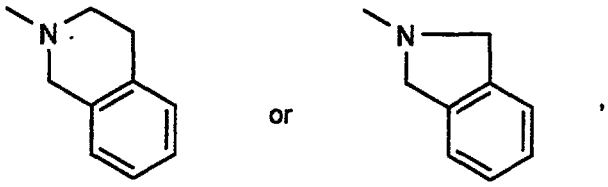
R^2 and R^3 are identical or different and
represent hydrogen, phenyl, benzyl, cyclopropyl, cyclopentyl or straight-chain or branched alkyl, acyl each having up to 5 carbon atoms, or a group of the formula $-CO-NR^{18}R^{19}$,

in which

R^{18} and R^{19} are identical or different and
denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl having up to 4 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a pyrryl, morpholinyl, pyrrolidinyl or piperidinyl ring or a radical of the formula

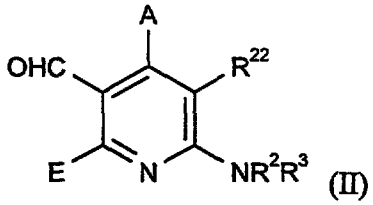


where the heterocycles are optionally substituted by hydroxyl, trifluoromethyl, fluorine, chlorine, bromine, hydroxyl, carboxyl, methylhydroxyl or straight-chain the branched alkxoy or alkoxy-carbonyl each having up to 3 carbon atoms,

and their salts.

Processes for the preparation of the compounds of the general formula (I) according to the invention have moreover been found, characterized in that

[A] the radical D is first introduced into the compounds of the general formula (II)



(II)

in which

A, E, R^2 and R^3 have the meaning indicated above

and

R^{22} has the meaning of R^1 indicated above, where the hydroxyl function is present in protected form, preferably by tetrahydropyranyl,

in the sense of Grignard/Wittig reactions, the substituents are optionally derivatized in this stage by customary methods, preferably by reductions, and the hydroxyl protective group is removed in a last step,

or

[B] compounds of the general formula (III)

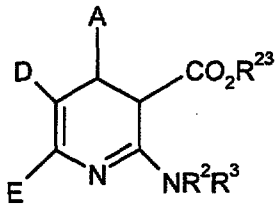
in which

A, D, E, R^2 and R^3 have the meaning indicated above

and

R^{23} represents C_1-C_4-alkyl,

are converted by oxidation into the compounds of the general formula (IV)



in which

A, D, E, R^{23}, R^2 and R^3 have the meaning indicated above,

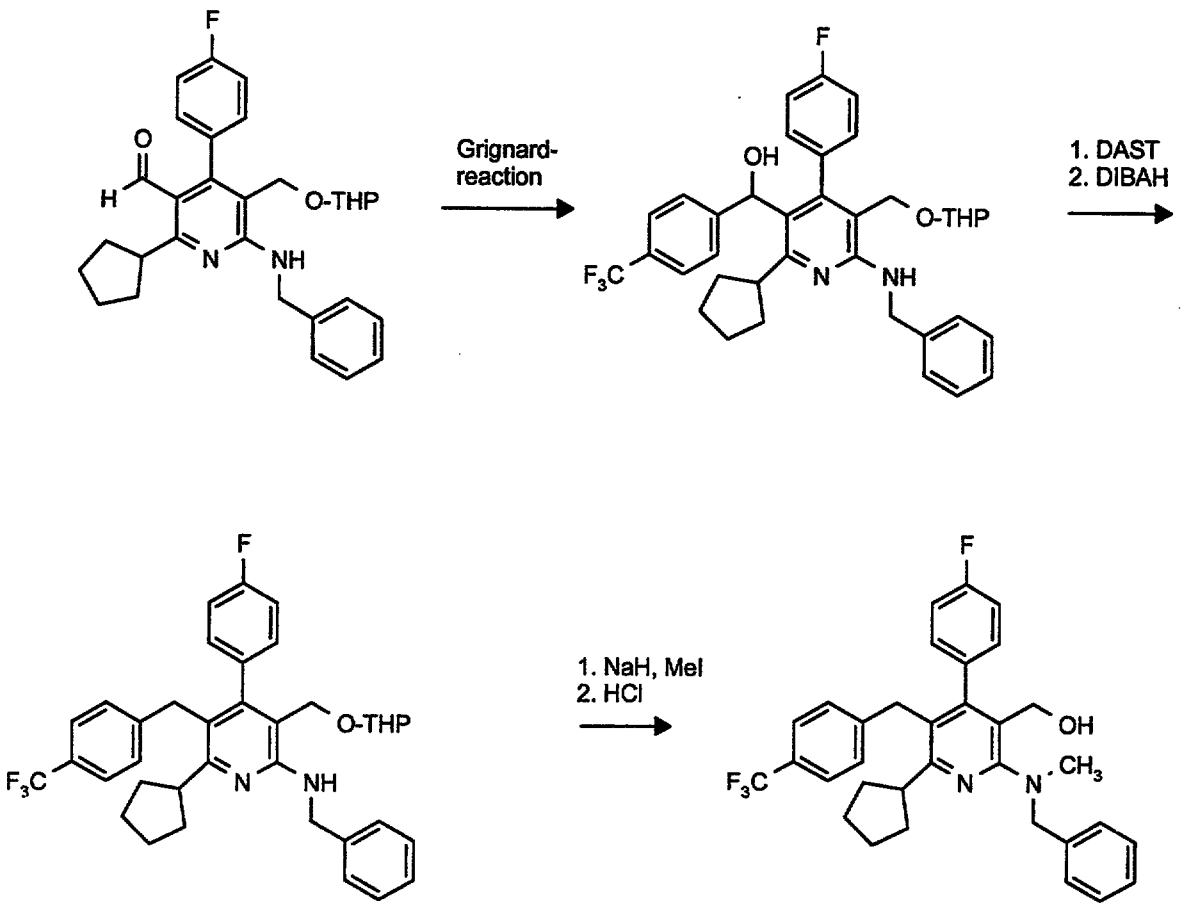
if appropriate the substituent D is varied in the stage

and finally the alkoxycarbonyl groups are reduced to the hydroxymethyl function under an argon atmosphere according to customary methods.

and, if appropriate, all substituents are varied and/or introduced according to customary methods.

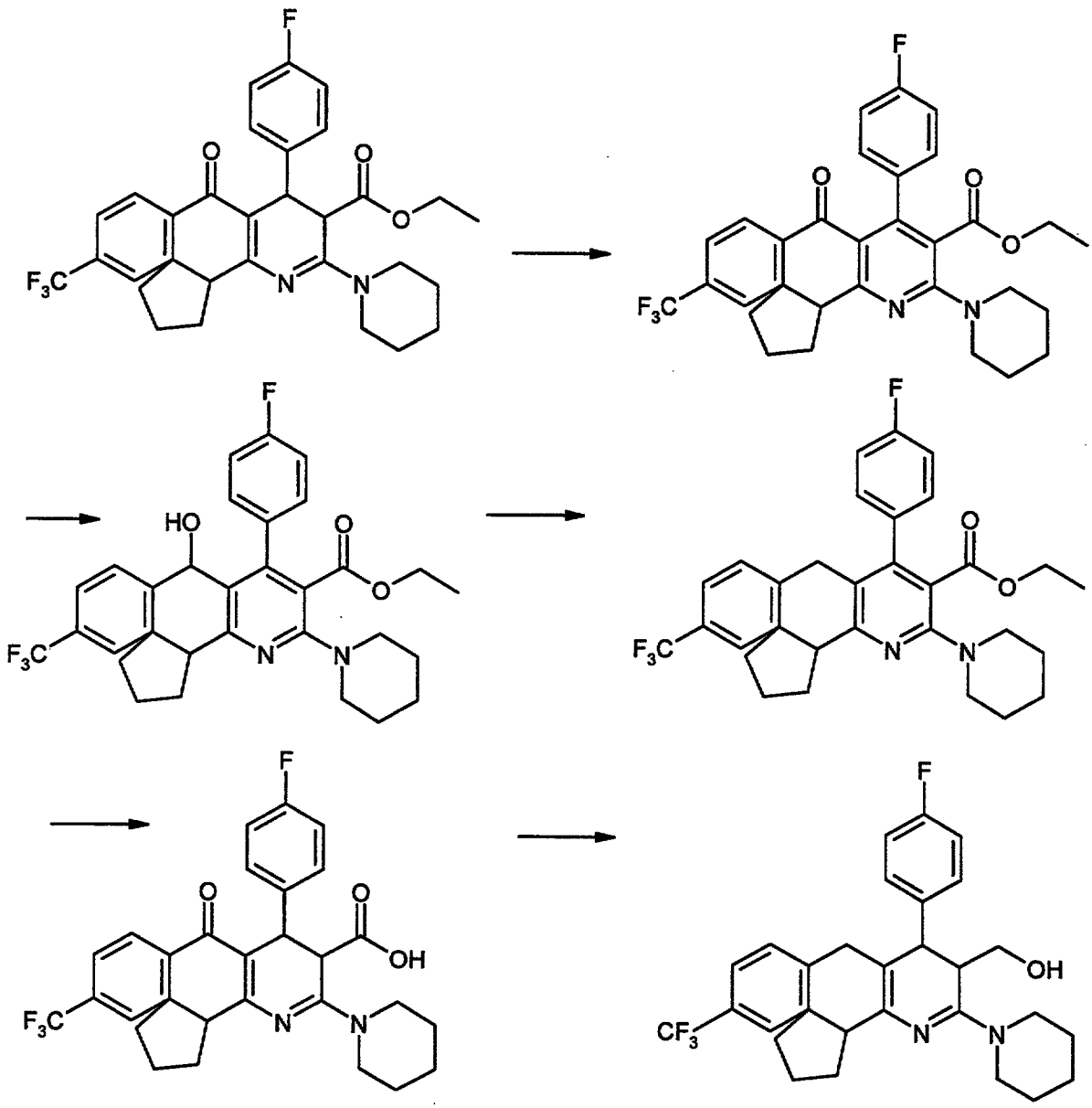
The process according to the invention can be illustrated by way of example by the following reaction schemes:

