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(51) International Patent Classification 4 : C07C 69/738, 69/732, 59/90 C07C 59/56, 59/34 C07D 309/30, A61K 31/365 A61K 31/22, 31/19	A1	(11) International Publication Number: WO 86/03488
		(43) International Publication Date: 19 June 1986 (19.06.86)

(21) International Application Number: PCT/EP85/00653

(22) International Filing Date: 29 November 1985 (29.11.85)

(31) Priority Application Number: 677,917

(32) Priority Date: 4 December 1984 (04.12.84)

(33) Priority Country: US

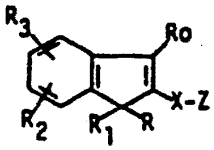
(71) Applicant: SANDOZ AG [CH/CH]; Lichtstrasse 35, CH-4002 Basel (CH).

(72) Inventors: KATHAWALA, Faizulla, G. ; 39 Woodland Avenue, Mountain Lakes, NJ 07946 (US). WATTANASIN, Sompong ; 39 3A Eagle Rock Village, Budd Lake, NJ 07828 (US).

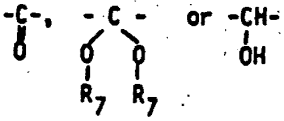
(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INDENE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF



(I)



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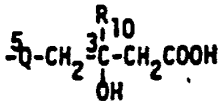

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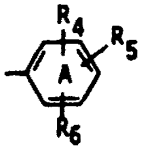

(II)

(V)

(57) Abstract

Compounds of formula (I), wherein R is hydrogen or primary or secondary C_{1-6}alkyl, R_1 is primary or secondary C_{1-6}alkyl or R and R_1 together are $(CH_2)_m$ or (Z)-CH_2-CH=CH-CH_2- wherein m is 2, 3, 4, 5 or 6, Ro is C_{1-6}alkyl, C_{3-7}cycloalkyl or ring A (II) each or R_2 and R_4 is independently hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, each of R_3 and R_5 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, R_6 is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, with the proviso that there may only be one each of trifluoromethyl, phenoxy or benzyloxy on each of the phenyl and indene rings X is -$(CH_2)_n$- or -$(CH_2)_q$CH=CH$(CH_2)_q$- wherein n is 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1, and Z is (III) wherein Q is (IV) wherein each R_7 is the same primary or secondary C_{1-6}alkyl or together they represent -$(CH_2)_2$-, -$(CH_2)_3$-, R_{10} is hydrogen or C_{1-3}alkyl, with the proviso that Q may be other than (V) only when X is -CH=CH- or -CH_2-CH=CH- and/or R_{10} is C_{1-3}alkyl, in free acid form, or in the form of an ester or -lactone thereof or in salt form as appropriate, which are indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

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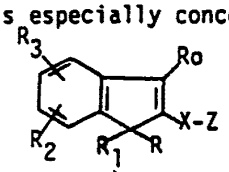
INDENE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

The invention concerns indene analogs of mevalonolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals in particular as hypolipoproteinemic and anti-atherosclerotic agents.

The invention is especially concerned with compounds of formula I



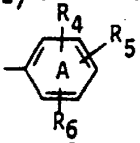
I

wherein R is hydrogen or primary or secondary C_{1-6}alkyl,

R_1 is primary or secondary C_{1-6}alkyl or

R and R_1 together are $(CH_2)_m$ or (Z)-CH_2-CH=CH-CH_2- wherein m is 2, 3, 4, 5 or 6,

Ro is C_{1-6}alkyl, C_{3-7}cycloalkyl or ring A



each of R_2 and R_4 is independently hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

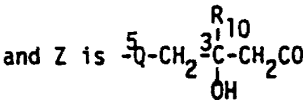
each of R_3 and R_5 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_6 is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,

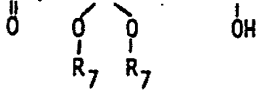
with the proviso that there may only be one each of trifluoromethyl, phenoxy or benzyloxy on each of the phenyl and indene rings

X is $-(CH_2)_n-$ or $-(CH_2)_qCH=CH(CH_2)_q-$

wherein n is 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1,

and Z is 

II

wherein Q is 

wherein each R_7 is the same primary or secondary C_{1-6}alkyl or together they represent $-(CH_2)_2-$, $-(CH_2)_3-$,

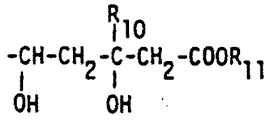
R_{10} is hydrogen or C_{1-3}alkyl,

with the proviso that Q may be other than $-\underset{\underset{OH}{|}}{CH}-$ only when X is -CH=CH- or $-CH_2-CH=CH-$ and/or R_{10} is C_{1-3}alkyl,

in free acid form, or in the form of an ester or -lactone thereof or in salt form as appropriate.

