US006114341A

United States Patent [19]

Müller et al.

[11] **Patent Number: 6,114,341**

[45] **Date of Patent: *Sep. 5, 2000**

[54] **PYRIMIDO[1,2-A]INDOLES**

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[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **08/829,015**

[22] Filed: **Mar. 31, 1997**

[30] **Foreign Application Priority Data**

Apr. 4, 1996 [DE] Germany 196 13 550

[51] **Int. Cl.**[7] **A01N 43/54**; C07D 239/00

[52] **U.S. Cl.** **514/267**; 544/252

[58] **Field of Search** 514/267; 544/252

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[57] **ABSTRACT**

The pyrimido[1,2-a]indoles according to the invention are prepared by reacting appropriately substituted phenylacetic acid derivatives with phenylglycinols. The pyrimido[1,2-a] indoles can be used as active compounds in medicaments, in particular in medicaments with antiatherosclerotic activity.

18 Claims, No Drawings

PYRIMIDO[1,2-A]INDOLES

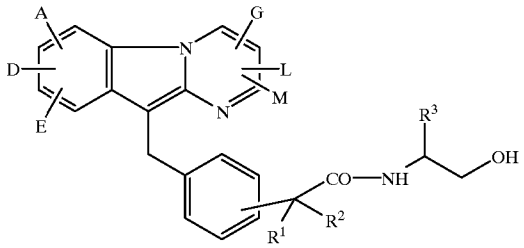
The present invention relates to pyrimido[1,2-a]indoles, to processes for their preparation and to their use as medicaments, in particular as antiatherosclerotic medicaments.

It is known that elevated blood levels of triglycerides (hypeitriglyceridaemia) and cholesterol (hypercholesterolaemia) are associated with the development of atherosclerotic changes in vessel walls and coronary heart disease.

There is, furthermore, a distinctly increased risk of developing coronary heart disease when these two risk factors occur in combination, which is in turn associated with an overproduction of apolipoprotein B-100. Hence there is a continuing pressing need to provide effective medicaments for controlling atherosclerosis and coronary heart disease.

The present invention relates to pyrimido[1,2-a]indoles of the general formula (I)

(I)



in which

A, D, E, G, L and M are identical or different and represent hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxycarbonyl with, in each case, up to 6 carbon atoms or straight-chain or branched alkyl with up to 6 carbon atoms, which in turn can be substituted by hydroxyl or by straight-chain or branched alkoxy with up to 4 carbon atoms,

R^1 and R^2 are identical or different and represent hydrogen, cycloalkyl with 3 to 8 carbon atoms or straight-chain or branched alkyl with up to 10 carbon atoms, which is optionally substituted by cycloalkyl with 3 to 6 carbon atoms, or represent phenyl which is optionally substituted by halogen or trifluoromethyl, or

R^1 and R^2 form, together with the carbon atom, a 4–8-membered cycloalkyl ring,

and

R^3 represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxycarbonyl with, in each case, up to 6 carbon atoms or by straight-chain or branched alkyl with up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl with, in each case, up to 6 carbon atoms, and/or is optionally substituted by a group of the formula —OR^4 or —NR^5R^6,

in which

R^4 is hydrogen or straight-chain or branched alkyl or alkenyl with, in each case, up to 6 carbon atoms,

R^5 and R^6 are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl with up to 6 carbon atoms, or denote straight-chain or branched acyl with up to 8 carbon atoms, which is optionally substituted by a group of the formula —NR^7R^8,

in which

R^7 and R^8 are identical or different and denote hydrogen or straight-chain or branched acyl with up to 8 carbon atoms;

where appropriate in an isomeric form and the salts thereof.

The pyrimido[1,2-a]indoles according to the invention can also be in the form of their salts. Salts which may be generally mentioned here are those with organic or inorganic bases or acids.

Physiologically acceptable salts are preferred for the purpose of the present invention. Physiologically acceptable salts of the compounds according to the invention may be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred examples are salts 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 may likewise be metal or ammonium salts of the compounds according to the invention which have a free carboxyl group. Particularly preferred examples are sodium, potassium, magnesium or calcium salts, and 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 are related as image and mirror image (enantiomers) or are not related as image and mirror image (diastereomers). The invention relates to the enantiomers or diastereomers or mixtures thereof in each case. These mixtures of enantiomers and diastereomers can be separated into the stereoisomerically pure components in a manner known per se.