[A]



THP = tetrahydropyranyl

[B]



[A]

Suitable solvents for the process are ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or hydrocarbons such as benzene, toluene, xylene, hexane, cylcohexane or petroleum fractions, or halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, or triethylamine, pyridine, dimethyl sulphoxide, dimethylformamide, hexamethylphosphoramide, acetonitrile, acetone or nitromethane. It is also possible to use mixtures of the solvents mentioned. Toluene or tetrahydrofuran are preferred.

Suitable bases for the individual steps are the customary strongly basic compounds. These preferably include organolithium compounds such as, for example, N-butyllithium, sec-butyllithium, tert-butyllithium or phenyllithium, or amides such as, for example, lithium diisopropylamide, sodium amide or potassium amide, or lithium hexamethylsilylamide, or alkali metal hydrides such as sodium hydride or potassium hydride. N-butyllithium, sodium hydride and lithium diisopropylamide are particularly preferably employed.

Suitable organometallic reagents are, for example, systems such as Mg/bromobenzotrifluoride and p-trifluoromethylphenyllithium.

Suitable Wittig reagents are the customary reagents. 3-Trifluoromethylbenzyltriphenylphosphonium bromide is preferred.

A suitable base is in general one of the abovementioned bases, preferably sodium amide.

The base is employed in an amount from 0.1 mol to 5 mol, preferably from 0.5 mol to 2 mol, in each case relative to 1 mol of the starting compound.

The reaction with Wittig reagents is in general carried out in a temperature range from 0°C to 150°C, preferably at 25°C to 40°C.

The Wittig reactions are in general carried out at normal pressure. However, it is also possible to carry out the process at reduced pressure or at elevated pressure (e.g. in a range from 0.5 to 5 bar).

Suitable solvents for the oxidation in process [B] are ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether, or hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, or triethylamine, pyridine, dimethyl sulphoxide, dimethylformamide, hexamethylphosphoramide, acetonitrile, acetone, nitromethane or water. It is also possible to use mixtures of the solvents mentioned. Acetonitrile and water are preferred.

Suitable oxidizing agents are, for example, cerium(IV) ammonium nitrate, 2,3-dichloro-5,6-dicyanobenzoquinone, pyridinium chlorochromate (PCC),

osmium tetroxide and manganese dioxide. Cerium(IV) ammonium nitrate is preferred.

The oxidizing agent is employed in an amount from 1 mol to 10 mol, preferably from 2 mol to 5 mol, relative to 1 mol of the compounds of the general formula (IV).

In general, the oxidation proceeds in a temperature range from -50°C to +100°C, preferably from 0°C to room temperature.

In general, the oxidation proceeds at normal pressure. However, it is also possible to carry out the oxidation at elevated or reduced pressure.

In general, the reductions are carried out using reducing agents, preferably using those which are suitable for the reduction of ketones to hydroxy compounds. In this context, reduction with metal hydrides or complex metal hydrides in inert solvents, if appropriate in the presence of a trialkylborane, is particularly suitable. The reduction is preferably carried out using complex metal hydrides such as, for example, lithium borohydride, sodium borohydride, potassium borohydride, zinc borohydride, lithium trialkylhydridoborohydride or lithium aluminium hydride or diisobutylaluminium hydride (DIBAH). The reduction is very particularly preferably carried out using sodium borohydride or DIBAH, in the presence of triethylborane.

In general, the reducing agent is employed in an amount from 4 mol to 10 mol, preferably from 4 mol to 5 mol, relative to 1 mol of the compounds to be reduced.

In general, the reduction proceeds in a temperature range from -78°C to +50°C, preferably from -78°C to 0°C, particularly preferably at -78°C, in each case depending on the choice of the reducing agent and solvent.

In general, the reduction proceeds at normal pressure, but it is also possible to work at elevated or reduced pressure.

In general, the reductions are carried out using reducing agents, preferably using those which are suitable for the reduction of ketones to hydroxy compounds. In this context, reduction with metal hydrides or complex metal hydrides in inert solvents, if appropriate in the presence of a trialkylborane, is particularly suitable. The

reduction is preferably carried out using complex metal hydrides such as, for example, lithium borohydride, sodium borohydride, potassium borohydride, zinc borohydride, lithium trialkylhydridoborohydride, diisobutylaluminium hydride or lithiumaluminium hydride. The reduction is very particularly preferably carried out using diisobutylaluminium hydride and sodium borohydride.

In general, the reducing agent is employed in an amount from 1 mol to 6 mol, preferably from 1 mol to 4 mol, relative to 1 mol of the compounds to be reduced.

In general, the reduction proceeds in a temperature range from -78°C to +50°C, preferably from -78°C to 0°C, in the case of DIBAH, 0°C, room temperature in the case of $NaBH_4$.

In general, the reduction proceeds at normal pressure, but it is also possible to work at elevated or reduced pressure.

In general, the protective group is removed in one of the abovementioned alcohols and THF, preferably methanol/THF in the presence of hydrochloric acid or p-toluenesulphonic acid in methanol in a temperature range from 0°C to 50°C, preferably at room temperature, and normal pressure.

The following types of reaction may be mentioned by way of example as derivatizations: reductions, hydrogenations, halogenation, Wittig/Grignard reactions, alkylations and amidations.

Suitable bases for the individual steps are the customary strongly basic compounds. These preferably include organolithium compounds such as, for example, N-butyllithium, sec-butyllithium, tert-butyllithium or phenyllithium, or amides such as, for example, lithium diisopropylamide, sodium amide or potassium amide, or lithium hexamethylsilylamide, or alkali metal hydrides such as sodium hydride or potassium hydride. N-Butyllithium, sodium hydride and lithium diisopropylamide are particularly preferably employed.

Suitable bases are moreover the customary inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal hydroxides such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates such as sodium carbonate or potassium carbonate or sodium

hydrogen-carbonate. Sodium hydroxide or potassium hydroxide are particularly preferably employed.

Suitable solvents for the individual reaction steps are also alcohols such as methanol, ethanol, propanol, butanol or tert-butanol. tert-Butanol is preferred.

If appropriate, it is necessary to carry out some reaction steps under a protective gas atmosphere.

In general, the halogenations are carried out in one of the abovementioned chlorinated hydrocarbons or toluene.

Suitable halogenating agents are, for example, diethylaminosulphur trifluoride (DAST) or $SOCl_2$.

