

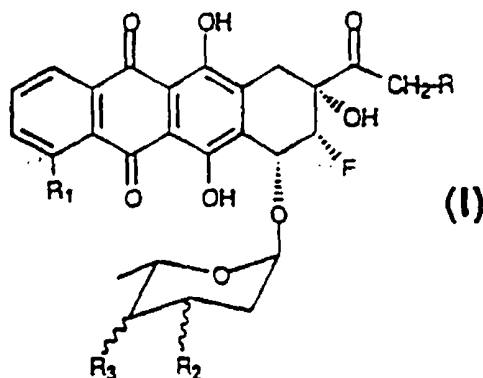


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8-FLUORO-ANTHRACYCLINES, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM
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EP 457215
WO 95/09173
- (57) Claim

1. Compounds of general formula (I)



(I)

wherein:

R is chosen in the group consisting of H, OH, OR₄ wherein R₄ is - COR₇,

wherein R₇ = H, alkyl C₁-C₅;

R₁ is chosen in the group consisting of: H, OH, OCH₃;

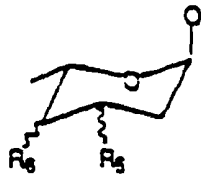
R₂ is chosen in the group consisting of: H, OH, NH₂

R₃ is chosen in the group consisting of: H, OH, NH₂, residue of formula

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(A)

wherein R_5 and R_6 , same or different, are chosen in the group consisting of: H, OH, NH_2 and the symbol (\sim) indicates that the substituents R_2 , R_3 , R_5 and R_6 can be in the axial or equatorial configuration; and wherein the groups 8-F and 9-OH are in position cis; and their pharmaceutically acceptable salts.

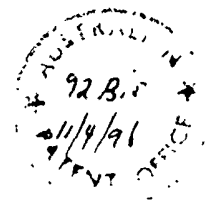
7. Method for the treatment of tumors wherein pharmaceutically acceptable quantities of a compound of formula (I) according to claim 1 are administered to the patient.

8-Fluoro-anthracyclines. processes for their preparation and pharmaceutical compositions containing them.

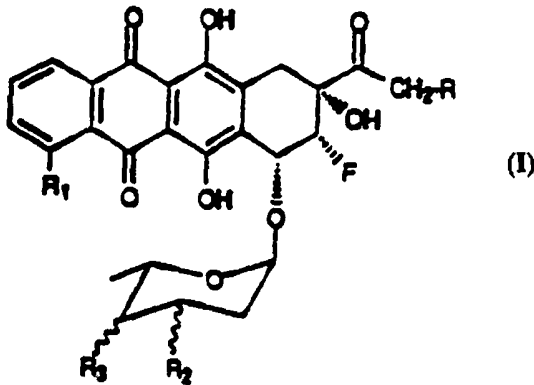


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see folio 3



(54) Title: 8-FLUORO-ANTHRACYCLINES, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(57) Abstract

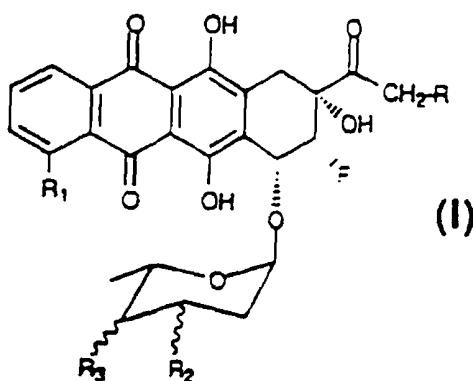
8-fluoro-anthracyclines of formula (I) having cis-stereochemistry between the groups 8-F and 9-OH, are described, such compounds present anti-tumor activity. Their preparation and pharmaceutical compositions containing them are also described.

8-Fluoro-anthracyclines, processes for their preparation and pharmaceutical compositions containing them.

Field of the invention

Glycosidic derivatives of 8-fluoro-anthracyclinone of general formula (I)

5 are described:



(I)

wherein:

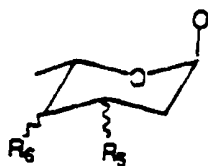
R is chosen in the group consisting of H, OH, OR₄ wherein R₄ is chosen in the group consisting of CHO, COCH₃, acyl derivative of a carboxylic acid containing up to 6 carbon atoms;

10 R₁ is chosen in the group consisting of: H, OH, OCH₃;

R₂ is chosen in the group consisting of: H, OH, NH₂

R₃ is chosen in the group consisting of: H, OH, NH₂, residue of formula

(A)



(A)

wherein R₅ and R₆, same or different, are chosen in the group consisting of: H, OH, NH₂ and the symbol (∩) indicates that the substituents R₂,

15

R₃, R₅ and R₆ can be in the axial or equatorial configuration;

and wherein the groups 8-F and 9-OH are in position cis;

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their pharmaceutically acceptable salts, processes for their preparation and pharmaceutical compositions containing them.

State of the art

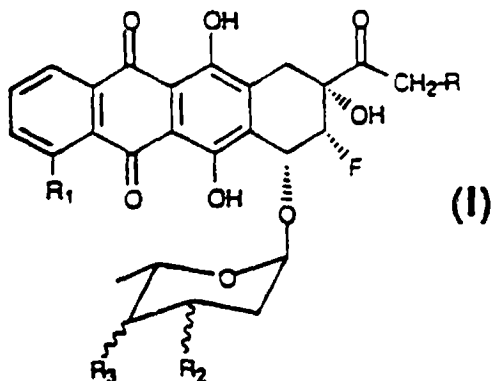
Daunorubicin (daunomicin) and 4-demethoxydaunorubicin (idarubicin), and their derivatives containing an hydroxylated lateral chain (doxorubicin), are glycosides presenting well-known anti-tumoral properties; their preparation and use were already described (F. Arcamone "Doxorubicin: Anticancer Antibiotics" Medicinal Chemistry Series Vol. 17, Academic press 1981).

