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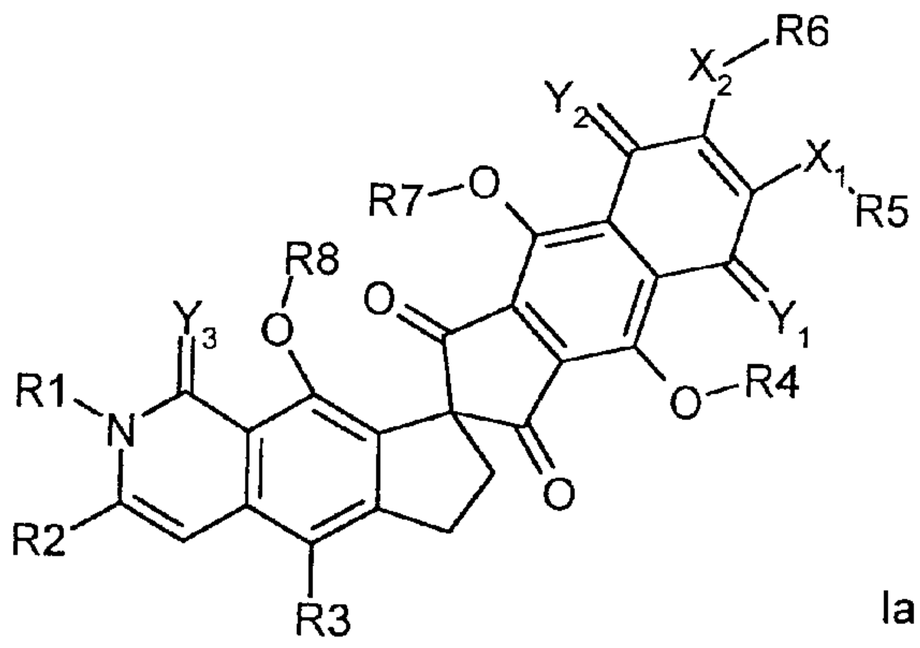
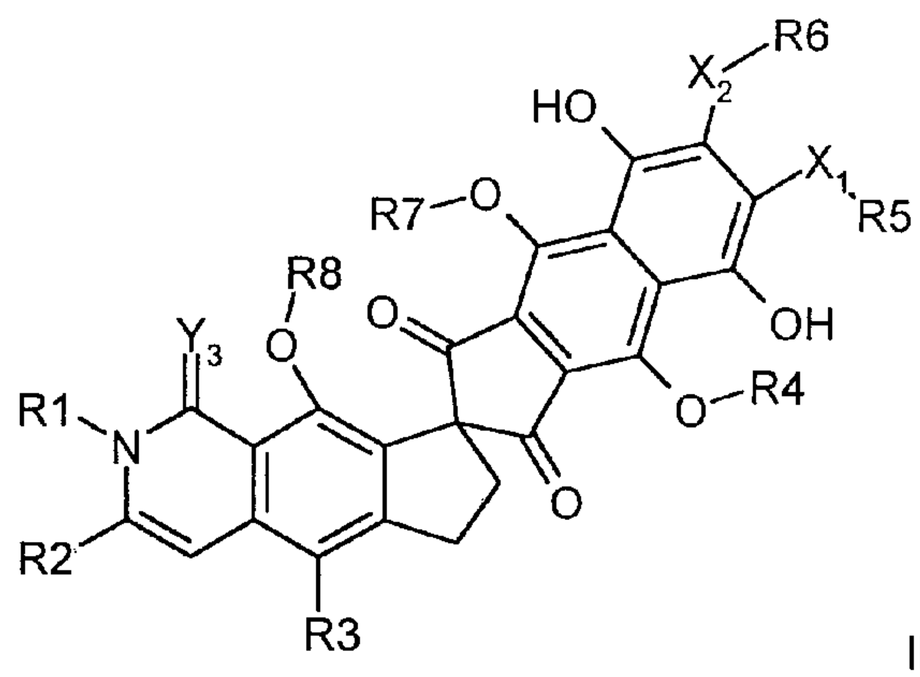
(54) Titre : DERIVES DE LA FREDERICAMYCINE EN TANT QU'ANTI-TUMORAUX
(54) Title: FREDERICAMYCIN DERIVATIVES AS DRUGS FOR TUMOR TREATMENT



