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WO 2004/028544 A1

(54) Title: USE OF MAS-COMPOUNDS FOR TREATING DISEASES ASSOCIATED WITH LIPID METABOLISM

(57) Abstract: Certain sterols can be used for increasing the HDL cholesterol to non-HDL cholesterol ratio, for treatment and/or prevention of artherosclerosis, for treatment and/or prevention of hyper-lipidemia, for treatment of diabetic dyslipididemia, for treatment of hyper-cholesterolemia, for treatment of diseases of illness related to metabolic dysfunction, for treatment of obesity or obesitas related diseases, and for the treatment of neurological diseases.

USE OF MAS-COMPOUNDS FOR TREATING DISEASES ASSOCIATED WITH LIPID METABOLISM

FIELD OF THE INVENTION

This invention relates to the use of novel compounds mentioned below for increasing the HDL cholesterol to non-HDL cholesterol ratio, for treatment and/or prevention of atherosclerosis, for treatment and/or prevention of hyperlipidemia, for treatment of diabetic dyslipididemia, for treatment of hyper-cholesterolemia, for treatment of diseases of illness related to metabolic dysfunction, for treatment of obesity or obesitas related diseases, and for treatment of neurological diseases, for example, Alzheimer, associated with lipid metabolism. The present invention also embraces pharmaceutical compositions and kits comprising these compounds and methods of using the compounds and their pharmaceutical compositions, for example, to humans.

BACKGROUND OF THE INVENTION

Herein the term lipoprotein covers any of the lipid-protein complexes in which lipids are transported in the blood. Lipoprotein particles consists of a spherical hydrophobic core of triglycerides or cholesteryl esters surrounded by an amphiphatic monolayer of phospholipids, cholesterol, and apolipoproteins. The expression HDL cholesterol covers high-density lipoprotein and the expression non-HDL cholesterol covers the remaining lipoproteins.

Atherosclerosis is an extremely common form of arteriosclerosis in which deposits of yellowish plaques (atheromas) containing cholesterol, lipid material, and lipophages are formed within the intima and inner media of large and medium-sized arteries. Arterosclerosis is a group of diseases characterized in thickening and loss of elasticity of arterial walls.

Hyperlipidemia is a general term for elevated concentrations of any or all of the lipids in the plasma, including, for example, hypertriglyceridema and hypercholesterolemia.

Diabetic dyslipidemia is the typical lipid disorder associated to type II diabetes characterized by low HDC, high LDC, and high small very dense lipid particles.

Hyper-cholesterolemia is the presence of an excess of cholesterol in the blood.

Metabolic dysfunctions cover the general term describing an inappropriate regulation of the glucose and lipid metabolism.

Alzheimer's disease is a progressive degenerative disease of the brain of unknown etiology characterized by diffuse atrophy throughout the cerebral cortex with distinctive histopathology changes termed "senile plaques" (microscopic lesions composed of fragmented

axon terminals and dendrites surrounding a core of amyloidal) and "neurofibrillary tangles" (intracellular knots or clums of neurofibrils).

In many countries, obesity is becoming a steadily increasing problem. Great effort has been devoted to this problem and the elevated health risk associated with obesity and metabolic imbalance. For example, over weighty people have an increased risk of developing diabetes. For several subgroups of the population, for example, diabetics, overweight increases the risks in connection with the parent disease. Recent research also revealed connections between cholesterol metabolism and diseases of the central nervous system. For example, it is possible to delaying or preventing the onset of Alzheimer disease by cholesterol synthesis inhibitors. Large portions of the health care budgets are nowadays used in obesity or obesity related fields.

Many steps in the cholesterol synthesis are known. For example, the cholesterol synthesis proceeds via the following compounds: HMG-CoA → evalonic acid → lanosterol → FF-MAS → T-MAS → desmosterol → cholesterol. Several statins, for example, Simvastatin, are known to interact on the HMG-CoA → evalonic acid step. The desmosterol → cholesterol is controlled by a sterol Δ^{24} reductase.

One object of this invention is to provide a medicament which can be used for increasing the HDL cholesterol to non-HDL cholesterol ratio.

Another object of this invention is to provide a medicament which can be used for treatment and/or prevention of artherosclerosis.

A further object of this invention is to provide a medicament which can be used for treatment and/or prevention of hyperlipidemia.

A still further object of this invention is to provide a medicament which can be used for treatment of diabetic dyslipididemia.

A still further object of this invention is to provide a medicament which can be used for treatment of hyper-cholesterolemia.

A still further object of this invention is to provide a medicament which can be used for treatment of diseases of illness related to metabolic dysfunction.

A still further object of this invention is to provide a medicament which can be used for treatment of obesity or obesitas related diseases.

A still further object of this invention is to provide a medicament which can be used for treatment of neurological diseases, e. g. Alzheimer disease.