The 8-fluoro-anthracyclines are a class of anthracyclines already known (see for example: EP-A-0436474; EP-A-0457215; WO 95/09173) for their higher activity and selectivity in respect of the corresponding non-fluorinated compounds.

It was now surprisingly found, and this is an object of the present application, that when the two substituents 8-F and 9-OH have cis-stereochemistry, the corresponding derivatives are surprisingly more active, especially in respect of tumoral cells resistant against the already known compounds.

Detailed description of the invention

The present invention refers to glycosidic derivatives of 8-fluoroanthracyclinone of general formula



(I)

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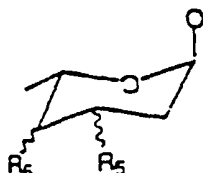
wherein:

R is chosen in the group consisting of H, OH, OR₄, wherein R₄ is - COR₇,
wherein R₇ = H, alkyl C₁-C₅;

R₁ is chosen in the group consisting of: H, OH, OCH₃;

5 R₂ is chosen in the group consisting of: H, OH, NH₂

R₃ is chosen in the group consisting of: H, OH, NH₂, residue of formula
(A)



10 (A)

wherein R₅ and R₆, same or different, are chosen in the group consisting
of: H, OH, NH₂ and the symbol (~~~~) indicates that the substituents R₂,
R₃, R₅ and R₆ can be in the axial or equatorial configuration;

and wherein the groups 8-F and 9-OH are in position cis;

15 their pharmaceutically acceptable salts, processes for their preparation
and pharmaceutical compositions containing them.

More particularly the present invention refers to the following
compounds:

1) 4-demethoxy-8-(R)-fluoro-daunorubicin

20 (I: R = R₁ = H; R₂ = NH₂; R₃ = OH)

2) 4-demethoxy-8-(R)-fluoro-3'-deamino-4'-deoxy-4'-amino-daunorubicin (I: R
= R₁ = R₂ = H; R₃ = NH₂)

3) 4-demethoxy-8-(R)-fluoro-3'-deamino-4'-deoxy-4'-epi-amino-daunorubicin
(I: R = R₁ = R₂ = H; R₃ = NH₂)

25 4) 4-demethoxy-8-(R)-fluoro-4'-epi-daunorubicin (I: R = R₁ = H;
R₂ = NH₂; R₃ = OH)

5) 4-demethoxy-8-(R)-fluoro-7-(daunosaminyl-fucosyl)-daunorubicinone (I:



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$R = R_1 = H; R_3 = A; R_2 = R_6 = OH; R_5 = NH_2$)

6) 4-demethoxy-8-(R)-fluoro-7-(daunosaminy-ramnosyl)-daunorubicinone (I:

$R = R_1 = H; R_3 = A; R_2 = R_6 = OH; R_5 = NH_2$)

7) 4-demethoxy-8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-

5 fucosyl)-daunorubicinone (I: $R = R_1 = R_5 = H; R_3 = A; R_2 = OH; R_6 = NH_2$)

8) 4-demethoxy-8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-

ramnosyl)-daunorubicinone (I: $R = R_1 = R_5 = H; R_3 = A; R_2 = OH; R_6 = NH_2$)

9) 4-demethoxy-8-(R)-fluoro-7-(fucosyl-4'-O-fucosyl)-daunorubicinone (I:

$R = R_1 = H; R_3 = A; R_2 = R_5 = R_6 = OH$)

10) 4-demethoxy-8-(R)-fluoro-7-fucosyl-4'-O-ramnosyl)-daunorubicinone (I:

$R = R_1 = H; R_3 = A; R_2 = R_5 = R_6 = OH$) 11) 8-(R)-fluoro-daunorubicin (I:

$R = H; R_1 = OCH_3; R_2 = NH_2; R_3 = OH$)

12) 8-(R)-fluoro-3'-deamino-4'-deoxy-4'-amino-daunorubicin (I: $R = R_2 = H;$

$R_1 = OCH_3; R_3 = NH_2$)

13) 8-(R)-fluoro-3'-deamino-4'-deoxy-4'-epi-amino-daunorubicin (I: $R = R_2$

$= H; R_1 = OCH_3; R_3 = NH_2$)

14) 8-(R)-fluoro-4'-epi-daunorubicin (I: $R = H; R_1 = OCH_3; R_2 =$

$NH_2; R_3 = OH$)

15) 8-(R)-fluoro-7-(daunosaminy-fucosyl)-daunorubicinone (I: $R = H; R_1 =$

20 $OCH_3; R_3 = A; R_2 = R_6 = OH; R_5 = NH_2$)

16) 8-(R)-fluoro-7-(daunosaminy-ramnosyl)-daunorubicinone (I: $R = H; R_1$

$= OCH_3; R_3 = A; R_2 = R_6 = OH; R_5 = NH_2$)

17) 8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-fucosyl)-

daunorubicinone (I: $R = R_5 = H; R_1 = OCH_3; R_3 = A; R_2 = OH; R_6 = NH_2$)

25 18) 8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-ramnosyl)-

daunorubicinone (I: $R = R_5 = H; R_1 = OCH_3; R_3 = A; R_2 = OH; R_6 = NH_2$)

19) 8-(R)-fluoro-7-(fucosyl-4'-O-fucosyl)-daunorubicinone (I: $R = H; R_1 =$

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OCH₃; R₃ = A; R₂ = R₅ = R₆ = OH)

20) 8-(R)-fluoro-7-fucosyl-4'-O-ramnosyl)-daunorubicinone (I: R = H; R₁ = OCH₃; R₃ = A; R₂ = R₅ = R₆ = OH)

21) 4-demethoxy-8-(R)-fluoro-doxorubicin and its esters in C-14 (I: R = R₃ = OH; R₁ = H; R₂ = NH₂)