Ia



Ib

(57) Abrégé/Abstract:
The invention relates to novel fredericamycin derivatives of general formula (Ia) or (Ib), to medicaments containing said derivatives or the salts of the same, and to the use of said fredericamycin derivatives for treating diseases, especially tumour diseases.

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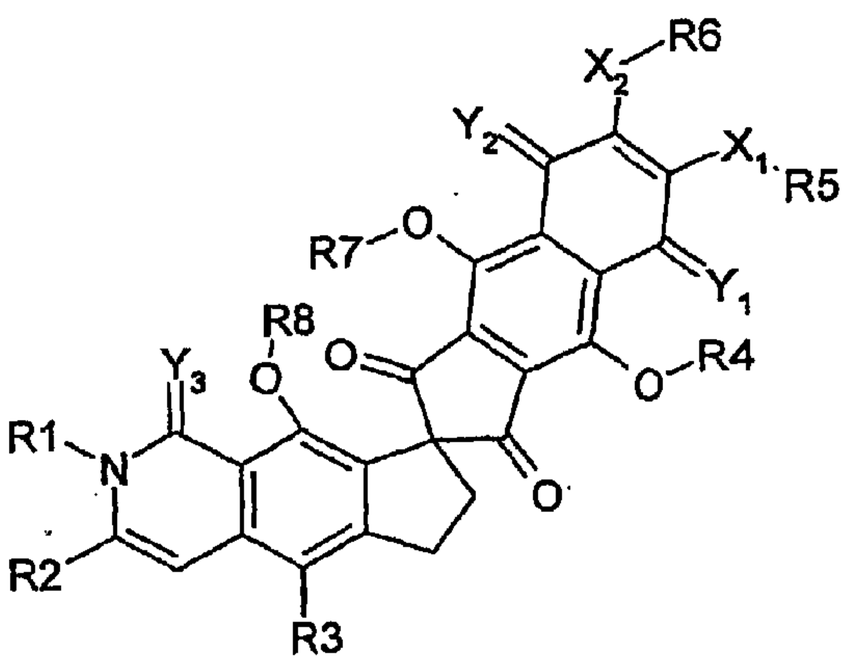
[Fortsetzung auf der nächsten Seite]

(54) **Title:** FREDERICAMYCIN DERIVATIVES AS MEDICAMENTS FOR TREATING TUMOURS

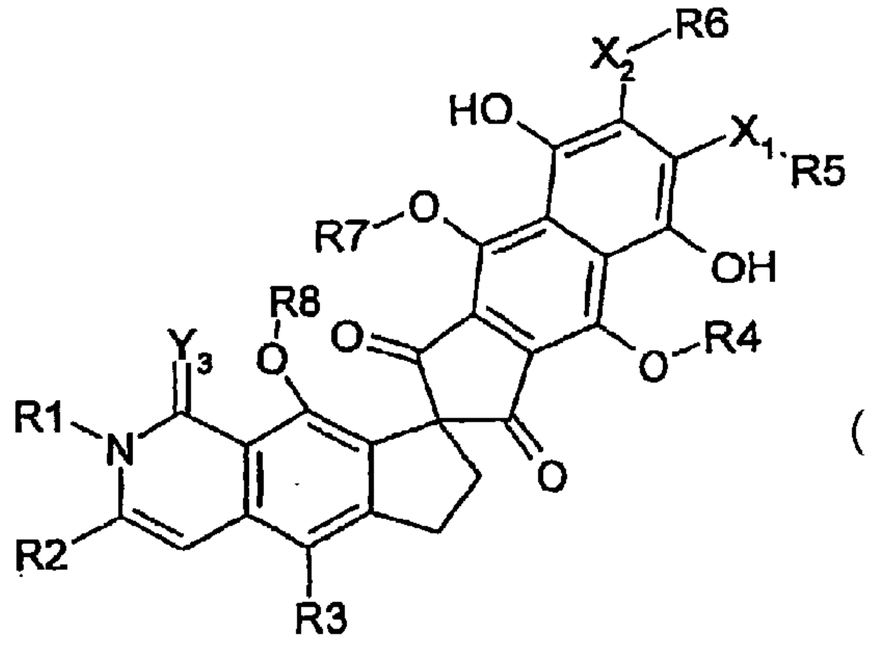
(54) **Bezeichnung:** FREDERICAMYCIN-DERIVATE ALS ARZNEIMITTEL ZUR TUMORBEHANDLUNG



