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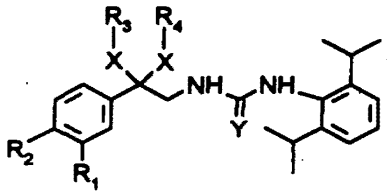
(54) Title: PHOSPHATE DERIVATIVES OF DISUBSTITUTED UREAS AND THIOUREAS

(57) Abstract

The present invention relates to a novel compound having ACAT inhibitory activity of formula (I), wherein: the X substituent, being the same, are O or S; Y is independently O or S; one of R_1 and R_2 is $OPO(OH)_2$ and the other is hydrogen, C_1-C_6 alkyl, halo, hydroxy, C_1-C_4 alkoxy or $OPO(OH)_2$; each of R_3 and R_4, being the same or different, is C_1-C_6 alkyl; or R_3 and R_4, taken together, form a C_2-C_4 alkylene chain in which each carbon atom can be optionally substitued by 1 or 2 substituents independently chosen from halo or C_1-C_3 alkyl; and the pharmaceutically acceptable salts thereof.



(I)

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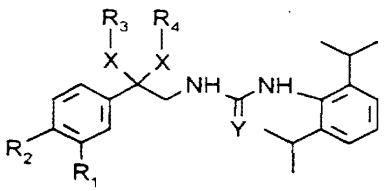
Phosphate derivatives of disubstituted ureas and thioureas

The present invention relates to novel compounds having ACAT inhibitory activity, to a process for their preparation and to pharmaceutical compositions containing them.

The inhibition of the enzime acylCoA:cholesterol acyltransferase is generally considered one of the most appealing approaches to the treatment of dyslipidemias and to the prevention of the atherosclerotic process (Exp. Opin. Invest. Drugs (1994) **3**(5) 427-436). ACAT inhibitors are well known in the art, for instance, the inventors of the present invention in EP 0500348 disclosed a new class of urea and thiourea derivatives endowed with high *in vitro* ACAT inhibitory activity. However such urea and thiourea derivatives, similarly to most of the known ACAT inhibitors, were characterized by high lipophilicity, extreme low aqueous solubility and low bioavailability; by consequence their effects on blood and tissutal cholesterol levels were indirect and appeared almost exclusively related to a reduction of the intestinal cholesterol absorption. Recently further experimental data demonstrated that the therapeutic potential of an ACAT inhibitor can be markedly enhanced when the compound directly affects ACAT activity in target tissues such as the liver and the arterial wall (Atherosclerosclerosis and Thrombosis (1994) **149**(9) 1498). Therefore a hydrosolubility sufficient to achieve high systemic bioavailability is now considered a crucial requirement for an ACAT inhibitor to be developed as a hypolipidemic as well as an antiatherosclerotic agent. The task to combine in the same molecule a high affinity for ACAT enzime and an adequate hydrosolubility cannot be achieved by merely introducing hydrophilic groups into the structure of *in vitro* active ACAT inhibitors, as this strategy results in most cases in a significant loss of the inhibitory activity.

It has now been discovered that new phosphate derivatives of a selected class of hydroxy compounds embraced by the general formula disclosed in EP 0500348, besides being highly hydrosoluble, are also potent *in vivo* ACAT inhibitors. By virtue of such properties the compounds of the present invention can be useful therapeutic agents in the treatment of dyslipidemias and atherosclerosis.

Accordingly, the present invention provides new compounds having the following general formula (I).



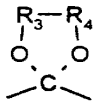
(I)

wherein:

the X substituents, being the same, are O or S;
Y is independently O or S;
one of R_1 and R_2 is $OPO(OH)_2$ and the other is hydrogen, C_1-C_6 alkyl, halo, hydroxy, C_1-C_4 alkoxy or $OPO(OH)_2$;
each of R_3 and R_4, being the same or different, is C_1-C_6 alkyl; or R_3 and R_4, taken together, form a C_2-C_4 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halo or C_1-C_3 alkyl;
and the pharmaceutically acceptable salts thereof.

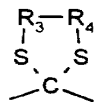
The alkyl and alkoxy groups may be branched or straight groups. Representative examples of C_1-C_6 alkyl groups include methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Representative examples of C_1-C_4 alkoxy groups include methoxy or ethoxy. A C_1-C_3 alkyl group is in particular methyl or ethyl. Halo includes fluoro, bromo, chlorine or iodine, in particular chlorine or bromine.

When R_3 and R_4, taken together, are a C_2-C_4 alkylene chain and X is oxygen, then the resulting pentatomic, hexatomic or heptatomic 1,3-dioxalkyl ring is respectively a 1,3-dioxolan, 1,3-dioxan or 1,3-dioxepan ring which may be represented by the formula



wherein R_3-R_4 represents a C_2-C_4 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halogen, in particular chlorine or C_1-C_3 alkyl, in particular methyl.

When R_3 and R_4, taken together, are a C_2-C_4 alkylene chain and X is sulfur, then the resulting pentatomic, hexatomic or heptatomic 1,3-dithialkyl ring is respectively a 1,3-dithiolan, 1,3-dithian or 1,3-dithiepan ring which may be represented by the formula



wherein R_3-R_4 represents a C_2-C_4 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halogen, in particular chlorine or C_1-C_3 alkyl, in particular methyl.

The pharmaceutically acceptable salts of the compounds of formula (I) include the salts of inorganic bases, for example hydroxides of alkaly metals, e.g. sodium or potassium, or alkaline-heart metals, e.g. calcium or magnesium, and the salts of organic bases organic

bases, such as for example aliphatic amines, e.g. methylamine, ethylamine, diethylamine, trimethylamine, or heterocyclic amines, e.g. piperidine.

The present invention also include within its scope all the possible isomers, stereoisomers, and their mixtures and both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

Preferred compounds of the invention are the compounds of formula (I) wherein:

X is O ;

Y is O ;

one of R_1 and R_2 is $OPO(OH)_2$ and the other is hydrogen;

R_3 and R_4, taken together, are a C_2-C_3 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halo or C_1-C_2 alkyl;

and the pharmaceutically acceptable salts thereof.

Examples of preferred compounds of the invention are the following:

4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate;

3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate;

3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-dimethyl-1,3-dioxan-2-yl}phenylphospate;

4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-diethyl-1,3-dioxan-2-yl}phenylphospate;

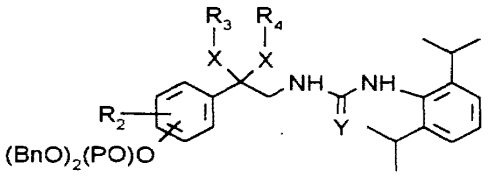
3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-diethyl-1,3-dioxan-2-yl}phenylphospate;

and

4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-dimethyl-1,3-dioxan-2-yl}phenylphospate;

if the case either as a single isomer or as a mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

The compounds of the invention and the salts thereof can be obtained by a process comprising the hydrogenolysis of a compound of formula (II)



(II)

wherein Bn means benzyl and R_2, R_3, R_4, Y and X are as defined above by reaction with hydrogen in the presence of a catalyst; and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or resolving a mixture of compounds of

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