22) 4-demethoxy-8-(R)-fluoro-3'-deamino-4'-deoxy-4'-amino-doxorubicin and its esters in C-14 (I: R = OH; R₁ = R₂ = H; R₃ = NH₂)

23) 4-demethoxy-8-(R)-fluoro-3'-deamino-4'-deoxy-4'-epi-amino-doxorubicin and its esters in C-14 (I: R = OH; R₁ = R₂ = H; R₃ = NH₂)

24) 4-demethoxy-8-(R)-fluoro-4'-epi-doxorubicin and its esters in C-14 (I: R = R₃ = CH; R₁ = H; R₂ = NH₂)

25) 4-demethoxy-8-(R)-fluoro-7-(daunosaminyl-fucosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = R₆ = OH; R₃ = A; R₁ = H; R₅ = NH₂)

26) 4-demethoxy-8-(R)-fluoro-7-(daunosaminyl-ramnosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = R₆ = OH; R₃ = A; R₁ = H; R₅ = NH₂)

27) 4-demethoxy-8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-fucosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = OH; R₃ = A; R₁ = R₅ = H; R₆ = NH₂)

28) 4-demethoxy-8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-ramnosyl)-doxorubicinone (I: R = R₂ = OH; R₃ = A; R₁ = R₅ = H; R₆ = NH₂)

29) 4-demethoxy-8-(R)-fluoro-7-(fucosyl-4'-O-fucosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = R₅ = R₆ = OH; R₃ = A; R₁ = H)

30) 4-demethoxy-8-(R)-fluoro-7-(fucosyl-4'-O-ramnosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = R₅ = R₆ = OH; R₃ = A; R₁ = H)

31) 8-(R)-fluoro-doxorubicin and its esters in C-14

(I: R = R₃ = OH; R₁ = OCH₃; R₂ = NH₂)

32) 8-(R)-fluoro-3'-deamino-4'-deoxy-4'-amino-doxorubicin and its esters in

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C-14 (I: R = OH; R₁ = OCH₃; R₂ = H; R₃ = NH₂)

33) 8-(R)-fluoro-3'-deamino-4'-deoxy-4'-epi-amino-doxorubicin and its esters in C-14 (I: R = OH; R₁ = OCH₃; R₂ = H; R₃ = NH₂)

34) 8-(R)-fluoro-4'-epi-doxorubicin and its esters in C-14 (I: R = R₃ = OH; R₁ = OCH₃; R₂ = NH₂)

35) 8-(R)-fluoro-7-(daunosaminyl-fucosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = R₆ = OH; R₁ = OCH₃; R₃ = A; R₅ = NH₂)

36) 8-(R)-fluoro-7-(daunosaminyl-ramnosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = R₆ = OH; R₃ = A; R₁ = OCH₃; R₅ = NH₂)

37) 8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-fucosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = OH; R₁ = OCH₃; R₃ = A; R₅ = H; R₆ = NH₂)

38) 8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-ramnosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = OH; R₁ = OCH₃; R₃ = A;

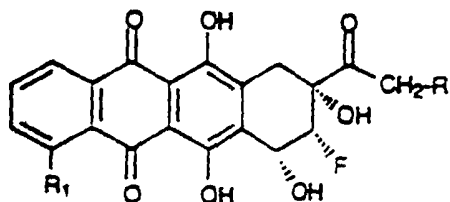
R₅ = H; R₆ = NH₂)

39) 8-(R)-fluoro-7-(fucosyl-4'-O-fucosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = R₅ = R₆ = OH; R₃ = A; R₁ = OCH₃)

40) 8-(R)-fluoro-7-fucosyl-4'-O-ramnosyl)-doxorubicinone and its esters in C-14 (I: R = R₂ = R₅ = R₆ = OH; R₁ = OCH₃; R₃ = A).

The compounds of formula (I) and their pharmaceutically acceptable salts are prepared by a process comprising the following steps.

Condensation between a 8-fluoro-anthracyclinone of formula (II):

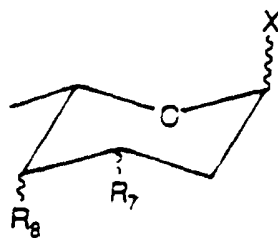


(II)

wherein R and R₁ are as above defined, and a compound of formula (III)

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(III)

wherein X is a leaving-group capable of generating, under the condensation conditions, a stable carbocation which can react with an hydroxyle in position C-7 of compound (II). Such leaving-group is suitably chosen among those used in the glycosidation reactions, for example halogen, p-nitro-benzoyloxy-group; R₇ is H or a group OH or NH₂ suitably protected; R₈ is H or OH or NH₂ suitably protected or a residue of formula (III'):

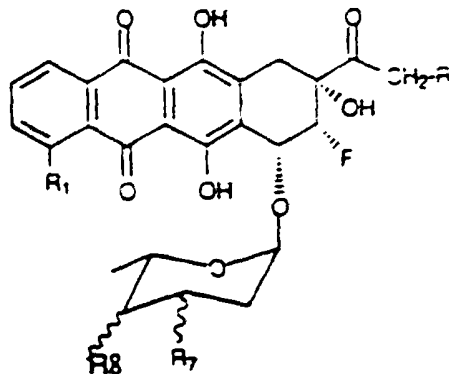


(III')

wherein R₉ and R₁₀, same or different, are chosen among H, OH and NH₂ suitably protected.

The groups OH are protected as p-nitrobenzoate or allyloxycarbonyle. The groups NH₂ are protected as allylcarboxamide or with trifluoroacetamide.

The symbol (~) indicates that the substituents R₇, R₈, R₉, R₁₀ can be in the axial and/or equatorial configuration. The condensation between compounds (II) and (III) gives the glycoside of formula (IV)



(IV)

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The glycosidation reaction is performed in an organic solvent in the presence of a condensing agent. The condensing agents used are, for example, silver trifluoromethanesulfate, silver perchlorate, mixtures of quicksilver oxide or bromide, boron halogenide, ion-exchanging resin as
5 Amberlite.

