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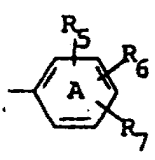
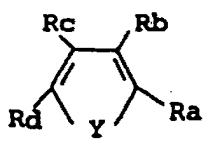
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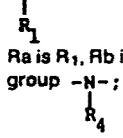
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(54) **Heterocyclic analogs of mevalonolactone and derivatives thereof, processes for their production and their use as pharmaceuticals.**

(57) **Compounds of formula**



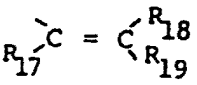
wherein  
 Ra is a group -X-Z, Rb is R<sub>2</sub>, Rc is R<sub>3</sub>, Rd is R<sub>4</sub> and Y is a group -N- or



Ra is R<sub>1</sub>, Rb is a group -X-Z, Rc is R<sub>2</sub>, Rd is R<sub>3</sub> and Y is O, S or a group -N-;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> independently are C<sub>1</sub>-alkyl not containing an asymmetric carbon atom, C<sub>3</sub>-cycloalkyl or a ring

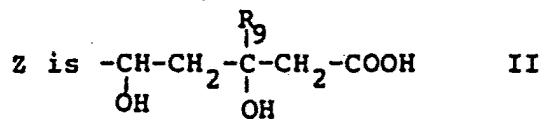
or in the case of R<sub>3</sub> and R<sub>4</sub> additionally hydrogen, or for R<sub>3</sub> when Y is O or S



whereby R<sub>17</sub> is hydrogen or C<sub>1</sub>-alkyl and R<sub>18</sub> and R<sub>19</sub> are independently hydrogen, C<sub>1</sub>-alkyl or phenyl; each R<sub>5</sub> is independently hydrogen, C<sub>1</sub>-alkyl, n-butyl, i-butyl, t-butyl, C<sub>1</sub>-alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy; each R<sub>6</sub> is independently hydrogen, C<sub>1</sub>-alkyl, C<sub>1</sub>-alkoxy, trifluoromethyl, fluoro, chloro, bromo, phenoxy or benzyloxy, and each R<sub>7</sub> is independently hydrogen, C<sub>1</sub>-alkyl, C<sub>1</sub>-alkoxy, fluoro or chloro.

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with the proviso that there may only be one each of trifluoromethyl, phenoxy or benzyloxy in each ring A present. X is  $(\text{CH}_2)_m$  or  $(\text{CH}_2)_q\text{CH}=\text{CH}(\text{CH}_2)_q$ , m is 0, 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1.



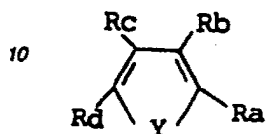
wherein  $\text{R}_9$  is hydrogen or  $\text{C}_1$ -alkyl, in free acid form, or in the form of an ester or  $\delta$ -lactone thereof or in salt form as appropriate, which compounds are indicated for use as pharmaceuticals in particular as hypolipoproteinemic and anti-atherosclerotic agents.

## 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



15 wherein

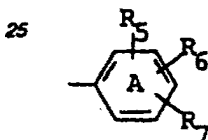
Ra is a group -X-Z, Rb is R<sub>2</sub>, Rc is R<sub>3</sub>, Rd is R<sub>4</sub> and Y is a group -N- or



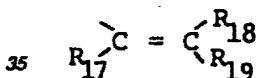
20 Ra is R<sub>1</sub>, Rb is a group -X-Z, Rc is R<sub>2</sub>, Rd is R<sub>3</sub> and Y is O, S or a group -N-;



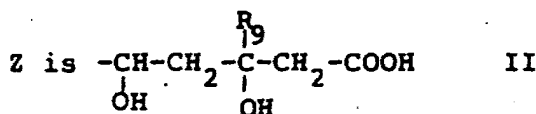
25 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> independently are C<sub>1</sub>-8alkyl not containing an asymmetric carbon atom, C<sub>3</sub>-7cycloalkyl or a ring



30 or in the case of R<sub>3</sub> and R<sub>4</sub> additionally hydrogen, or for R<sub>3</sub> when Y is O or S



