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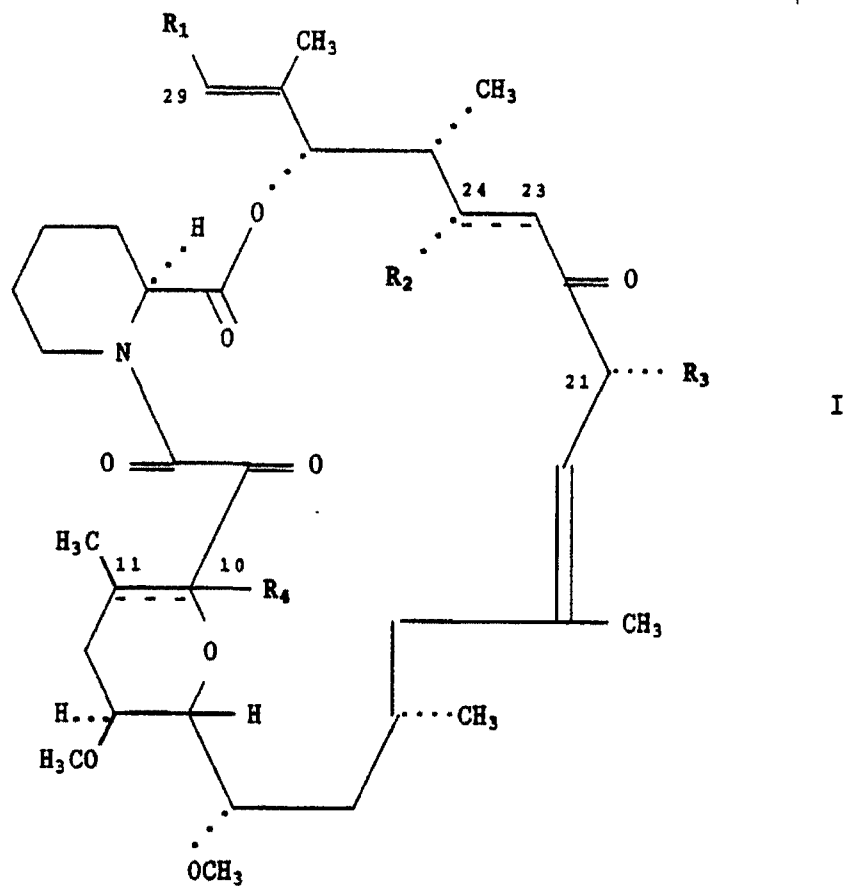
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Heteroatoms-containing tricyclic compounds.