(1a)

(57) **Abstract:** The invention relates to novel fredericamycin derivatives of general formula (Ia) or (Ib), to medicaments containing said derivatives or the salts of the same, and to the use of said fredericamycin derivatives for treating diseases, especially tumour diseases.

(57) **Zusammenfassung:** Die Erfindung betrifft neue Fredericamycin-Derivate gemäss allgemeiner Formel (Ia) oder (Ib) Arzneimittel die diese oder deren Salze enthalten, und die Verwendung der Fredericamycin-Derivate zur Behandlung von Erkrankungen, insbesondere Tumorerkrankungen.



(1b)

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Veröffentlicht:

— *mit internationalem Recherchenbericht*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

Fredericamycin derivatives as drugs for tumor treatment

The invention relates to novel fredericamycin derivatives, to drugs containing said derivatives or the salts thereof, and to the use of the fredericamycin derivatives for treating diseases, particularly tumor diseases.

Fredericamycin has been isolated 1981 from *Streptomyces griseus,* and demonstrates anti-tumor activity.

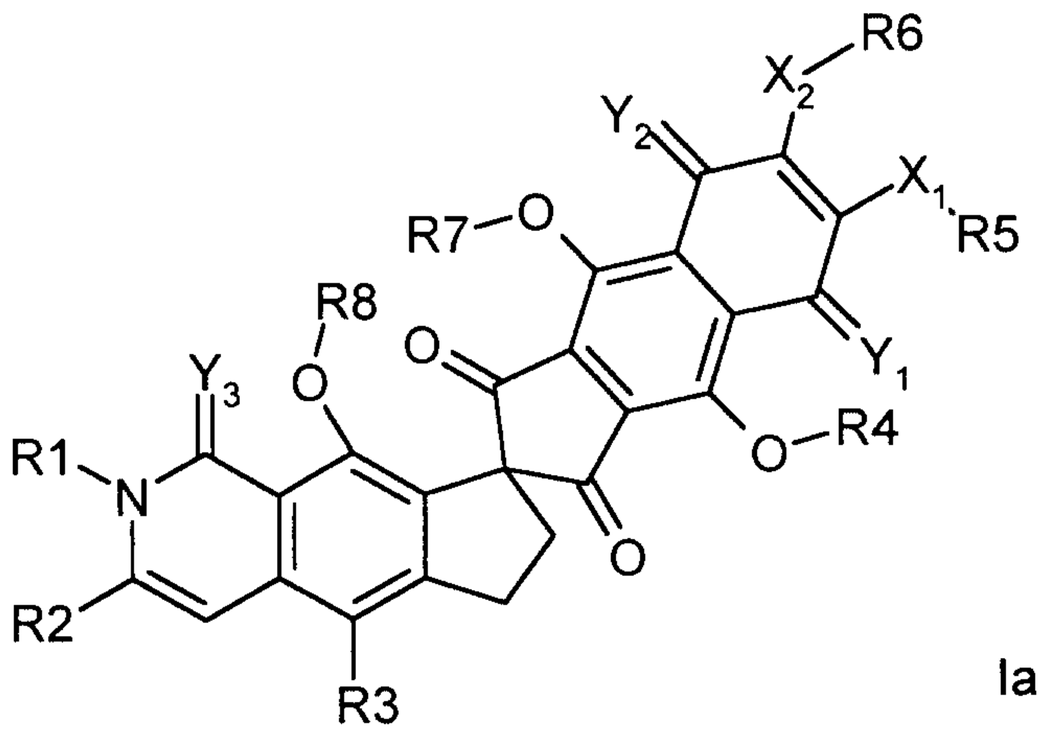
Fredericamycin and several fredericamycin derivatives are known.