Other objects of the present invention will become apparent upon reading the present description.

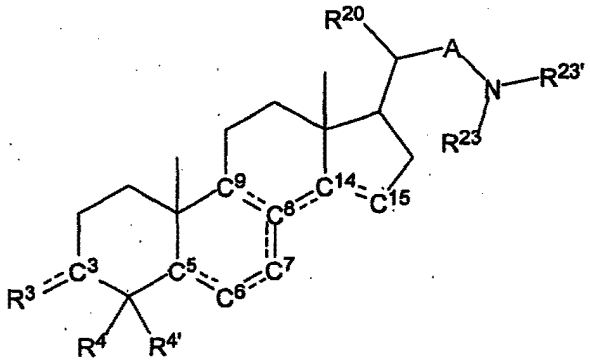
DEFINITIONS

Herein, FF-MAS is 4,4-dimethyl-5α-cholesta-8,14,24-triene-3β-ol, T-MAS is 4,4-dimethyl-5α-cholesta-8,24-diene-3β-ol (also designated 4,4-dimethylzymosterol), and ZK 255884 is (20S)-20-[(piperidin-1-yl)methyl]-4,4-dimethyl-5α-pregna-8,14-dien-3β-ol (compound No. 2 in the list below).

DESCRIPTION OF THE INVENTION

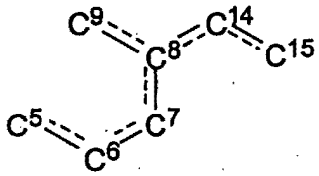
It has now, surprisingly been found that certain compounds hereinafter designated MAS compound which are defined below can be used for increasing the HDL cholesterol to non-HDL cholesterol ratio, for treatment and/or prevention of artherosclerosis, for treatment and/or prevention of hyperlipidemia, for treatment of diabetic dyslipididemia, for treatment of hyper-cholesterolemia, for treatment of diseases of illness related to metabolic dysfunction, and for treatment of obesity or obesitas related diseases.

Herein MAS compounds are all compounds of the general formula I, Ia, Ib, and Ic mentioned in any of the international patent applications having the international publication number WO 96/00235 (our ref.: 4228), WO 97/00884 (our ref.: 4475), WO 98/28323 (our ref.: 5141), WO 99/32506 (earliest priority: 971218), WO 98/52965 (earliest priority: 970516), WO 99/67273 (our ref.: 5558), WO 99/58549 (our ref.: 5509), or WO 2000/47604 (our ref.: 5769), WO 2000/68245 (our ref.: 6238), or WO 2001/62771 (our ref.: 6239), preferably all the specific compounds mentioned specifically in said WO specifications covered by said formula, as well as compounds of the general formula X shown below:



X

wherein in the moiety of the following formula



XA

each bond between C^5 and C^6, between C^8 and C^7, between C^7 and C^8, between C^8 and C^9, between C^8 and C^{14} and between C^{14} and C^{15}, independently, is a single bond or a double bond, at least one of these bonds being a double bond, and wherein each carbon atom C^5, C^6, C^7, C^8, C^9, C^{14} and C^{15} is bonded to each neighbouring C atom by a single bond or at the most by one double bond, and wherein between all other carbon atoms of the steroid skeleton are single bonds, and C^3R^3 is a) C^3=O or b) C^3H-O$R^{3'}$, wherein $R^{3'}$ is selected from the group, comprising hydrogen, unsubstituted or substituted, linear or branched C_1 - C_{10} alkyl and C^3(O)-$R^{3''}$, bonded to the CH-O moiety via the C(O) moiety, wherein $R^{3''}$ is selected from the group, comprising i) substituted or unsubstituted, linear or branched C_1 - C_{10} alkyl, ii) substituted or unsubstituted, linear or branched C_1 - C_{10} fluoro alkyl, iii) unsubstituted or substituted C_6 - C_{10} aryl, iv) unsubstituted or substituted C_5 - C_{10} heteroaryl, v) unsubstituted or substituted, linear or branched C_1 - C_{10} alkyloxy and vi) unsubstituted or substituted, linear or branched C_1 - C_{10} alkylamino, or c) C^3H-SO_2-$R^{3''}$ or C^3=N$OR^{3''}$, wherein $R^{3''}$ has the same meaning as above, or d) C^3H-O-$R^{3'''}$, wherein $R^{3'''}$ is unsubstituted or substituted, linear or branched C_2 - C_{10} alkylen and forms a cyclic ether both with the C atom of the steroid skeleton and the O atom, or e) a cyclic ring structure with the C^3 atom, wherein R^3 is unsubstituted or substituted, linear or branched C_2 - C_{10} alkylen, or f) C^3H-Hal, wherein Hal is F, Cl, Br or I,

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