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(54) **Analogs of mevalolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.**

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TETRAHEDRON LETTERS, vol. 23, no. 42, 1982, Pergamon Press, Oxford, GB YUH-LIN YANG et al.: "Mevinic acids and analogues: preparation of a key chiral intermediate", p. 4305, 4308

(73) Proprietor: **SANDOZ AG**
Lichtstrasse 35
CH-4002 Basel (CH)
(84) **BE CH FR GB IT LI LU NL SE**

(73) Proprietor: **SANDOZ-PATENT-GMBH**
Humboldtstrasse 3
D-7850 Lörrach (DE)
(84) **DE**

(73) Proprietor: **SANDOZ-ERFINDUNGEN Verwaltungsgesellschaft m.b.H.**
Brunner Strasse 59
A-1235 Wien (AT)
(84) **AT**

(72) Inventor: **Kathawala, Faizulla Gulamhusein**
39 Woodland Avenue
Mountain Lakes, N.J., 07946 (US)

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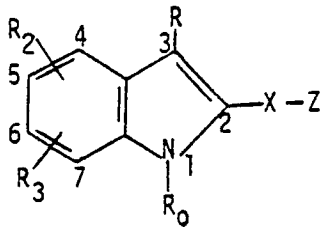
Description

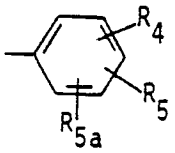
The invention concerns heterocyclic analogs of mevalono-lactone and derivatives thereof, process for their production, pharmaceutical compositions containing them and their use as pharmaceuticals, in particular as hypolipoproteinemic and antiatherosclerotic agents.

The invention is especially concered with compounds of formula I



(I)

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,

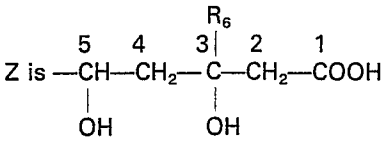
R_{5a} is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and

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,

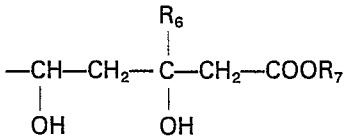
X is $—(CH_2)_n—$ or —CH=CH— (n=0, 1, 2 or 3), and



II

wherein R_6 is hydrogen or C_{1-3}alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester of a δ-lactone thereof or in salt form.

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 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. Preferred such esters as Z can be represented together with the free acid by formula IIa

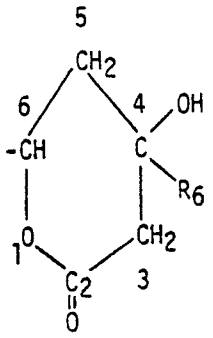


IIa

wherein R_7 is hydrogen, C_{1-4}alkyl or benzyl, preferably hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl and R_6 is as defined above.

When in salt form R_7 represents a cation.

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



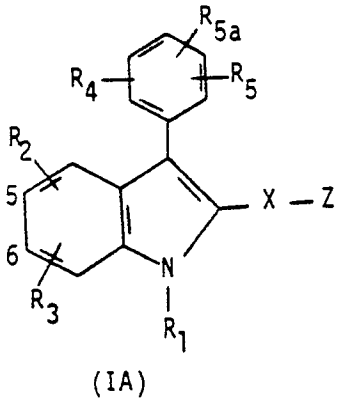
IIb

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 partiuclar their pharmaceutically acceptable salts. Such pharmaceutically acceptable salts include e.g. alkali metal salts such as the sodium and potassium salts and ammonium salts.

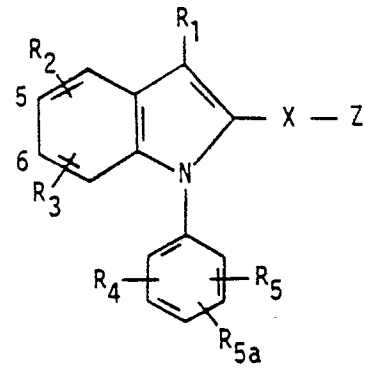
References to compounds of formula I and sub-species thereof are intended to cover all forms unless otherwise stated.