Preferably the glycosidation reaction is carried out using an inert organic solvent as benzene, toluene, ethylether, tetrahydrofuran, dioxan, chloroform, methylene chloride or dichloroethane and their mixtures.

The reaction temperature can vary between -40°C and 40°C , preferably
10 between -20°C and 20°C , and the time requested for the reaction can vary between 5 min. and 2 hours.

In the reaction mixture a dehydrator, as activated molecular sieves, can be present.

During the reaction, or at its end, an organic base as pyridine,
15 collidine, triethylamine can be added to the reaction mixture.

The removal of the protecting groups from the groups OH and/or NH_2 in the compounds of formula (IV), in order to obtain the wanted compounds of formula (I), can vary according to the protecting group used.

When R_7 and/or R_8 and/or R_9 and/or R_{10} , same or different, are a NH_2
20 group protected as trifluoroacetamide and/or a OH group protected as p-nitrobenzoate, the deprotecting reaction is carried out in a polar solvent as water, methanole, ethanole, pyridine, dimethylformamide or their mixtures in the presence of a stoichiometric quantity, or an excess, of an inorganic base as NaOH, KOH, LiOH, $\text{Ba}(\text{OH})_2$ and their
25 carbonates. The reaction temperature can vary from 0°C to 50°C and the reaction-time can vary from 3 hours and 3 days.

When R_7 and/or R_8 and/or R_9 and/or R_{10} , same or different, are a NH_2

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group protected as allylcarboxamide and/or a group OH protected as allyloxycarbonate, the deprotection reaction is carried out in an inert solvent and in the presence of a metallic complex as (tetrakis-triphenylphosphine)Pd, as described for example in Tetrahedron Letters, 30 (1989), 3773 or (tetracarbonyl)Ni, as described for example in J.Org.Chem. 38 (1973) 3233.

If preferred the compounds of formula (I) wherein R_1 , R_2 and R_3 are as above defined and R is the group OH, can be prepared starting from glycosides of formula (I) or their pharmaceutically acceptable salts where R_1 , R_2 and R_3 and the symbol (\sim) are as above defined and R is H, by bromuration of the carbon atom in position 14 with bromine in chloroform followed by hydrolysis of the so obtained 14-bromo-derivatives with sodiumformiate at room temperature for 48 hours.

The same product can also be obtained by bromuration of the carbon atom in position 14, according to the above described procedure, of the aglycon of formula (II) wherein R_1 is as above defined and R is H. This compound, after hydrolysis, which transforms R in the group OH, is glycosilated with a compound of formula (III) as above defined by a glycosidation reaction as above described in order to obtain the wanted product.

If preferred, glycosides of formula (I) can be transformed in the corresponding pharmaceutically acceptable salts, for example hydrochlorides, by treatment with hydrochloric acid in methanol.

Another object of the present application are the 8-fluoro-anthracyclinones of formula (II) wherein the group 8-F and 9-OH are mutually in position cis and wherein R and R_1 are as above defined, and their preparation process.

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The process is illustrated in the joined Schema.

The first step is the bromofluoruration of an allyl alcohol of formula (V), wherein R_1 is as above defined, in order to obtain a compound of formula (VI).

5 The bromofluoruration of (V) can be carried out according to various methods, described in literature (ex. Gazz. Chim. It. 121 (1991) 537-545; J.O.C. 58 (1993) 2791-2796), for the bromo-fluoruration of the alkenes.

The second step is the epoxide formation, starting from bromidrine (VI), in order to obtain the compound of formula (VII) wherein R_1 is as above
10 defined. This reaction can be carried out using a strong base, according to the known methods described in literature in respect of this kind of reaction.

The third step is the opening of the epoxide in order to obtain the product of formula (VII) wherein R_1 is as above defined. Also in this
15 case the reaction methods are described in the literature referring to the opening of an epoxide to give a diol by acid catalysis, preferably mixtures of water, mineral acids and inert organic solvents.

The fourth step is the reaction of oxidation of diol (VIII) to the hydroxyketone of formula (IX). The oxidation reaction can be carried out
20 according to known procedures. Preferred are the methods comprising the use of dimethylsulfoxide, as for example the Moffat-oxidation reaction and similar, or of complexes pyridine-chrome, as the chlorochromate of pyridinium.

The last step is the transformation of the fluorohydroxyketone of formula
25 (IX) into the compound of formula (II). This can be carried out according to known methods as the bromuration and solvolysis, when necessary with the possible protection of the keto-group (Can. J. Chem. 49 (1973) 2712;

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J.A.C.S. 98 (1976) 1969; J.A.C.S. 98 (1976) 1967).

The present invention refers also to pharmaceutical compositions containing as active principle an anthracyclin-glycoside of formula (I) or a pharmaceutically acceptable salt thereof.

5 A therapeutically active quantity of a compound according to the present invention (between 2 and 20 mg/m² of body surface, or 0.05 - 0.5 mg/kg body weight if the product is administered endovenously, or 10 - 200 mg/m² of body surface or 0.25 - 5 mg/kg body weight in the case of oral administration) is combined with an inert vector. Conventional vectors
10 can be used and the composition is formulated according to known procedures.

Compositions suitable for endovenous or oral administration are preferred.

The compounds according to the invention are useful in the therapeutical
15 treatment in men and animals. In particular the compounds according to the invention are useful as anti-tumor agents for the administration of therapeutically active quantities of the compound to the patient under treatment.

In particular the compounds showed a surprising activity against a wide
20 number of solid tumors (for example: ovary, breast, lung, uterus tumor) also against those which developed resistance towards the known and normally used anti-tumor agents.

The following example are given to better illustrate the invention but have no limiting purpose.

25 EXAMPLE I

9-(1'-Hydroxyethyl)-7,10-dihydro-6,11-dihydroxy-8-fluoro-9-bromo-5,12-naphthacene-dione ((VI), R₁ = H).