In general, the halogenation proceeds in a temperature range from -78°C to +50°C, preferably from -78°C to 0°C.

In general, the halogenation proceeds at normal pressure, but it is also possible to work at elevated or reduced pressure.

In this context, suitable solvents for the amidation are inert organic solvents which do not change under the reaction conditions. These include ethers, such as diethyl ether or tetrahydrofuran, halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, nitromethane, dimethylformamide, acetone, acetonitrile or hexamethylphosphoramide. It is also possible to employ mixtures of the solvents. Dichloromethane, tetrahydrofuran, acetone or dimethylformamide are particularly preferred.

In general, bases which can be employed for the amidation are inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkali metal or alkaline earth metal alkoxides such as sodium methoxide or potassium methoxide, sodium ethoxide or potassium ethoxide or potassium tert-

butoxide, or organic amines (trialkyl-(C_1-C_6)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, diaminopyridine, methyl-piperidine or morpholine. It is also possible to employ alkali metals such as sodium and their hydrides such as sodium hydride as bases. Sodium carbonate and potassium carbonate and triethylamine are preferred.

The base is employed in an amount from 1 mol to 5 mol, preferably from 1 mol to 3 mol, relative to 1 mol of the compound of the compound to be amidated.

In general, the amidation is carried out in a temperature range from 0°C to 150°C, preferably from +20°C to +110°C.

The amidation can be carried out at normal, elevated or reduced pressure (e.g. 0.5 to 5 bar). In general, the reaction is carried out at normal pressure.

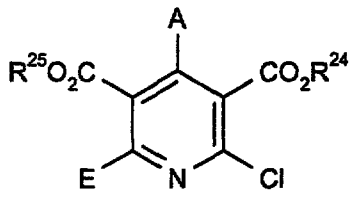
Suitable solvents for the alkylation are customary organic solvents which do not change under the reaction conditions. These preferably include ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimehyl ether, or hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenohydrocarbons, such as dichloromethane, trichloromethane, tetrachloro-methane, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, or triethylamine, pyridine, dimethyl sulphoxide, dimethylformamide, hexamethyl-phosphoramide, acetonitrile, acetone or nitromethane. It is also possible to use mixtures of the solvents mentioned. Dimethylformamite is preferred.

The alkylation is carried out in one of the abovementioned solvents at temperatures from 0°C to +150°C, preferably at room temperature to +100°C, at normal pressure.

The reductions are carried out according to the abovementioned methods.

The compounds of the general formula (II) are known in some cases or are new and can then be prepared, for example, by

first converting compounds of the general formula (V)



(V)

in which

A and E have the meaning indicated above

and

R^{24} and R^{25} are identical or different and represent C_1-C_4-alkyl,

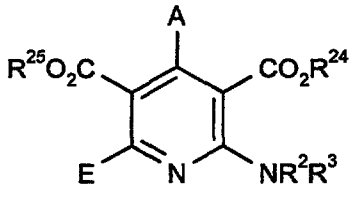
by reaction with amines of the general formula (VI)

$$HNR^2R^3 \qquad (VI)$$

in which

R^2 and R^3 have the meaning indicated above,

into the compounds of the general formula (VII)



(VII)

in which

A, E, R^2, R^3, R^{23} and R^{24} have the meaning indicated above,

in a further step first reducing the alkoxycarbonyl group CO_2R^{24} to the corresponding alkylhydroxyl function

and finally reacting the other alkoxycarbonyl function to give the formyl group.

Suitable solvents for all processes are ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether, or hydrocarbons such as benzene, toluene, xylene, hexane, cylcohexane or petroleum fractions, or halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, or triethylamine, pyridine, dimethyl sulphoxide, dimethylformamide, hexamethylphosphoramide, acetonitrile, acetone or nitromethane. It is also possible to use mixtures of the solvents mentioned. Acetonitrile and dimethylformamide are preferred.

Suitable bases for the individual steps are the customary strongly basic compounds. These preferably include organolithium compounds such as, for example, N-butyllithium, sec-butyllithium, tert-butyllithium or phenyllithium, or amides such as, for example, lithium diisopropylamide, sodium amide or potassium amide, or lithium hexamethylsilylamide, or alkali metal hydrides such as sodium hydride or potassium hydride.

In general, the base is employed in an amount of from 1 mol to 10 mol, preferably from 1 mol to 3 mol, in each case relative to 1 mol of the compounds of the general formula (V).

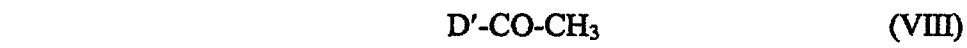
In general, the reaction proceeds in a temperature from room temperature to +120°C, preferably from 80°C to 120°C, in each case depending on the choice of the solvent.

In general, the reaction proceeds at normal pressure, but it is also possible to work at elevated or reduced pressure.

The compounds of the general formula (V) and (VI) are known per se or can be prepared by customary methods.

The compounds of the general formula (VI) are known in some cases or are new and can then be prepared as described above.

The compounds of the general formula (III) are new in some cases and can be prepared by first converting compounds of the general formula (VIII)



(VIII)

in which

D′ denotes the aryl radical mentioned above under D,

by reaction with compounds of the general formula (IX)

$$E\text{-}CO_2\text{-}R^{26} \qquad (IX)$$

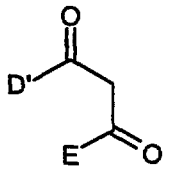
in which

E has the meaning indicated above

and

R^{26} represents C_1-C_4-alkyl,

into the compounds of the general formula (X)



(X)

in which

D′ and E have the meaning indicated above,

in inert solvents, in the presence of a base,

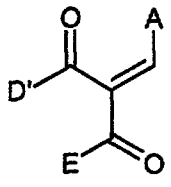
in a second step reacting with aldehydes of the general formula (XI)

$$A\text{-}CHO \qquad (XI)$$

in which

A has the meaning indicated above,

to give the compounds of the general formula (XII)



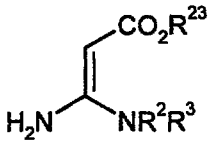
(XII)

in which

A, D' and E have the meaning indicated above,

and finally

reacting with compounds of the general formula (XIII)



(XIII)

in which

R^{23}, R^2 and R^3 have the meaning indicated above.

Suitable solvents for the reactions are, for the individual steps, water or ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether, or hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, or triethylamine, pyridine, dimethyl sulphoxide, dimethylformamide, hexamethylphosphoramide, acetonitrile, acetone or nitromethane or alcohols, such as, for example, methanol, ethanol or propanol. It is also possible to use mixtures of the solvents mentioned. Toluene is preferred.

In general, the reaction is carried out at normal pressure. However, it is also possible to carry out the process at reduced pressure or at elevated pressure (e.g. in a range from 0.5 to 5 bar).

The compounds of the general formula (VIII), (IX), (XI) and (XIII) are known in some cases or can be prepared by customary methods.

The compounds of the general formula (X) and (XII) are new in some cases and can be prepared as described above.

The compounds of the general formula (I) according to the invention have an unforseeable spectrum of pharmacological action.

The compounds of the general formula (I) according to the invention have valuable pharmacological properties which are superior in comparison with the prior art, in particular they are highly effective inhibitors of the cholesterol ester transfer protein (CETP) and stimulate reverse cholesterol transport. The active compounds according to the invention bring about a lowering of the LDL cholesterol level in the blood with simultaneous increase in the HDL cholesterol level. They can therefore be employed for the treatment of hyperlipoproteinaemia, hypolipoproteinaemia, dyslipidaemias, hypertriglyceridaemias, combined hyperlipidaemias or arteriosclerosis.

The pharmacological action of the substances according to the invention were determined in the following test:

CETP inhibition testing

Obtainment of CETP

CETP is obtained in partially purified form from human plasma by differential centrifugation and column chromatography and used for the test. For this, human plasma is adjusted with NaBr to a density of 1.21 g per ml and centrifuged at 4°C for 18 h at 50,000 rpm. The bottom fraction (d > 1.21 g/ml) is applied to a Sephadex® phenyl-Sepharose 4B (Pharmacia) column, washed with 0.15 M NaCl/0.001 M tris HCl pH 7.4 and then eluted with dist. water. The CETP-active fractions are pooled, dialysed against 50 mM Na acetate pH 4.5 and applied to a CM-Sepharose® (Pharmacia) column. Elution is then carried out using a linear gradient (0-1 M NaCl). The pooled CETP fractions are dialysed against 10 mM tris HCl pH 7.4 and then purified further by chromatography on a Mono Q® column (Pharmacia).

