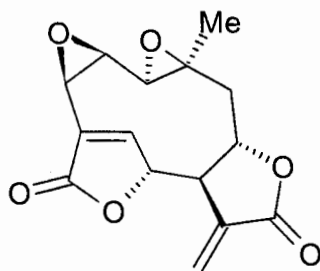


DERIVATIVES OF MIKANOLIDE, THEIR PREPARATION AND THEIR THERAPEUTIC USES

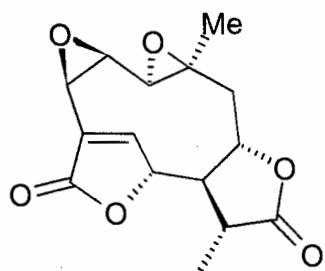
A subject of the invention is new derivatives of mikanolide, their preparation processes as well as their therapeutic uses, in particular as anticancerous, antibacterial and antiviral agents.

5 Tropical plants of the *Mikania* genus such as *M. cordata*, *M. scandens* or *M. micrantha* are part of certain traditional pharmacopeia of India, South America and Central America. Under the names of *guaco*, *bejuco de finca*, *cepu*, *liane françois*, *matafinca*, or also *vedolin*, the extracts of *Mikania* are used as antibiotics and anti-inflammatories.

10 Active substances originating from extracts of *Mikania* have been isolated and characterized: these are mikanolide and dihydromikanolide (see their structures in the figure below), and to a lesser extent scandenolides. These are sesquiterpenes of the germacrane family, i.e. having 4-isopropyl-1,7-dimethylcyclodecane as a hydrocarbon skeleton (Herz et al., *Tetrahedron Lett.* (1967) 3111-3115; Kiang et al., *Phytochemistry* (1968) 7: 1035-1037; Cuenca et al., *J. Nat. Prod.* (1988), **51**, 625-626).



mikanolide

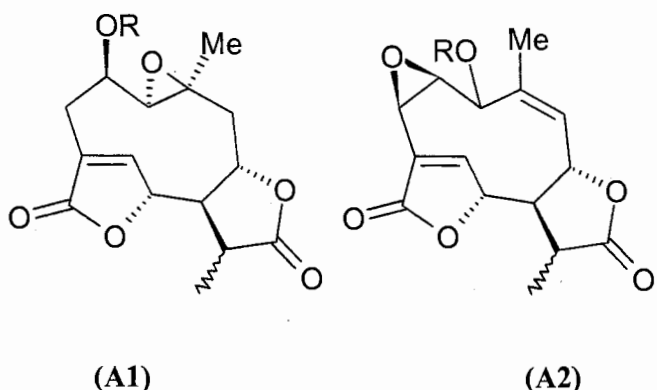


dihydromikanolide

15 Studies of the extracts of *Mikania* report an antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* (Facey et al., *J. Pharm. Pharmacol.* (1999) **51**, 1455-1460; Mathur et al., *Rev. Latinoam. Quim.* (1975), **6**, 201-205). Molluscicidal, piscicidal and bactericidal activities have also been described for dihydromikanolide (Vasquez et al., AG Meeting, Amsterdam, Netherlands, 26-30 July 1999, poster No. 316).

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For the purpose of elucidating structures, certain simple derivatives of mikanolide and dihydromikanolide, and in particular the compounds of general formulae (A1) and (A2) represented below



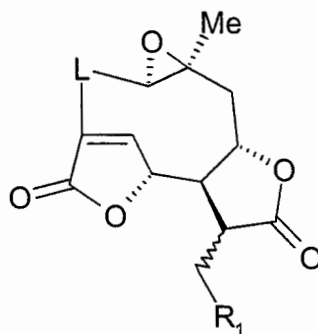
in which R represents a hydrogen atom or the acetyl group, have been synthesized and described in Herz et al., *J. Org. Chem.* (1970), **35**, 1453-1464. However, no pharmacological activity has been disclosed for these compounds.

The Applicant recently described in PCT Patent Application WO 01/39720 that mikanolide and dihydromikanolide are endowed with an antiproliferative activity linked to the inhibition of DNA-polymerase. However, mikanolides do not possess all the physico-chemical properties desirable for medicamentous use as they are neither very water soluble, nor very stable, which renders their pharmaceutical use relatively difficult, in particular in injectable form.

The Applicant has now developed new semi-synthetic mikanolide derivatives, which can be used for the treatment of diseases due to abnormal cell proliferation, in particular for the treatment of cancer, viral diseases and bacterial and parasitic infections. These compounds have the advantage of better solubility and better stability than that of mikanolide and dihydromikanolide while retaining an activity similar to or even greater than that of the latter.

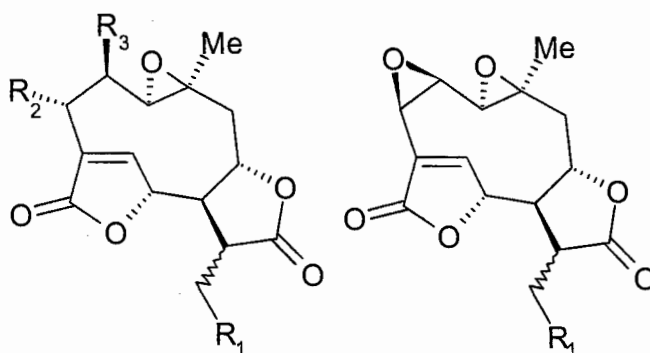
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A subject of the invention is the compounds of general formula (I)



(I)

corresponding to general sub-formulae (I)₁ and (I)₂

(I)₁(I)₂

in which

R₁ represents a hydrogen atom or an SR₄ or NR₄R₅ radical;

5 R₂ represents SR₆ or NR₆R₇;

R₃ represents OH, O(CO)R₁₄, OSiR₁₅R₁₆R₁₇, O(CO)OR₁₈ or O(CO)NHR₁₈;

R₄ and R₆ represent, independently, an alkyl radical, a cycloalkyl, cycloalkylalkyl, hydroxyalkyl radical or also one of the aryl or aralkyl radicals optionally substituted on their aryl group by one or more radicals chosen from the alkyl, hydroxy or alkoxy radicals,

10 R₅ and R₇ represent, independently, a hydrogen atom, an alkyl radical, a cycloalkyl, cycloalkylalkyl, hydroxyalkyl radical or also one of the aryl or aralkyl radicals

optionally substituted on their aryl group by one or more radicals chosen from the alkyl, hydroxy or alkoxy radicals,

R_4 and R_5 being able to form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional members being chosen from the
5 - CR_8R_9 -, - NR_{10} -, -O- and -S- radicals, it being understood however that there can only be one member chosen from -O- or -S- in said heterocycle,

and R_6 and R_7 being able to form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional members being chosen from the
10 - $CR_{11}R_{12}$ -, - NR_{13} -, -O- and -S- radicals, it being understood however that there can only be one member chosen from -O- or -S- in said heterocycle,

R_8 , R_{10} , R_{11} and R_{13} represent, independently each time they are involved, a hydrogen atom or an alkyl, alkoxy carbonyl or aralkyl radical,

R_9 and R_{12} representing, independently each time they are involved, a hydrogen atom or each of R_9 and R_{12} being able to form respectively together with R_8 and R_{11} an
15 -O-(CH₂)₂-O- radical attached on either side to the carbon atom which carries them, such a radical only being present however once at most per NR_4R_5 or NR_6R_7 radical, represent, independently each time they are involved, a hydrogen atom or an alkyl radical;

R_{14} represents an alkyl, cycloalkyl or adamantyl radical or one of the aryl, heteroaryl, aralkyl or heteroaralkyl radicals optionally substituted on their aryl or heteroaryl group
20 by one or more radicals chosen from a halogen atom and the alkyl, haloalkyl, nitro, hydroxy, alkoxy, alkylthio or phenyl radicals,

or also R_{14} is such that R_{14} -COOH represents a natural amino acid or the optical enantiomer of such an amino acid;

25 R_{15} , R_{16} and R_{17} represent, independently, an alkyl radical or a phenyl radical;

R_{18} represents an alkyl, cycloalkyl or adamantyl radical or one of the aryl, heteroaryl, aralkyl or heteroaralkyl radicals optionally substituted on their aryl or heteroaryl group by one or more radicals chosen from a halogen atom and the alkyl, haloalkyl, nitro, hydroxy, alkoxy, alkylthio or phenyl radicals;

30 it being understood however that when the compounds correspond to general sub-formula (I)₂, then R_1 does not represent a hydrogen atom;

or the salts of the latter.

By alkyl, unless otherwise specified, is meant a linear or branched alkyl radical containing 1 to 12 carbon atoms, and preferably 1 to 6 carbon atoms. By cycloalkyl, unless otherwise specified, is meant a monocyclic carbon system containing 3 to 7 carbon atoms. By haloalkyl, is meant an alkyl radical at least one of the hydrogen atoms (and optionally all) of which is replaced by a halogen atom. By carbocyclic or heterocyclic aryl, unless otherwise specified, is meant a carbocyclic or heterocyclic system comprising one to three condensed rings at least one of which is an aromatic ring, a system being referred to as heterocyclic when at least one of the rings comprising it contains one or more heteroatoms (O, N or S). By aryl, unless otherwise specified, is meant a carbocyclic aryl radical. By heteroaryl is meant a heterocyclic aryl radical. By haloalkyl, is meant an alkyl radical at least one of the hydrogen atoms (and optionally all) of which is replaced by a halogen atom. Finally, by halogen atom is meant the fluorine, chlorine, bromine or iodine atoms.

By alkoxy, hydroxyalkyl, cycloalkylalkyl, aralkyl and heteroaralkyl radicals, is meant respectively the alkoxy, hydroxyalkyl, cycloalkylalkyl and aralkyl radicals the alkyl, cycloalkyl, aryl and heteroaralkyl radicals of which have the meanings indicated previously.

By natural amino acid, is understood valine (Val), leucine (Leu), isoleucine (Ile), methionine (Met), phenylalanine (Phe), asparagine (Asn), glutamic acid (Glu), glutamine (Gln), histidine (His), lysine (Lys), arginine (Arg), aspartic acid (Asp), glycine (Gly), alanine (Ala), serine (Ser), threonine (Thr), tyrosine (Tyr), tryptophane (Trp), cysteine (Cys) or proline (Pro).

By linear or branched alkyl having 1 to 6 carbon atoms, is meant in particular the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, pentyl, neopentyl, isopentyl, hexyl, isohexyl radicals. By alkoxy, is meant in particular the methoxy, ethoxy and isopropoxy radicals, and in particular the methoxy and ethoxy radicals. By cycloalkyl is meant in particular the cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl radicals. By haloalkyl is meant in particular the trifluoromethyl radical. By carbocyclic aryl is meant in particular the phenyl, naphthyl and phenanthryl radicals, preferably the phenyl and naphthyl radicals and more preferentially the phenyl radical. By heterocyclic aryl is meant in particular the pyrrolyl, furanyl, benzofuranyl, thienyl, benzothienyl, pyridyl, pyrimidinyl, triazinyl, imidazolyl, oxazolyl, thiazolyl, indolyl and quinolyl radicals, and preferably the furanyl, benzofuranyl, thienyl and benzothienyl radicals. By aralkyl is meant in particular a phenalkyl radical, and preferably the benzyl radical. By heteroaralkyl is meant in particular a thienylalkyl, furanylalkyl, pyrrolylalkyl and thiazolylalkyl radical (the alkyl radical of said radicals

- 6 -

being preferably a methyl radical), and preferably a thienylalkyl radical (preferably thienylmethyl).

A compound of general formula **(I)** having at least one of the following characteristics is preferred:

- 5
- the compound corresponds to general sub-formula **(I)₁**;
 - R_1 represents a hydrogen atom or an NR_4R_5 radical;
 - R_2 represents an NR_6R_7 radical;
 - R_3 represents OH , or an $O(CO)R_{14}$, $OSiR_{15}R_{16}R_{17}$ or $O(CO)NHR_{18}$ radical.

10 More preferentially, a compound of general formula **(I)** will be such that it has at least one of the following characteristics:

- the compound corresponds to general sub-formula **(I)₁**;
- R_1 represents a hydrogen atom;
- R_2 represents an NR_6R_7 radical;
- R_3 represents an $O(CO)R_{14}$, $OSiR_{15}R_{16}R_{17}$ or $O(CO)NHR_{18}$ radical.