The compounds of formula I may be divided into two groups, the compounds of formulae IA and IB:



(IA)

and



(IB)

wherein

R_1 is primary or secondary C_{1-6}alkyl, C_{3-6}cycloalkyl or phenyl-$(CH_2)_m$—, and

R_2—R_{5a}, X, Z and m are as defined above.

The compounds of formula IA may be divided into a two sub-groups, the compounds wherein Z is a group of formula II in other than lactone form (Group IAa) and those wherein Z is a group of formula (Group IAb) IIb. Likewise, the compounds of formula IB may be divided into two sub-groups, the compounds wherein Z is a group of formula II in other than lactone form (Group IBa) and those wherein Z is a group of formula IIb (Group IBb).

As is self-evident to those in the art, each compound of formula I (and every sub-scope and species thereof) has at least two centers of asymmetry (e.g. 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 these lead to four stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers). These four stereoisomes 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. Depending on the nature of substituents further asymmetric carbon atoms may be present and the resulting isomers and mixtures thereof also form part of the invention. Compounds containing only two centres of asymmetry (four mentioned stereoisomers) are preferred.

R_1 is preferably primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, 1-ethylpropyl, neopentyl and n-hexyl), more preferably C_{1-3}alkyl and most preferably methyl, ethyl or i-propyl, especially i-propyl.

Alkyl as R_2 is preferably C_{1-3} or n-, i- or t-butyl and alkoxy C_{1-3} or n- or i-butoxy. R_2 is preferably R_2', where R_2' is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, more preferably R_2'', where R_2'' is hydrogen, C_{1-3}alkyl, methoxy, fluoro, chloro or 4-, 5- or 6-benzyloxy, and most preferably R_2''', where R_2''' is hydrogen, C_{1-3}alkyl or 4- or 6-benzyloxy, especially hydrogen or methyl and most especially hydrogen.

R_3 is preferably R_3', where R_3' is hydrogen, C_{1-3}alkyl, C_{1-2}alkoxy, fluoro or chloro, more preferably R_3'',

where R_3'' is hydrogen or C_{1-3}alkyl and most preferably R_3''', where R_3''' is hydrogen or methyl, especially hydrogen. R_3 (R_3', etc.) must be hydrogen when R_2 (R_2', etc.) is hydrogen.

Preferably, when R_2 (R_2', R_2'', etc.) is other than hydrogen and R_3 (R_3', R_3'', etc.) is hydrogen, R_2 (R_2', etc.) is in the 4-, 5- or 6-position.

Preferably, when both R_2 (R_2', R_2'', etc.) and R_3 (R_3', R_3'', etc.) are other than hydrogen, at least one of them is in the 5- or 6-position, neither of them is in the 7-position, and not more than one of them is a member of the group consisting of t-butyl, C_{3-6}cycloalkyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, they are not *ortho* to each other when neither of them is a member of the group consisting of methyl, methoxy, fluoro and chloro. Most preferably, one is in the 4-position and the other is in the 6-position.

Except where otherwise indicated: (a) Any C_{1-4}alkyl or C_{3-6}cycloalkyl group as R_2, R_2', R_3, R_3', etc. is more preferably in the 4- or 6-position. (b) Any C_{1-4}alkoxy, fluoro or chloro substituent as R_2, R_2', R_3, R_3', etc. is more preferably in the 5-position. (c) Any benzyloxy as R_2, R_2', R_3, R_3', etc. is more preferably in the 4-, 5- or 6-position and most preferably in the 4- or 6-position, especially the 6-position.

Alkyl as R_4 is preferably C_{1-3} or n-, i- or t-butyl and alkoxy C_{1-3} or n- or i-butoxy. R_4 is preferably R_4', where R_4' is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, more preferably R_4'', where R_4'' is hydrogen, methyl, methoxy, fluoro or chloro, and most preferably R_4''', where R_4''' is hydrogen, methyl or fluoro, especially R_4'''', where R_4'''' is hydrogen, 3- or 4-methyl or 4-fluoro and most especially 4-fluoro.

R_5 is preferably R_5', where R_5' is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, more preferably R_5'', where R_5'' is hydrogen, methyl, methoxy, fluoro or chloro, and most preferably R_5''', where R_5''' is hydrogen or methyl, especially hydrogen. R_5 (R_5', R_5'', etc.) must be hydrogen when R_4 (R_4', R_4'', etc.) is hydrogen.