Obtainment of radiolabelled HDL

50 ml of fresh human EDTA plasma are adjusted with NaBr to a density of 1.12 and centrifuged at 4°C in a Ty 65 rotor for 18 h at 50,000 rpm. The upper phase is used for the obtainment of cold LDL. The lower phase is dialysed against 3 × 4 l of PDB buffer (10 mM tris/HCl pH 7.4, 0.15 mM NaCl, 1 mM EDTA, 0.02% NaN_3). 20 µl of 3H-cholesterol (Dupont NET-725; 1 µC/µl dissolved in ethanol!) are then added per 10 ml of retentate volume and the mixture is incubated under nitrogen for 72 h at 37°C.

The batch is then adjusted to the density 1.21 using NaBr and centrifuged at 20°C in a Ty 65 rotor for 18 h at 50,000 rpm. The upper phase is recovered and the lipoprotein fractions are purified by gradient centrifugation. For this, the isolated, labelled lipoprotein fraction is adjusted to a density of 1.26 using NaBr. Each 4 ml of this solution are covered with a layer of 4 ml of a solution of the density 1.21 and 4.5 ml of a solution of 1.063 (density solutions of PDB buffer and NaBr) in centrifuge tubes (SW 40 rotor) and then centrifuged in the SW 40 rotor for 24 h at 38,000 rpm and 20°C. The intermediate layer containing the labelled HDL lying between the density 1.063 and 1.21 is dialysed against 3 × 100 volumes of PDB buffer at 4°C. The retentate contains radiolabelled ^{3}H-CE-HDL, which is used for the test adjusted to about 5×10^6 cpm per ml.

CETP test

For the testing of the CETP activity, the transfer of ^{3}H-cholesterol ester from human HD lipoproteins to biotinylated LD lipoproteins is measured. The reaction is ended by addition of streptavidin-SPA® beads (Amersham) and the transferred radioactivity is determined directly in a liquid scintillation counter.

In the test batch, 10 µl of HDL-^{3}H-cholesterol ester (~ 50,000 cpm) are incubated at 37°C for 18 h with 10 µl of biotin-LDL (Amersham) in 50 mM Hepes/0.15 M NaCl/0.1% bovine serum albumin/0.05% NaN_3 pH 7.4 [lacuna] with 10 µl of CETP (1 mg/ml) and 3 µl of the substance to be tested (dissolved in 10% DMSO/1% RSA). 200 µl of the SPA-streptavidin bead solution (TRKQ 7005) are then added, and the mixture is further incubated for 1 h with shaking and then measured in a scintillation counter. The controls used are corresponding incubations with 10 µl of buffer, 10 µl of CETP at 4°C and 10 µl of CETP at 37°C.

The activity transferred in the control batches with CETP at 37°C is rated as 100% transfer. The substrate concentration at which this transfer is reduced to one half is indicated as the IC_{50} value.

The following table indicates the IC_{50} values (mol/l) for CETP inhibitors:

Example No.	**IC_{50} value (mol/l)**
6	2.4×10^{-7}
9	6×10^{-8}
10	6×10^{-7}

Ex-vivo activity of the compounds according to the invention

Syrian golden hamsters from in-house breeding are anaesthetized (0.8 mg/kg atropine, 0.8 mg/kg Ketavet® s.c., 30' later 50 mg/kg Nembutal i.p.) after fasting for 24 hours. The jugular vein is then exposed and cannulated. The test substance is dissolved in a suitable solvent (as a rule Adalat placebo solution: 60 g of glycerol, 100 ml of H_2O, PEG-400 to 1000 ml) and administered to the animals via a PE catheter inserted in the

jugular vein. The control animals receive the same volume of solvent without test substance. The vein is then tied off and the wound is closed.

The test substances can also be administered p.o. by administering the substances dissolved in DMSO or suspended in 0.5% Tylose orally by means of a stomach tube. The control animals receive identical volumes of solvent without test substance.

After various times - up to 24 hours after administration - blood (about 250 µl) is taken from the animals by puncture of the retro-orbital venous plexus. Clotting is completed by incubation at 4°C overnight, then the blood is centrifuged at 6000 × g for 10 minutes. The CETP activity in the serum thus obtained is determined by the modified CETP test. As described for the CETP test above, the transfer of ^{3}H-cholesterol ester from HD lipoproteins to biotinylated LD lipoproteins is measured.

The reaction is completed by addition of Streptavidin-SPA^R beads (Amersham) and the transferred radioactivity is determined directly in a liquid scintlation counter.

The test batch is carried out as described under "CETP test". Only for the testing of the serum 10 µl of CETP are replaced by 10 µl of the corresponding serum samples. The controls used are corresponding incubations with sera of untreated animals.

The activity transferred in the control batches with control sera is rated as 100% transfer. The substance concentrations at which this transfer is reduced to one half is indicated as the ED_{50} value.

In-vivo activity of the compounds according to the invention

In experiments for the determination of the oral action on the lipoproteins and triglycerides, test substance dissolved in DMSO and suspended [lacuna] 0.5% Tylose is administered orally by means of a stomach tube to Syrian golden hamsters from in-house breeding. For the determination of the CETP activity, blood (about 250 µl) is taken before the start of the experiment by retro-orbital puncture. The test substances are then administered orally by means of a stomach tube. The control animals receive identical volumes of solvent without test substance. The feed is then withdrawn from the animals and blood is taken at various times - up to 24 hours after substance administration - by puncture of the retro-orbital venus plexus.

Clotting is completed by incubation of 4°C overnight, then the blood is centrifuged at 6000 × g for 10 minutes. The content of cholesterol and triglycerides in the serum thus obtained is determined with the aid of modified commercially available enzyme tests (cholesterol enzymatic 14366 Merck, triglycerides 14364 Merck). Serum is diluted in a suitable manner using physiological saline solution.

100 µl of serum dilution are mixed with 100 µl of test substance in 96-hole plates and incubated at room temperature for 10 minutes. The optical density is then determined at a wavelength of 492 nM using an automatic plate-reading apparatus. The triglyceride or cholesterol concentration contained in the samples is determined with the aid of a standard curve measured in parallel.

After precipitation of the ApoB-containing lipoproteins, the determination of the content of HDL cholesterol is carried out according to the manufacturer's instructions by means of a reagent mixture (Sigma 352-4 HDL cholesterol reagent).

In-vivo activity on transgenic hCETP mice

Transgenic mice from in-house breading (Dinchuck, Hart, Gonzalez, Karmann, Schmidt, Wirak; BBA (1995), 1295, 301) were administered the substances to be tested in the feed. Before the start of the experiment, blood was taken from the mice retro-orbitally in order to determine cholesterol and triglycerides in the serum. The serum was obtained as described above for hamsters by incubation at 4°C overnight and subsequent centrifugation at 6000 × g. After a week, blood was again taken from the mice in order to determine lipoproteins and triglycerides. The change in the measured parameters are expressed as a percentage change compared with the starting value.

The invention moreover relates to the combination of 2-amino-substituted pyridines of the general formula (I) with a glucosidase and/or amylase inhibitor for the treatment of familial hyperlipidaemias, of obesity (adiposity) and of diabetes mellitus. Glucosidase and/or amylase inhibitors in the context of the invention are, for example, acarbose, adiposine, voglibose, miglitol, emiglitate, MDL-25637, camiglibose (MDL-73945), tendamistate, AI-3688, trestatin, pradimicin-Q and salbostatin.

The combination of acarbose, miglitol, emiglitate or voglibose with one of the abovementioned compounds of the general formula (I) according to the invention is preferred.

The compounds according to the invention can furthermore be combined in combination with cholesterol-lowering vastatins or ApoB-lowering principles in order to treat dyslipidaemias, combined hyperlipidaemias, hypercholesterolaemias or hypertriglycerideaemias.

The combinations mentioned can also be employed for the primary or secondary prevention of coronary heart diseases (e.g. myocardial infarct).