15 Quite particularly, a compound of general formula **(I)** is such that it has at least one of the following characteristics:

- the compound corresponds to general sub-formula **(I)₁**;
- R_1 represents a hydrogen atom;
- R_2 represents an NR_6R_7 radical and preferably an NR_6R_7 radical in which R_6 and R_7 are chosen independently from a hydrogen atom and an alkyl radical;
- R_3 represents an $O(CO)R_{14}$, $OSiR_{15}R_{16}R_{17}$ or $O(CO)NHR_{18}$ radical.

Moreover, R_2 will quite preferentially represent an NR_6R_7 radical in which R_6 and R_7 are alkyl radicals, and in particular an NR_6R_7 radical in which R_6 and R_7 are methyl radicals. R_3 will quite preferentially represent an $O(CO)NHR_{18}$ radical.

25 Preferably also, R_4 will represent an alkyl or aralkyl radical, and R_5 will represent a hydrogen atom or an alkyl radical, or also R_4 and R_5 will form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional

members being chosen from the $-CR_8R_9-$, $-NR_{10}-$, $-O-$ and $-S-$ radicals. Preferably, R_8 will represent, independently each time it is involved, a hydrogen atom or an alkyl radical (and preferably a hydrogen atom) and R_9 will represent, independently each time it is involved, a hydrogen atom. Preferably, R_{10} will represent, independently each time it is involved, a hydrogen atom or an alkyl radical.

Preferably also, R_6 will represent an alkyl or aralkyl radical, and R_7 will represent a hydrogen atom or an alkyl radical, or also R_6 and R_7 will form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional members being chosen from the $-CR_{11}R_{12}-$, $-NR_{13}-$, $-O-$ and $-S-$ radicals. Preferably, R_{11} will represent, independently each time it is involved, a hydrogen atom or an alkyl or alkoxy carbonyl radical (and preferably a hydrogen atom) or also R_{11} and R_{12} will represent, once together, an $-O-(CH_2)_2-O-$ radical attached on either side to the carbon atom which carries it. Preferably, R_{13} will represent, independently each time it is involved, a hydrogen atom or an alkyl radical.

Moreover, R_{14} will preferably represent an alkyl or cycloalkyl radical, or one of the aryl or heteroaryl radicals optionally substituted by a halogen atom or a haloalkyl or phenyl radical. More preferentially, R_{14} will represent a cycloalkyl radical or one of the aryl or heteroaryl radicals optionally substituted by a halogen atom or a haloalkyl radical. In a more preferred manner, R_{14} will represent a cyclohexyl radical or one of the phenyl, thienyl or benzothienyl radicals optionally substituted by a halogen atom.

Finally, R_{15} , R_{16} and R_{17} will preferably represent alkyl radicals. In a particularly preferred manner, one of the R_{15} , R_{16} and R_{17} radicals will represent a *tert*-butyl radical and the other two will represent methyl radicals.

Finally, R_{18} will preferably represent an alkyl, cycloalkyl or adamantyl radical, or one of the aryl or heteroaryl radicals optionally substituted by a halogen atom or an alkyl, haloalkyl, alkoxy, alkylthio or phenyl radical. More preferentially, R_{18} will represent a cycloalkyl radical or one of the aryl or heteroaryl radicals optionally substituted by an alkyl, alkoxy or alkylthio radical. Still more preferably, R_{18} will represent one of the phenyl, thienyl or benzothienyl radicals optionally substituted by an alkyl, alkoxy or alkylthio radical.

Moreover, when R_4 and R_5 form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the NR_4R_5 radical preferably represents one of the pyrrolyl, piperidyl, piperazinyl, morpholinyl or thiomorpholinyl radicals optionally substituted by an alkyl radical (the latter being preferably a methyl or ethyl radical, and more preferentially a methyl radical) on one of its carbon or nitrogen atoms, or by an

-O-(CH₂)₂-O- radical attached on either side to a carbon atom. More preferentially, when R₄ and R₅ form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the NR₄R₅ radical will represent one of the pyrrolyl, piperidyl, piperazinyl, morpholinyl or thiomorpholinyl radicals optionally substituted by an alkyl radical (the latter being preferably a methyl radical) on one of its carbon or nitrogen atoms.

Similarly, when R₆ and R₇ form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the NR₆R₇ radical preferably represents one of the pyrrolyl, piperidyl, piperazinyl, morpholinyl or thiomorpholinyl radicals optionally substituted by an alkyl radical (the latter preferably being a methyl or ethyl radical, and more preferentially a methyl radical) on one of its carbon or nitrogen atoms, or by an -O-(CH₂)₂-O- radical attached on either side to a carbon atom. More preferentially, when R₆ and R₇ form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the NR₆R₇ radical will represent one of the pyrrolyl, piperidyl, piperazinyl, morpholinyl or thiomorpholinyl radicals optionally substituted by an alkyl radical (the latter preferably being a methyl radical) on one of its carbon or nitrogen atoms.

The invention relates in particular to the following compounds described in the examples:

- 20 - 12-diisopropylaminomethyl-7-methyl-3,6,10,15-tetraoxapentacyclo
[12.2.1.0^{2,4}.0^{5,7}.0^{9,13}]heptadec-1(17)-ene-11,16-dione;
- 12-dimethylamino-3-dimethylaminomethyl-11-hydroxy-8-methyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-benzyl(methyl)amino-3-benzyl(methyl)aminomethyl-11-hydroxy-8-methyl-
25 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-8-methyl-12-morpholino-3-morpholinomethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-dimethylamino-11-hydroxy-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 30 - 11-hydroxy-3,8-dimethyl-12-(4-methylpiperidino)-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-3,8-dimethyl-12-pyrrolidino-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;

- ethyl 1-[11-hydroxy-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-12-yl]-
4-piperidinecarboxylate;
- 12-(4-benzylpiperidino)-11-hydroxy-3,8-dimethyl-
5 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-3,8-dimethyl-12-piperidino-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)-11-hydroxy-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 10 - 11-hydroxy-3,8-dimethyl-12-morpholino-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-(*tert*-butyldimethylsiloxy)-12-dimethylamino-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-
15 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl acetate;
- 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-11-phenylcarbonyloxy-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene;
- ethyl 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl carbonate;
- 20 - 11-hydroxy-12-isobutylsulphanyl-3-isobutylsulphanylmethyl-8-methyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-12-isobutylsulphanyl-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
25 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl benzoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl acetate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl
30 cyclohexanecarboxylate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-fluorobenzoate;

- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl heptanoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-(trifluoromethyl)benzoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thiophenecarboxylate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 3,3-dimethylbutanoate;
- 10 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 1-benzothiophene-2-carboxylate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-furoate;
- 15 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 5-nitro-2-furoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thienylacetate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl phenoxyacetate;
- 20 - 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 4-*tert*-butylphenylcarbamate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-2-ylcarbamate;
- 25 - 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-methoxyphenylcarbamate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-c]oxireno[f]oxacycloundecin-9-yl 2(methylthio)phenylcarbamate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-ethoxyphenylcarbamate;
- 30 - 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-3-ylcarbamate;

- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylcarbamate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-*c*]oxireno[f]oxacycloundecin-9-yl *N*-(*ter*-butoxycarbonyl)glycinate;
- 5 - 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl thien-3-ylacetate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylacetate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl thiophene-3-carboxylate;
- 10 - 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 5-phenylthien-2-ylcarbamate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 1-adamantylcarbamate;
- 15 - 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 2-naphthylcarbamate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 2-*tert*-butyl-6-methylphenylcarbamate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 2,5-dimethoxyphenylcarbamate;
- 20

as well as their salts.

The invention quite particularly relates to the following compounds:

- 12-dimethylamino-11-hydroxy-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 25 - 11-(*tert*-butyldimethylsiloxy)-12-dimethylamino-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl benzoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl cyclohexanecarboxylate;
- 30 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-fluorobenzoate;

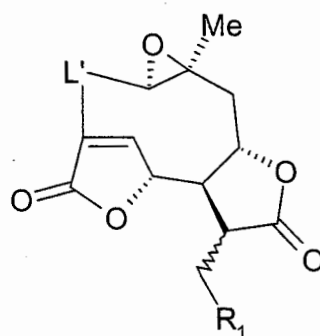
- 12 -

- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thiophenecarboxylate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 3,3-dimethylbutanoate;
- 5 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 1-benzothiophene-2-carboxylate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 4-*tert*-butylphenylcarbamate;
- 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-ethoxyphenylcarbamate;
- 10 as well as their salts.

As regards the salts of compounds of general formula (I), the maleates, fumarates, methanesulphonates and hydrochlorides of compounds of general formula (I) are preferred, and in particular those described in the examples, namely:

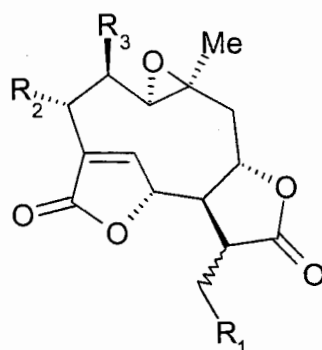
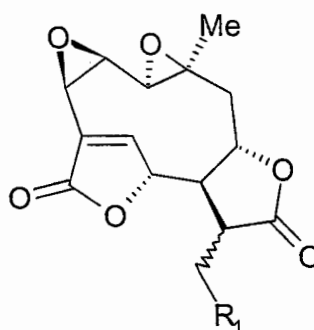
- 15 - 11-hydroxy-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-12-yl(dimethyl)ammonium maleate;
- 11-hydroxy-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-12-yl(dimethyl)ammonium fumarate;
- 11-hydroxy-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-12-yl(dimethyl)ammonium methanesulphonate;
- 20 - 11-[[*tert*-butyl(dimethyl)silyl]oxy]-12-(dimethylamino)-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione hydrochloride; and
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thiophenecarboxylate hydrochloride.
- 25 A subject of the invention is also the compounds of general formula (I)'

- 13 -



(I)'

corresponding to general sub-formulae (I)'₁ and (I)'₂

(I)'₁(I)'₂

in which

R₁ represents a hydrogen atom or an SR₄ or NR₄R₅ radical;

5 R₂ represents SR₆ or NR₆R₇;

R₃ represents OH, O(CO)R₁₄, O(CO)OR₁₄, or OSiR₁₅R₁₆R₁₇;

R₄, and R₆ represent, independently, an alkyl radical, a cycloalkyl, cycloalkylalkyl, hydroxyalkyl radical or also one of the aryl or aralkyl radicals optionally substituted on their aryl group by one or more radicals chosen from the alkyl, hydroxy or alkoxy radicals,

10

R₅ and R₇ represent, independently, a hydrogen atom, an alkyl radical, a cycloalkyl, cycloalkylalkyl, hydroxyalkyl radical or also one of the aryl or aralkyl radicals

optionally substituted on their aryl group by one or more radicals chosen from the alkyl, hydroxy or alkoxy radicals,

R₄ and R₅ being able to form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional members being chosen from the
5 -CR₈R₉-, -NR₁₀-, -O- and -S- radicals, it being understood however that there can only be one member chosen from -O- or -S- in said heterocycle,

and R₆ and R₇ being able to form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional members being chosen from the
10 -CR₁₁R₁₂-, -NR₁₃-, -O- and -S- radicals, it being understood however that there can only be one member chosen from -O- or -S- in said heterocycle,

R₈, R₁₀, R₁₁ and R₁₃ represent, independently each time they are involved, a hydrogen atom or an alkyl, alkoxy carbonyl or aralkyl radical,

R₉ and R₁₂ representing, independently each time they are involved, a hydrogen atom or each of R₉ and R₁₂ being able to form respectively with R₈ and R₁₁ an -O-(CH₂)₂-O-
15 radical attached on either side to the carbon atom which carries them, such a radical only being present however once at most per NR₄R₅ or NR₆R₇ radical,

represent, independently each time they are involved, a hydrogen atom or an alkyl radical;

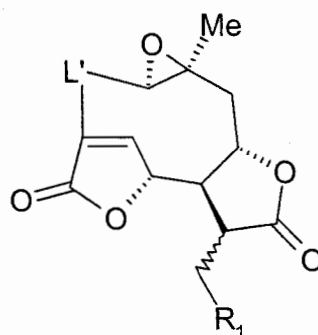
R₁₄ represents an alkyl or cycloalkyl radical or one of the aryl, heteroaryl, aralkyl or
20 heteroaralkyl radicals optionally substituted on their aryl or heteroaryl group by one or more radicals chosen from a halogen atom and the alkyl, haloalkyl, nitro, hydroxy or alkoxy radicals;

R₁₅, R₁₆ and R₁₇ represent, independently, an alkyl radical or a phenyl radical;

it being understood however that when the compounds correspond to general sub-
25 formula (I)'₂, then R₁ does not represent a hydrogen atom;

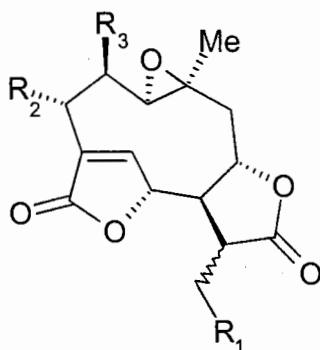
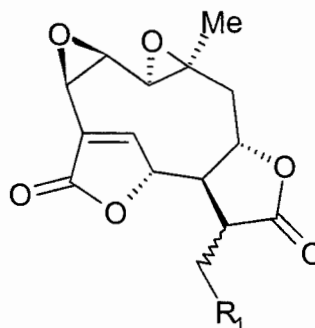
or the salts of the latter.