Preferred compounds of the general formula (I) are those in which

A, D, E, G, L and M are identical or different and represent hydrogen, fluorine, chlorine, bromine, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxycarbonyl with, in each case, up to 4 carbon atoms or straight-chain or branched alkyl with up to 4 carbon atoms, which can in turn be substituted by hydroxyl or by straight-chain or branched alkoxy with up to 3 carbon atoms,

R^1 and R^2 are identical or different and represent hydrogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or straight-chain or branched alkyl with up to 8 carbon atoms, which is optionally substituted by cyclopropyl, cyclopentyl or cyclohexyl, or represent phenyl which is optionally substituted by fluorine, chlorine or bromine, or

R^1 and R^2 form, together with the carbon atom, a 4–7-membered cycloalkyl ring,

and

R^3 represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, fluorine, chlorine, bromine, cyano, by straight-chain or branched alkenyl or alkoxycarbonyl with, in each case, up to 4 carbon atoms or by straight-chain or branched alkyl with up to 5 carbon atoms, which is optionally

substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl with, in each case, up to 5 carbon atoms, and/or is optionally substituted by a group of the formula —OR^4 or —NR^5R^6,

in which

R^4 denotes hydrogen or straight-chain or branched alkyl or alkenyl with, in each case, up to 4 carbon atoms,

R^5 and R^6 are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl with up to 5 carbon atoms, or straight-chain or branched acyl with up to 6 carbon atoms, which is optionally substituted by a group of the formula —NR^7R^8,

in which

R^7 and R^8 are identical or different and denote hydrogen or straight-chain or branched acyl with up to 6 carbon atoms,

where appropriate in an isomeric form and the salts thereof.

Particularly preferred compounds of the general formula (I) are those in which

A, D, E, G, L and M are identical or different and represent hydrogen, fluorine, chlorine, bromine, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxycarbonyl with, in each case, up to 3 carbon atoms or represents straight-chain or branched alkyl with up to 3 carbon atoms,

R^1 and R^2 are identical or different and represent hydrogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or represent straight-chain or branched alkyl with up to 6 carbon atoms, which is optionally substituted by cyclopentyl or cyclohexyl, or represent phenyl which is optionally substituted by fluorine, chlorine or bromine, or

R^1 and R^2 form, together with the carbon atom, a 5–7-membered cycloalkyl ring,

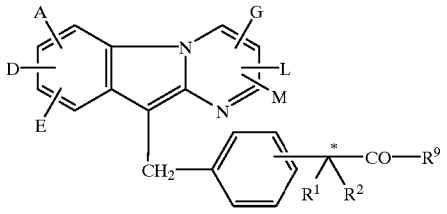
and

R^3 represents phenyl which is optionally substituted up to 3 times, identically or differently, by hydroxyl, trifluoromethyl, trifluoromethoxy, carboxyl, or by straight-chain or branched alkoxy, alkyl or alkoxycarbonyl with, in each case, up to 3 carbon atoms,

where appropriate in an isomeric form and the salts thereof.

A process for the preparation of the compounds of the general formula (I) according to the invention has also been found and is characterized in that racemic or else already enantiomerically pure carboxylic acids or their activated derivatives of the general formula (II)

(II)



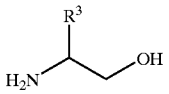
racemic or enantiomerically pure in which

A, D, E, G, L, M, R^1 and R^2 have the indicated meaning, and

R^9 represents hydroxyl or represents an activating radical, preferably chlorine,

are amidated with phenylglycinols of the general formula (III)

(III)

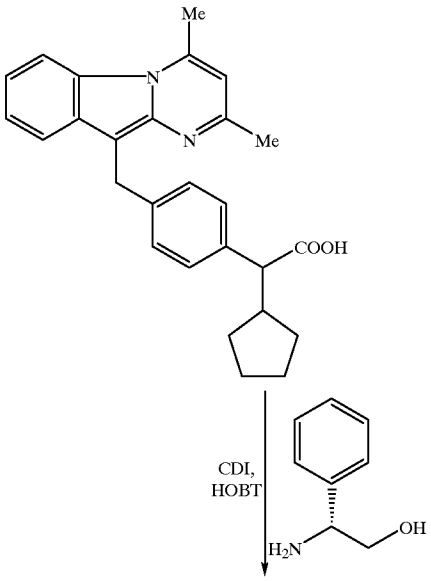


in which

R^3 has the indicated meaning,

in inert solvents, where appropriate in the presence of bases and/or ancillary substances.