Vastatins in the context of the invention are, for example, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin. ApoB-lowering agents are, for example, MTB inhibitors.

The combination of cerivastatin or ApoB inhibitors with one of the above-mentioned compounds of the general formula (I) according to the invention is preferred.

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, non-toxic, pharmaceutically suitable excipients or solvents. In this connection, the therapeutically active compound should in each case be present in a concentration of approximately 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds using solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, it optionally being possible, for example, if water is used as a diluent to use organic solvents as auxiliary solvents.

Administration is carried out in a customary manner intravenously, parenterally, perlingually or orally, preferably orally.

In the case of parenteral administration, solutions of the active compound can be employed using suitable liquid excipients.

In general, it has proved advantageous in the case of intravenous administration to administer amounts of approximately 0.001 to 1 mg/kg, preferably approximately 0.01 to 0.5 mg/kg, of body weight to achieve effective results, and in the case of oral administration the daily dose is approximately 0.01 to 20 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

In spite of this, if appropriate it may be necessary to depart from the amounts mentioned, namely depending on the body weight or the type of administration route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned has to be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these into a number of individual doses over the course of the day.

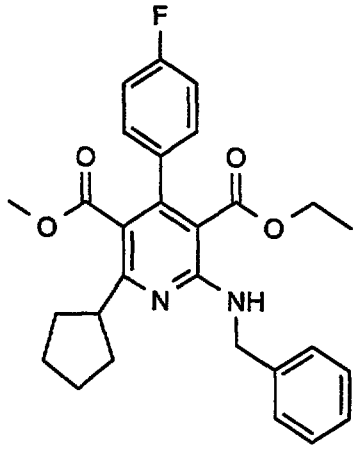
Abbreviations used:

CY	= cyclohexane
EA	= ethyl acetate
PE	= petroleum ether
THF	= tetrahydrofuran
DAST	= dimethylaminosulphur trifluoride
PTS	= para-toluenesulphonic acid
PDC	= pyridinium dichromate
PE/EA	= petroleum ether/ethyl acetate
DIBAH	= diisobutylaluminium hydride
HCl	= hydrochloric acid

Starting compounds

Example I

3-Ethyl 5-methyl 2-benzylamino-6-cyclopentyl-4-(4-fluoro-phenyl)-pyridine-3,5-dicarboxylate



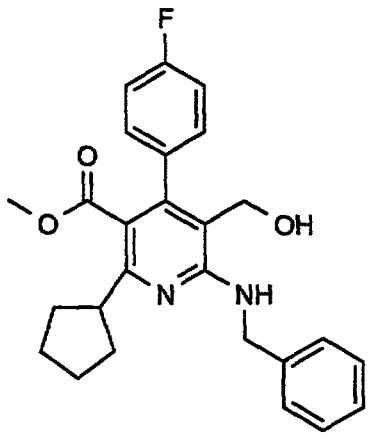
26 g (64 mmol) of 3-ethyl 5-methyl 2-chloro-6-cyclopentyl-4-(4-fluorophenyl)-pyridine-3,5-dicarboxylate, 14 ml (130 mmol) of benzylamine and 17 g (160 mmol) of sodium carbonate are stirred under reflux for 2 days in 220 ml of acetonitrile. 6.9 ml (64 mmol) of benzylamine and 6.8 g (64 mmol) of sodium carbonate are additionally added and the mixture is stirred under reflux for a further 20 hours. After cooling to room temperature, it is filtered off with suction through silica gel and the silica gel is washed with 100 ml of ethyl acetate. After concentrating in vacuo, the partially crystallizing residue is taken up in 100 ml of petroleum ether with stirring. The precipitated solid is filtered off with suction, washed with some petroleum ether and dried in a high vacuum. The mother liquor which remains is concentrated and chromatographed on silica gel (200 g of silica gel 230-400 mesh, d = 3.5 cm, eluent toluene).

Yield: 25.1 g (82% of theory)

R_f = 0.54 (PE/EA 8:1)

Example II

Methyl 6-benzylamino-2-cyclopentyl-4-(4-fluoro-phenyl)-5-hydroxymethyl-nicotinate



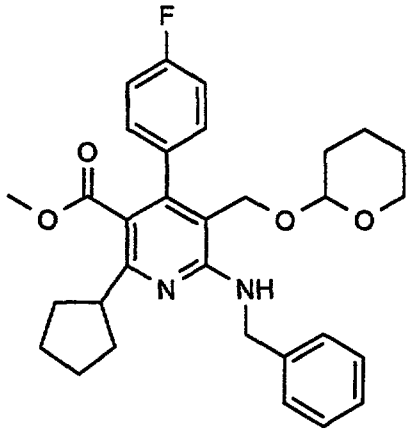
A solution of 14.8 g (31.1 mmol) of the compound from Example I is added dropwise at -40°C to 32.6 ml of a 1.0 M solution of $LiAlH_4$ in THF under argon over the course of 5 minutes and the mixture is allowed to warm to room temperature in the course of 40 minutes. It is stirred for 30 minutes, cooled to -15°C and the reaction is quenched by addition of 5.0 ml of H_2O. The resulting mixture is filtered off with suction through kieselguhr and the residue is washed with ethyl acetate. The combined organic phases are washed with H_2O (2 ×) and saturated NaCl solution, dried using Na_2SO_4, filtered and concentrated, and the product is chromatographed on silica gel 60 (petroleum ether/ethyl acetate = 5/1).

Yield: 13.2 g (97% of theory)

R_f = 0.25 (petroleum ether/ethyl acetate = 5/1)

Example III

Methyl 6-benzylamino-2-cyclopentyl-4-(4-fluoro-phenyl)-5-(tetrahydro-pyran-2-yloxymethyl)-nicotinate



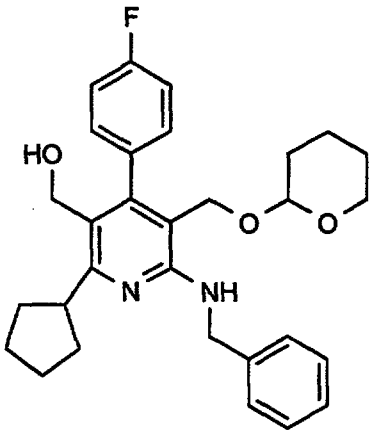
779 mg (3.1 mmol) of pyridinium p-toluenesulphonate (PPTS) and 8.8 ml (93 mmol) of 3,4-dihydro-2H-pyran are added to a solution of 13.5 g (31.0 mmol) of the compound from Example II in 300 ml of dry CH_2Cl_2 and the mixture is stirred at room temperature for 16 h. It is diluted with ether and washed with saturated NaCl solution. The organic phase is dried over Na_2SO_4 and concentrated, and the crude product is chromatographed on silica gel 60 (petroleum ether/ethyl acetate = 20/1, then ethyl acetate).

Yield: 9.9 g (59% of theory)

R_f = 0.53 (petroleum ether/ethyl acetate = 5/1)

Example IV

[6-Benzylamino-2-cyclopentyl-4-(4-fluoro-phenyl)-5-(tetrahydro-pyran-2-yloxy-methyl)-pyridin-3-yl]methanol



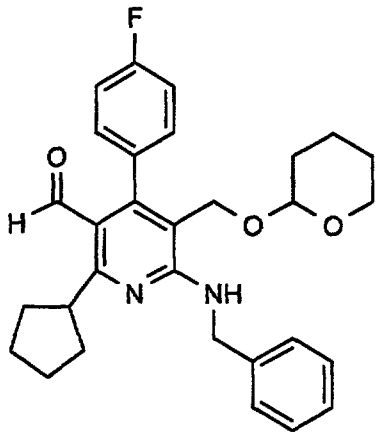
23 ml (34.3 mmol) of a 1.5 M solution of diisobutylaluminium hydride (DIBAH) in toluene are slowly added dropwise to a solution of 4.21 g (8.58 mmol) of the compound from Example III under argon over the course of 10 minutes. The mixture is allowed to warm to 0°C and is stirred at this temperature for 1 h, and 5.7 ml of a 1.5 M DIBAH solution are added again. After 1 h, the mixture is hydrolysed with 10 ml of water and extracted by stirring with 2 × 300 ml of ethyl acetate. The gelatinous aqueous phase is filtered off with suction through kieselguhr and washed 2 × with H_2O and 3 × with ethyl acetate. After separation of the phases, the combined organic phases are washed with saturated NaCl solution, dried over Na_2SO_4, concentrated and chromatographed on silica gel 60 (CH_2Cl_2, then ethyl acetate).