A subject of the invention is also the compounds of general formula (I)''



(I)''

corresponding to the general sub-formulae (I)''₁ and (I)''₂

(I)''₁(I)''₂

in which

5 R₁ represents a hydrogen atom or an SR₄ or NR₄R₅ radical;

R₂ represents SR₆ or NR₆R₇;

R₃ represents OH, O(CO)R₁₄, O(CO)OR₁₄, or OSiR₁₅R₁₆R₁₇;

10 R₄, R₅, R₆ and R₇ represent, independently, a hydrogen atom, an alkyl radical, a cycloalkyl, cycloalkylalkyl, hydroxyalkyl radical or also one of the aryl or aralkyl radicals optionally substituted on their aryl group by one or more radicals chosen from the alkyl, hydroxy or alkoxy radicals,

R₄ and R₅ can form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional members being chosen from the -CR₈R₉-, -NR₁₀-,

-O- and -S- radicals, it being understood however that only one member chosen from -O- or -S- can be found in said heterocycle,

and R_6 and R_7 can form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional members being chosen from the
 5 - $CR_{11}R_{12}$ -, - NR_{13} -, -O- and -S- radicals, it being understood however that only one member chosen from -O- or -S- can be found in said heterocycle,

R_8 , R_{10} , R_{11} and R_{13} represent, independently each time they are involved, a hydrogen atom or an alkyl, alkoxycarbonyl or aralkyl radical,

R_9 and R_{12} representing, independently each time they are involved, a hydrogen atom or
 10 each of R_9 and R_{12} can form with R_8 and R_{11} respectively an -O-(CH₂)₂-O- radical attached on either side to the carbon atom which carries it, such radical however only being present at most once per NR_4R_5 or NR_6R_7 radical, represent, independently each time they are involved, a hydrogen atom or an alkyl radical;

R_{14} , R_{15} , R_{16} and R_{17} represent, independently, a hydrogen atom, an alkyl radical or one
 15 of the aryl or aralkyl radicals optionally substituted on their aryl group by one or more radicals chosen from the alkyl, hydroxy or alkoxy radicals;

it being understood however that when the compounds correspond to the general sub-formula (I)'', then R_1 does not represent a hydrogen atom;

or the salts of the latter.

20 The compounds of the present invention can inhibit abnormal cell proliferation in a patient, for example a mammal such as man, by administration to this patient of a therapeutically effective quantity of a compound of general formula (I), (I)' or (I)'' or of a pharmaceutically acceptable salt of such a compound.

The compounds of general formula (I), (I)' or (I)'' have an anti-tumoral activity. They
 25 can be used for the treatment of tumors in a patient by administration to said patient of a therapeutically effective quantity of a compound of general formula (I), (I)' or (I)'' or of a pharmaceutically acceptable salt of such a compound. Examples of tumors or cancers include cancers of the oesophagus, stomach, intestines, rectum, buccal cavity, pharynx, larynx, lung, colon, breast, cervix uteri, *corpus endometrium*, ovaries,
 30 prostate, testicles, bladder, kidneys, liver, pancreas, bone, connective tissues, skin, for example melanomas, eyes, brain and central nervous system, as well as cancer of the thyroid, leukemia, Hodgkin's disease, lymphomas other than those of Hodgkin's disease, multiple myelomas and others.

They can also be used for the treatment of parasitic infections by inhibition of the hemoflagellates (for example in trypanosomia or leishmania infections) or by inhibition of the plasmodia (such as for example in malaria), but also the treatment of viral infections and diseases.

5 These properties make the compounds of the invention suitable for pharmaceutical use. A subject of the invention is therefore also, as medicaments, the compounds of general formula (I), (I)' or (I)'' described previously or their pharmaceutically acceptable salts. It also relates to pharmaceutical compositions containing these compounds or their pharmaceutically acceptable salts. A further subject of the invention is the use of these
10 compounds or their pharmaceutically acceptable salts in order to produce medicaments intended to inhibit DNA polymerases, and in particular to treat diseases due to abnormal cell proliferation (in particular cancer or atherosclerosis, benign hyperplasia of the prostate and fibroses), as well as viral diseases and parasitic diseases, in particular those caused by protozoans (for example malaria) or protists (for example
15 diseases caused by amoebae). Finally, the invention relates to the use of the compounds of general formula (I), (I)' or (I)'' described previously or their pharmaceutically acceptable salts for preparing a medicament intended to treat diseases of bacterial origin.

By pharmaceutically acceptable salt is meant in particular addition salts of inorganic
20 acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, diphosphate and nitrate or organic acids such as acetate, maleate, fumarate, tartrate, succinate, citrate, lactate, methanesulphonate, p-toluenesulphonate, pamoate and stearate. The salts formed from bases such as sodium or potassium hydroxide also fall within the scope of the present invention, when they can be used. For other examples of
25 pharmaceutically acceptable salts, reference can be made to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), 33, 201-217.

The pharmaceutical compositions containing a compound of the invention can be in solid form such as, for example, powders, pills, granules, tablets, liposomes, gelatin capsules or suppositories. The pills, tablets or gelatin capsules can be coated with a
30 substance capable of protecting the composition from the action of the gastric acid or the enzymes in the subject's stomach for a sufficient period of time to allow this composition to pass undigested into the subject's small intestine. The compound can also be administered locally, for example at the precise location of a tumor. The compound can also be administered according to a sustained release process (for
35 example using a sustained release composition or a perfusion pump). Appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, magnesium

carbonate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone and wax.

The pharmaceutical compositions containing a compound of the invention can also be presented in liquid form such as, for example, solutions, emulsions, suspensions or a
5 sustained release formulation. Appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols such as polyethylene glycol, as well as their mixtures, in varying proportions, in water.

The administration of a medicament according to the invention can be carried out by topical, oral, parenteral route, by intramuscular injection, etc.

10 The dose of a compound according to the present invention, to be provided for the treatment of the diseases or disorders indicated above, varies according to the method of administration, the age and the body weight of the subject to be treated as well as the latter's state, and the final decision is made by the attending doctor or veterinary surgeon. Such a quantity determined by the attending doctor or veterinary surgeon is
15 here referred to as "therapeutically effective quantity".

The same preferences as those indicated previously for the compounds of general formula (I) are applicable *mutatis mutandis* to the compounds of general formula (I)' or (I)", to the medicaments of general formula (I), (I)' or (I)", to the pharmaceutical compositions containing a compound of general formula (I), (I)' or (I)" and to the uses
20 of a compound of general formula (I), (I)' or (I)" for preparing medicaments.

According to the invention, the compounds of general formula (I), (I)' or (I)" can be prepared by the processes described hereafter.

Preparation of compounds of general formula (I), (I)' or (I)" and their salts

25 **Preparation of compounds of general sub-formula (I)₁:**

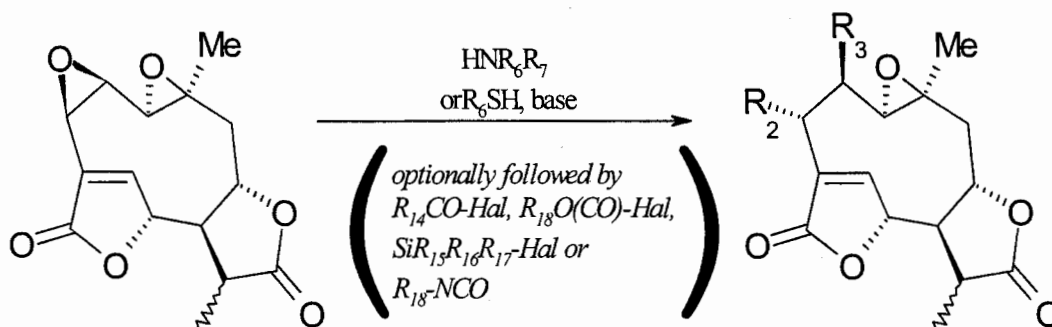
CASE 1: R₁ = H:

The preparation of this type of compound is summarized in Diagram 1 hereafter. The dihydromikanolide by adding a nucleophile such as a primary or secondary amine HNR₆R₇, or also a thiol R₆SH in the presence of a base, in an inert solvent such as
30 tetrahydrofuran or acetone, at a temperature preferably comprised between 0 °C and 50 °C, and more preferentially at ambient temperature.

In the case where R_3 is not OH, the intermediate obtained is treated with one of the reagents of general formula $R_{14}(\text{CO})\text{-Hal}$ (or an equivalent reagent such as for example the anhydride $(R_{14}(\text{CO}))_2\text{O}$), $R_{18}\text{O}(\text{CO})\text{-Hal}$, $\text{Hal-Si } R_{15}R_{16}R_{17}$ (Hal representing a halogen atom) or $R_{18}\text{-NCO}$ in order to obtain the desired final compound. Generally,

5 this reaction is carried out in an aprotic solvent such as dichloromethane, trichloroethane, acetonitrile, tetrahydrofuran or toluene, at a temperature preferably comprised between 0°C and 110°C and optionally in the presence of a base such as triethylamine or 4-dimethylaminopyridine. These types of reaction are well known to a person skilled in the art (who can in particular usefully consult the following reference

10 publication: Greene et al., "*Protective groups in Organic Synthesis*", 2nd edition, Wiley, New-York, 1991) owing to their frequent use for protecting an alcohol or amine function. For example, as regards the silylation reaction, this is generally carried out by treatment of an alcoholic compound with a silyl chloride in the presence of a base, in an aprotic solvent at a temperature comprised between 0°C and 50°C .

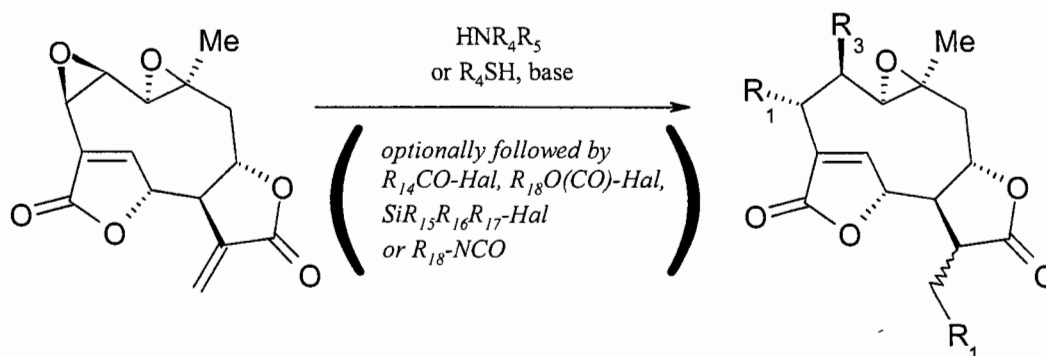
**Diagram 1**

- 15 An additional method for obtaining compounds with $R_3 = \text{OCOR}_{14}$ consists of treating the intermediate alcohol with the acid $R_{14}\text{-COOH}$ in the presence of a base, such as for example dimethylaminopyridine, and a coupling agent, such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl).

CASE 2: $R_1 = R_2 \neq \text{H}$:

- 20 The compounds of formula **(I)₁** in which $R_1 = R_2 \neq \text{H}$ and R_3 represents a hydroxyl group can be prepared from mikanolide by adding a nucleophilic such as a primary or secondary amine HNR_4R_5 , or also a thiol R_4SH in the presence of a base, in an inert solvent such as tetrahydrofuran or acetone, at a temperature preferably comprised between 0°C and 50°C , and more preferentially at ambient temperature.

