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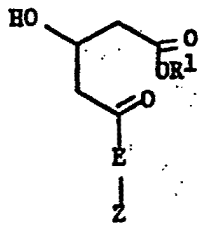
1136M/0619A

TITLE OF THE INVENTION

OXO-ANALOGS OF MEVINOLIN-LIKE ANTIHYPERCHOLESTEROLEMIC AGENTS

SUMMARY OF THE INVENTION

This invention is concerned with novel compounds of structural formula I:



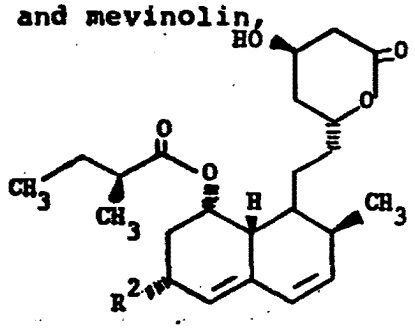
I

wherein Z is a variety of mono- and bi-carbocyclic moieties with various substituents well known to those skilled in the art of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors useful in the treatment of familial hypercholesterolemia, hyperlipemia and atherosclerosis.

The invention is also concerned with novel processes for the preparation of the novel compounds; pharmaceutical formulations comprising a novel compound as active ingredient; and a method of treating familial hypercholesterolemia, hyperlipemia, and atherosclerosis.

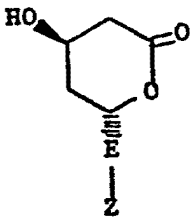
BACKGROUND OF THE INVENTION

Over the past several years a number of structurally related antihypercholesterolemic agents acting by inhibition of HMG-CoA reductase have been reported in the patent literature and elsewhere. The compounds have varied from the natural fermentation products, compactin and mevinolin,

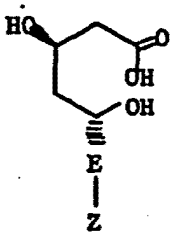


Compactin (R^2=H)
Mevinolin (R^2=CH_3)

to di- and tetrahydro derivatives thereof; to analogs with different esters in the 8-position of the polyhydronaphthalene moiety, to totally synthetic analogs, wherein the polyhydronaphthalene moiety is replaced by substituted mono- and bicyclic aromatics, and biphenyls. But in all instances the active compound included a 4-hydroxytetrahydropyran-2-one ring or the corresponding 3,5-dihydroxy acid, or derivatives thereof, formed by opening the pyranone ring such as:



or



II IIa

4-hydroxytetrahydropyran-2-one 3,5-dihydroxy-acid

In all of these compounds the 3,5-dihydroxy acid or corresponding lactone moiety is present and the particular stereochemistry depicted is essential for manifestation of the optimum enzyme inhibitory activity.

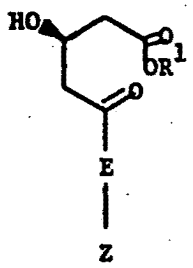
Now with the present invention there are provided compounds structurally related to those lactones and dihydroxy acids that do not have the 5-hydroxy functionality, do not form a lactone ring, and are incapable of stereochemical variation at the 5-position of the acid because the 5-carbon is not asymmetric. On the contrary, the 5-carbon carries an oxo function which greatly facilitates the total synthesis of active compounds in that by eliminating one asymmetric center it is unnecessary to separate diastereoisomers or to conduct a stereoselective synthesis to obtain optimum enzyme inhibitory activity. It is believed that structures I are reduced in situ to generate the "active" inhibitors of structure II or IIa.

The active compounds of this invention are useful in either the racemic form or as the 3(R)-isomer. Those compounds produced by total synthesis are obtained initially as racemates, but

may be resolved by standard methods into 3(R)- and 3(S)-isomers. Compounds of Structure I which are synthesized starting from natural fermentation products such as mevinolin and its analogs are obtained as the optically pure 3(R)-isomers.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention have structural formula:

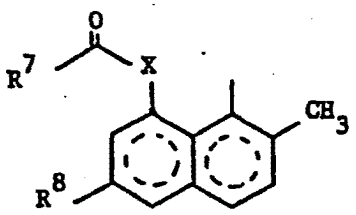


wherein

R^1 is
1) hydrogen,
2) C_{1-4}alkyl,
3) 2,3-dihydroxypropyl,
4) alkali metal cation, such as Na^+, or K^+, or
5) ammonium of formula $\overset{+}{N}R^3R^4R^5R^6$ wherein R^3, R^4, R^5 and R^6 are independently hydrogen or C_{1-4}alkyl or two of R^3, R^4, R^5 and R^6 are joined together to form a 5 or 6-membered heterocycle such as pyrrolidino or piperidino with the nitrogen to which they are attached;

E is $-CH_2CH_2-$, -CH=CH-, or $(CH_2)_3-$; and

Z is 1)

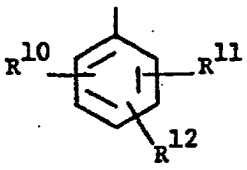


wherein the dotted lines represent all of the possible oxidation states of the bicyclic system such as naphthalene, dihydro-, tetrahydro-, hexahydro-, octahydro-, and decahydronaphthalene;

X is -O- or $>NR^9$ wherein

R^9 is H or C_{1-3}alkyl;
R^7 is C_{2-8}alkyl; and
R^8 is H or $-CH_3$;

2)



wherein R^{10}, R^{11} and R^{12} are independently

a) hydrogen,
b) halogen, such as bromo, chloro or fluoro,
c) C_{1-4}alkyl,
d) halo-C_{1-4}alkyl,
e) phenyl either unsubstituted or substituted with one or more of
i) C_{1-4}alkoxy,
ii) C_{1-4}alkyl,
iii) C_{2-8}alkanoyloxy, or
iv) halo-C_{1-4}alkyl,

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