Yield: 3.5 g (83% of theory)

R_f = 0.31 (petroleum ether/ethyl acetate = 5/1)

Example V

6-Benzylamino-2-cyclopentyl-4-(4-fluoro-phenyl)-5-(tetrahydro-pyran-2-yloxy-methyl)-pyridine-3-carbaldehyde



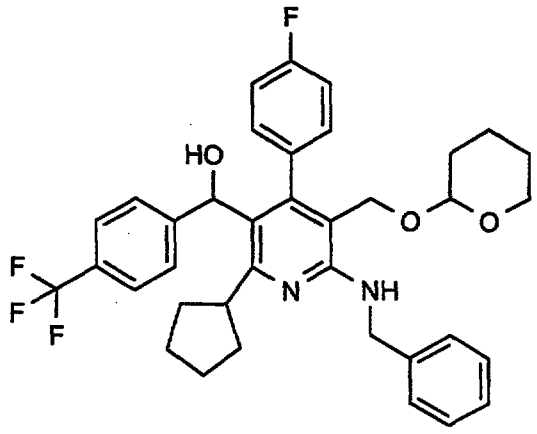
8.5 g (22.2 mmol) of pyridinium dichromate (PDC) are added at 0°C in 6 portions to a solution of 3.6 g (7.3 mmol) of the compound from Example IV in 200 ml of abs. CH_2Cl_2 over the course of 3 hours and the mixture is stirred at room temperature for 30 minutes. The reaction mixture is added to 50 g of silica gel 60 and the product is eluted with CH_2Cl_2/triethylamine 100:1. After concentration, the residue is chromatographed on silica gel 60 (petroleum ether/ethyl acetate = 20/1, then 2/1).

Yield: 1.64 g (45% of theory) + 417 mg (11% of theory) of recovered starting material.

R_f = 0.50 (petroleum ether/ethyl acetate = 10/1)

Example VI

[6-Benzylamino-2-cyclopentyl-4-(4-fluoro-phenyl)-5-(tetrahydro-pyran-2-yloxy-methyl)-pyridin-3-yl]-(4-trifluoromethyl-phenyl)-methanol



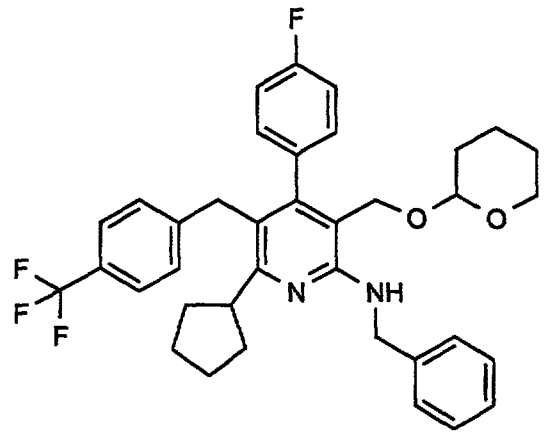
32 ml (4.6 mmol) of a freshly prepared 0.144 M solution of p-trifluoromethyl-phenyl-magnesium bromide in THF are added at -20°C to 800 mg (1.64 mmol) of the compound from Example V in abs. THF under argon. The mixture is stirred at room temperature for 2 h, 30 ml of 10% NH_4Cl solution are added and it is extracted with ethyl acetate. After washing with H_2O and saturated NaCl solution, drying over Na_2SO_4 and concentrating, the residue is chromatographed on silica gel 60 (CH_2Cl_2, then ethyl acetate).

Yield: 559 mg (54% of theory)

R_f = 0.53 (petroleum ether/ethyl acetate = 2/1)

Example VII

Benzyl-[6-cyclopentyl-4-(4-fluoro-phenyl)-3-(tetrahydro-pyran-2-yloxymethyl)-5-(4-trifluoromethyl-benzyl)-pyridin-2-yl]-amine



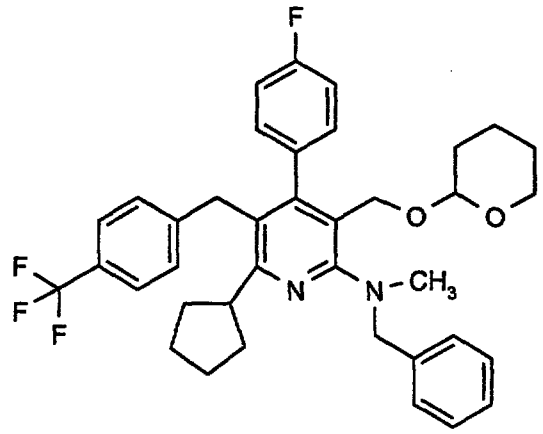
171 µl (1.3 mmol) of diethylaminosulphur trifluoride (DAST) are added at -30°C to a solution of 549 mg (0.865 mmol) of the compound from Example VI in abs. CH_2Cl_2, the mixture is stirred at this temperature for 3 h and 2.6 ml (3.89 mmol) of a 1.5 M solution of DIBAH in toluene are then added at this temperature. The cooling bath is removed, and the mixture is stirred at room temperature for 90 minutes and quenched at 0°C by addition of 2 ml of saturated NaCl solution. The mixture is filtered off with suction through kieselguhr and the residue is washed with H_2O, CH_2Cl_2 and ethyl acetate. After separation of the phases, the aqueous phase is washed with CH_2Cl_2, and the combined organic phases are dried over Na_2SO_4 and concentrated. Further purification is carried out by chromatography on silica gel 60 (petroleum ether/ ethyl acetate = 40/1).

Yield: 482 mg (90% of theory)

R_f = 0.43 (petroleum ether/ethyl acetate = 10/1)

Example VIII

Benzyl-[6-cyclopentyl-4-(4-fluoro-phenyl)-3-(tetrahydro-pyran-2-yloxymethyl)-5-(4-trifluoromethyl-benzyl)-pyridin-2-yl]-methyl-amine



0.36 ml of methyl iodide (5.82 mmol) is added to a solution of 60 mg (0.097 mmol) of the compound from Example VII and 109 mg (0.97 mmol) of potassium tert-butoxide (KOtBu) in 2 ml of abs. DMF and the mixture is stirred for 40 minutes. 3 ml of saturated $NaHCO_3$ solution are added, the mixture is extracted 3 × with ether, and the combined organic phases are washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated. Further purification is carried out by chromatography on silica gel 60 (petroleum ether/ethyl acetate = 40/1).

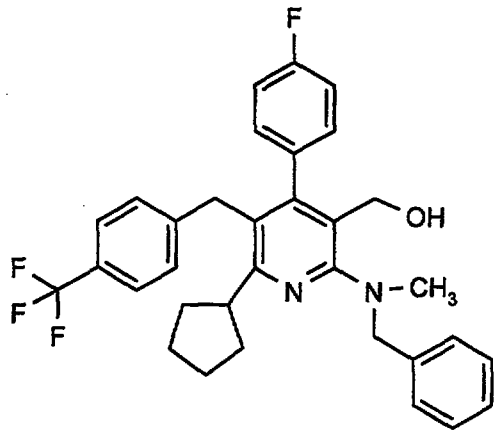
Yield: 35 mg (57% of theory)

R_f = 0.18 (petroleum ether/ethyl acetate = 10/1)

Preparation Examples

Example 1

[2-Benzyl-methyl-amino-6-cyclopentyl-4-(4-fluoro-phenyl)-5-(4-trifluoromethyl-benzyl)-pyridin-3-yl]-methanol

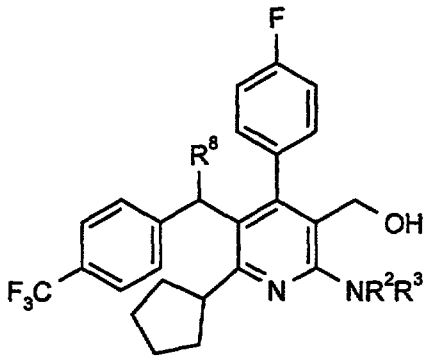


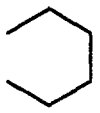
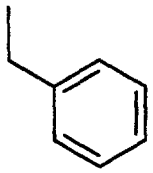
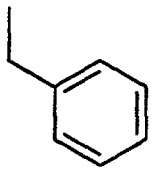
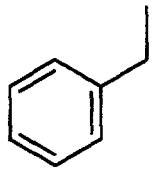
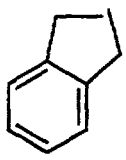
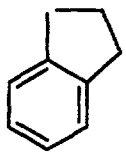
A solution of 32 mg (0.051 mmol) of the compound from Example VIII in 2 ml of THF is treated with 0.5 ml of 3 M HCl and stirred at room temperature for 90 minutes. 4 ml of saturated $NaHCO_3$ solution are added, the mixture is extracted with ethyl acetate (3 ×), and the combined organic phases are washed with H_2O and saturated NaCl solution, dried over Na_2SO_4 and concentrated. Further purification is carried out by chromatography on silica gel 60 (petroleum ether/ethyl acetate = 20/1).