The process according to the invention can be illustrated by way of example by the following formula diagram:



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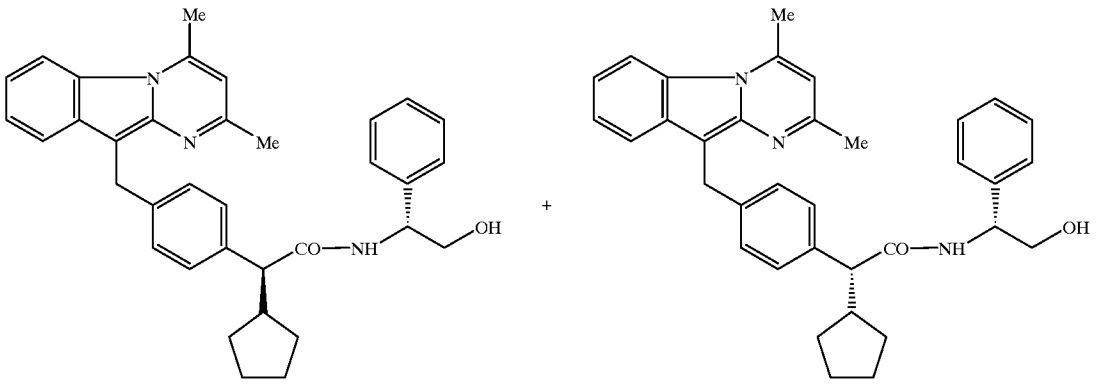


Suitable solvents for the amidation in this case are inert organic solvents which are not changed under the reaction conditions. These include ethers such as diethyl ether or tetrahydrofuiran, halogenated hydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, 1,2- dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethylene or trichloroethylene, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane, or petroleum fractions, nitromethane, dimethylformamide, acetone, acetonitrile or hexamethylphosphoric triamide. It is likewise possible to employ mixtures of the solvents. Dichloromethane, tetrahydrofuran, acetone or dimethylformamide are particularly preferred.

Bases which can be employed for the process according to the invention are, in general, 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 alcoholates such as sodium or potassium methanolate, sodium or potassium ethanolate 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, dimethylaminopyridine, methylpiperidine or morpholine. It is also possible to employ as bases alkali metals such as sodium and hydrides thereof such as sodium hydride. Sodium and potassium carbonates and triethylamine are preferred.

The base is employed in an amount of from 1 mol to 5 mol, preferably from 1 mol to 3 mol, based on 1 mol of the compound of the general formula (II).

The reaction is generally carried out at a temperature in the range from 0° C. to 150° C., preferably from +20° C. to +110° C.

The reaction can be carried out under atmospheric, elevated or reduced pressure (for example 0.5 to 5 bar). Atmospheric pressure is generally employed.

The reaction can, where appropriate, also take a course via the activated stage of the acid halides which can be prepared from the corresponding acids by reaction with thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus tribromide or oxalyl chloride.

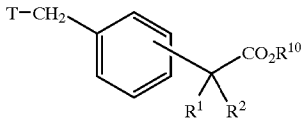
The bases listed above may also be employed as acid-binding aids for the amidation.

Likewise suitable as ancillary substances are dehydrating reagents. These include, for example, carbodiimides such as diisopropylcarbodiimide, dicyclohexylcarbodiimideorN-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride or carbonyl compounds such as carbonyldiimidazole or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3'-sulphonate or propanephosphonic anhydride or isobutyl chloroformate or benzotriazolyloxy (dimethylamino)phosphonium hexafluorophosphate or diphenylphosphoryl azide or methanesulphonyl chloride, where appropriate in the presence of bases such as triethylamine or N-ethylmorpholine or N-methylpiperidine or dicyclohexylcarbodiimide and N-hydroxysuccinimide.

The ancillary substances are generally employed in an amount of from 0.5 to 3 mol, preferably from 1 to 1.5 mol, based on 1 mol of the appropriate carboxylic acids.

