(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 221 025**
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **86810470.4**

(22) Date of filing: **21.10.86**

(51) Int. Cl.[4]: **C 07 D 207/337**
C 07 D 307/54,
C 07 D 333/24, A 61 K 31/34,
A 61 K 31/38, A 61 K 31/40

(30) Priority: **25.10.85 US 791198 07.01.86 US 816664**

(43) Date of publication of application:
06.05.87 Bulletin 87/19

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: **SANDOZ AG**
Lichtstrasse 35
CH-4002 Basel (CH)

(84) Designated Contracting States:
BE CH ES FR GB GR IT LI LU NL SE

(71) Applicant: **SANDOZ-PATENT-GMBH**
Humboldtstrasse 3
D-7850 Lörrach (DE)

(84) Designated Contracting States: **DE**

(71) Applicant: **SANDOZ-ERFINDUNGEN**
Verwaltungsgesellschaft m.b.H.
Brunner Strasse 59
A-1235 Wien (AT)

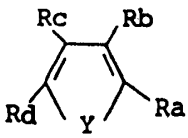
(84) Designated Contracting States: **AT**

(72) Inventor: **Wareing, James Richard**
402 Millbrook Avenue
Randolph, N.J. 07801 (US)

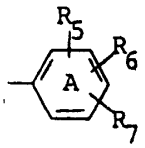
Damon, Robert Edson
23156 West View
Wharton, N.J. 07885 (US)

(54) **Heterocyclic analogs of mevalonolactone and derivatives thereof, processes for their production and their use as pharmaceuticals.**

(57) Compounds of formula

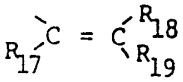


I



wherein
Ra is a group -X-Z, Rb is R_2, Rc is R_3, Rd is R_4 and Y is a group -N- or
R_1
Ra is R_1, Rb is a group -X-Z, Rc is R_2, Rd is R_3 and Y is O, S or a group -N-;
R_4
R_1, R_2, R_3, and R_4 independently are C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-7}cycloalkyl or a ring

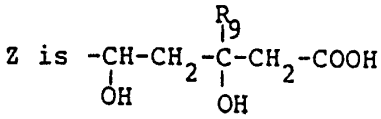
or in the case of R_3 and R_4 additionally hydrogen, or for R_3 when Y is O or S



whereby R_{17} is hydrogen or C_{1-3}alkyl and R_{18} and R_{19} are independently hydrogen C_{1-3}alkyl or phenyl; each R_5 is independently hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy; each R_6 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, bromo, phenoxy or benzyloxy, and each R_7 is independently hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro.

EP 0 221 025 A1

with the proviso that there may only be one each of trifluoromethyl, phenoxy or benzyloxy in each ring A present. X is $(CH_2)_m$ or $(CH_2)_qCH=CH-(CH_2)_q$, m is 0, 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1.

Z is  II

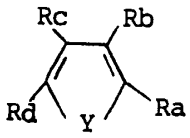
wherein R_9 is hydrogen or C_{1-3}alkyl.
in free acid form, or in the form of an ester or δ-lactone thereof or in salt form as appropriate, which compounds are indicated for use as pharmaceuticals in particular as hypolipoproteinemic and anti-atherosclerotic agents.

Description

HETEROCYCLIC ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF, PROCESSES FOR THEIR PRODUCTION AND THEIR USE AS PHARMACEUTICALS

The present invention concerns heterocyclic analogs of mevalonolactone and derivatives thereof, processes for their preparation, pharmaceutical compositions containing them and their use as pharmaceuticals especially as agents for treating hyper-lipoproteinemia and atherosclerosis.

More particularly the invention concerns compounds of formula I



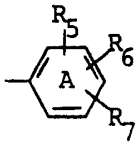
I

wherein

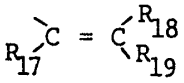
Ra is a group -X-Z, Rb is R_2, Rc is R_3, Rd is R_4 and Y is a group $-\overset{|}{\underset{R_1}{N}}-$ or

Ra is R_1, Rb is a group -X-Z, Rc is R_2, Rd is R_3 and Y is O, S or a group $-\overset{|}{\underset{R_4}{N}}-$;