- 12 -

To a suspension of 9-(1'-hydroxyethyl)-7,10-dihydro-6,11-dihydroxy-5,12-naphthacene dione ((V), $R_1 = H$) (9.4 g, 28 μ moles) in methylene chloride (900 ml), a solution of tetrabutylammonium-dihydrogen (18.4 g, at 55%; 33.6 μ moles) in methylene chloride is added under stirring at $-5^\circ C$,
5 thereafter, always at $-5^\circ C$ and maintaining the reactor in the darkness. N-bromo-succinimide (6.0 g; 33.6 μ moles) is added. The reaction goes on for 5 hours. Longer reaction time does not increase the yield. A solution of $NaHCO_3$ 10% is added up to neutral pH. The organic phase is dried on Na_2SO_4 , filtered and evaporated. The residue is purified by
10 flash chromatography using $CHCl_3$ as eluent.

3.6 g (yield 29%) of compound (VI) ($R_1 = H$) are obtained.

NMR ($CDCl_3$, δ): 1.45 (3H, d); 3.0-3.5 (2H, q); 3.2-3.4 (2H,
q); 3.93 (1H, m); 5.4-5.6 (1H, d); 7.90 (2H,
m); 8.30 (2H, m); 13.36 (1H, s); 13.46 (1H,
15 s).

By analogous procedure

4-methoxy-9-(1'-hydroxyethyl)-7,10-dihydro-6,11-dihydroxy-8-fluoro-9-bromo-5,12-naphthacene dione ((VI), $R_1 = OCH_3$) was obtained.

EXAMPLE II

20 9-(9-1'-Epoxyethyl)-7,10-dihydro-6,11-dihydroxy-8-fluoro-5,12-naphthacene-dione ((VII), $R_1 = H$).

A solution of 9-(1'-hydroxyethyl)-7,10-dihydro-6,11-dihydroxy-8-fluoro-9-bromo-5,12-naphthacene-dione (3.6 g, 8.3 μ moles), obtained according to the Example 1, in $NaOH$ 5% (16 ml) is left under stirring for 2 hours at
25 room temperature. The reaction is treated with HCl 1N and the product extracted with $CHCl_3$; the organic phase is dried on Na_2SO_4 , filtered and evaporated. The obtained residue is purified by flash chromatography

- 13 -

using CHCl_3 as eluent. 1.6 g (yield 57%) of the title compound are obtained.

NMR (CDCl_3 , δ): 1.4 (3H, d); 2.62-3.48 (2H, q); 2.9-3.1 (2H, q); 3.26-3.68 (2H, m); 3.10 (1H, m); 4.80-
5 4.96 (1H, d); 7.80 (2H, m); 8.40 (2H, m);
13.35 (1H, s); 14.42 (1H, s).

By analogous procedure:

4-Methoxy-9-(9-1'-epoxyethyl)-7,10-dihydro-6,11-dihydroxy-8-fluoro-5,12-naphthacene-dione ((VII), $R_1 = \text{OCH}_3$)

10 ESEMPIO III

9-(1'-hydroxyethyl)-7,10-dihydro-6,9,11-trihydroxy-8-fluoro-5,12-naphthacene-dione ((VIII), $R_1 = \text{H}$).

To a solution of 9-(9-1'-Epoxyethyl)-7,10-dihydro-6,11-dihydroxy-8-fluoro-5,12-naphthacene-dione (1.6 g; 4.7 μmoles), obtained according to
15 example II, in dioxane (700 ml) H_2O (700 ml) is added and thereafter, maintaining the reactor in a bath at 0°C , oleum (700 ml) is slowly dropped therein. At the end of the oleum addition the temperature is left to raise up to room temperature and the solution is stirred for 6 h. A
20 solution of NaHCO_3 is added to the mixture up to neutral pH and the product is extracted with CH_2Cl_2 . The organic phase, dried on Na_2SO_4 , is evaporated. The title product is obtained (1.7 g; 100% yield).

NMR (CDCl_3 , δ): 1.40 (3H, d); 2.8-3.1 (2H, q); 3.0-3.3 (2H, q); 4.05 (1H, q); 5.0-5.2 (1H, q); 7.80
25 (2H, m); 8.30 (2H, m); 13.30 (1H, s); 13.32 (1H, s).

By analogous procedure

4-methoxy-9-(1'-hydroxyethyl)-7,10-dihydro-6,9,11-trihydroxy-8-fluoro-

- 14 -

5,12-naphthacene-dione ((VIII), $R_1 = OCH_3$).

EXAMPLE IV

9-Acetyl-8(8H)-fluoro-7,10-dihydro-6,9,11-trihydroxy-5,12-naphthacene-dione ((IX), $R_1 = H$).

5 9-(1'-hydroxyethyl)-7,10-dihydro-6,9,11-trihydroxy-8-fluoro-5,12-naphthacene-dione (1.7 g; 4.7 mmol), prepared according to example III, in anhydrous conditions, is solubilized in DMSO (90 ml), then a mixture of pyridine (1.14 ml; 14.1 mmol) and trifluoroacetic acid (0.83 ml; 10.8 mmol) in DMSO (16 ml) is added to the solution. Acetic anhydride
10 (4.44 ml; 47 mmol) is added to the mixture and the solution is left under stirring at room temperature for 4 h. Thereafter H_2O is added to the solution, the desired product precipitates.

More product possibly present in the solution is recovered by extraction with $CHCl_3$. The so obtained crude is purified by flash chromatography
15 using $CHCl_3$ as eluent. The title compound is obtained (1.2 g; yield 70%).
NMR ($CDCl_3$, δ): 2.48 (3H, s); 3.18 (2H, s); 3.1-3.6 (2H, m)
3.90 (1H, s); 5.2-5.4 (1H, s); 7.82 (2H, m); 8.38 (2H, m); 13.34 (1H, s); 13.36 (1H, s).