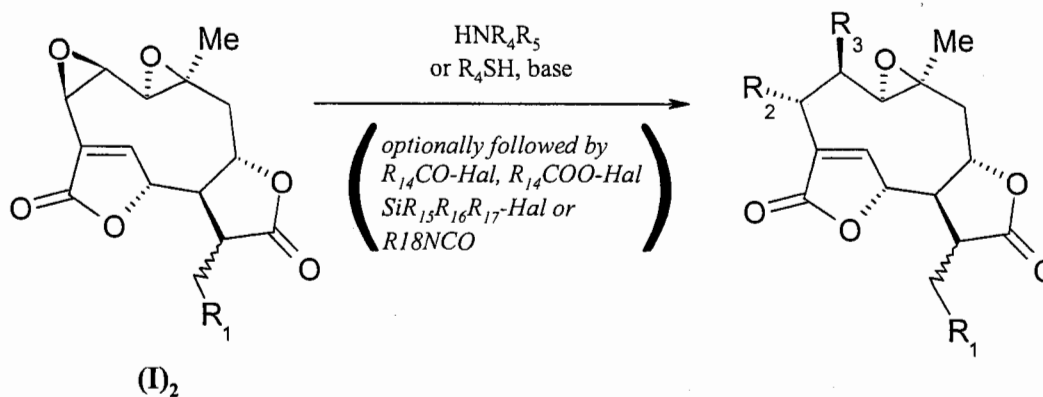
In the case where R_3 is not OH, a second reaction is carried out using a compound of general formula $R_{14}(\text{CO})\text{-Hal}$ (or an equivalent reagent such as for example $(R_{14}(\text{CO}))_2\text{O}$), $R_{18}\text{O}(\text{CO})\text{-Hal}$ or $\text{Hal-SiR}_{15}\text{R}_{16}\text{R}_{17}$ anhydride (Hal representing a halogen atom) or $R_{18}\text{-NCO}$ in order to obtain the desired final compound. This reaction can be carried out in a manner analogous to that disclosed in CASE 1.

**Diagram 2**

An additional method for obtaining compounds with $R_3 = \text{OCOR}_{14}$ consists of treating the intermediate alcohol with the acid $R_{14}\text{-COOH}$ in the presence of a base, such as for example dimethylaminopyridine, and of a coupling agent, such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl).

CASE 3: $R_1 \neq \text{H}$ and $R_1 \neq R_2$:

In this case, the compound of general formula **(I)₂** is subjected to the same reactions as in CASE 1 in order to produce the desired final compound in which $R_1 \neq R_2$.

**Diagram 3**

Preparation of compounds of general sub-formula (I)₂:

The compounds of sub-formula (I)₂ can be prepared, Diagram 4, from mikanolide by adding a nucleophile such as a primary or secondary amine HNR_6R_7 , or also a thiol R_6SH in the presence of a base, in an inert solvent such as tetrahydrofuran or acetone, at a temperature preferably comprised between 0 °C and 50 °C, and more preferentially at ambient temperature.

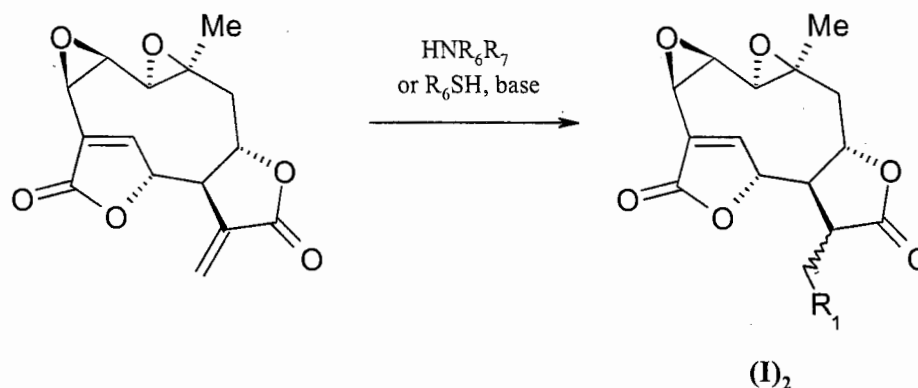


Diagram 4

Salts of compounds of general formula (I):

Certain compounds of the invention can be prepared in the form of pharmaceutically acceptable salts according to the usual methods. As regards these salts, a person skilled in the art can usefully consult the article by Gould et al., "Salt selection for basic drugs", *Int. J. Pharm.* (1986), **33**, 201-217.

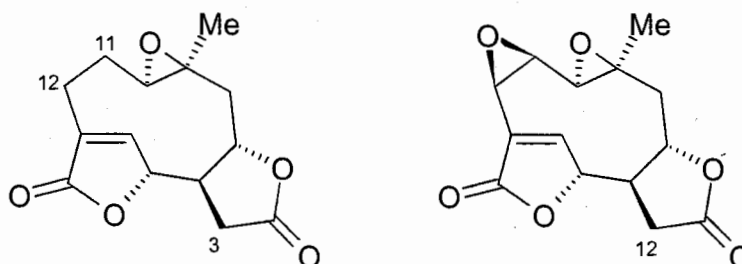
Unless otherwise specified, all the technical and scientific terms used here have the same meaning as that usually understood by an ordinary specialist in the field to which this invention belongs. Similarly, all the publications, patent applications, all the patents and all other references mentioned here are incorporated by way of reference.

The following examples are presented in order to illustrate the above procedures and should in no event be considered as a limit to the scope of the invention.

EXAMPLES

The nomenclature used for the examples in principle conforms with the IUPAC standards. It was determined using the ACD/Name[®] software (version 4.53) for examples 1 to 36 and using the ACD/Name[®] software (version 5.00) for examples 37 to 52.

The numbering indicated in the figure below is used for examples 1 to 36 as regards the positions of the substituents $-CH_2-R_1$, R_2 and R_3 on the polycycles of general formulae (I)₁ and (I)₂:



Example 1: 12-diisopropylaminomethyl-7-methyl-3,6,10,15-tetraoxapentacyclo[12.2.1.0^{2,4}.0^{5,7}.0^{9,13}]heptadec-1(17)-ene-11,16-dione:

Diisopropylamine (500 μ mol; 70 μ l) is added to a solution of mikanolide (100 μ mol; 29 mg) in acetone (1 ml). The reaction mass is stirred for 30 minutes at ambient temperature then the solvent is eliminated by evaporation under reduced pressure. The residue is taken up in ether, filtered and dried under vacuum. 10 mg of product is obtained in the form of a white powder.

NMR-¹H (DMSO): 0.90-1.30 (m, 15H); 1.85 (m, 2H); 2.15 (t, 2H); 3.15-3.50 (m, 4H); 3.95 (s, 1H); 4.75 (m, 1H); 5.50 (s, 1H); 6.00 (s, 1H); 6.25 (s, 1H); 7.60 (s, 1H).

Example 2: 12-dimethylamino-3-dimethylaminomethyl-11-hydroxy-8-methyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

A solution of dimethylamine (160 μ mol; 80 μ l; 2M in THF) is added to a solution of mikanolide (30 μ mol; 9 mg) in acetone (0.3 ml). The reaction mass is stirred for 30 minutes at ambient temperature then concentrated under reduced pressure. The residue is taken up in ether, filtered and dried under vacuum. 6 mg of expected compound is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.11 (s, 3H); 1.94-1.97 (m, 2H); 2.20 (s, 6H); 2.47 (s, 6H); 2.67 (m, 2H); 2.85 (t, 1H); 3.07 (d, 1H); 3.15 (m, 1H); 3.52 (d, 1H); 3.63 (m, 1H); 4.62 (m, 1H); 5.36 (s, 1H); 5.47 (s, 1H); 8.00 (s, 1H).

NMR-¹³C (DMSO): 20.68; 42.85; 43.37; 44.71; 45.92; 49.95; 57.84; 58.24; 61.61;
5 62.97; 67.94; 77.09; 80.67; 131.46; 151.01; 172.03; 174.98.

Example 3: 12-benzyl(methyl)amino-3-benzyl(methyl)aminomethyl-11-hydroxy-8-methyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 2. The expected product is obtained in the form of a white
10 powder.

NMR-¹H (DMSO): 1.12 (s, 3H); 1.96 (m, 2H); 2.10 (m, 1H); 2.15 (s, 3H); 2.47 (m, 2H); 2.83 (d, 2H); 2.89 (d, 1H); 3.22 (d, 1H); 3.26 (m, 1H); 3.58 (dd, 2H); 3.69 (m, 1H); 3.89 (d, 1H); 3.93 (s, 2H); 4.73 (m, 1H); 5.47 (d, 1H); 5.52 (s, 1H); 7.23-7.40 (m, 10H); 8.10 (s, 1H).

15 NMR-¹³C (DMSO): 20.65; 39.08; 40.54; 42.09; 43.09; 43.52; 50.18; 56.57; 57.85; 60.17; 61.14; 62.21; 62.33; 68.37; 77.22; 81.01; 126.07; 128.30; 131.48; 138.88; 139.67; 150.35; 172.16; 175.18.

Example 4: 11-hydroxy-8-methyl-12-morpholino-3-morpholinomethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

20 This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 2. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.13 (s, 3H); 1.85-2.10 (m, 2H); 2.36 (m, 2H); 2.40 (m, 2H); 2.74 (m, 4H); 2.88 (t, 1H); 2.95 (m, 2H); 3.10 (d, 1H); 3.24 (m, 1H);
25 3.50-3.70 (m, 10H); 4.64 (m, 1H); 5.49 (s, 1H); 5.50 (d, 1H); 8.01 (s, 1H).

Example 5: 12-dimethylamino-11-hydroxy-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

A solution of dimethylamine (500 μmol, 250 μl, 2M in THF) is added to a solution of dihydromikanolide (100 μmol, 29 mg) in acetone (1 ml). The reaction mass is stirred
30 for 2 hours at ambient temperature then the solvent is eliminated by evaporation under reduced pressure. The residue is taken up in ether, filtered and dried under vacuum. 25 mg of product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.10 (s, 3H); 1.25 (d, 3H); 1.90 (dd, 1H); 1.99 (t, 1H); 2.49 (s, 6H); 2.58 (t, 1H); 2.94 (m, 1H); 3.06 (d, 1H); 3.51 (m, 1H); 3.63 (m, 1H); 4.62 (m, 1H); 5.34 (s, 1H); 5.37 (d, 1H); 8.00 (s, 1H).

Example 6: 11-hydroxy-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo
[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-12-yl(dimethyl)ammonium maleate:

A solution of maleic acid (0.1 mmol; 11.6 mg) in acetone (0.5 ml) is added to a solution of the compound of Example 5 (0.1 mmol; 34 mg) in acetone (0.5 ml). The precipitate is filtered, washed with acetone and dried under reduced pressure. 24 mg of the expected product is obtained in the form of a white powder. Melting point: 178.5 °C.

10 NMR-¹H (DMSO): 1.09 (s, 3H); 1.28 (d, 3H); 1.94 (dd, 1H); 2.05 (m, 1H); 2.63 (t, 1H); 2.70-3.70 (m, 9H); 3.79 (t, 1H); 4.38 (s, 1H); 4.68 (m, 1H); 5.45 (s, 1H); 6.07 (s, 2H); 8.31 (s, 1H).

Example 7: 11-hydroxy-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo
[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-12-yl(dimethyl)ammonium fumarate:

15 A solution of fumaric acid (0.1 mmol; 11.6 mg) in acetone (3 ml) is added to a solution of the compound of Example 5 (0.1 mmol; 34 mg) in acetone (0.5 ml). The precipitate is filtered, washed with acetone and dried under reduced pressure. 15 mg of the expected product is obtained in the form of a white powder. Melting point: 159 °C.

NMR-¹H (DMSO): 1.11 (s, 3H); 1.25 (d, 3H); 1.92 (dd, 1H); 2.02 (m, 1H); 2.58 (t, 1H);
 20 2.80-4.00 (m, 11H); 4.64 (m, 1H); 5.34 (s, 1H); 6.61 (s, 2H); 8.01 (s, 1H).

Example 8: 11-hydroxy-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo
[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-12-yl(dimethyl)ammonium
methanesulphonate:

25 A solution of methanesulphonic acid (0.1 mmol; 1 ml; 0.1N in acetone) is added to a solution of the compound of Example 5 (0.1 mmol; 34 mg) in acetone (2 ml). The precipitate is filtered, washed with acetone and dried under reduced pressure. 24 mg of the expected product is obtained in the form of a white powder. Melting point: 220 °C.

NMR-¹H (DMSO): 1.09 (s, 3H); 1.29 (d, 3H); 1.97 (dd, 1H); 2.07 (m, 1H); 2.30 (s, 3H); 2.65 (t, 1H); 2.80-3.15 (m, 7H); 3.28 (d, 1H); 3.85 (t, 1H);
 30 4.66-4.72 (m, 2H); 5.49 (s, 1H); 6.94 (s, 1H); 8.44 (s, 1H); 10.04 (s, 1H).

