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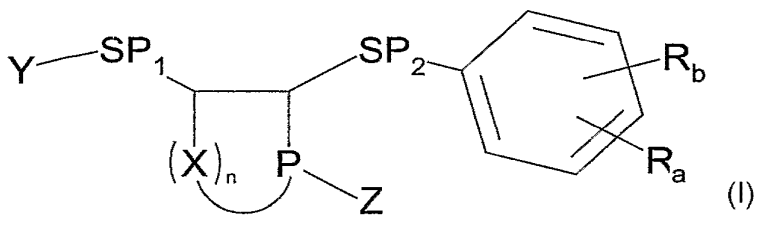
(54) Title: NOVEL HYPOCHOLESTEROLEMIC COMPOUNDS



(I)

(57) Abstract: The present invention relates to novel hypocholesterolemic compounds of formula (I) useful in the treatment and prevention of atherosclerosis and for the reduction of cholesterol levels as well as to pharmaceutical compositions comprising said compounds alone or in combination with other active agents.

Novel hypocholesterolemic compounds

The present invention relates to novel hypocholesterolemic compounds useful in the treatment and prevention of atherosclerosis and for the reduction of cholesterol levels as well as to pharmaceutical compositions comprising said compounds alone or in combination with other active agents.

Atherosclerotic coronary heart disease represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigarette smoke as well as serum cholesterol. Elevated concentrations of serum cholesterol have been demonstrated by a number of clinical studies to be a major contributing factor in the development and progression of atherosclerosis, which is characterized by the formation of cholesterol-containing plaques in the aorta and lesser arteries.

In mammals, 1/3 of the serum cholesterol is derived from exogenous dietary sources which enters the body through absorption in the intestine and 2/3 of the serum cholesterol are derived through endogenous de novo synthesis in the liver involving a complex set of enzyme-catalyzed reactions and regulatory mechanisms.

Recently it has been shown that intestinal cholesterol absorption is an energy-independent, protein-mediated process (Hauser, H. et al, *Biochemistry* **1998**, *37*, 17843-17850; Schulthess, G. et al, *Biochemistry* **2000**, *39*, 12623-12631; Werder, M. et al, *Biochemistry* **2001**, *40*, 11643-11650) rather than a passive diffusion process. The proteins facilitating intestinal cholesterol absorption were identified as two brush border membrane-resident scavenger receptors (Hauser, H. et al, *Biochemistry* **1998**, *37*,

17843-17850; Werder, M. et al, *Biochemistry* **2001**, *40*, 11643-11650). Both *in vitro* and *in vivo* animal experiments confirmed the presence of these two scavenger receptors in the intestinal BBM and proved that they are responsible for the protein-mediated cholesterol uptake.

Various 2-azetidinone compounds have been reported as being useful in lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls: For example WO 93/02048, WO 94/17038, WO 95/08532, PCT/US95/03196, U.S. Pat. No.5,633,246 describe 2-azetidinone compounds with different substituents at the 3-position, and U.S. Pat. No. 5,756,470 discloses 2-azetidinones having varying substituents at the 4 position. Other azetidinone derivatives include for example elastase inhibitory substituted azetidinones disclosed in European Patent 199,630B1 and European Patent Application 337,549A1. The most prominent representative of these 2-azetidinones, Ezetimibe (also known under trade names Zetia™ and Ezetrol®), has been in use as a cholesterol-lowering drug in monotherapy and in dual therapy combined with a statin. It is the first representative of the new class of cholesterol-lowering drugs that inhibit intestinal cholesterol absorption by targeting the two scavenger receptors in the intestinal brush border membrane described above.

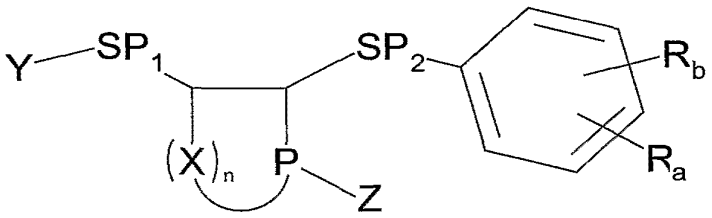
However, it has been shown that the 2-azetidinones upon administration are readily absorbed and extensively metabolized into the pharmalogically active glucuronide of which over 95% remained in the intestinal wall upon direct administration as the glucuronide (van Heek, M. et al. *Br. J. Pharmacol.* **2000**, *129*, 1748-1754). In addition side effects such as allergic reactions including rash and angiodema have been reported.