Yield: 24 mg (86% of theory)

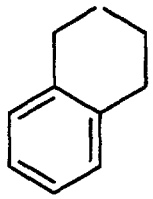
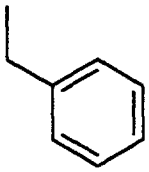
R_f = 0.28 (petroleum ether/ethyl acetate = 10/1)

Table 1:



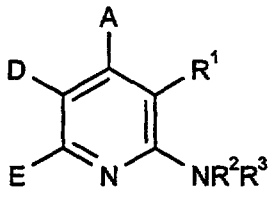
Ex. No.	R^2	R^3	R^8	R_f *
2			H	0.41 PE/EA (5:1
3	C_2H_5		H	0.30 EA/PE (1:10)
4	$(CH_2)_3CH_3$		H	0.40 EA / PE (1:10)
5	CH_2-C_6H_5		H	0.35 EA / PE (1:10)
6			OCH_3	0.38 Cy / EA (8:2)
7			F	0.33 Cy / EA (8:2)

5

Ex. No.	R^2	R^3	R^8	R_f *
8			H	0.25 Cy / EA (9:1)
9			H	0.37 Cy / EA (8:1)
10		H	H	0.47 Tol/EA (9:1)
11	H		H	

Patent Claims

1. 2-Amino-substituted pyridines of the general formula (I)



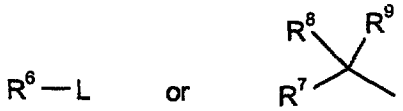
in which

A represents aryl having 6 to 10 carbon atoms, which is optionally identically or differently substituted up to 5 times by halogen, hydroxyl, trifluoromethyl, nitro, trifluoromethoxy or by straight-chain or branched alkyl, acyl, hydroxyalkyl or alkoxy each having up to 7 carbon atoms, or by a group of the formula $-NR^4R^5$,

in which

R^4 and R^5 are identical or different and
denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

D represents aryl having 6 to 10 carbon atoms, which is optionally substituted by nitro, halogen, trifluoromethyl or trifluoromethoxy, or represents a radical of the formula



in which
R^6 and R^7 are identical or different and
denote cycloalkyl having 3 to 6 carbon atoms, or
denote aryl having 6 to 10 carbon atoms or form a 5- to 7-membered, optionally benzo-fused, saturated or unsaturated,

* C L M S *

mono-, bi- or tricyclic heterocycle having up to 4 carbon atoms from the group consisting of S, N and/or O,
where the cyclic systems are optionally substituted, in the case of the nitrogen-containing rings also via the N function, identically or differently up to 5 times by halogen, trifluoromethyl, hydroxyl, nitro, cyano, carboxyl, trifluoromethoxy, straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms, by aryl having 6 to 10 carbon atoms or by an optionally benzo-fused, aromatic 5- to 7-membered heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O,
and/or are substituted by a group of the formula $-OR^{10}$, $-SR^{11}$, $-SO_2R^{12}$ or $-NR^{13}R^{14}$,

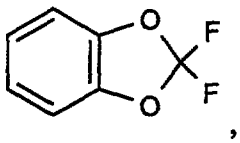
in which

R^{10}, R^{11} and R^{12} are identical or different and
denote aryl having 6 to 10 carbon atoms, which for its part can be identically or differently substituted up to 2 times by phenyl, halogen or by straight-chain or branched alkyl having up to 4 carbon atoms,

R^{13} and R^{14} are identical or different and have the meaning of R^4 and R^5 indicated above,

or

R^6 or R^7 denote a radical of the formula



,

L denotes straight-chain or branched alkyl or alkenyl each having 2 to 10 carbon atoms, each of which is optionally substituted up to 2 times by hydroxyl,

* C L M S *

R^8 denotes hydrogen or halogen,

and

R^9 denotes hydrogen, halogen, azido, trifluoromethyl, hydroxyl, trifluoromethoxy, straight-chain or branched alkoxy having up to 5 carbon atoms or a radical of the formula $-NR^{15}R^{16}$,

in which

R^{15} and R^{16} are identical or different and have the meaning of R^4 and R^5 indicated above,

or

R^8 and R^9 together form a radical of the formula =O or $=NR^{17}$,

in which

R^{17} denotes hydrogen or straight-chain or branched alkyl, alkoxy or acyl each having up to 6 carbon atoms,

E represents cycloalkyl having 3 to 8 carbon atoms, or
represents straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 8 carbon atoms or hydroxyl, or
represents phenyl which is optionally substituted by halogen or trifluoromethyl,

R^1 represents straight-chain or branched alkyl having up to 6 carbon atoms, which is substituted by hydroxyl,

R^2 and R^3 are identical or different and
represent hydrogen, phenyl, benzyl, cycloalkyl having 3 to 7 carbon atoms or straight-chain or branched alkyl, acyl each having up to 6 carbon atoms, or a group of the formula $-CO-NR^{18}R^{19}$,

in which

* C L M S *

R^{18} and R^{19} are identical or different and
denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl having up to 6 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a 5- to 7-membered saturated, partially unsaturated or unsaturated, optionally benzo-fused, mono- or bicyclic heterocycle having up to 4 heteroatoms from the group consisting of S, N and/or O, which can optionally be identically or differently substituted up to three times by nitro, cyano, halogen, trifluoromethyl, hydroxyl, carboxyl, straight-chain or branched alkxoy or alkoxycarbonyl each having up to 5 carbon atoms, phenyl or by straight-chain or branched alkyl having up to 5 carbon atoms, which for its part can be substituted by hydroxyl,
and/or the heterocycle is substituted by a group of the formula $-NR^{20}R^{21}$,

in which

R^{20} and R^{21} have the meaning of R^{18} and R^{19} indicated above and are identical to or different from this,

and their salts.

2. Compound of the general formula (I) according to Claim 1, in which

A represents naphthyl or phenyl, each of which is optionally substituted identically or differently up to 3 times by fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, nitro, trifluoromethoxy or by straight-chain or branched alkyl, acyl or alkoxy each having up to 6 carbon atoms, or by a group of the formula $-NR^4R^5$,

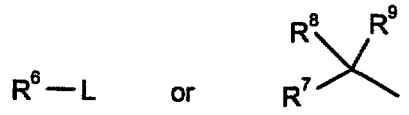
in which

R^4 and R^5 are identical or different and

* C L M S *

denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

D represents phenyl which is optionally substituted by nitro, fluorine, chlorine, bromine, trifluoromethyl or trifluoromethoxy, or
represents a radical of the formula



in which

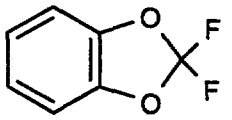
R^6 and R^7 are identical or different and
denote cyclopropyl, cyclopentyl or cyclohexyl, or
denote phenyl, napthyl, pyridyl, tetrazolyl, pyrimidyl, pyrazinyl, pyrrolidinyl, indolyl, morpholinyl, imidazolyl, benzothiazolyl, phenoxathiin-2-yl, benzoxazolyl, furyl, quinolyl or purin-8-yl,
where the cyclic systems are optionally identically or differently substituted up to 3 times, in the case of the nitrogen-containing rings also via the N function, by fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, cyano, carboxyl, trifluoromethoxy, straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms, triazolyl, tetrazolyl, benzoxathiazolyl or phenyl,
and/or are substituted by a group of the formula $-OR^{10}$, $-SR^{11}$ or $-SO_2R^{12}$,

in which

R^{10}, R^{11} and R^{12} are identical or different and
denote phenyl which for its part is identically or differently substituted up to 2 times by phenyl, fluorine or chlorine or by straight-chain or branched alkyl having up to 4 carbon atoms,

or

R^6 or R^7 denote a radical of the formula



,

L denotes straight-chain or branched alkyl or alkenyl each having 2 to 8 carbon atoms, each of which is optionally substituted up to 2 times by hydroxyl,