Example 9: 11-hydroxy-3,8-dimethyl-12-(4-methylpiperidino)-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 5. The expected product is obtained in the form of a white powder. Melting point: 210 °C.

NMR-¹H (DMSO): 0.80-3.50 (m, 23H); 3.60-3.75 (m, 2H); 4.62 (m, 1H); 5.32 (s, 2H); 8.01 (s, 1H).

Example 10: 11-hydroxy-3,8-dimethyl-12-pyrrolidino-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 5. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.12 (s, 3H); 1.25 (d, 3H); 1.69 (m, 4H); 1.91 (dd, 1H); 2.00 (m, 1H); 2.60 (t, 1H); 2.80 (m, 4H); 2.95 (m, 1H); 3.02 (d, 1H); 3.45 (s, 1H); 3.63 (m, 1H); 4.61 (m, 1H); 5.34 (s, 1H); 5.42 (d, 1H); 7.97 (s, 1H).

Example 11: ethyl 1-[11-hydroxy-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-12-yl]-4-piperidinecarboxylate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 5. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.00-4.00 (m, 25H); 4.04 (q, 2H); 4.64 (m, 1H); 5.35 (s, 1H); 5.48 (d, 1H); 8.07 (s, 1H).

Example 12: 12-(4-benzylpiperidino)-11-hydroxy-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 5. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.00-1.80 (m, 12H); 1.85-2.10 (m, 2H); 2.35-4.00 (m, 6H); 4.63 (m, 1H); 5.33 (m, 2H); 7.00-7.20 (m, 5H); 8.03 (s, 1H).

Example 13: 11-hydroxy-3,8-dimethyl-12-piperidino-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 5. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.11 (s, 3H); 1.26 (d, 3H); 1.35-1.70 (m, 6H); 1.85-2.14 (m, 2H); 2.57-3.18 (m, 7H); 3.50-3.75 (m, 2H); 4.64 (m, 1H); 5.34 (m, 2H); 8.04 (s, 1H).

Example 14: 12-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)-11-hydroxy-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 5. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.11 (s, 3H); 1.26 (d, 3H); 1.40-1.80 (m, 6H); 1.85-2.05 (m, 2H); 2.58-4.00 (m, 17H); 4.67 (m, 1H); 5.37 (s, 1H); 5.44 (d, 1H); 8.08 (s, 1H).

Example 15: 11-hydroxy-3,8-dimethyl-12-morpholino-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 5. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.10 (s, 3H); 1.25 (d, 3H); 1.89 (dd, 1H); 2.01 (m, 1H); 2.61 (t, 1H); 2.75 (m, 2H); 3.95 (m, 3H); 3.08 (d, 1H); 3.55-3.75 (m, 5H); 4.63 (1H); 5.33 (s, 1H); 5.54 (d, 1H); 8.04 (s, 1H).

Example 16: 11-(tert-butyldimethylsiloxy)-12-dimethylamino-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

Terbutyldimethylsilyl chloride (80 μmol, 12 mg) is added to a solution of the compound of Example 5 (80 μmol; 27 mg) and imidazole (160 μmol; 11 mg) in DMF (0.5 ml). The solution obtained is stirred for 20 hours then the reaction mass is poured into water. The aqueous phase is extracted twice with ethyl acetate, the organic phase is washed with water then with a solution of sodium chloride. The organic phase is dried over magnesium sulphate, filtered then evaporated. The residue is eluted on silica with a mixture of isopropyl acetate and dichloromethane (20/80). 20 mg of product is obtained in the form of a white powder.

NMR-¹H (DMSO): 0.04 (s, 3H); 0.07 (s, 3H); 0.89 (s, 9H); 1.14 (s, 3H); 1.25 (d, 3H); 1.90 (dd, 1H); 1.99 (dd, 1H); 2.48 (s, 6H); 2.63 (t, 1H); 2.93-2.98 (m, 1H); 3.12 (d, 1H); 3.43 (m, 1H); 3.80 (m, 1H); 4.61 (m, 1H); 5.36 (s, 1H); 8.03 (s, 1H).

Example 17: 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-

5 **5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl acetate:**

Acetic anhydride (150 μmol; 15 μl) is added to a solution of the compound of Example 9 (100 μmol; 40 mg) in pyridine (0.5 ml). The solution obtained is stirred for 20 hours then the reaction mass is poured into water. The aqueous phase is extracted twice with ethyl acetate and the organic phase obtained is washed with water then with a solution
10 of sodium chloride. The organic phase is dried over magnesium sulphate, filtered then evaporated. The residue is eluted on silica with a mixture of isopropyl acetate and dichloromethane (20/80). 16 mg of product is obtained in the form of a white powder.
NMR-¹H (DMSO): 0.90 (d, 3H); 1.11 (s, 3H); 1.26 (d, 3H); 1.35 (m, 1H); 1.60 (m, 2H); 1.94 (dd, 1H); 2.03 (d, 1H); 2.09 (s, 3H); 2.43 (t, 1H); 2.60 (t, 1H); 2.98
15 (d, 1H); 2.94-3.05 (m, 2H); 3.36-3.45 (m, 4H); 4.07 (d, 1H); 4.64 (dd, 1H); 4.70 (m, 1H); 5.38 (s, 1H); 8.12 (s, 1H).

Example 18: 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-

11-phenylcarbonyloxy-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene:

Benzoyl chloride (400 μmol; 46 μl) is added to a solution of the compound of Example 9 (100 μmol; 40 mg) in pyridine (0.5 ml). The reaction mass is stirred for 2 hours then
20 treated in the same manner as for the preparation of the compound of Example 17. 25 mg of product is obtained in the form of a white powder. Melting point: 234 °C.
NMR-¹H (DMSO): 0.73 (d, 3H); 1.18 (s, 3H); 1.25 (m, 1H); 1.27 (d, 3H); 1.45-1.60 (m, 2H); 2.00 (dd, 1H); 2.10 (m, 1H); 2.65 (t, 1H); 2.92-3.15 (m, 3H);
25 3.45 (m, 2H); 3.54 (d, 1H); 4.18 (d, 1H); 4.36 (t, 1H); 4.74 (m, 1H); 4.95 (t, 1H); 5.41 (s, 1H); 7.58 (t, 2H); 7.70 (t, 1H); 8.01 (d, 2H); 8.19 (s, 1H).

Example 19: ethyl 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-

5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl carbonate:

Ethyl chloroformate (300 μmol; 28 μl) is added to a solution of the compound of Example 9 (100 μmol; 40 mg) in pyridine (0.5 ml). The reaction mass is stirred for 2
30 hours then treated in the same manner as for the preparation of the compound of Example 17. 20 mg of product is obtained in the form of a white powder.

NMR-¹H (DMSO): 0.88 (d, 3H); 1.10-1.40 (m, 12H); 1.59 (m, 2H); 2.90-2.10 (m, 2H); 2.35-2.50 (m, 2H); 2.58 (t, 1H); 2.80 (d, 1H); 2.95-3.07 (m, 2H); 3.40 (d, 1H); 4.11-4.25 (m, 3H); 4.43 (dd, 1H); 4.70 (m, 1H); 5.39 (s, 1H); 8.13 (s, 1H).

Example 20: 11-hydroxy-12-isobutylsulphanyl-3-isobutylsulphanylmethyl-8-methyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

2-methyl-1-propanethiol (500 μmol; 54 μl) is added to a solution of mikanolide (100 μmol; 30 mg) and dimethylaminopyridine (10 μmol; 1.2 mg) in acetone (1 ml). The reaction mass is stirred for two hours at ambient temperature then the solvent is evaporated off under reduced pressure. The residue is taken up in ether, the precipitate is filtered, washed with ether and dried under vacuum. 35 mg of product is obtained in the form of a white powder.

NMR-¹H (DMSO): 0.96 (m, 12H); 1.15 (s, 3H); 1.77 (m, 2H); 1.93 (d, 2H); 2.50 (m, 4H); 2.80-2.98 (m, 4H); 3.39 (m, 1H); 3.76 (m, 1H); 4.07 (d, 1H); 4.62 (q, 1H); 5.52 (s, 1H); 5.62 (s, 1H); 8.06 (s, 1H).

Example 21: 11-hydroxy-12-isobutylsulphanyl-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione:

2-methyl-1-propanethiol (500 μmol; 54 μl) is added to a solution of dihydromikanolide (100 μmol; 30 mg) and dimethylaminopyridine (10 μmol; 1.2 mg) in acetone (1 ml). The reaction mass is stirred for two hours at ambient temperature then the solvent is evaporated off under reduced pressure. The residue is taken up in ether then the precipitate formed is filtered, washed with ether and dried under vacuum. 25 mg of product is obtained in the form of a white powder.

NMR-¹H (DMSO): 0.96 (t, 6H); 1.13 (s, 3H); 1.25 (d, 3H); 1.78 (m, 1H); 1.89 (dd, 1H); 2.00 (t, 1H); 2.48 (m, 2H); 2.62 (t, 1H); 2.82 (d, 1H); 2.98 (m, 1H); 3.78 (m, 1H); 4.07 (d, 1H); 4.57 (m, 1H); 5.40 (s, 1H); 5.61 (d, 1H); 8.06 (s, 1H).

Example 22: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl benzoate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.21 (s, 3H); 1.28 (d, 3H); 1.98 (dd, 1H); 2.08 (t, 1H); 2.48 (s, 6H); 2.66 (t, 1H); 3.01 (m, 1H); 3.51 (d, 1H); 4.04 (d, 1H); 4.71 (m, 1H); 5.06 (dd, 1H); 4.43 (s, 1H); 7.58 (m, 2H); 7.70 (t, 1H); 8.01 (d, 2H); 8.20 (s, 1H).

Example 23: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl acetate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 17. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.14 (s, 3H); 1.26 (d, 3H); 1.94 (dd, 1H); 2.05 (t, 1H); 2.08 (s, 3H); 2.45 (s, 6H); 2.62 (t, 1H); 3.97 (m, 1H); 3.32 (m, 1H); 3.90 (d, 1H); 4.68 (m, 1H); 4.78 (m, 1H); 5.39 (s, 1H); 8.12 (s, 1H).

Example 24: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl cyclohexanecarboxylate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.14 (s, 3H); 1.26 (d, 3H); 1.08-1.48 (m, 5H); 1.58 (m, 1H); 1.68 (m, 2H); 1.84 (t, 2H); 1.93 (dd, 1H); 2.03 (t, 1H); 2.37 (m, 1H); 2.44 (s, 6H); 2.61 (t, 1H); 2.98 (m, 1H); 3.32 (t, 1H); 3.87 (d, 1H); 4.66 (m, 1H); 4.77 (dd, 1H); 5.40 (s, 1H); 8.12 (s, 1H).

Example 25: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-fluorobenzoate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.20 (s, 3H); 1.28 (d, 3H); 1.97 (dd, 1H); 2.08 (t, 1H); 2.46 (s, 6H); 2.65 (t, 1H); 3.00 (m, 1H); 3.50 (d, 1H); 4.04 (d, 1H); 4.71 (m, 1H); 5.04 (dd, 1H); 5.43 (s, 1H); 7.41 (t, 2H); 8.06 (dd, 2H); 8.20 (s, 1H).

Example 26: 11-{{tert-butyl(dimethyl)silyl}oxy}-12-(dimethylamino)-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione hydrochloride:

A solution of hydrochloric acid (0.3 mmol; 0.3 ml; 1N in ether) is added to a solution of the compound of Example 16 (0.22 mmol; 100 mg) in acetone (2 ml). The precipitate is filtered, washed with a little acetone, with ether and dried under reduced pressure. 70mg of the expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 0.14 (d, 6H); 0.90 (s, 9H); 1.15 (s, 3H); 1.27 (d, 3H); 1.85 (dd, 1H); 2.05 (t, 1H); 2.72 (t, 1H); 2.90-3.25 (m, 7H); 3.72 (m, 1H); 3.93 (m, 1H); 4.76 (m, 2H); 5.46 (s, 1H); 8.70 (d, 1H); 11.64 (s, 1H).

Example 27: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl heptanoate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 0.86 (t, 3H); 1.14 (s, 3H); 1.20-1.35 (m, 9H); 1.55 (m, 2H); 1.95 (dd, 1H); 2.02 (t, 1H); 2.35 (t, 2H); 2.44 (s, 6H); 2.61 (t, 1H); 2.96 (m, 1H); 3.33 (t, 1H); 3.89 (d, 1H); 4.68 (m, 1H); 4.77 (dd, 1H); 5.40 (s, 1H); 8.12 (s, 1H).