The invention concerns the compounds of formula I

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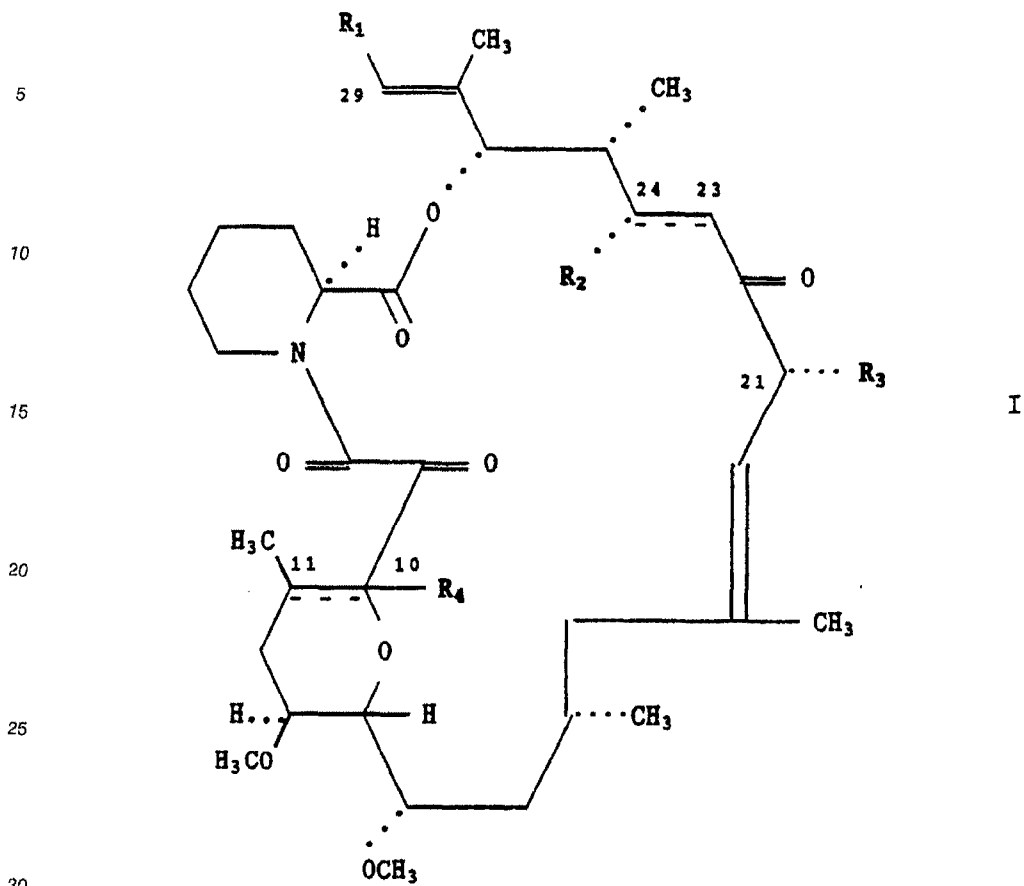
wherein the substituents have various significances.

They are prepared by several processes including epimerizing replacement, treatment with cyanogen bromide or thiophosgene, treatment with an acid having a non-nucleophilic anion, treatment with dimethylsulfoxide and acetic anhydride, acylation, treatment with an oxalyl derivative and ammonia, methylation, oxidation, deprotection and protection.

They possess interesting pharmacological activity as antiinflammatory, immunosuppressant, antiproliferative and chemotherapeutic drug resistance reversing agents.

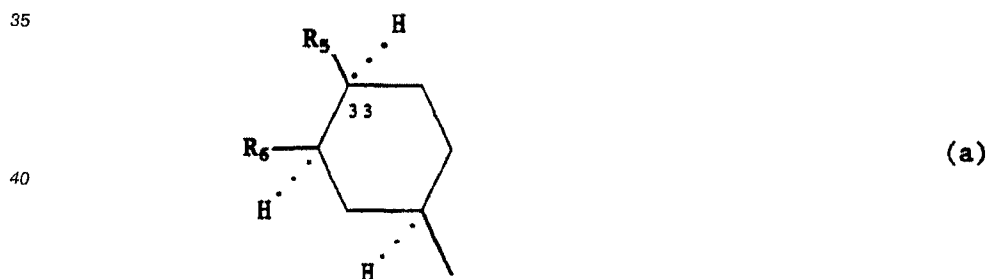
HETEROATOMS-CONTAINING TRICYCLIC COMPOUNDS

The invention relates to the field of macrolides. It concerns the compounds of formula I



wherein

either R₁ is a group (a) of formula



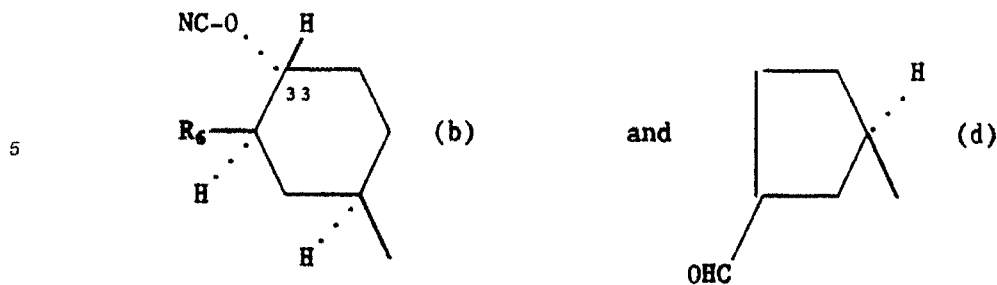
wherein R₅ is chloro, bromo, iodo or azido and