40 whereby R<sub>17</sub> is hydrogen or C<sub>1</sub>-3alkyl and R<sub>18</sub> and R<sub>19</sub> are independently hydrogen C<sub>1</sub>-3alkyl or phenyl; each R<sub>5</sub> is independently hydrogen, C<sub>1</sub>-3alkyl, n-butyl, i-butyl, t-butyl, C<sub>1</sub>-3alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy; each R<sub>6</sub> is independently hydrogen, C<sub>1</sub>-3alkyl, C<sub>1</sub>-3alkoxy, trifluoromethyl, fluoro, chloro, bromo, phenoxy or benzyloxy, and each R<sub>7</sub> is independently hydrogen, C<sub>1</sub>-2alkyl, C<sub>1</sub>-2alkoxy, 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<sub>2</sub>)<sub>m</sub> or (CH<sub>2</sub>)<sub>q</sub>CH=CH-(CH<sub>2</sub>)<sub>q</sub>, m is 0, 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1.



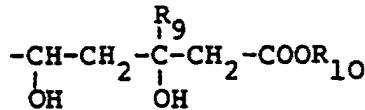
50 wherein R<sub>9</sub> is hydrogen or C<sub>1</sub>-3alkyl,

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.

55 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

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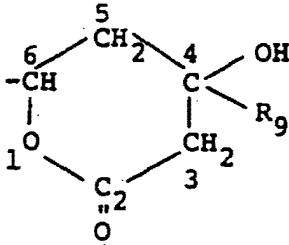


wherein

R<sub>9</sub> is hydrogen or C<sub>1</sub>-alkyl and

R<sub>10</sub> is hydrogen, a physiologically acceptable ester forming group (R<sub>11</sub>) or a pharmaceutically acceptable cation (M).

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

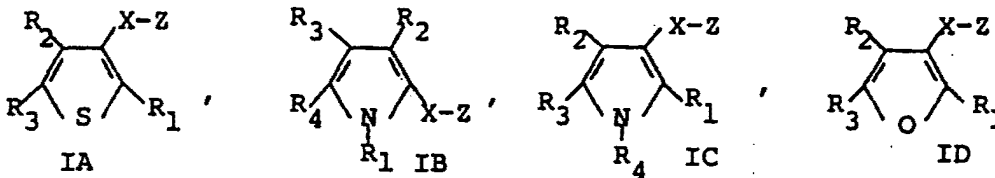


and reference to "lactone" hereinafter refer to δ-lactones.

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



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 stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers). 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 mentioned stereoisomers) are preferred.

Preferably in compounds IA-ID one of R<sub>1</sub> and R<sub>2</sub> is C<sub>1</sub>-alkyl not containing an asymmetric carbon atom and the other is a Ring A. Also preferably in compounds IB and IC, one of R<sub>3</sub> and R<sub>4</sub> is a Ring A and the other is hydrogen or C<sub>1</sub>-alkyl not containing an asymmetric carbon atom, preferably hydrogen or C<sub>1</sub>-2alkyl and most preferably hydrogen except that R<sub>4</sub> 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<sub>1</sub> is preferably R<sub>1Bx</sub>, where R<sub>1Bx</sub> is Ring A, more preferably R<sub>1' Bx</sub>, where R<sub>1' Bx</sub> is Ring A wherein R<sub>5</sub> is R<sub>5'</sub>, R<sub>6</sub> is R<sub>6'</sub>, and R<sub>7</sub> is R<sub>7'</sub>, even more preferably R<sub>1'' Bx</sub>, where R<sub>1'' Bx</sub> is Ring A wherein R<sub>5</sub> is R<sub>5''</sub>, R<sub>6</sub> is R<sub>6''</sub>, and R<sub>7</sub> is hydrogen, and most preferably phenyl, 4-fluorophenyl or 3,5-dimethylphenyl, especially