In Heterocycles 37 (1994) 1893 – 1912, J. Am. Chem. Soc. 116 (1994) 9921 – 9926, J. Am. Chem. Soc. 116 (1994) 11275 – 11286, J. Am. Chem. Soc. 117 (1995) 11839 – 11849, and in J. Am. Chem. Soc. 123 (2001), various total syntheses of fredericamycin A have been described, some being enantio-selective.

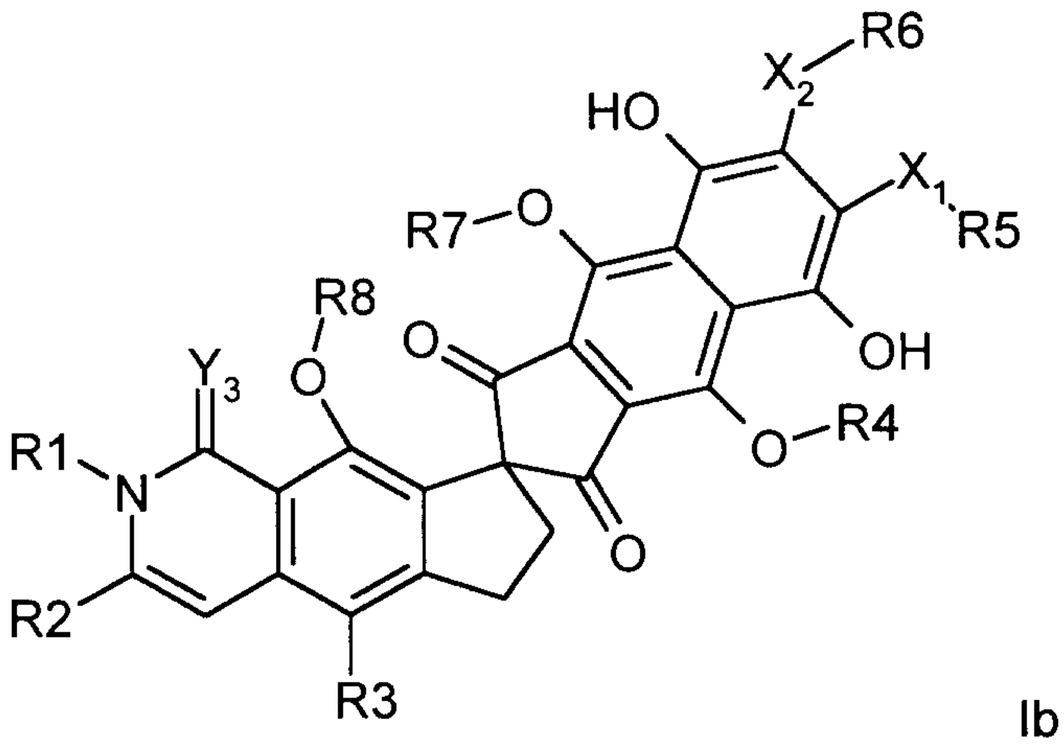
In US 4673768, alkali salts of the fredericamycin A are described. In US 4584377, fredericamycin derivatives are described, particularly derivatives acylated at ring E and F. In US 5,166,208, fredericamycin derivatives are described as well, particularly derivatives carrying thio and amino substituents in ring F. The derivatives are generated semi-synthetically or fully synthetically.