R^8 denotes hydrogen, fluorine, chlorine or bromine,

and

R^9 denotes hydrogen, fluorine, chlorine, bromine, azido, trifluoromethyl, hydroxyl, trifluoromethoxy, straight-chain or branched alkoxy having up to 4 carbon atoms or a radical of the formula $-NR^{15}R^{16}$,

in which

R^{15} and R^{16} are identical or different and have the meaning of R^4 and R^5 indicated above,

or

R^8 and R^9 together form a radical of the formula =O or $=NR^{17}$,

in which

R^{17} denotes hydrogen or straight-chain or branched alkyl, alkoxy or acyl each having up to 4 carbon atoms,

E represents cyclopropyl, -butyl, -pentyl, -hexyl or -heptyl, or
represents straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by cyclopropyl, -butyl, -hexyl,

-pentyl, -heptyl or by hydroxyl, or represents phenyl which is optionally substituted by fluorine, chlorine or trifluoromethyl,

R^1 represents straight-chain or branched alkyl having up to 5 carbon atoms, which is substituted by hydroxyl,

R^2 and R^3 are identical or different and

represent hydrogen, phenyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl or represent straight-chain or branched alkyl, acyl each having up to 5 carbon atoms, or a group of the formula -CO-$NR^{18}R^{19}$,

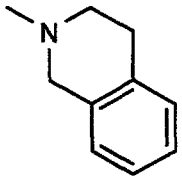
in which

R^{18} and R^{19} are identical or different and

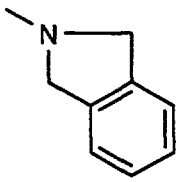
denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl having up to 5 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a pyrryl, imidazolyl, pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl ring or a radical of the formula



or



,

where the heterocycles are optionally substituted by hydroxyl, trifluoromethyl, fluorine, chlorine, bromine, hydroxyl, carboxyl, methylhydroxyl or straight-chain the branched alkxoy or alkoxy-carbonyl each having up to 4 carbon atoms,

and their salts.

3. Compounds of the general formula (I) according to Claim 1, in which

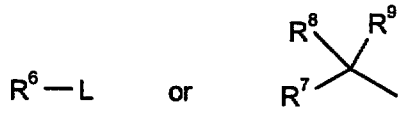
* C L M S *

A represents naphthyl or phenyl, each of which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, nitro, trifluoromethoxy or by straight-chain or branched alkyl, acyl or alkoxy each having up to 5 carbon atoms, or by a group of the formula $-NR^4R^5$,

in which

R^4 and R^5 are identical or different and
denote hydrogen, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

D represents phenyl which is optionally substituted by nitro, fluorine, chlorine or bromine, or
represents a radical of the formula



in which

R^6 and R^7 are identical or different and
denote cyclopropyl, cyclopentyl or cyclohexyl, or
denote phenyl, napthyl, pyridyl, tetrazolyl, pyrimidyl, pyrazinyl, phenoxathiin-2-yl, indolyl, imidazolyl, pyrrolidinyl, morpholinyl, benzothiazolyl, benzoxazolyl, furyl, quinolyl or purin-8-yl,
where the cyclic systems are optionally identically or differently substituted up to 3 times, in the case of the nitrogen-containing rings also via the N function, by fluorine, chlorine, trifluoromethyl, hydroxyl, cyano, carboxyl, trifluoromethoxy, straight-chain or branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms, triazolyl, tetrazolyl, benzothiazolyl or phenyl,
and/or are substituted by a group of the formula $-OR^{10}$, $-SR^{11}$ or $-SO_2R^{12}$,

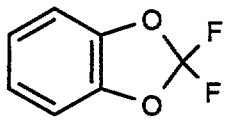
in which

R^{10}, R^{11} and R^{12} are identical or different and

denote phenyl which for its part is identically or differently substituted up to 2 times by phenyl, fluorine, chlorine or by straight-chain or branched alkyl having up to 3 carbon atoms,

or

R^6 or R^7 denote a radical of the formula



,

L denotes straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms, each of which is optionally substituted up to 2 times by hydroxyl,

R^8 denotes hydrogen or fluorine,

and

R^9 denotes hydrogen, fluorine, chlorine, bromine, azido, trifluoromethyl, hydroxyl, trifluoromethoxy, methoxy or a radical of the formula $-NR^{15}R^{16}$,

in which

R^{15} and R^{16} are identical or different and have the meaning of R^4 and R^5 indicated above,

or

R^8 and R^9 together form a radical of the formula =O or $=NR^{17}$,

in which

* C L M S *

R^{17} denotes hydrogen or straight-chain or branched alkyl, alkoxy or acyl each having up to 3 carbon atoms,

E represents cyclopropyl, cyclopentyl or cyclohexyl, or phenyl which is optionally substituted by fluorine or trifluoromethyl, or
represents straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,

R^1 represents straight-chain or branched alkyl having up to 4 carbon atoms, which is substituted by hydroxyl,

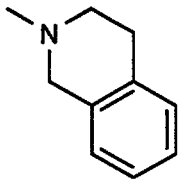
R^2 and R^3 are identical or different and
represent hydrogen, phenyl, benzyl, cyclopropyl, cyclopentyl or straight-chain or branched alkyl, acyl each having up to 5 carbon atoms, or a group of the formula $-CO-NR^{18}R^{19}$,

in which

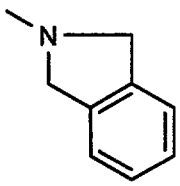
R^{18} and R^{19} are identical or different and
denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl having up to 4 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a pyrryl, morpholin, pyrrolidinyl or piperidinyl ring or a radical of the formula



or



,

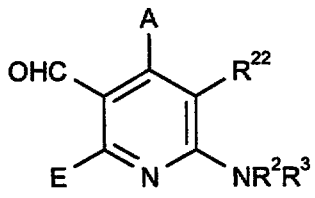
where the heterocycles are optionally substituted by hydroxyl, trifluoromethyl, fluorine, chlorine, bromine, hydroxyl, carboxyl, methylhydroxyl or straight-chain the branched alkxoy or alkoxy-carbonyl each having up to 3 carbon atoms,

* C L M S *

and their salts.

4. Process for the preparation of compounds of the general formula (I) according to Claim 1, characterized in that

[A] the radical D is first introduced into the compounds of the general formula (II)



in which

A, E, R^2 and R^3 have the meaning indicated above

and

R^{22} has the meaning of R^1 indicated above, where the hydroxyl function is present in protected form, preferably by tetrahydropyranyl,

in the sense of Grignard/Wittig reactions, the substituents are optionally derivatized in this stage by customary methods, preferably by reductions, and the hydroxyl protective group is removed in a last step,

[lacuna]

and, if appropriate, all substituents are varied and/or introduced according to customary methods.

5. Medicaments comprising at least one 2-amino-substituted pyridine according to Claims 1 to 3 and pharmacologically acceptable auxiliaries.

6. Pharmaceuticals according to Claim 5 for the treatment of arteriosclerosis.

* C L M S *

7. Pharmaceuticals according to Claim 5 for the treatment of hyperlipoproteinaemia.

8. Use of 2-amino-substituted pyridines according to Claims 1 to 3 for the production of medicaments.

9. Use according to Claim 8 for the production of medicaments for the treatment of arteriosclerosis.

10. Use according to Claim 8 for the production of medicaments for the treatment of hyperlipoproteinaemia.

* C L M S *