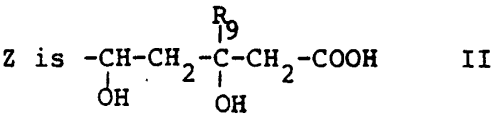
R_1, R_2, R_3 and R_4 independently are C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-7}cycloalkyl or a ring



or in the case of R_3 and R_4 additionally hydrogen, or for R_3 when Y is O or S



whereby R_{17} is hydrogen or C_{1-3}alkyl and R_{18} and R_{19} are independently hydrogen C_{1-3}alkyl or phenyl; each R_5 is independently hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy; each R_6 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, bromo, phenoxy or benzyloxy, and each R_7 is independently 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 in each ring A present, X is $(CH_2)_m$ or $(CH_2)_qCH=CH-(CH_2)_q$, m is 0, 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1,



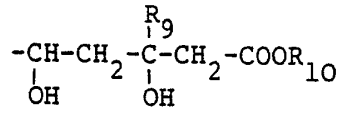
II

wherein R_9 is hydrogen or C_{1-3}alkyl,

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

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

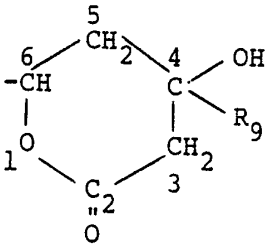
By the term "physiologically-hydrolysable and -acceptable ester is meant an ester of a compound in accordance with the invention in which the carboxyl moiety if present is esterified, and which is hydrolysable under physiological conditions to yield an alcohol which is itself physiologically acceptable,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



a

wherein
R_9 is hydrogen or C_{1-3}alkyl and
R_{10} is hydrogen, a physiologically acceptable ester forming group (R_{11}) or a pharmaceutically acceptable cation (M).

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



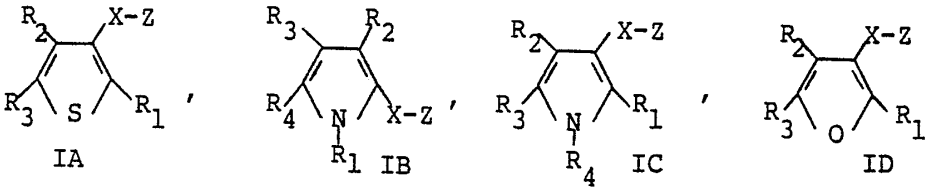
b

and reference 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 formulae I and IA-ID and subscopes thereof are intended to cover all forms unless otherwise stated.

Depending on the nature of the various substituents the compounds of formula I may be divided into four main groups, namely



IA IB IC ID

These four groups may be further divided into two sub-groups each depending on the significance of Z as either a group of formula II in other than lactone form (sub-group "a") or a group of formula b (sub-group "b"). The resulting eight sub-groups are designated as formulae IAa, IAb, IBa, IBb, ICa, ICb, IDa, IDb respectively.

As is self-evident to those skilled in the art, each compound of formula I (and every sub-group and species thereof) has at least two centres of asymmetry (e.g. the two carbon atoms bearing the hydroxy groups in the group of formula a and the carbon atom bearing the hydroxy group and the carbon atom having the free valence in the group of formula b) and these lead (e.g. with two centres) to four stereoisomic forms (enantiomers) of each compound (two racemates or pairs of diasteroisomers). In preferred compounds having only two such centres of asymmetry these 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. 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 menmentioned stereoisomers) are preferred.

Preferably in compounds IA-ID one of R_1 and R_2 is C_{1-6}alkyl not containing an asymmetric carbon atom and the other is a Ring A. Also preferably in compounds IB and IC, one of R_3 and R_4 is a Ring A and the other is hydrogen or C_{1-6}alkyl not containing an asymmetric carbon atom, preferably hydrogen or C_{1-2}alkyl and most preferably hydrogen except that R_4 in compounds IC is preferably other than hydrogen. More preferably, the preferences of both preceding sentences occur simultaneously. Thus, the preferred compounds IB and IC and each of the sub-scopes thereof are those having attached to the pyrrole ring two Rings A and two alkyl groups or in compounds IB especially one alkyl group and one hydrogen. Even more preferably the two Rings A are ortho to each other. Also preferably the pyrrole ring does not bear two ortho tertiary alkyl groups.