Example 28: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-(trifluoromethyl)benzoate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.21 (s, 3H); 1.28 (d, 3H); 2.01 (dd, 1H); 2.06 (t, 1H); 2.48 (s, 6H); 2.66 (t, 1H); 3.00 (m, 1H); 3.55 (d, 1H); 4.09 (d, 1H); 4.73 (m, 1H); 5.04 (dd, 1H); 5.44 (s, 1H); 7.96 (d, 2H); 8.19 (d, 2H); 8.21 (s, 1H).

Example 29: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thiophenecarboxylate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.20 (s, 3H); 1.27 (d, 3H); 1.99 (m, 1H); 2.07 (t, 1H); 2.49 (s, 6H); 2.65 (t, 1H); 3.00 (m, 1H); 3.47 (d, 1H); 4.00 (d, 1H); 4.70 (m, 1H); 5.01 (dd, 1H); 5.43 (s, 1H); 7.26 (t, 1H); 7.87 (d, 1H); 8.01 (dd, 1H); 8.18 (s, 1H).

Example 30: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 3,3-dimethylbutanoate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.00 (s, 9H); 1.15 (s, 3H); 1.26 (d, 3H); 1.94 (dd, 1H); 2.03 (t, 1H); 2.24 (dd, 2H); 2.45 (s, 6H); 2.62 (t, 1H); 2.98 (m, 1H); 3.32 (d, 1H); 3.86 (d, 1H); 4.65 (m, 1H); 4.81 (dd, 1H); 5.40 (s, 1H); 8.12 (s, 1H).

Example 31: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 1-benzothiophene-2-carboxylate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.22 (s, 3H); 1.28 (d, 3H); 2.01 (dd, 1H); 2.08 (m, 1H); 2.50 (s, 6H); 2.66 (t, 1H); 3.00 (m, 1H); 3.52 (d, 1H); 4.05 (d, 1H); 4.71 (m, 1H); 5.06 (dd, 1H); 5.44 (s, 1H); 7.50 (t, 1H); 7.56 (t, 1H); 8.09 (t, 2H); 8.21 (s, 1H); 8.27 (s, 1H).

Example 32: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-furoate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.19 (s, 3H); 1.27 (d, 3H); 1.97 (dd, 1H); 2.07 (t, 1H); 2.47 (s, 6H); 2.64 (t, 1H); 3.00 (m, 1H); 3.46 (d, 1H); 4.00 (d, 1H); 4.70 (m, 1H); 4.98 (dd, 1H); 5.43 (s, 1H); 6.72 (d, 1H); 7.36 (d, 1H); 8.03 (s, 1H); 8.18 (s, 1H).

Example 33: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 5-nitro-2-furoate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.19 (s, 3H); 1.28 (d, 3H); 1.98 (dd, 1H); 2.08 (t, 1H); 2.45 (s, 6H); 2.64 (t, 1H); 3.00 (m, 1H); 3.53 (d, 1H); 4.08 (d, 1H); 4.72 (m, 1H); 4.97 (dd, 1H); 5.44 (s, 1H); 7.65 (d, 1H); 7.80 (d, 1H); 8.21 (s, 1H).

Example 34: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thiophenecarboxylate hydrochloride:

A solution of hydrochloric acid (0.8 mmol; 0.8 ml; 1N in ether) is added to a solution of the compound of Example 29 (0.44 mmol; 196 mg) in acetone (4 ml). The precipitate is

filtered, washed with a little acetone, with ether and dried under reduced pressure. 180 mg of the expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.23 (s, 3H); 1.29 (d, 3H); 1.90 (dd, 1H); 2.13 (t, 1H); 2.76 (t, 1H); 2.85-3.25 (m, 7H); 3.95 (m, 1H); 4.78 (m, 1H); 5.02 (m, 1H);
 5 5.38 (m, 1H); 5.51 (s, 1H); 7.29 (t, 1H); 7.97 (s, 1H); 8.08 (d, 1H); 8.86 (s, 1H); 12.12 (s, 1H).

Example 35: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thienylacetate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.14 (s, 3H); 1.26 (d, 3H); 1.94 (dd, 1H); 2.04 (m, 1H); 2.38 (s, 6H); 2.61 (t, 1H); 2.97 (m, 1H); 3.37 (d, 1H); 3.88 (d, 1H); 4.00 (d, 2H); 4.68 (m, 1H); 4.78 (dd, 1H); 5.39 (s, 1H); 6.98 (m, 2H); 7.43 (d, 1H); 8.12 (s, 1H).

Example 36: 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl phenoxyacetate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.23 (s, 3H); 1.35 (d, 3H); 2.04 (dd, 1H); 2.13 (t, 1H); 2.58 (s, 6H); 2.67 (t, 1H); 3.06 (m, 1H); 3.48 (d, 1H); 4.08 (d, 1H); 4.77 (m, 1H); 4.86 (m, 1H); 4.96 (dd, 2H); 5.50 (s, 1H); 7.05 (m, 3H); 7.38 (m, 2H); 8.23 (s, 1H).

Example 37: 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 4-tert-butylphenylcarbamate:

4-terbutylphenylisocyanate (250 μmol; 44 mg) is added to a solution of the compound of Example 5 (200 μmol; 67 mg) in 1,2-dichloroethane (10 ml). The solution obtained is stirred for 20 hours at 60 °C before evaporating the solvent under reduced pressure. The residue is eluted on silica using a mixture of acetone and dichloromethane (20/80). The residue is taken up in ether, filtered and dried under vacuum. 36 mg of product is
 30 obtained in the form of a white powder.

NMR-¹H (DMSO): 1.18 (s, 3H); 1.25 (s, 9H); 1.27 (d, 3H); 1.95 (dd, 1H); 2.08 (t, 1H); 2.48 (s, 6H); 2.64 (t, 1H); 2.98 (m, 1H); 3.37 (m, 1H); 3.91 (d, 1H); 4.69

(m, 1H); 4.80 (dd, 1H); 5.40 (s, 1H); 7.29 (d, 2H); 7.38 (d, 2H); 8.12 (s, 1H); 9.67 (s, 1H).

Example 38: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-2-ylcarbamate:

- 5 This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.18 (s, 3H); 1.26 (d, 3H); 1.95 (m, 1H); 2.06 (m, 1H); 2.48 (s, 6H); 2.64 (t, 1H); 2.97 (m, 1H); 3.36 (m, 1H); 3.90 (m, 1H); 4.68 (m, 1H); 4.79
10 (m, 1H); 5.40 (s, 1H); 6.61 (s, 1H); 6.82 (s, 1H); 6.94 (s, 1H); 8.13 (s, 1H); 10.78 (s, 1H).

Example 39: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-methoxyphenylcarbamate:

- 15 This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.17 (s, 3H); 1.27 (d, 3H); 1.94 (dd, 1H); 2.05 (t, 1H); 2.48 (s, 6H); 2.63 (t, 1H); 2.98 (m, 1H); 3.37 (m, 1H); 3.80 (s, 3H); 3.87 (d, 1H); 4.68
20 (m, 1H); 4.80 (dd, 1H); 5.40 (s, 1H); 6.90 (t, 1H); 7.02 (d, 1H); 7.09 (t, 1H); 7.59 (d, 1H); 8.12 (s, 1H); 8.59 (s, 1H).

Example 40: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2(methylthio)phenylcarbamate:

- 25 This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.17 (s, 3H); 1.27 (d, 3H); 1.95 (dd, 1H); 2.08 (t, 1H); 2.40 (s, 3H); 2.48 (s, 6H); 2.63 (t, 1H); 2.98 (m, 1H); 3.37 (s, 1H); 3.84 (d, 1H); 4.67
(m, 1H); 4.80 (dd, 1H); 5.39 (s, 1H); 7.15-7.25 (m, 3H); 7.32 (t, 1H); 8.10 (s, 1H); 8.90 (s, 1H).

Example 41: 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-ethoxyphenylcarbamate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.17 (s, 3H); 1.27 (d, 3H); 1.35 (t, 3H); 1.95 (dd, 1H); 2.05 (t, 1H); 2.48 (s, 6H); 2.63 (t, 1H); 2.98 (m, 1H); 3.34 (m, 1H); 3.90 (d, 1H); 4.07 (q, 2H); 4.67 (m, 1H); 4.79 (dd, 1H); 5.40 (s, 1H); 6.90 (t, 1H); 7.01 (d, 1H); 7.07 (t, 1H); 7.58 (d, 1H); 8.12 (s, 1H); 8.46 (s, 1H).

Example 42: 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-3-ylcarbamate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.18 (s, 3H); 1.27 (d, 3H); 1.95 (dd, 1H); 2.05 (m, 1H); 2.48 (s, 6H); 2.64 (t, 1H); 2.98 (m, 1H); 3.36 (m, 1H); 3.90 (d, 1H); 4.68 (m, 1H); 4.80 (dd, 1H); 5.40 (s, 1H); 7.04 (d, 1H); 7.22 (s, 1H); 7.43 (t, 1H); 8.12 (s, 1H); 10.08 (s, 1H).

Example 43: 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylcarbamate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 18. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.20 (s, 3H); 1.28 (d, 3H); 1.98 (dd, 1H); 2.07 (m, 1H); 2.48 (s, 6H); 2.65 (t, 1H); 2.98 (m, 1H); 3.40 (m, 1H); 3.97 (d, 1H); 4.70 (m, 1H); 4.82 (dd, 1H); 5.40 (s, 1H); 7.40 (m, 2H); 7.65 (s, 1H); 7.95 (d, 1H); 8.14 (m, 2H); 10.00 (s, 1H).

Example 44: 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl N-(*ter*-butoxycarbonyl)glycinate:

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (200 μmol; 38 mg), N-*ter*-butoxycarbonyl-glycine (200 μmol; 35mg), triethylamine (200 μmol; 28μl) and dimethylaminopyridine (10 μmol; 3mg) are added to a solution of the compound of Example 5 (200 μmol; 60 mg) in dichloromethane (5 ml). The solution is stirred for three hours at ambient temperature, poured into a solution of NaHCO₃ then extracted

with ethyl acetate. The organic phase is washed with water then with a saturated solution of sodium chloride before being dried over MgSO_4 and filtered. The solvent is eliminated by distillation under reduced pressure. The residue is eluted on silica using a mixture of acetone and dichloromethane (40/60). The residue is taken up in ether,
 5 filtered and dried under vacuum. 25 mg of product is obtained in the form of a white powder.

NMR- ^1H (DMSO): 1.15 (s, 3H); 1.26 (d, 3H); 1.39 (s, 9H); 1.92 (dd, 1H); 2.05 (t, 1H); 2.43 (s, 6H); 2.62 (t, 1H); 2.98 (m, 1H); 3.35 (t, 1H); 3.75 (t, 2H); 3.84 (d, 1H); 4.67 (m, 1H); 4.81 (dd, 1H); 5.40 (s, 1H); 7.25 (t, 1H); 8.13 (s, 1H).

10 **Example 45: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-3-ylacetate:**

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 44. The expected product is obtained in the form of a white powder.

15 NMR- ^1H (DMSO): 1.14 (s, 3H); 1.26 (d, 3H); 1.94 (dd, 1H); 2.05 (m, 1H); 2.37 (s, 6H); 2.61 (t, 1H); 2.97 (m, 1H); 3.33 (t, 1H); 3.77 (s, 2H); 3.88 (d, 1H); 4.67 (m, 1H); 4.78 (dd, 1H); 5.39 (s, 1H); 7.04 (d, 1H); 7.36 (s, 1H); 7.50 (t, 1H); 8.11 (s, 1H).

20 **Example 46: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylacetate:**

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 44. The expected product is obtained in the form of a white powder.

25 NMR- ^1H (DMSO): 1.13 (s, 3H); 1.25 (d, 3H); 1.94 (dd, 1H); 2.04 (t, 1H); 2.26 (s, 6H); 2.60 (t, 1H); 2.96 (m, 1H); 3.32 (m, 1H); 3.88 (d, 1H); 4.04 (s, 2H); 4.67 (m, 1H); 4.74 (dd, 1H); 5.38 (s, 1H); 7.40 (m, 2H); 7.64 (s, 1H); 7.79 (d, 1H); 7.99 (d, 1H); 8.09 (s, 1H).