R₆ is hydroxy or methoxy;

R₂ is oxo and there is a single bond in 23,24 position; optionally protected hydroxy and there is a single or a double bond in 23,24 position; or absent and there is a double bond in 23,24 position; and

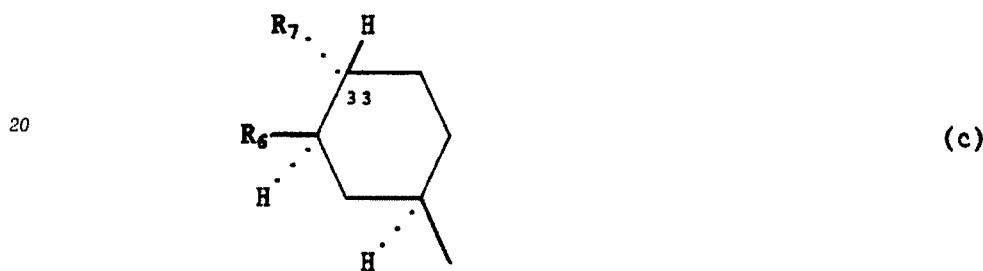
50 R₄ is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;

or R₁ is a group (b) or (d) of formula



wherein R_6 is as defined above;
 R_2 is as defined above; and
 R_4 is hydroxy and there is a single bond in 10,11 position;
 or R_1 is a group (c) of formula

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wherein R_6 is as defined above and
 R_7 is oxo; optionally protected hydroxy; methoxy; methylthiomethoxy; isobutanoyloxy; aminooxalyloxy;
 $R_8R_9CHCOO^-$ wherein R_8 is optionally protected hydroxy or optionally protected amino and R_9 is hydrogen
 or methyl; or p-tolyloxythiocarbonyloxy;
 R_2 is oxo and there is a single bond in 23,24 position; absent and there is a double bond in 23,24 position;
 or is optionally protected hydroxy, methoxy, methylthiomethoxy, isobutanoyloxy, aminooxalyloxy or R_8R_9CH
 COO^- wherein R_8 and R_9 are as defined above, and there is a single or a double bond in 23,24 position;
 whereby for group (c)

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- 35
- 1) when R_7 is oxo, unprotected hydroxy or methoxy
 then R_2 is other than absent and other than unprotected hydroxy or methoxy, and
 there is a single bond in 23,24 position;
 - 2) when R_6 is methoxy and R_7 is methylthiomethoxy
 then R_2 is other than absent and other than unprotected hydroxy;
 - 40 3) when R_6 is methoxy and R_7 is protected hydroxy
 then R_2 is other than optionally protected hydroxy; and
 - 4) when R_6 is hydroxy
 then R_7 is other than optionally protected hydroxy; and
 R_4 is hydroxy and there is a single bond in 10,11 position; and
 - 45 R_3 is methyl, ethyl, n-propyl or allyl;
 in free form and, where such forms exist, in salt form,
 hereinafter referred to as "the compounds of the invention".

As is evident from formula I and the definition of the substituents when there is a single bond in 10,11
 position the carbon atom to which the methyl group in 11 position is attached has the β -configuration and
 there is a hydrogen atom with the α -configuration attached to the carbon atom in 11 position; when there is
 a double bond in 10,11 position this methyl group lies in the plane of the paper and there is no hydrogen
 atom in 11 position. When R_2 is oxo no hydrogen atom is attached to the carbon atom in 24 position. When
 R_7 is oxo the hydrogen atom shown in group (c) attached to the same carbon atom as R_7 is absent.