20 By analogous procedure

4-Methoxy-9-acetyl-8(8H)-fluoro-7,10-dihydro-6,9,11-trihydroxy-5,12-naphthacene-dione ((IX), $R_1 = OCH_3$)
is obtained.

EXAMPLE V

25 9-Acetyl-8(8H)-fluoro-10-hydro-6,7(7H),9,11-tetrahydroxy-5,12-naphthacene dione (II; $R_1 = H$)

In a flask equipped with Dean Stark, to a suspension of 9-acetyl-8(8H)-

- 15 -

fluoro-7,10-dihydro-6,9,11-trihydroxy-5,12-naphthacene-dione
(1.2 g; 3.3. μ moles) prepared according to the Example IV, in anhydrous
benzene (200 ml), ethylene glycol (5 ml) and a catalytic quantity of p-
toluensulphonic acid (60 mg; 0.3 μ moles) are added. The mixture is
5 refluxed at 120°C for 15 h. The carbonyl-function in position 13 is
protected by ketalization. When the reaction is finished the temperature
is raised to room temperature and the product precipitates and is
collected and washed with water.

The so obtained product is bromurated in position 7 with PPHP and AIB in
10 CCl_4 by refluxing at 120°C in N_2 current, for 8 hours. The temperature of
the reaction mixture is raised up to room temperature, the precipitate is
filtered and the solution is evaporated. The residue is hydrolyzed with
trifluoroacetic acid (240 ml) and water (60 ml) by refluxing for 1 h.

The temperature is raised at room temperature, then is cooled at 7°C.
15 The product precipitates, is washed with water and dried. It results to
be a mixture of epimers in position 7 (a = 70%, b = 30%). The wanted
epimer is isolated by HPLC in order to obtain the title product (312 mg;
yield 24%).

NMR (CDCl_3 , δ): 2.50 (3H, s); 3.1-3.4 (2H, m); 3.85 (1H, d)
20 4.82 (1H, s); 5.04-5.22 (1H, q); 5.50 (1H, m); 7.85 (2H, m); 8.40 (2H,
m); 13.28 (1H, s); 14.54 (1H, s).

By analogous procedure

4-Methoxy-9-acetyl-8(8H)-fluoro-10-hydro-6,7(7H),9,11-tetrahydroxy-5,12-
naphthacene dione (II; $\text{R}_1 = \text{OCH}_3$)

25 EXAMPLE VI

Protected 4-demethoxy-8(R)-fluoro-daunorubicin (IV, $\text{R} = \text{R}_1 = \text{H}$, $\text{R}_7 =$
 $\text{NHCO}_2\text{CH}_2\text{CH}=\text{CH}_2$, $\text{R}_8 = \text{p-CO-C}_6\text{H}_4\text{-NO}_2$).

- 16 -

To a solution of 9-acetyl-8(8H)-fluoro-10-hydro-6.7(7H),9.11-tetrahydroxy-5.12-naphthacene dione (77 mg.; 0.2 mmoles), obtained according to example V and protected daunosamine ((III), X = R₈ = OCOC₆H₄NO₂; R₇ = NHCO₂CH₂CH=CH₂) (127 mg; 0.24 mmoles) in anhydrous methylene chloride (40 ml) and anhydrous ethyleter (10 ml) molecular sieves 4°A (1.2 g) are added. To this solution, maintained at -10°C and under anhydrous nitrogen current, trimethyl-silyl-triflate (107 mg; 0.48 mmoles) is added. The reaction is carried out at -10°C for 30 minutes.

5 The solution is treated with a solution of NaHCO₃, the organic phase is extracted, dried on Na₂SO₄ and evaporated. The so obtained crude is purified by flash chromatography (CHCl₃ + 1% iPrOH). 61 mg (yield 40%) of the title compound are obtained.

NMR (CDCl₃, δ): 1.2 (3H, d); 2.0 (2H, m); 2.5 (3H, d); 3.1-
15 3.5 (2H,q); 4.2-4.7 (5H, m); 5.0-5.3 (3H, m); 5.4-5.6 (2H, m); 5.8 (1H, s); 5.9 (1H, m); 7.8 (2H, m); 8.3 (6H, m); 13.7 (1H, s); 13.2 (1H,s).

By analogous procedure

20 Protected 8-(R)-fluoro-daunorubicin ((IV) R = H, R₁ = OCH₃, R₇ = NHCO₂CH₂CH=CH₂, R₈ = p-CO-C₆H₄-NO₂) is obtained.

EXAMPLE VII

4-demethoxy-8-(R)-fluoro-daunorubicin hydrochloride ((I) R = R₁ = H; R₂ = NH₂.HCl, R₃ = OH).

25 The product described in example VI, must undergo two deprotections in order to be transformed in the corresponding compound I.

The product obtained in example VI (61 mg; 0.08 mmoles) is suspended in MeOH/H₂O and treated with a solution of K₂CO₃ 0.5 M in order to

- 17 -

deprotect the hydroxy-group in 4'.

The obtained product, by treatment with Ph_3P , Tetrakis, 2-methyl-butirric acid in CH_2Cl_2 , under anhydrous conditions, in the darkness, at room temperature, gives, by deprotection of the amino-group in 3', the wanted
5 compound (32 mg; 75%).