Example 47: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thiophene-3-carboxylate:

30 This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 44. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.19 (s, 3H); 1.27 (d, 3H); 1.97 (dd, 1H); 2.07 (t, 1H); 2.48 (s, 6H); 2.65 (t, 1H); 2.99 (m, 1H); 3.46 (d, 1H); 3.98 (s, 1H); 4.70 (m, 1H); 5.02 (m, 1H); 5.43 (s, 1H); 7.49 (s, 1H); 7.69 (s, 1H); 8.18 (s, 1H); 8.40 (s, 1H).

Example 48: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 5-phenylthien-2-ylcarbamate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 37. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.20 (s, 3H); 1.27 (d, 3H); 1.97 (dd, 1H); 2.03 (t, 1H); 2.38 (s, 6H); 2.67 (m, 1H); 2.98 (m, 1H); 3.37 (d, 1H); 3.94 (m, 1H); 4.69 (m, 1H); 4.81 (m, 1H); 5.41 (s, 1H); 6.60 (s, 1H); 7.22 (m, 2H); 7.36 (t, 2H); 7.55 (d, 2H); 8.14 (s, 1H); 10.93 (s, 1H).

Example 49: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 1-adamantylcarbamate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 37. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.14 (s, 3H); 1.26 (d, 3H); 1.60 (s, 6H); 1.80-1.94 (m, 6H); 1.94-2.09 (m, 4H); 2.47 (s, 6H); 2.62 (t, 1H); 2.96 (m, 1H); 3.21 (d, 1H); 3.38 (s, 1H); 3.76 (s, 1H); 4.64 (m, 2H); 5.37 (s, 1H); 6.96 (s, 1H); 8.05 (s, 1H).

Example 50: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-naphthylcarbamate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 37. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.20 (s, 3H); 1.28 (d, 3H); 1.96 (dd, 1H); 2.07 (t, 1H); 2.48 (s, 6H); 2.66 (t, 1H); 3.01 (m, 1H); 3.37 (m, 1H); 3.95 (d, 1H); 4.70 (m, 1H); 4.87 (dd, 1H); 5.42 (s, 1H); 7.38 (t, 1H); 7.46 (t, 1H); 7.55 (d, 1H); 7.82 (m, 3H); 8.10 (s, 1H); 8.14 (s, 1H); 10.01 (s, 1H).

Example 51: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-tert-butyl-6-methylphenylcarbamate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 37. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.14 (s, 3H); 1.20-1.42 (m, 12H); 1.92 (dd, 1H); 2.05 (m, 1H); 2.25 (s, 3H); 2.52 (s, 6H); 2.62 (m, 1H); 2.95 (m, 1H); 3.36 (m, 1H); 3.88 (m, 1H); 4.80-4.95 (m, 2H); 5.40 (s, 1H); 7.13 (m, 2H); 7.22 (s, 1H); 8.13 (s, 1H); 8.69 (s, 1H).

Example 52: 8-(dimethylamino)-3,10a -dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxa-cycloundecin-9-yl 2,5-dimethoxyphenylcarbamate:

This compound is obtained by a procedure similar to that described for the synthesis of the compound of Example 37. The expected product is obtained in the form of a white powder.

NMR-¹H (DMSO): 1.17 (s, 3H); 1.27 (d, 3H); 1.94 (dd, 1H); 2.06 (m, 1H); 2.48 (s, 6H); 2.64 (t, 1H); 2.98 (m, 1H); 3.33 (m, 1H); 3.69 (s, 3H); 3.76 (s, 3H); 3.89 (d, 1H); 4.68 (m, 1H); 4.80 (dd, 1H); 5.40 (s, 1H); 6.63 (d, 1H); 6.94 (d, 1H); 7.32 (s, 1H); 8.12 (s, 1H); 8.58 (s, 1H).

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

The usefulness of the compounds of the invention can be demonstrated in particular by the effect of a treatment with these compounds on:

- the incorporation of cytosine labelled with ³²P in a DNA fragment in the presence of DNA polymerase of *E. Coli* (acellular system);
- the incorporation of tritiated thymidine in the DNA of HT29 tumor cells in division over a period of 3 hours (cell system); and
- the proliferation of two human cell lines Mia-Paca2 and DU145.

1) Procedures

Cell lines

DU-145 (human prostate cancer cells), HT29 (cancer of the colon) and Mia-PaCa2 (human pancreatic cancer cells) were acquired from the American Tissue Culture Collection (Rockville, Maryland, USA).

5 *Incorporation of deoxycytidine 5'-[alpha-³²P]-triphosphate into a DNA in the presence of DNA polymerase in an acellular system*

Labelling of the DNA is carried out on a DNA fragment which incorporates nucleotides by way of the activity of the DNA polymerase enzyme. From these nucleotides, the dCTP is labelled with radioactive phosphorus (³²P).

10 Plasmidal DNA (pc DNA 3, invitrogen, Netherlands) is diluted to a concentration of 2 ng in 45 µl of TE solution (10 mM Tris-HCl, pH 8, 1mM EDTA) and denatured by heating to 100 °C for 10 minutes before being replaced directly in ice. The denatured DNA is placed in the tube which contains the buffer solution of dATP, dGTP, dTTP, the Klenow DNA polymerase enzyme and the random primers (Rediprime II random prime labelling system, RPN 1633, RPN 1634, Amersham pharmacia biotech). 2 µl of
15 Redivue deoxycytidine 5'-[alpha-³²P]-triphosphate (250 µCi specific activity Amersham, Orsay, France) is added to start the reaction. The reaction is carried out in the presence or absence of the compound to be tested for 10 minutes at 37°. The reaction is stopped by adding 5 µl of EDTA (0.2M). The labelled DNA is recovered in 200 µl of isopropanol after centrifugation for 10 minutes at 12,000 rpm then washed
20 with 70% ethanol. After drying completely, the DNA is solubilized in 50 µl of TE. 10 µL is counted in 5 ml of scintillator (Instagel plus and scintillation counter Packard, Rungis, France). The results are expressed as a percentage of the inhibition of incorporation of the labelled nucleotide in the sample with respect to the control: 100 – [(DPM of the sample treated/ control DPM) x 100].

25 *Incorporation of thymidine labelled with tritium into DNA cells in exponential growth phase*

HT29 cells are seeded in 96-well plates (culturPlate-96, Packard, Rungis, France) (4000 cells per well) with the medium (DME, Gibco BRL, Cergy-Pontoise, France) complemented with 10% of foetal calf serum, Gibco BRL, Cergy-Pontoise, France). On
30 day 3, the medium is removed and replaced with medium containing the tritiated thymidine (5'-thymidine TRK.328, 1 mCi, 0.6 µCi / well, Amersham, Orsay, France) with or without the compound. The treatments are carried out for 3 hours. The medium is then removed and the cells are washed twice with 200µl of PBS (Gibco BRL, Cergy-Pontoise, France). The lysis solution (SDS 1.25%, EDTA 5 mM) is added for 10
35 minutes at ambient temperature, then 75 µl of scintillating liquid (microscint 40,

Packard, Rungis, France) is added. The plates are read using Topcount (Packard, Rungis, France). These tests are carried out in duplicate and the results are expressed with respect to the incorporation of the labelled nucleotide in the sample treated with the compound over the incorporation of the labelled nucleotide in the control sample (sample DPM / control DPM).

Measurement of cell proliferation

The cells placed in 80 μ l of Dulbecco's modified Eagle medium (Gibco-BRL, Cergy-Pontoise, France) completed with 10% of foetal calf serum inactivated by heating (Gibco-BRL, Cergy-Pontoise, France), 50000 units/l of penicillin and 50 mg/l streptomycin (Gibco-BRL, Cergy-Pontoise, France), and 2 mM of glutamine (Gibco-BRL, Cergy-Pontoise, France) were seeded on a 96-well plate on day 0. The cells were treated on day 1 for 96 hours with increasing concentrations of each of the compounds to be tested. At the end of the of this period, quantification of the cell proliferation is evaluated by a colorimetric test based on the cleavage of the tetrazolium salt WST1 by mitochondrial dehydrogenases in viable cells leading to the formation of formazan (Boehringer Mannheim, Meylan, France). These tests are carried out in duplicate with 8 determinations per concentration tested. The products are solubilised in dimethylsulphoxide (DMSO) at 10^{-2} M and finally used in culture with 0.5% DMSO.

2) Results

At a concentration of 100 μ g/ml, the compound of Example 16, like dihydromikanolide, inhibits the activity of DNA polymerase in an acellular system (Table I).

% inhibition of incorporation	
Dihydromikanolide	77 $\pm$ 11
Example 16	70 $\pm$ 8

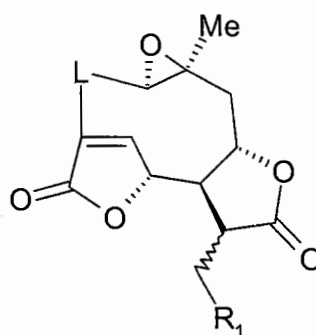
Table I

Moreover, the compound of Example 16, like dihydromikanolide, inhibits the incorporation of tritiated thymidine in the DNA of human HT29 cells (Table II).

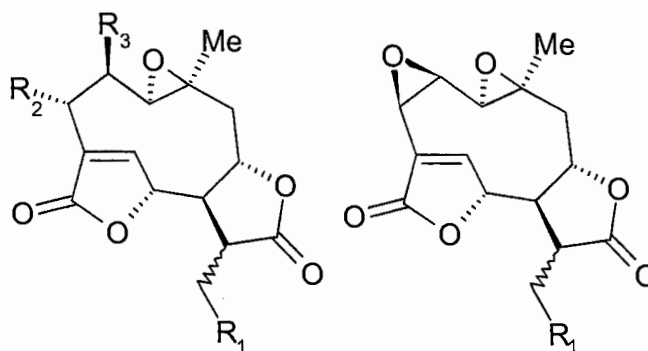
(sample dpm / control dpm)			
Concentration $\mu\text{g/ml}$	100	50	25
Dihydromikanolide	0.14	0.22	0.98
Example 16	0.52	0.58	0.71

Table II

Finally, the compounds of Examples 1 to 3, 9, 16, 18, 22, 24 to 32 and 39 to 43 inhibit the proliferation of DU-145 cell lines with an IC_{50} inhibitory concentration lower than or equal to 30 μM , whereas the compounds of Examples 1 to 10, 12, 16 to 20, 22, 24 to 37 and 39 to 44 inhibit the proliferation of the Mia-Paca2 cell lines with an IC_{50} inhibitory concentration lower than or equal to 30 μM .

Claims**1. Compound of general formula (I)****(I)**

corresponding to general sub-formulae (I)₁ and (I)₂

**(I)₁****(I)₂**

in which

5 R_1 represents a hydrogen atom or an SR_4 or NR_4R_5 radical;

R_2 represents SR_6 or NR_6R_7 ;

R_3 represents OH , $O(CO)R_{14}$, $OSiR_{15}R_{16}R_{17}$, $O(CO)OR_{18}$ or $O(CO)NHR_{18}$;

R_4 and R_6 represent, independently, an alkyl radical, a cycloalkyl, cycloalkylalkyl, hydroxyalkyl radical or also one of the aryl or aralkyl radicals optionally substituted on

their aryl group by one or more radicals chosen from the alkyl, hydroxy or alkoxy radicals,

R₅ and R₇ represent, independently, a hydrogen atom, an alkyl radical, a cycloalkyl, cycloalkylalkyl, hydroxyalkyl radical or also one of the aryl or aralkyl radicals
 5 optionally substituted on their aryl group by one or more radicals chosen from the alkyl, hydroxy or alkoxy radicals,

R₄ and R₅ being able to form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional members being chosen from the -CR₈R₉-, -NR₁₀-, -O- and -S- radicals, it being understood however that it there can
 10 only be one member chosen from -O- or -S- in said heterocycle,

and R₆ and R₇ being able to form together with the nitrogen atom which carries them a heterocycle with 5 to 7 members, the additional members being chosen from the -CR₁₁R₁₂-, -NR₁₃-, -O- and -S- radicals, it being understood however that there can only be one member chosen from -O- or -S- in said heterocycle,

15 R₈, R₁₀, R₁₁ and R₁₃ represent, independently each time they are involved, a hydrogen atom or an alkyl, alkoxycarbonyl or aralkyl radical,

R₉ and R₁₂ representing, independently each time they are involved, a hydrogen atom or each of R₉ and R₁₂ being able to form respectively together with R₈ and R₁₁ an -O-(CH₂)₂-O- radical attached on either side to the carbon atom which carries it, such a
 20 radical only being present however once at most per NR₄R₅ or NR₆R₇ radical, represent, independently each time they are involved, a hydrogen atom or an alkyl radical;

R₁₄ represents an alkyl, cycloalkyl or adamantyl radical or one of the aryl, heteroaryl, aralkyl or heteroaralkyl radicals optionally substituted on their aryl or heteroaryl group
 25 by one or more radicals chosen from a halogen atom and the alkyl, haloalkyl, nitro, hydroxy, alkoxy, alkylthio or phenyl radicals;

or also R₁₄ is such that R₁₄-COOH represents a natural amino acid or the optical enantiomer of such an amino acid;

R₁₅, R₁₆ and R₁₇ represent, independently, an alkyl radical or a phenyl radical;

30 R₁₈ represents an alkyl, cycloalkyl or adamantyl radical or one of the aryl, heteroaryl, aralkyl or heteroaralkyl radicals optionally substituted on their aryl or heteroaryl group by one or more radicals chosen from a halogen atom and the alkyl, haloalkyl, nitro, hydroxy, alkoxy, alkylthio or phenyl radicals;

it being understood however that when the compounds correspond to general sub-
 35 formula (I)₂, then R₁ does not represent a hydrogen atom;

- 43 -

or a salt of a compound of general formula (I).