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R_1 preferably is a group (c) or (d). R_2 preferably is unprotected hydroxy and there is a single bond in
 23,24 position. R_3 preferably is ethyl or allyl. R_4 preferably is hydroxy. R_5 preferably is chloro. R_6
 preferably is methoxy. R_7 preferably is isobutanoyloxy, aminooxalyloxy or $R_8R_9CHCOO^-$. R_8 preferably is
 unprotected hydroxy or unprotected amino, especially unprotected hydroxy. R_9 preferably is hydrogen.
 When R_9 is other than hydrogen the carbon atom to which it is attached preferably has the (S)

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configuration.

Protected hydroxy preferably is hydroxy protected by a conventional hydroxy-protecting group such as formyl, tert-butoxycarbonyl, or trialkylsilyl; it especially is tert-butyldimethylsilyloxy.

Optionally protected hydroxy as defined above under formula I for R₂ and R₇ should not be understood as including a group R₂ or R₇ which is otherwise specified, such as e.g. aminooxalyloxy or R₈R₉CHCOO-.

Protected amino preferably is amino protected by a conventional amino-protecting group such as benzyloxycarbonyl or trialkylsilyl; it especially is tert-butoxycarbonyl.

A compound of the invention preferably is in free form. It preferably is in unprotected form.

A subgroup of compounds of the invention is the **compounds Ip₁**, i.e. the compounds of formula I
10 wherein

R₁ is a group (a) wherein R₆ is methoxy and
either R₅ is chloro or bromo and
R₄ is hydroxy and there is a single bond in 10,11 position
or R₅ is azido and

15 R₄ is hydroxy and there is a single bond in 10,11 position or absent and there is a double bond in 10,11 position;

R₂ is optionally protected hydroxy and there is a single or a double bond in 23,24 position; and
R₃ is as defined above under formula I;

in free form and, where such forms exist, in salt form.

20 A further subgroup of compounds of the invention is the **compounds Ip₂**, i.e. the compounds of formula I wherein

R₁ is a group (c) wherein R₆ is methoxy and R₇ is oxo; optionally protected hydroxy; methoxy; methylthiomethoxy; aminooxalyloxy; R₈CH₂COO- wherein R₈ is optionally protected amino; or p-tolylox-ythiocarbonyloxy;

25 R₂ is absent and there is a double bond in 23,24 position; or optionally protected hydroxy, methoxy, methylthiomethoxy or aminooxalyloxy and there is a single or double bond in 23,24 position;

whereby

1) when R₇ is oxo, unprotected hydroxy or methoxy
then R₂ is other than absent and other than unprotected hydroxy or methoxy, and
30 there is a single bond in 23,24 position;

2) when R₇ is methylthiomethoxy
then R₂ is other than absent and other than unprotected hydroxy; and

3) when R₇ is protected hydroxy
then R₂ is other than optionally protected hydroxy; and

35 R₄ is hydroxy and there is a single bond in 10,11 position; and
R₃ is as defined above under formula I;

in free form and, where such forms exist, in salt form.

A further subgroup of compounds of the invention is the **compounds Ip₃**, i.e. the compounds of formula I wherein

40 R₁ is a group (b) wherein R₆ is methoxy,

R₂ is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R₄ is hydroxy and there is a single bond in 10,11 position; and

R₃ is as defined above under formula I;

45 in free form and, where such forms exist, in salt form.

A further subgroup of compounds of the invention is the **compounds Ip₄**, i.e. the compounds of formula I wherein

R₁ is a group (d),

50 R₂ is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R₄ is hydroxy and there is a single bond in 10,11 position; and

R₃ is as defined above under formula I;

in free form and, where such forms exist, in salt form.

A preferred subgroup of compounds of the invention is the compounds of formula I wherein

55 R₁ is a group (a) wherein R₅ is as defined above under formula I and R₆ is methoxy;

R₂ is optionally protected hydroxy and there is a single bond in 23,24 position;

R₄ is hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 10,11 position; and

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