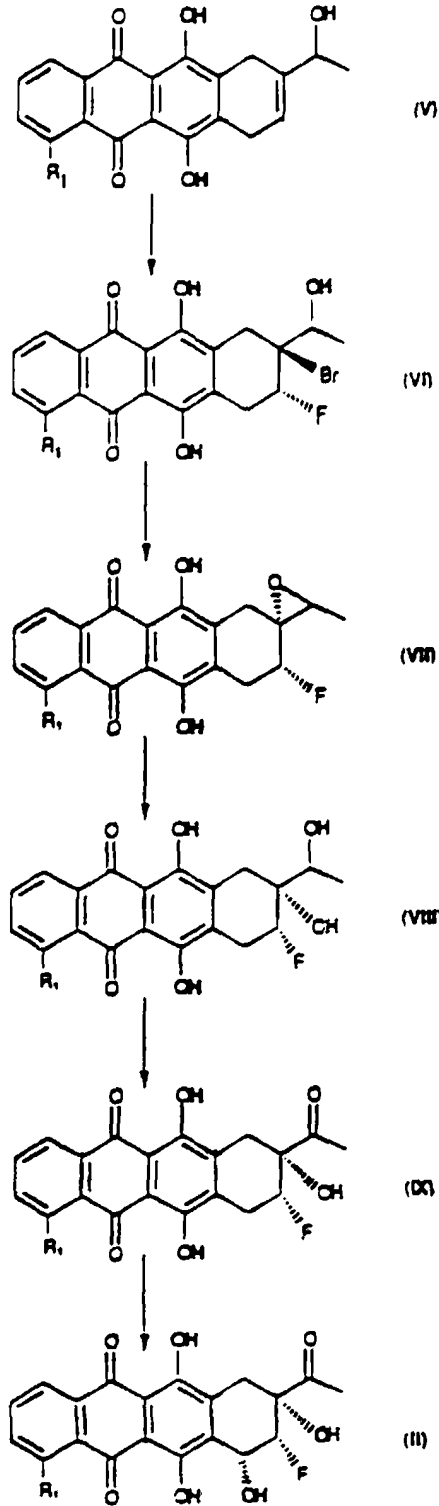
This product, by treatment with HCl 0.01 N, is salified to title compound.

NMR (CDCl_3 , δ): 1.3 (3H, d); 2.0-2.2 (2H, m); 2.5 (3H, s);
3.2-3.4 (2H, m); 3.6-3.8 (2H, m); 4.4-4.5
10 (1H, m); 5.2-5.4 (1H, m); 5.5 (1H, m); 5.7
(1H, m); 8.0 (2H, s); 8.4 (2H, s)

By analogous procedure

8-(R)-fluoro-daunorubicin hydrochloride (I, R = H; $\text{R}_1 = \text{OCH}_3$; $\text{R}_2 = \text{NH}_2 \cdot \text{HCl}$, $\text{R}_3 = \text{OH}$).

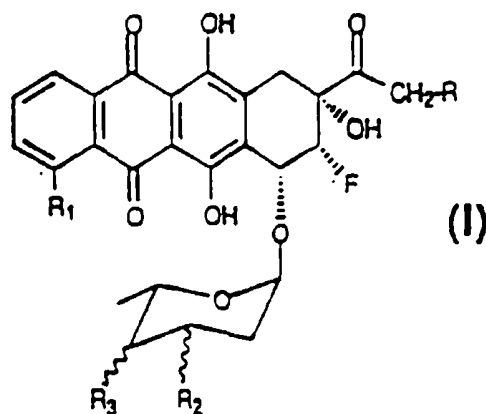
REACTION SCHEMA



CLAIMS

1. Compounds of general formula (I)

5



10

(I)

wherein:

R is chosen in the group consisting of H, OH, OR₄ wherein R₄ is - COR₇, wherein R₇ = H, alkyl C₁-C₅;

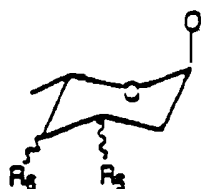
R₁ is chosen in the group consisting of: H, OH, OCH₃;

15

R₂ is chosen in the group consisting of: H, OH, NH₂

R₃ is chosen in the group consisting of: H, OH, NH₂, residue of formula (A)

20



(A)

wherein R₅ and R₆, same or different, are chosen in the group consisting of: H, OH, NH₂ and the symbol (wavy line) indicates that the substituents R₂, R₃, R₅ and R₆ can be in the axial or equatorial configuration;

25

and wherein the groups 8-F and 9-OH are in position cis; and their pharmaceutically acceptable salts.

2. Compounds according to claim 1 represented by:

4-demethoxy-8-(R)-fluoro-daunorubicin



- 20 -

- 3 4-demethoxy-8-(R)-fluoro-3'-deamino-4'deoxy-4' amino-daunorubicin
- 4 4-demethoxy-8-(R)-fluoro-3'-deamino-4'deoxy-4'-epi-amino-daunorubicin
- 5 4-demethoxy-8-(R)-fluoro-3'-deamino-4'epi-daunorubicin
- 6 4-demethoxy-8-(R)-fluoro-7-(daunosaminyl-fucosyl)-daunorubicinone
- 7 4-demethoxy-8-(R)-fluoro-7-(daunosaminyl-ramnosyl)-daunorubicinone
- 8 4-demethoxy-8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-
- 9 fucosyl)-daunorubicinone
- 10 4-demethoxy-8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-
- 11 ramnosyl)-daunorubicinone
- 12 4-demethoxy-8-(R)-fluoro-7-(fucosyl-4'-O-fucosyl)-daunorubicinone
- 13 4-demethoxy-8-(R)-fluoro-7-(fucosyl-4'-O-ramnosyl)-daunorubicinone
- 14 8-(R)-fluoro-daunorubicin
- 15 8-(R)-fluoro-3'-deamino-4'deoxy-4' amino-daunorubicin
- 16 8-(R)-fluoro-3'-deamino-4'deoxy-4'-epi-amino-daunorubicin
- 17 8-(R)-fluoro-4'epi-daunorubicin 8-(R)-fluoro-7-(daunosaminyl-
- 18 fucosyl)-daunorubicinone
- 19 8-(R)-fluoro-7-(daunosaminyl-ramnosyl)-daunorubicinone
- 20 8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-fucosyl)-
- 21 daunorubicinone
- 22 8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-ramnosyl)-
- 23 daunorubicinone
- 24 8-(R)-fluoro-7-(fucosyl-4'-O-fucosyl)-daunorubicinone
- 25 8-(R)-fluoro-7-(fucosyl-4'-O-ramnosyl)-daunorubicinone
- 26 4-demethoxy-8-(R)-fluoro-doxorubicin and its esters in C-14
- 27 4-demethoxy-8-(R)-fluoro-3'-deamino-4'deoxy-4' amino-doxorubicin and its
- 28 esters in C-14
- 29 4-demethoxy-8-(R)-fluoro-3'-deamino-4'deoxy-4'-epi-amino-doxorubicin and