4-fluorophenyl; or

R<sub>1</sub> is preferably R<sub>1B<sub>y</sub></sub>, where R<sub>1B<sub>y</sub></sub> is C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom, more preferably R<sub>1<sup>1</sup><sub>B<sub>y</sub></sub>, where R<sub>1<sup>1</sup><sub>B<sub>y</sub></sub> is C<sub>1-4</sub>alkyl not containing an asymmetric carbon atom, and most preferably i-propyl.</sub></sub>

R<sub>2</sub> is preferably R<sub>2B<sub>x</sub></sub>, where R<sub>2B<sub>x</sub></sub> is C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom, more preferably R<sub>2<sup>1</sup><sub>B<sub>x</sub></sub>, where R<sub>2<sup>1</sup><sub>B<sub>x</sub></sub> is C<sub>1-4</sub>alkyl not containing an asymmetric carbon atom, and most preferably i-propyl; or</sub></sub>

R<sub>2</sub> is preferably R<sub>2B<sub>y</sub></sub>, where R<sub>2B<sub>y</sub></sub> is Ring A, more preferably R<sub>2<sup>1</sup><sub>B<sub>y</sub></sub>, where R<sub>2<sup>1</sup><sub>B<sub>y</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>1</sup></sub>, R<sub>6</sub> is R<sub>6<sup>1</sup></sub>, and R<sub>7</sub> is R<sub>7<sup>1</sup></sub>, even more preferably R<sub>2<sup>2</sup><sub>B<sub>y</sub></sub>, where R<sub>2<sup>2</sup><sub>B<sub>y</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>2</sup></sub>, R<sub>6</sub> is R<sub>6<sup>2</sup></sub> and R<sub>7</sub> is hydrogen, and most preferably phenyl, 4-fluorophenyl or 3,5-dimethylphenyl, especially 4-fluorophenyl.</sub></sub></sub></sub>

R<sub>3</sub> is preferably R<sub>3B<sub>x</sub></sub>, where R<sub>3B<sub>x</sub></sub> is hydrogen or C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom, more preferably R<sub>3<sup>1</sup><sub>B<sub>x</sub></sub>, where R<sub>3<sup>1</sup><sub>B<sub>x</sub></sub> is hydrogen or C<sub>1-2</sub>alkyl, even more preferably R<sub>3<sup>2</sup><sub>B<sub>x</sub></sub>, where R<sub>3<sup>2</sup><sub>B<sub>x</sub></sub> is hydrogen or methyl, and most preferably hydrogen; or</sub></sub></sub></sub>

R<sub>3</sub> is preferably R<sub>3B<sub>y</sub></sub>, where R<sub>3B<sub>y</sub></sub> is Ring A, more preferably R<sub>3<sup>1</sup><sub>B<sub>y</sub></sub>, where R<sub>3<sup>1</sup><sub>B<sub>y</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>1</sup></sub>, R<sub>6</sub> is R<sub>6<sup>1</sup></sub>, and R<sub>7</sub> is R<sub>7<sup>1</sup></sub>, even more preferably R<sub>3<sup>2</sup><sub>B<sub>y</sub></sub>, where R<sub>3<sup>2</sup><sub>B<sub>y</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>2</sup></sub>, R<sub>6</sub> is R<sub>6<sup>2</sup></sub>, and R<sub>7</sub> is hydrogen, and most preferably phenyl.</sub></sub></sub></sub>

R<sub>4</sub> is preferably R<sub>4B<sub>x</sub></sub>, where R<sub>4B<sub>x</sub></sub> is Ring A, more preferably R<sub>4<sup>1</sup><sub>B<sub>x</sub></sub>, where R<sub>4<sup>1</sup><sub>B<sub>x</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>1</sup></sub>, R<sub>6</sub> is R<sub>6<sup>1</sup></sub>, and R<sub>7</sub> is R<sub>7<sup>1</sup></sub>, even more preferably R<sub>4<sup>2</sup><sub>B<sub>x</sub></sub>, where R<sub>4<sup>2</sup><sub>B<sub>x</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>2</sup></sub>, R<sub>6</sub> is R<sub>6<sup>2</sup></sub>, and R<sub>7</sub> is hydrogen, and most preferably phenyl; or R<sub>4</sub> is preferably R<sub>4B<sub>y</sub></sub>, where R<sub>4B<sub>y</sub></sub> is hydrogen or C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom, more preferably R<sub>4<sup>1</sup><sub>B<sub>y</sub></sub>, where R<sub>4<sup>1</sup><sub>B<sub>y</sub></sub> is hydrogen or C<sub>1-2</sub>alkyl, even more preferably R<sub>4<sup>2</sup><sub>B<sub>y</sub></sub>, where R<sub>4<sup>2</sup><sub>B<sub>y</sub></sub> is hydrogen or methyl, and most preferably hydrogen.</sub></sub></sub></sub></sub></sub></sub></sub>