In Formula IB:

R_1 is preferably R_{1Bx}, where R_{1Bx} is Ring A, more preferably $R'_{1\ Bx}$, where $R'_{1\ Bx}$ is Ring A wherein R_5 is R'_5, R_6 is R'_6, and R_7 is R'_7, even more preferably $R''_{1\ Bx}$, where $R''_{1\ Bx}$ is Ring A wherein R_5 is R''_5, R_6 is R''_6, and R_7 is hydrogen, and most preferably phenyl, 4-fluorophenyl or 3,5-dimethylphenyl, especially

4-fluorophenyl; or

R_1 is preferably R_{1By}, where R_{1By} is C_{1-6}alkyl not containing an asymmetric carbon atom, more preferably $R'_{1\ By}$, where $R'_{1\ By}$ is C_{1-4}alkyl not containing an asymmetric carbon atom, and most preferably i-propyl.

R_2 is preferably R_{2Bx}, where R_{2Bx} is C_{1-6}alkyl not containing an asymmetric carbon atom, more preferably $R'_{2\ Bx}$, where $R'_{2\ Bx}$ is C_{1-4}alkyl not containing an asymmetric carbon atom, and most preferably i-propyl, or

R_2 is preferably R_{2By}, where R_{2By} is Ring A, more preferably $R'_{2\ By}$, where $R'_{2\ By}$ is Ring A wherein R_5 is R'_5, R_6 is R'6, and R_7 is R'7, even more preferably $R''_{2\ By}$, where $R''_{2\ By}$ is Ring A wherein R_5 is R"5, R_6 is R"6 and R_7 is hydrogen, and most preferably phenyl, 4-fluorophenyl or 3,5-dimethylphenyl, especially 4-fluorophenyl.

R_3 is preferably R_{3Bx}, where R_{3Bx} is hydrogen or C_{1-6}alkyl not containing an asymmetric carbon atom, more preferably $R'_{3\ Bx}$, where $R'_{3\ Bx}$ is hydrogen or C_{1-2}alkyl, even more preferably $R''_{3\ Bx}$, where $R''_{3\ Bx}$ is hydrogen or methyl, and most preferably hydrogen; or

R_3 is preferably R_{3By}, where R_{3By} is Ring A, more preferably $R'_{3\ By}$, where $R'_{3\ By}$ is Ring A wherein R is R'5, R_6 is R'6, and R_7 is R'7, even more preferably $R''_{3\ By}$, where $R''_{3\ By}$ is Ring A wherein R_5 is R"5, R_6 is R"6, and R_7 is hydrogen, and most preferably phenyl.

R_4 is preferably R_{4Bx}, where R_{4Bx} is Ring A, more preferably $R'_{4\ Bx}$ where $R'_{4\ Bx}$ is Ring A wherein R_5 is R'5, R_6 is R'6, and R_7 is R'7, even more preferably $R''_{4\ Bx}$, where $R''_{4\ Bx}$ is Ring A wherein R_5 is R"5, R_6 is R"6, and R_7 is hydrogen, and most preferably phenyl; or R_4 is preferably R_{4By}, where R_{4By} is hydrogen or C_{1-6}alkyl not containing an asymmetric carbon atom, more preferably $R'_{4\ By}$, where $R'_{4\ By}$ is hydrogen or C_{1-2}alkyl, even more preferably $R''_{4\ By}$, where $R''_{4\ By}$ is hydrogen or methyl. and most preferably hydrogen.

In Formulae IA, IC and ID:

R_1 is preferably R_{1Cx}, where R_{1Cx} is C_{1-6}alkyl not containing an asymmetric carbon atom, more preferably $R'_{1\ Cx}$, where $R'_{1\ Cx}$ is C_{1-4}alkyl not containing an asymmetric carbon atom, and most preferably i-propyl, or

R_1 is preferably R_{1Cy}, where R_{1Cy} is Ring A, more preferably $R'_{1\ Cy}$, where $R'_{1\ Cy}$ is Ring A wherein R_5 is R'_5, R_6 is R'_6 and R_7 is R'_7, even more preferably $R''_{1\ Cy}$, where $R''_{1\ Cy}$ is Ring A wherein R_5 is R''_5, R_6 is R''_6, and R_7 is hydrogen, and most preferably phenyl, 4-fluorophenyl or 3,5-dimethylphenyl, especially 4-fluorophenyl.

