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None

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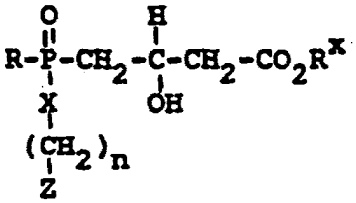
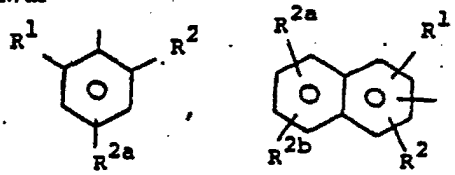
(54) Phosphorus-containing HMG–CoA reductase inhibitors

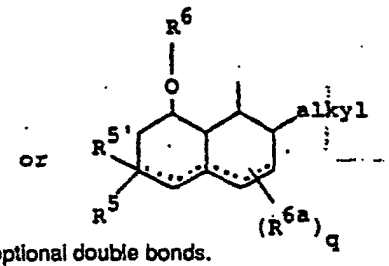
(57) Compounds which are useful as inhibitors of cholesterol biosynthesis and thus as hypocholesterolemic agents have the structure



including salts thereof, wherein R is OH, lower alkoxy or lower alkyl;
R^x is H or alkyl;
X is –O– or –NH–;
n is 1 or 2
Z is a hydrophobic anchor, such as



or



wherein the dotted lines represent optional double bonds.

New intermediates used in preparing the above compounds, e.g. compounds in which the OH group is silane blocked, pharmaceutical compositions containing such compounds and a method for using such compounds to inhibit

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PHOSPHORUS-CONTAINING HMG-CoA REDUCTASE INHIBITORS, NEW INTERMEDIATES AND METHOD

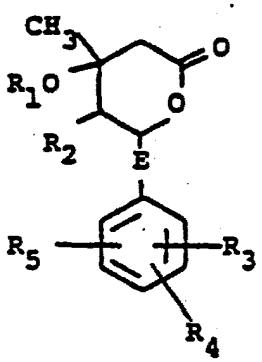
The present invention relates to new phosphorus-containing compounds which inhibit the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and thus is useful in inhibiting cholesterol biosynthesis, to hypocholesterolemic compositions containing such compounds, to new intermediates formed in the preparation of such compounds and to a method of using such compounds for such purposes.

F. M. Singer et al., Proc. Soc. Exper. Biol. Med., 102, 370 (1959) and F. H. Hulcher, Arch. Biochem. Biophys., 146, 422 (1971) disclose that certain mevalonate derivatives inhibit the biosynthesis of cholesterol.

Endo et al in U. S. Patents Nos. 4,049,495, 4,137,322 and 3,983,140 disclose a fermentation

product which is active in the inhibition of cholesterol biosynthesis. This product is called compactin and was reported by Brown et al., (J. Chem. Soc. Perkin I. 1165 (1976)) to have a complex mevalonolactone structure.

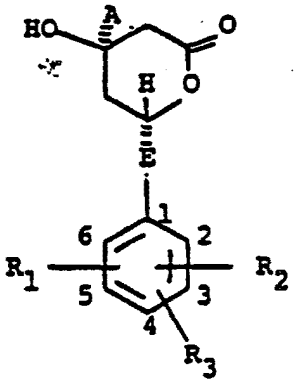
GB 1,586,152 discloses a group of synthetic compounds of the formula



in which E represents a direct bond, a C_{1-3} alkylene bridge or a vinylene bridge and the various R's represent a variety of substituents.

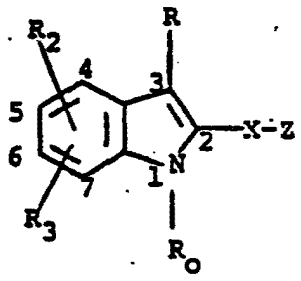
The activity reported in the U.K. patent is less than 1% that of compactin.

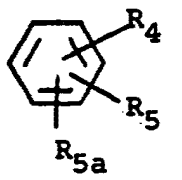
U. S. Patent No. 4,375,475 to Willard et al discloses hypocholesterolemic and hypolipemic compounds having the structure



wherein A is H or methyl; E is a direct bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH=CH-$; R_1, R_2 and R_3 are each selected from H, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, phenyl, phenyl substituted by halogen, C_{1-4} alkoxy, C_{2-8} alkanoyloxy, C_{1-4} alkyl, or C_{1-4} haloalkyl, and OR_4 in which R_4 is H, C_{2-8} alkanoyl, benzoyl, phenyl, halophenyl, phenyl C_{1-3} alkyl, C_{1-9} alkyl, cinnamyl, C_{1-4} haloalkyl, allyl, cycloalkyl-C_{1-3}-alkyl, adamantyl-C_{1-3}-alkyl, or substituted phenyl C_{1-3}-alkyl in each of which the substituents are selected from halogen, C_{1-4} alkoxy, C_{1-4} alkyl, or C_{1-4} haloalkyl; and the corresponding dihydroxy acids resulting from the hydrolytic opening of the lactone ring, and the pharmaceutically acceptable salts of said acids, and the C_{1-3} alkyl and phenyl, dimethylamino or acetylamino substituted C_{1-3}-alkyl esters of the dihydroxy acids; all of the compounds being the enantiomers having a 4 R configuration in the tetrahydropyran moiety of the trans racemate shown in the above formula.

WO 84/02131 (PCT/EP83/00308) (based on U. S. application Serial No. 443,668, filed November 22, 1982, and U. S. application Serial No. 548,850, filed November 4, 1983), filed in the name of Sandoz AG discloses heterocyclic analogs of mevalono lactone and derivatives thereof having the structure



wherein one of R and R_o is  and the other is primary or secondary C_{1-6} alkyl, C_{3-6} cycloalkyl or phenyl-$(CH_2)_m$-,

wherein R_4 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_5 is hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_{5a} is hydrogen, C_{1-2} alkyl, C_{1-2} alkoxy, fluoro or chloro, and

m is 1, 2 or 3,

with the provisos that both R_5 and R_{5a} must be hydrogen when R_4 is hydrogen, R_{5a} must be hydrogen when R_5 is hydrogen, not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy and not more than one of R_4 and R_5 is benzyloxy,

R_2 is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_3 is hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R_3 must be hydrogen when R_2 is hydrogen, not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy.

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