R_{5a} is preferably R_{5a}', where R_{5a}' is hydrogen or methyl, and most preferably hydrogen. R_{5a} (R_{5a}', etc.) must be hydrogen when at least one of R_4 (R_4', R_4'', etc.) and R_5 (R_5', R_5'', etc.) is hydrogen.

Preferably, when R_4 (R_4', R_4'', etc.) is other than hydrogen and R_5 (R_5', R_5'', etc.) and R_{5a} (R_{5a}', etc.) are both hydrogen, R_4 (R_4', etc.) is in a *meta* or *para* position, more preferably the *para* position. The most preferred monosubstituted phenyl group is 4-fluorophenyl.

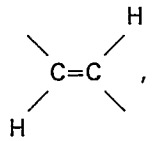
Preferably, when both R_4 (R_4', R_4'', etc.) and R_5 (R_5', R_5'', etc.) are other than hydrogen and R_{5a} (R_{5a}', etc.) is hydrogen, at least one of R_4 (R_4', etc.) and R_5 (R_5', etc.) is in a *meta* or *para* position (more preferably both are), and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, R_4 (R_4', etc.) and R_5 (R_5', etc.) are not *ortho* to each other when neither of them is a member of the group consisting of methyl, methoxy, fluoro and chloro. The most preferred disubstituted phenyl groups are 3,4- and 3,5-dimethylphenyl and 4-fluoro-3-methylphenyl, especially 3,5-dimethylphenyl and 4-fluoro-3-methylphenyl.

Preferably, when each of R_4 (R_4', etc.), R_5 (R_5', etc.) and R_{5a} (R_{5a}', etc.) is other than hydrogen, at least two of them (more preferably, all three) are in *meta* or *para* positions, and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, no two fo them are *ortho* to each other unless at least one member of the or each pair of substituents that are *ortho* to each other is a member of the group consisting of methyl, methoxy, fluoro and chloro. The most preferred trisubsituted phenyl group is 3,5-dimethyl-4-fluorophenyl.

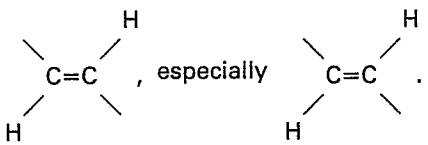
R_6 is preferably R_6', where R_6' is hydrogen or C_{1-2}alkyl, more preferably R_6'', where R_6'' is hydrogen or methyl, and most preferably hydrogen.

R_7 is preferably R_7', where R_7' is hydrogen or C_{1-3}alkyl, more preferably R_7'', where R_7'' is hydrogen or C_{1-2}alkyl. Such compounds wherein Z is of formula II or IIa are most preferably in salt form. Preferred salt-forming cations are those free from centres of asymmetry, especially e.g. sodium, potassium or ammonium, most preferably sodium.

X is preferably X', where X is $-(CH_2)_m-$ or



more preferably X'', where X'' is $-CH_2CH_2-$ or



Z is preferably a group of formula IIa wherein R_6 is R_6' and R_7 is R_7' or a group of formula IIb where in R_6 is R_6', more preferably a group of formula IIa wherein R_6 is R_6'' and R_7 is R_7'' or a group of formula IIb

wherein R_6 is R_6'' most preferably a group of formula IIa wherein R_6 is hydrogen and R_7 is R_7'' or a group of formula IIb wherein R_6 is hydrogen, especially a group of formula IIa wherein R_6 is hydrogen in salt form, particularly in sodium salt form, or a group of formula IIb wherein R_6 is hydrogen.

n is preferably m, where m is 1, 2 or 3, preferably 2 or 3 and most preferably 2.

Insofar as the compounds of Groups IAa and IBa are concerned, the *erythro* isomers are generally preferred over the *threo* isomers, *erythro* and *threo* referring to the relative positions of the hydroxy groups in the 3- and 5-positions (of the group of formula II or IIa).

As between compounds of formula I having identical R, R_o, R_2, R_3, R_6 and X groups, free acid, salt and ester forms are generally preferred to lactone forms.