R_2 is preferably R_{2Cx}, where R_{2Cx} is Ring A, more preferably $R'_{2\ Cx}$, where $R'_{2\ Cx}$ is Ring A wherein R_5 is R'_5, R_6 is R'6 and R_7 is R'7, even more preferably $R''_{2\ Cx}$, where $R''_{2\ Cx}$ is Ring A wherein R_5 is R"5, R_6 is R''_6, and R_7 is hydrogen, and most preferably phenyl, 4-fluorophenyl or 3,5-dimethylphenyl, especially 4-fluorophenyl; or

R_2 is preferably R_{2Cy}, where R_{2Cy} is C_{1-6}alkyl not containing an asymmetric carbon atom, more preferably $R'_{2\ Cy}$, where $R'_{2\ Cy}$ is C_{1-4}alkyl not containing an asymmetric carbon atom, and most preferably i-propyl.

R_3 is preferably R_{3Cx}, where R_{3Cx} is Ring A, more preferably $R'_{3\ Cx}$, where $R'_{3\ Cx}$ is Ring A wherein R_5 is R'5, R_6 is R'6, and R_7 is R'7, even more preferably $R''_{3\ Cx}$, where $R''_{3\ Cx}$ is Ring A wherein R_5 is R"5, R_6 is R"6, and R_7 is hydrogen, and most preferably phenyl; or

R_3 is preferably R_{3Cy}, where R_{3Cy} is hydrogen or C_{1-6}alkyl not containing an asymmetric carbon atom, more preferably $R'_{3\ Cy}$, where $R'_{3\ Cy}$ is hydrogen or C_{1-2}alkyl, and even more preferably $R''_{3\ Cy}$, where $R''_{3\ Cy}$ is hydrogen or methyl, especially hydrogen.

In the compounds of formulae IA and ID, especially the former, R_{3cy}, R_{3cy}' and R_{3cy}" include $-CH=C(CH_3)_2$.

In formula IC:

R_4 is preferably R_{4Cx}, where R_{4Cx} is hydrogen or C_{1-6}alkyl not containing an asymmetric carbon atom, more preferably $R'_{4\ Cx}$, where $R'_{4\ Cx}$ C_{1-2}alkyl, even more preferably methyl, or

R_4 is preferably R_{4Cy}, where R_{4Cy} is Ring A, more preferably $R'_{4\ Cy}$, where $R'_{4\ Cy}$ is Ring A wherein R is R'5, R_6 is R'6, and R_7 is R'7, even more preferably $R''_{4\ Cy}$, where $R''_{4\ Cy}$ is Ring A wherein R_5 is R"5, R_6 is R"6, and R_7 is hydrogen, and most preferably phenyl.

In addition, in the compounds IA and ID R_2 is preferably C_{1-6}alkyl not containing an asymmetric carbon atom, especially isopropyl or t-butyl, or phenyl or p-substituted phenyl, especially p-fluorophenyl and R_1 is preferably phenyl or p-substituted phenyl especially p-fluorophenyl.

Of IA and ID the former are preferred.

In each of IA, IB, IC and ID the following preferences apply.

Each R_5 independently is preferably R_5' where R_5' is hydrogen, C_{1-3}alkyl, C_{1-2}alkoxy, trifluoromethyl, fluoro or chloro, more preferably R_5" where R_5" is hydrogen methyl or fluoro. In the case of R_1 and R_2 being a Ring A each R''_5 is preferably fluoro, especially 4-fluoro. In the case of R_3 and R_4 being a Ring A R_5" is preferably hydrogen.

Each R_6 independently is preferably R_6' where R_6' is hydrogen, C_{1-2}alkyl, fluoro or chloro more preferably R_6" where R_6" is hydrogen or methyl, most preferably hydrogen.

Each R_7 independently is preferably R_7' where R_7' is hydrogen or methyl, most preferably hydrogen.

Preferably, each Ring A, independently bears a maximum of one substituent selected from the group consisting of t-butyl, trifluoromethyl, phenyl, phenoxy and benzyloxy. More preferably, when any two or all three of the substituents on each Ring A independently are ortho to each other, at least one member of each pair that are ortho to each other is a member of the group consisting of hydrogen, methyl, methoxy, fluoro and

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.