The carboxylic acids of the general formula (II) are novel and can be prepared by initially preparing, by reacting compounds of the general formula (IV)

(IV)



in which

R^1 and R^2 have the indicated meaning,

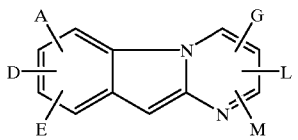
T represents a typical leaving group such as, for example, chlorine, bromine, iodine, tosylate or mesylate, and preferably represents bromine,

and

R^{10} represents (C_1–C_4)-alkyl,

with compounds of the general formula (V)

(V)

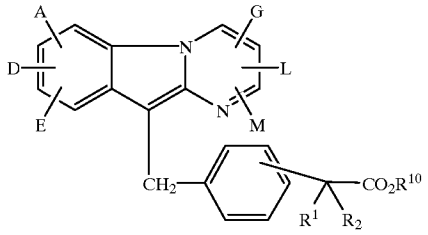


in which

A, D, E, G, L and M have the indicated meaning,

the compounds of the general formula (VI)

(VI)



in which

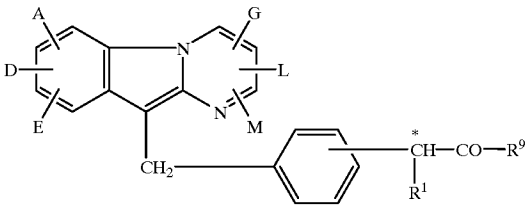
A, D, E, G, L, M, R^1, R^2 and R^{10} have the abovementioned meaning,

in inert solvents, where appropriate in the presence of bases,

and subsequently hydrolysing the esters by conventional methods.

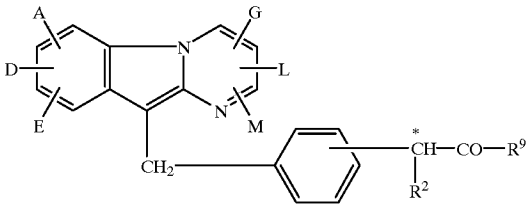
Enantiomerically pure acids of the formula (IIa) or (IIb):

(IIa)



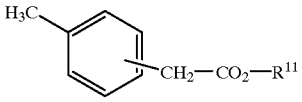
or

(IIb)



in which R^1 and R^2 are not hydrogen and R^9 represents hydroxyl, are furthermore obtained by preparing, from the D- or L-menthyl esters of the general formula (VII)

(VII)



in which

R^{11} represents D- or L-menthyl,

by reaction with compounds of the general formula (VIIIa) or (VIIIb) R^1—Z (VIIIa) or R^2—Z (VIIIb)

in which

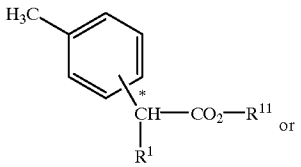
R^1 and R^2 have the indicated meaning,

and

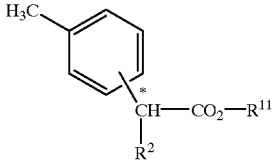
Z represents halogen, preferably bromine,

the enantiomerically pure menthyl esters of the general formula (IXa) or (IXb)

(IXa)



(IXb)

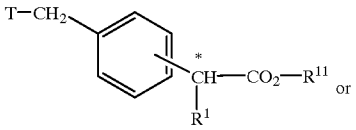


in which

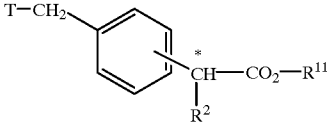
R^1, R^2 and R^{11} have the indicated meaning,

converting the latter in a next step by a halogenation into the compounds of the general formula (Xa) or (Xb)

(Xa)



(Xb)

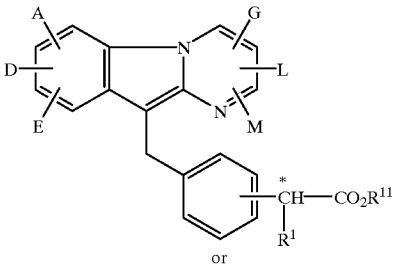


in which

R^1, R^2, and R^{11} have the indicated meaning, and T represents halogen,

subsequently preparing, by reaction with the compounds of the general formula (V), the enantiomerically pure compounds of the general formula (XIa) or (XIb)

(XIa)



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