The preferred stereoisomers of the compounds having only two assymetric carbons wherein X is a direct bond or —CH=CH—, and Z is in other than lactone form are the 3R,5S and 3R,5R isomers and the racemate of which each is a constituent, i.e., the 3R,5S-3S,5R (*erythro*) and 3R,5R-3S,5S (*threo*) racemates, with the 3R,5S isomer and the racemate of which it is a constituent being more preferred and the 3R,5S isomer being most preferred.

The preferred stereoisomers of the compounds having only two assymetric carbons wherein X is $—(CH_2)_m—$, and Z is in other than lactone form are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, *i.e.,* the 3R,5R-3S,5S (*erythro*) and 3R,5S-3S,5R (*threo*) racemates, with the 3R,5R isomer and the racemate of which it is a constituent being more preferred and the 3R,5R isomer being most preferred.

The preferred stereoisomers of the compounds having only two assymetric carbons wherein X is a direct bond or —CH=CH—, and Z is a group of formula IIb are the 4R,6S and 4R,6R isomers and the racemate of which each is a constituent, *i.e.*, the 4R,6S-4S,6R (*trans* lactone) and 4R,6R-4S,6S (*cis* lactone) racemates, with the 4R,6S isomer and the racemate of which it is a constituent being more preferred and the 4R,6S isomer being most preferred.

The preferred stereoisomers of the compounds having only two assymetric carbons wherein X is $—(CH_2)_m—$, and Z is a group of formula IIb are the 4R,6R and 4R,6S isomers and the racemate of which each is a constituent, *i.e.,* the 4R,6R-4S,6S (*trans* lactone) and 4R,6S-4S,6R (*cis* lactone) racemates, with the 4R,6R isomer and the racemate of which it is a constituent being more preferred and the 4R,6R isomer being most preferred.

Each of the preferences set forth above applies, not only to the compounds of formula I but also to the compounds of formulae IA and IB and those of Groups IAa, IAb, IBa and IBb as well as to every other subgroup thereof set forth *infra, e.g.,* Groups (i)-(cxiv), unless otherwise indicated. When any preference contains a variable, the preferred significances of that variable apply to the preference in question, unless otherwise indicated.

Preferred groups of compounds of formula I include the compounds

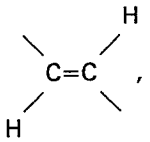
(i) of Group IAa wherein R_1 is R_1', R_2 is R_2', R_3 is R_3', R_4 is R_4', R_5 is R_5', R_{5a} is R_{5a}', R_6 is R_6', R_7 is R_7', and X is X'.

(ii) of (i) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both R_2' and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is hydrogen, at least one of R_4' and R_5' is in a *meta* or *para* position; and when each of R_4', R_5' and R_{5a}' is other than hydrogen, at least two of them are in *meta* or *para* positions.

(iii)—(iv) of (i) and (ii) wherein R_6 is R_6'', especially hydrogen,

(v)—(vi) of (i) and (ii) wherein R_1 is C_{1-3}alkyl, R_2 is R_2'', R_3 is R_3'', R_4 is R_4'', R_5 is R_5'', R_6 is R_6'', especially hydrogen, R_7 is R_7'', and X is X''.

(vii) of (i) wherein R_1 is C_{1-3}alkyl, R_2 is R_2'', R_3 is R_3''', R_4 is R_4''', R_5 is R_5''', R_{5a} is hydrogen, R_6 is hydrogen, R_7 is R_7'', and X is



(viii)—(xiii) of (i)—(vi) wherein any salt is a sodium, potassium or ammonium salt,

(xiv) of Group IAb wherein R_1 is R_1', R_2 is R_2', R_3 is R_3', R_4 is R_4', R_5 is R_5', R_{5a} is R_{5a}', R_6 is R_6' and X is X,

(xv) of (xiv) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both R_2' and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is hydrogen, at least one of R_4' and R_5' is in a *meta* or *para* position; and when each of R_4', R_5' and R_{5a} is other than hydrogen, at least two of them are in *meta* or *para* positions,

(xvi)—(xvii) of (xiv) and (xv) wherein R_6 is R_6'', especially hydrogen,

(xviii)—(xix) of (xiv) and (xv) wherein R_1 is C_{1-3}alkyl, R_2 is R_2'', R_3 is R_3'', R_4 is R_4'', R_5 is R_5'', R_6 is R_6'', especially hydrogen, and X is X'',

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