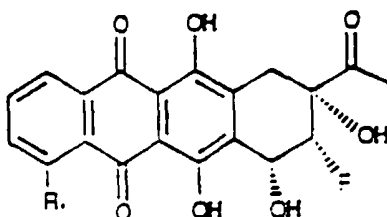
- 30 its esters in C-14
- 31 4-demethoxy-8-(R)-fluoro-4'epi-doxorubicin and its esters in C-14
- 32 4-demethoxy-8-(R)-fluoro-7-(daunosaminyl-fucosyl)-doxorubicinone and its
33 esters in C-14
- 34 4-demethoxy-8-(R)-fluoro-7-(daunosaminyl-ramnosyl)-doxorubicinone and its
35 esters in C-14
- 36 4-demethoxy-8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-
37 fucosyl)-doxorubicinone and its esters in C-14
- 38 4-demethoxy-8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-
39 ramnosyl)-doxorubicinone and its esters in C-14
- 40 4-demethoxy-8-(R)-fluoro-7-(fucosyl-4'-O-fucosyl)-doxorubicinone and its
41 esters in C-14
- 42 4-demethoxy-8-(R)-fluoro-7-(fucosyl-4'-O-ramnosyl)-doxorubicinone and its
43 esters in C-14
- 44 8-(R)-fluoro-doxorubicin and its esters in C-14
- 45 8-(R)-fluoro-3'-deamino-4'deoxy-4' amino-doxorubicin and
46 its esters in C-14
- 47 8-(R)-fluoro-3'-deamino-4'deoxy-4'-epi-amino-doxorubicin and its esters
48 in C-14
- 49 8-(R)-fluoro-3'-deamino-4'epi-doxorubicin and its esters in C-14
- 50 8-(R)-fluoro-7-(daunosaminyl-fucosyl)-doxorubicinone and its esters in C-
51 14
- 52 8-(R)-fluoro-7-(daunosaminyl-ramnosyl)-doxorubicinone and its esters in
53 C-14
- 54 8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-fucosyl)-
55 doxorubicinone and its esters in C-14
- 56 8-(R)-fluoro-7-(2",3",4"-trideoxy-4"-amino-esapiranosyl-ramnosyl)-

doxorubicinone and its esters in C-14

8-(R)-fluoro-7-(fucosyl-4'-O-fucosyl)-doxorubicinone and its esters in C-14

8-(R)-fluoro-7-(fucosyl-4'-O-ramnosyl)-doxorubicinone and its esters in C-14

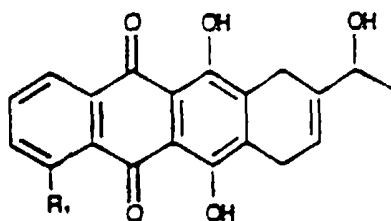
3. Compounds of formula II



(II)

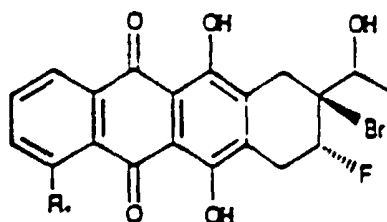
wherein R and R₁ are as defined in claim 1, and the groups 8-F and 9-OH have relative stereochemistry cis.

4. A process for the preparation of compounds of formula (II) according to claim 3 wherein an allyl alcohol of formula (V)



(V)

is bromofluorurated to give a compound of formula (VI)



(VI)

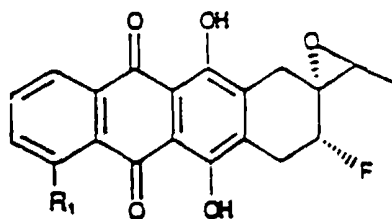
which treated with a base is transformed into the epoxide of formula

(VII)



5

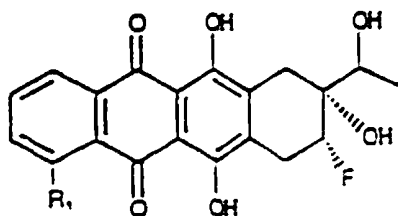
(VII)



which is transformed, by treatment with acids in aqueous solution, into the corresponding diol of formula (VIII)

10

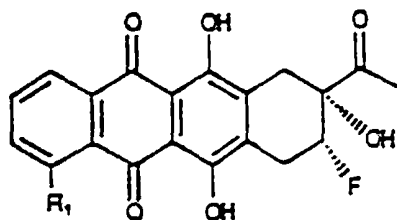
(VIII)



which is oxidized to a fluoro-hydroxy-keton of formula (IX)

15

(IX)



which is finally bromurated and subjected to solvolysis in position 7 by conventional agents giving the aglycon (II).

20

5. Pharmaceutical composition containing as active principle a therapeutically active quantity of a compound of formula (I) according to claim 1, or its pharmaceutically acceptable salts, in combination with a pharmaceutically acceptable vector or diluent.

25

6. Composition according to claim 5 when used for the treatment of tumors.

7. Method for the treatment of tumors wherein pharmaceutically acceptable quantities of a compound of formula (I) according to claim 1 are administered to the patient.



- 24 -

8-Fluoro-anthracyclines, processes for their preparation and pharmaceutical compositions containing them.

Abstract

8-fluoro-anthracyclines of formula (I) having cis-stereochemistry between
5 the groups 8-F and 9-OH, are described, such compounds present anti-tumor
activity. Their preparation and pharmaceutical compositions containing
them are also described.