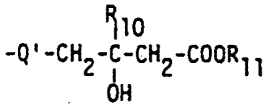
Suitable esters include physiologically acceptable esters e.g. physiologically hydrolysable and -acceptable esters.

By the term "physiologically-hydrolysable and -acceptable ester" is meant an ester of a compound in accordance with the invention in which the carboxyl moiety if present is esterified, and which is hydrolysable under physiological conditions to yield an alcohol which is itself physiologically acceptable, e.g. non-toxic at desired dosage levels. For the avoidance of doubt, throughout this application it is the right hand side of the X radical that is attached to the Z group. Preferred such esters as Z can be represented together with the free acid by formula IIa



IIa

or formula IIc



IIc

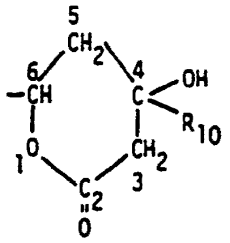
wherein R_{11} is hydrogen, C_{1-4}alkyl or benzyl preferably hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl,

Q' is $-\overset{\overset{O}{\|}}{C}-$ or $\begin{matrix} -C- \\ O \quad O \\ | \quad | \\ R_7 \; R_7 \end{matrix}$ and

R_7 and R_{10} are as defined above with the further proviso that R_{11} is other than hydrogen when Q' is $\begin{matrix} -C- \\ O \quad O \\ | \quad | \\ R_7 \; R_7 \end{matrix}$

When IIa is in salt form R_{11} represents a cation.

When Z is in lactone form it forms a δ-lactone of formula IIb



IIb

and references to "lactone" hereinafter refer to δ-lactones.

Salts of the compounds of the invention, e.g. of the compounds of formula I, include in particular their pharmaceutically acceptable salts. Such pharmaceutically acceptable salts include e.g. alkali metal salts such as the sodium and potassium salts and salts with ammonium.

References to compounds of formula I, II, IIa, IIb and IIc and sub-species thereof are intended to cover all forms unless otherwise stated.

Depending on the nature of R_1 and R the compounds of formula I may be divided into two main groups, namely, those wherein R is hydrogen or primary or secondary C_{1-6}alkyl (Group IA) and those wherein R_1 and R together represent $-(CH_2)_m-$ or $(Z)-CH_2-CH=CH-CH_2-$ (Group IB). These groups may be further divided depending on the nature of Z, namely when Q is $-\underset{OH}{CH}-$ and the Z is in other than lactone form (sub-group "a"); when Z is a group of formula IIb (sub-group "b"); and when Q is $-\overset{O}{\overset{\|}{C}}-$ or $-C\begin{matrix}O-R_7\\O-R_7\end{matrix}$ and Z is in other than lactone form (sub-group "c").

The resulting six groups are designated as IAa, IAb, IAc, IBa, IBb, IBc.

As is self-evident to those in the art, each compound of Groups IAa, IAb, IBa and IBb (and every subscope and species thereof) has two centres of asymmetry (the two carbon atoms bearing the hydroxy groups in the group of formula IIa and the carbon atom bearing the hydroxy group and the carbon atom having the free valence in the group of formula IIb and, therefore, there are four stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers), provided that R and R_1 are identical or taken together are $-(CH_2)_m-$ or $(Z)-CH_2-CH=CH-CH_2-$ and that R_{11} does not contain any centre of asymmetry. The four stereoisomers may be designated as the R,R, R,S, S,R and S,S enantiomers, all four stereoisomers being within the scope of this invention. When R and R_1 are different and/or R_{11} contains one or more centres of asymmetry, there are eight or more stereoisomers.

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