(12) UK Patent Application (19) GB (11) 2 205 837 (13) A

(43) Application published 21 Dec 1988

(21) Application No 8811929

(22) Date of filing 20 May 1988

(30) Priority data
(31) 053281 (32) 22 May 1987 (33) US
109680 19 Oct 1987

(51) INT CL⁴
C07F 9/26 // 7/18

(52) Domestic classification (Edition J):
C2P 1L1 1L2 2E12B 2E18C 2E19A 2E19B 2E19C 2E19D 2E23 2E25A 2E26B 3B12B 3B14A 3B14B 3B16 3B18C 3B19A 3B19B 3B19C 3B19D 5B7 9A
C2R S121 S122 S131 S143 S173 S211 S361 SQA
U1S 1317 C2P C2R

(56) Documents cited
None

(58) Field of search
C2P

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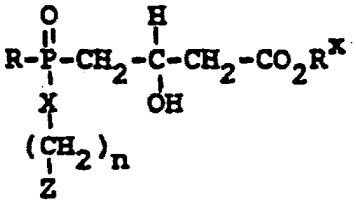
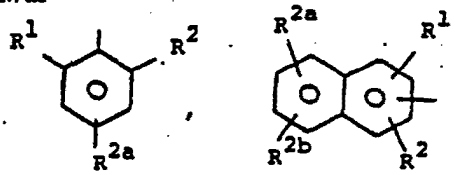
# (54) Phosphorus-containing HMG–CoA reductase inhibitors

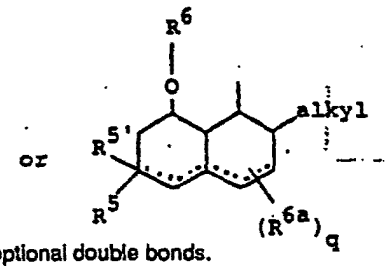
(57) Compounds which are useful as inhibitors of cholesterol biosynthesis and thus as hypocholesterolemic agents have the structure



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

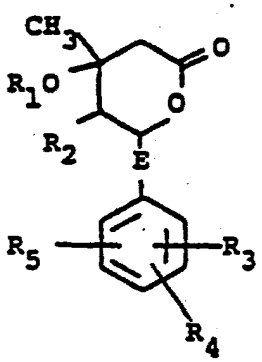
The present invention relates to new phosphorus-containing compounds which inhibit the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and thus is useful in inhibiting cholesterol biosynthesis, to hypocholesterolemic compositions containing such compounds, to new intermediates formed in the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

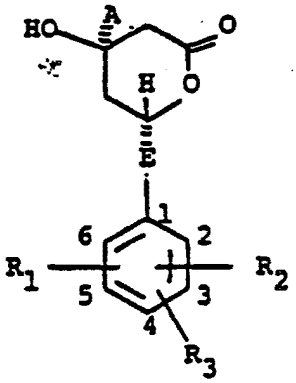
GB 1,586,152 discloses a group of synthetic compounds of the formula



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.

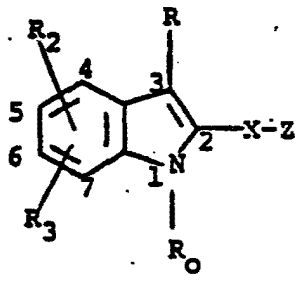
The activity reported in the U.K. patent is less than 1% that of compactin.

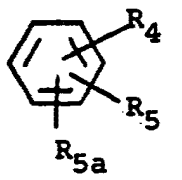
U. S. Patent No. 4,375,475 to Willard et al discloses hypocholesterolemic and hypolipemic compounds having the structure



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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