2. Compound according to claim 1, characterized in that it corresponds to general sub-formula (I)₁ or is a salt of such a compound.

3. Compound according to claim 2, characterized in that:

- 5 • R₁ represents a hydrogen atom or an NR₄R₅ radical;
- R₂ representing an NR₆R₇ radical;
- R₃ represents OH or an O(CO)R₁₄, OSiR₁₅R₁₆R₁₇ or O(CO)NHR₁₈ radical.

4. Compound according to claim 1, characterized in that it corresponds to general sub-formula (I)₂.

10 5. Compound according to claim 1, characterized in that it is one of the following compounds:

- 12-diisopropylaminomethyl-7-methyl-3,6,10,15-tetraoxapentacyclo
[12.2.1.0^{2,4}.0^{5,7}.0^{9,13}]heptadec-1(17)-ene-11,16-dione;
- 12-dimethylamino-3-dimethylaminomethyl-11-hydroxy-8-methyl-
15 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-benzyl(methyl)amino-3-benzyl(methyl)aminomethyl-11-hydroxy-8-methyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-8-methyl-12-morpholino-3-morpholinomethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 20 - 12-dimethylamino-11-hydroxy-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-3,8-dimethyl-12-(4-methylpiperidino)-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-3,8-dimethyl-12-pyrrolidino-
25 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- ethyl 1-[11-hydroxy-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-12-yl]-
4-piperidinecarboxylate;
- 12-(4-benzylpiperidino)-11-hydroxy-3,8-dimethyl-
30 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;

- 11-hydroxy-3,8-dimethyl-12-piperidino-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)-11-hydroxy-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 5 - 11-hydroxy-3,8-dimethyl-12-morpholino-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-(*tert*-butyldimethylsiloxy)-12-dimethylamino-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-
10 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl acetate;
- 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-11-phenylcarbonyloxy-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene;
- ethyl 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl carbonate;
- 15 - 11-hydroxy-12-isobutylsulphanyl-3-isobutylsulphanylmethyl-8-methyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-12-isobutylsulphanyl-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
20 5,9,15-trioxatetracyclo[11.2.1.02.6.08.10]hexadec-13(16)-en-11-yl benzoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.02.6.08.10]hexadec-13(16)-en-11-yl acetate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl
25 cyclohexanecarboxylate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-fluorobenzoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl heptanoate;
- 30 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-
(trifluoromethyl)benzoate;

- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thiophenecarboxylate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 3,3-dimethylbutanoate;
- 5 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 1-benzothiophene-2-carboxylate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-furoate;
- 10 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 5-nitro-2-furoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.02.6.08.10]hexadec-13(16)-en-11-yl 2-thienylacetate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.02.6.08.10]hexadec-13(16)-en-11-yl phenoxyacetate;
- 15 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 4-*tert*-butylphenylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-2-ylcarbamate;
- 20 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-methoxyphenylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-c]oxireno[f]oxacycloundecin-9-yl 2(methylthio)phenylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-ethoxyphenylcarbamate;
- 25 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-3-ylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylcarbamate;
- 30 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-c]oxireno[f]oxacycloundecin-9-yl *N*-(*ter*-butoxycarbonyl)glycinate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-3-ylacetate;

- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylacetate;
 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thiophene-3-carboxylate;
 - 5 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 5-phenylthien-2-ylcarbamate;
 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 1-adamantylcarbamate;
 - 10 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-naphthylcarbamate;
 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-*tert*-butyl-6-methylphenylcarbamate;
 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2,5-dimethoxyphenylcarbamate;
 - 15 or a salt of one of the latter.
6. As a medicament, a compound of general formula (I) as defined in claim 1 or a pharmaceutically acceptable salt of the latter.
7. Medicament according to claim 6, characterized in that it is one of the following compounds:
- 20 - 12-diisopropylaminomethyl-7-methyl-3,6,10,15-tetraoxapentacyclo[12.2.1.0^{2,4}.0^{5,7}.0^{9,13}]heptadec-1(17)-ene-11,16-dione;
 - 12-dimethylamino-3-dimethylaminomethyl-11-hydroxy-8-methyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
 - 12-benzyl(methyl)amino-3-benzyl(methyl)aminomethyl-11-hydroxy-8-methyl-
 - 25 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
 - 11-hydroxy-8-methyl-12-morpholino-3-morpholinomethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
 - 12-dimethylamino-11-hydroxy-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
 - 30 - 11-hydroxy-3,8-dimethyl-12-(4-methylpiperidino)-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;

- 11-hydroxy-3,8-dimethyl-12-pyrrolidino-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- ethyl 1-[11-hydroxy-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-12-yl]-
5 4-piperidinecarboxylate;
- 12-(4-benzylpiperidino)-11-hydroxy-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-3,8-dimethyl-12-piperidino-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 10 - 12-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)-11-hydroxy-3,8-dimethyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-3,8-dimethyl-12-morpholino-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-(*tert*-butyldimethylsiloxy)-12-dimethylamino-3,8-dimethyl-
15 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl acetate;
- 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-11-phenylcarbonyloxy-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene;
- 20 - ethyl 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-ylcarbonate;
- 11-hydroxy-12-isobutylsulphanyl-3-isobutylsulphanylmethyl-8-methyl-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-12-isobutylsulphanyl-3,8-dimethyl-
25 5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.02.6.08.10]hexadec-13(16)-en-11-yl benzoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.02.6.08.10]hexadec-13(16)-en-11-yl acetate;
- 30 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-
5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl
cyclohexanecarboxylate;

- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-fluorobenzoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl heptanoate;
- 5 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-(trifluoromethyl)benzoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thiophenecarboxylate;
- 10 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 3,3-dimethylbutanoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 1-benzothiophene-2-carboxylate;
- 15 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-furoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 5-nitro-2-furoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thienylacetate;
- 20 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl phenoxyacetate;
- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 4-*tert*-butylphenylcarbamate;
- 25 - 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-2-ylcarbamate;
- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-methoxyphenylcarbamate;
- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2(methylthio)phenylcarbamate;
- 30 - 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-ethoxyphenylcarbamate;

- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl thien-3-ylcarbamate;
- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylcarbamate;
- 5 - 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-*c*]oxireno[f]oxacycloundecin-9-yl *N*-(*ter*-butoxycarbonyl)glycinate;
- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl thien-3-ylacetate;
- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylacetate;
- 10 - 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl thiophene-3-carboxylate;
- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 5-phenylthien-2-ylcarbamate;
- 15 - 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 1-adamantylcarbamate;
- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 2-naphthylcarbamate;
- 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 2-*tert*-butyl-6-methylphenylcarbamate;
- 20 - 8-(dimethylamino)-3.10a-dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-*c*]oxireno[f]oxacycloundecin-9-yl 2,5-dimethoxyphenylcarbamate;

or a pharmaceutically acceptable salt of one of the latter.

8. Pharmaceutical composition containing, as active ingredient, a compound of general formula (I) as defined in claim 1 or a pharmaceutically acceptable salt of the latter.

9. Pharmaceutical composition according to claim 8, characterized in that it contains, as active ingredient, one of the following compounds:

- 12-diisopropylaminomethyl-7-methyl-3,6,10,15-tetraoxapentacyclo[12.2.1.0^{2,4}.0^{5,7}.0^{9,13}]heptadec-1(17)-ene-11,16-dione;
- 30 - 12-dimethylamino-3-dimethylaminomethyl-11-hydroxy-8-methyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;

- 12-benzyl(methyl)amino-3-benzyl(methyl)aminomethyl-11-hydroxy-8-methyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-8-methyl-12-morpholino-3-morpholinomethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 5 - 12-dimethylamino-11-hydroxy-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-3,8-dimethyl-12-(4-methylpiperidino)-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-3,8-dimethyl-12-pyrrolidino-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 10 - ethyl 1-[11-hydroxy-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-12-yl]-4-piperidinecarboxylate;
- 12-(4-benzylpiperidino)-11-hydroxy-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 15 - 11-hydroxy-3,8-dimethyl-12-piperidino-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 12-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)-11-hydroxy-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 20 - 11-hydroxy-3,8-dimethyl-12-morpholino-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-(*tert*-butyldimethylsiloxy)-12-dimethylamino-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl acetate;
- 25 - 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-11-phenylcarbonyloxy-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene;
- ethyl 3,8-dimethyl-12-(4-methylpiperidino)-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl carbonate;
- 30 - 11-hydroxy-12-isobutylsulphanyl-3-isobutylsulphanylmethyl-8-methyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;
- 11-hydroxy-12-isobutylsulphanyl-3,8-dimethyl-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-ene-4,14-dione;

- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl benzoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl acetate;
- 5 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl cyclohexanecarboxylate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-fluorobenzoate;
- 10 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl heptanoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 4-(trifluoromethyl)benzoate;
- 15 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thiophenecarboxylate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 3,3-dimethylbutanoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 1-benzothiophene-2-carboxylate;
- 20 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-furoate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 5-nitro-2-furoate;
- 25 - 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl 2-thienylacetate;
- 12-(dimethylamino)-3,8-dimethyl-4,14-dioxo-5,9,15-trioxatetracyclo[11.2.1.0^{2,6}.0^{8,10}]hexadec-13(16)-en-11-yl phenoxyacetate;
- 30 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 4-*tert*-butylphenylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-2-ylcarbamate;

- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-methoxyphenylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-c]oxireno[f]oxacycloundecin-9-yl 2(methylthio)phenylcarbamate;
- 5 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-ethoxyphenylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-3-ylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylcarbamate;
- 10 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-c]oxireno[f]oxacycloundecin-9-yl *N*-(*ter*-butoxycarbonyl)glycinate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thien-3-ylacetate;
- 15 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 1-benzothien-3-ylacetate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl thiophene-3-carboxylate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 5-phenylthien-2-ylcarbamate;
- 20 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 1-adamantylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-methenofuro[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-naphthylcarbamate;
- 25 - 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-c]oxireno[f]oxacycloundecin-9-yl 2-*tert*-butyl-6-methylphenylcarbamate;
- 8-(dimethylamino)-3,10a-dimethyl-2,6-dioxodecahydro-4,7-metheno-furo[3,2-c]oxireno[f]oxacycloundecin-9-yl 2,5-dimethoxyphenylcarbamate;

or a pharmaceutically acceptable salt of one of the latter.

- 30 **10.** Use of a compound of general formula **(I)** as defined in claim 1 or a pharmaceutically acceptable salt of the latter for preparing a medicament intended to inhibit DNA polymerases.

11. Use of a compound of general formula **(I)** as defined in claim 1 or a pharmaceutically acceptable salt of the latter for preparing a medicament intended to treat diseases due to abnormal cell proliferation.
12. Use according to claim 11, characterized in that the disease due to abnormal cell proliferation is cancer.
13. Use according to claim 11, characterized in that the disease due to abnormal cell proliferation is chosen from atherosclerosis, benign hyperplasia of the prostate and fibroses.
14. Use of a compound of general formula **(I)** as defined in claim 1 or a pharmaceutically acceptable salt of the latter for preparing a medicament intended to treat viral diseases.
15. Use of a compound of general formula **(I)** as defined in claim 1 or a pharmaceutically acceptable salt of the latter for preparing a medicament intended to treat parasitic diseases.
16. Use of a compound of general formula **(I)** as defined in claim 1 or a pharmaceutically acceptable salt of the latter for preparing a medicament intended to treat diseases of bacterial origin.