In Formulae IA, IC and ID:

R<sub>1</sub> is preferably R<sub>1C<sub>x</sub></sub>, where R<sub>1C<sub>x</sub></sub> is C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom, more preferably R<sub>1<sup>1</sup><sub>C<sub>x</sub></sub>, where R<sub>1<sup>1</sup><sub>C<sub>x</sub></sub> is C<sub>1-4</sub>alkyl not containing an asymmetric carbon atom, and most preferably i-propyl, or</sub></sub>

R<sub>1</sub> is preferably R<sub>1C<sub>y</sub></sub>, where R<sub>1C<sub>y</sub></sub> is Ring A, more preferably R<sub>1<sup>1</sup><sub>C<sub>y</sub></sub>, where R<sub>1<sup>1</sup><sub>C<sub>y</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>1</sup></sub>, R<sub>6</sub> is R<sub>6<sup>1</sup></sub>, and R<sub>7</sub> is R<sub>7<sup>1</sup></sub>, even more preferably R<sub>1<sup>2</sup><sub>C<sub>y</sub></sub>, where R<sub>1<sup>2</sup><sub>C<sub>y</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>2</sup></sub>, R<sub>6</sub> is R<sub>6<sup>2</sup></sub>, and R<sub>7</sub> is hydrogen, and most preferably phenyl, 4-fluorophenyl or 3,5-dimethylphenyl, especially 4-fluorophenyl.</sub></sub></sub></sub>

R<sub>2</sub> is preferably R<sub>2C<sub>x</sub></sub>, where R<sub>2C<sub>x</sub></sub> is Ring A, more preferably R<sub>2<sup>1</sup><sub>C<sub>x</sub></sub>, where R<sub>2<sup>1</sup><sub>C<sub>x</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>1</sup></sub>, R<sub>6</sub> is R<sub>6<sup>1</sup></sub> and R<sub>7</sub> is R<sub>7<sup>1</sup></sub>, even more preferably R<sub>2<sup>2</sup><sub>C<sub>x</sub></sub>, where R<sub>2<sup>2</sup><sub>C<sub>x</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>2</sup></sub>, R<sub>6</sub> is R<sub>6<sup>2</sup></sub>, and R<sub>7</sub> is hydrogen, and most preferably phenyl, 4-fluorophenyl or 3,5-dimethylphenyl, especially 4-fluorophenyl; or</sub></sub></sub></sub>

R<sub>2</sub> is preferably R<sub>2C<sub>y</sub></sub>, where R<sub>2C<sub>y</sub></sub> is C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom, more preferably R<sub>2<sup>1</sup><sub>C<sub>y</sub></sub>, where R<sub>2<sup>1</sup><sub>C<sub>y</sub></sub> is C<sub>1-4</sub>alkyl not containing an asymmetric carbon atom, and most preferably i-propyl.</sub></sub>

R<sub>3</sub> is preferably R<sub>3C<sub>x</sub></sub>, where R<sub>3C<sub>x</sub></sub> is Ring A, more preferably R<sub>3<sup>1</sup><sub>C<sub>x</sub></sub>, where R<sub>3<sup>1</sup><sub>C<sub>x</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>1</sup></sub>, R<sub>6</sub> is R<sub>6<sup>1</sup></sub>, and R<sub>7</sub> is R<sub>7<sup>1</sup></sub>, even more preferably R<sub>3<sup>2</sup><sub>C<sub>x</sub></sub>, where R<sub>3<sup>2</sup><sub>C<sub>x</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>2</sup></sub>, R<sub>6</sub> is R<sub>6<sup>2</sup></sub>, and R<sub>7</sub> is hydrogen, and most preferably phenyl; or</sub></sub></sub></sub>