Applicants have now discovered that the compounds of the present invention with the structural characteristics as depicted in

formula I and in particular formulas II and III are able to inhibit the protein-mediated process mentioned above by which cholesterol absorption is mediated, while overcoming the above described disadvantages of compounds known in the art. Thus the compounds of the present invention are particularly useful in the treatment and prevention of atherosclerosis and for the reduction of cholesterol levels.

In a first aspect, the present invention thus relates to novel hypocholesterolemic compounds of formula I, and in particular to compounds of formulas II and III having a four- or five-membered ring, respectively.

In one embodiment, the present invention is directed to a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof,



I

wherein

P represents -N< or -C=,

X represents independently of each other $-CH_2-$, CR_1 (sp_2-hybridised), O, -NH-, =N-, -CO- or -CS-, wherein R_1 represents H or NR_2, wherein R_2 represents H or lower alkyl, which optionally is linked to Z such that a bicyclic structure is formed;

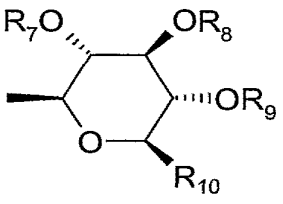
n represents 1 or 2,

R_a represents H, lower alkyl, $-OR_3$, $-O(CO)R_3$, $-O(CO)OR_3$, $-O(CO)NR_3R_4$, $-NR_3R_4$, $-NR_3(CO)R_4$, $-COOR_3$, $-CONR_3R_4$, -

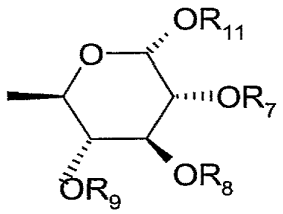
$CH=CHCOOR_3$, $-CF_3$, $-CN$, $-NO_2$, SO_3H, PO_3H or halogen, wherein R_3 and R_4 represent H or lower alkyl,

R_b represents H, OH, $-OSO_2Me$, $-OSO_2W$ wherein W represents optionally substituted aryl or heteroaryl, $-OCO(CHOH)_2COOR_5$ wherein R_5 represents H or lower alkyl; or represents the formula $-Sp_3-R_6$,

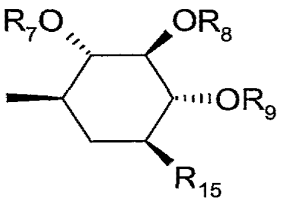
wherein Sp_3 represents a covalent bond, $-O-$, $-OCH_2-$, $-OSO_2CH_2-$, $-OSO_2-$, $-OSO_2-(p)C_6H_4O-$ and R_6 represents one of carbohydrate structures A-D:



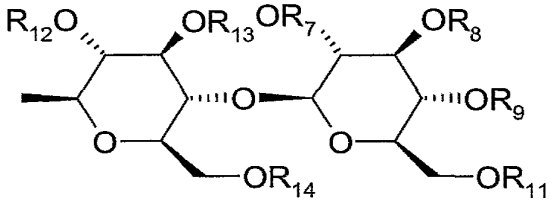
A



B



C



D

wherein

R_7, R_8, R_9, R_{11}, R_{12}, R_{13} and R_{14} represent independently of each other H, lower alkyl, aryl(lower alkyl), -CO-lower alkyl, $-CO$-aryl, $-SO_3^-$ or $-PO_3^-$,

R_{10} represents $-CH_2OR_{16}$ or $-COOR_{17}$, and

R_{15} represents $-CH_2OR_{16}$, $-COOR_{17}$, $-CH_2NH_2$, $-CH_2OPO_3^-$ or $-CH_2OSO_3^-$, wherein R_{16} and R_{17} independently of each other represent H, lower alkyl, aryl(lower alkyl), -CO-lower alkyl, $-CO$-aryl, $-SO_3^-$ or $-PO_3^-$,

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