R<sub>3</sub> is preferably R<sub>3C<sub>y</sub></sub>, where R<sub>3C<sub>y</sub></sub> is hydrogen or C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom, more preferably R<sub>3<sup>1</sup><sub>C<sub>y</sub></sub>, where R<sub>3<sup>1</sup><sub>C<sub>y</sub></sub> is hydrogen or C<sub>1-2</sub>alkyl, and even more preferably R<sub>3<sup>2</sup><sub>C<sub>y</sub></sub>, where R<sub>3<sup>2</sup><sub>C<sub>y</sub></sub> is hydrogen or methyl, especially hydrogen.</sub></sub></sub></sub>

In the compounds of formulae IA and ID, especially the former, R<sub>3C<sub>y</sub></sub>, R<sub>3C<sub>y</sub></sub>' and R<sub>3C<sub>y</sub></sub>" include -CH=C(CH<sub>3</sub>)<sub>2</sub>.

In formula IC:

R<sub>4</sub> is preferably R<sub>4C<sub>x</sub></sub>, where R<sub>4C<sub>x</sub></sub> is hydrogen or C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom, more preferably R<sub>4<sup>1</sup><sub>C<sub>x</sub></sub>, where R<sub>4<sup>1</sup><sub>C<sub>x</sub></sub> is C<sub>1-2</sub>alkyl, even more preferably methyl, or</sub></sub>

R<sub>4</sub> is preferably R<sub>4C<sub>y</sub></sub>, where R<sub>4C<sub>y</sub></sub> is Ring A, more preferably R<sub>4<sup>1</sup><sub>C<sub>y</sub></sub>, where R<sub>4<sup>1</sup><sub>C<sub>y</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>1</sup></sub>, R<sub>6</sub> is R<sub>6<sup>1</sup></sub>, and R<sub>7</sub> is R<sub>7<sup>1</sup></sub>, even more preferably R<sub>4<sup>2</sup><sub>C<sub>y</sub></sub>, where R<sub>4<sup>2</sup><sub>C<sub>y</sub></sub> is Ring A wherein R<sub>5</sub> is R<sub>5<sup>2</sup></sub>, R<sub>6</sub> is R<sub>6<sup>2</sup></sub>, and R<sub>7</sub> is hydrogen, and most preferably phenyl.</sub></sub></sub></sub>

In addition, in the compounds IA and ID R<sub>2</sub> is preferably C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom, especially isopropyl or t-butyl, or phenyl or p-substituted phenyl, especially p-fluorophenyl and R<sub>1</sub> 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<sub>5</sub> independently is preferably R<sub>5<sup>1</sup></sub> where R<sub>5<sup>1</sup></sub> is hydrogen, C<sub>1-3</sub>alkyl, C<sub>1-2</sub>alkoxy, trifluoromethyl, fluoro or chloro, more preferably R<sub>5<sup>2</sup></sub> where R<sub>5<sup>2</sup></sub> is hydrogen methyl or fluoro. In the case of R<sub>1</sub> and R<sub>2</sub> being a Ring A each R<sub>5<sup>1</sup></sub> is preferably fluoro, especially 4-fluoro. In the case of R<sub>3</sub> and R<sub>4</sub> being a Ring A R<sub>5<sup>1</sup></sub> is preferably hydrogen.

Each R<sub>6</sub> independently is preferably R<sub>6<sup>1</sup></sub> where R<sub>6<sup>1</sup></sub> is hydrogen, C<sub>1-2</sub>alkyl, fluoro or chloro more preferably R<sub>6<sup>2</sup></sub> where R<sub>6<sup>2</sup></sub> is hydrogen or methyl, most preferably hydrogen.

Each R<sub>7</sub> independently is preferably R<sub>7<sup>1</sup></sub> where R<sub>7<sup>1</sup></sub> 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

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