Surprisingly it was found that fredericamycin derivatives, especially those derivatized in ring E, in ring F, or at rings E and F, represent potent drugs. Also, a possibility was found to introduce such residues in ring E, in ring F, or at both rings E and F semi-synthetically, with which the water solubility, among others, of the derivatives can be significantly increased. Other derivatisation methods known from the art can also be performed with the derivatives according to the invention. Furthermore, an alternative method was found to make fredericamycin derivatives water-soluble by generating cyclodextrin inclusion compounds.

The invention relates to novel fredericamycin derivatives with the general Formula Ia or Ib:



Ia



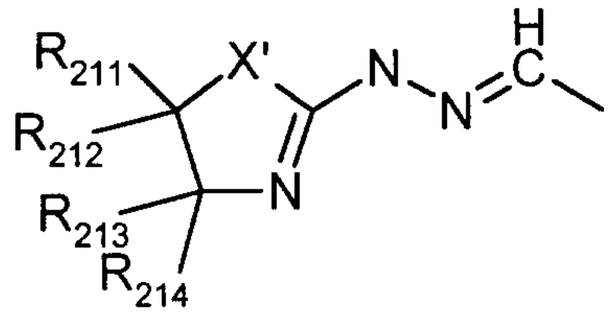
Ib

wherein in each,

R1 means H, C_1-C_6 alkyl, cycloalkyl, C_1-C_4 alkylcycloalkyl,

R2 means C_1-C_{14} alkyl, C_2-C_{14} alkenyl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkyl heteroaryl, cycloalkyl, C_1-C_4 alkyl-cycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y = independently from each other selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH, SR21), $CH_2NHCOR21$, $CH_2NHCSR21$, $CH_2S(O)nR21$, with n = 0, 1, 2, $CH_2SCOR21$, CH_2OSO_2-R21, CHO, CH=NOH, CH(OH)R21, -CH=NOR21, -CH=NOCOR21, -

$CH=NOCH_2CONR21R22$, $-CH=NOCH(CH_3)CONR21R22$, $-CH=NOC(CH_3)_2CONR21R22$, $-CH=N-NHCO-R23$, $-CH=N-NHCO-CH_2NHCOR21$, $-CH=N-O-CH_2NHCOR21$, $-CH=N-NHCS-R23$, $-CH=CR24R25$ (trans or cis), COOH, $COOR21$, $CONR21R22$, $-CH=NR21$, $-CH=N-NR21R22$,



(with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently from each other H or C_1-C_6 alkyl), $-CH=N-NHSO_2$ aryl, $-CH=N-NHSO_2$ heteroaryl,

R21, R22 are independently from each other C_1-C_{14} alkyl, C_1-C_{14} alkanoyl, C_1-C_6 alkylhydroxy, C_1-C_6 alkylamino, C_1-C_6 alkylamino-C_1-C_6 alkyl, C_1-C_6 alkylamino-di-C_1-C_6 alkyl, cycloalkyl, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, aryl, aryloyl, C_1-C_4 alkylaryl, heteroaryl, heteroaryloyl, C_1-C_4 alkylheteroaryl, cycloalkanoyl, C_1-C_4 alkanoylcycloalkyl, heterocycloalkanoyl, C_1-C_4 alkanoylheterocycloalkyl, C_1-C_4 alkanoylaryl, C_1-C_4 alkanoylheteroaryl, mono- and di-sugar residues linked through a C atom which would carry an OH residue in the sugar, wherein the sugars are independently from each other selected from the group consisting of glucuronic acid and its stereo isomers at all optical C-atoms, aldopentoses, aldohexoses, including their desoxy compounds (such as e.g. glucose, desoxyglucose, ribose, desoxyribose),

R23 independently of R21, has the same meanings as R21, or CH_2-pyridinium salts, CH_2-tri-C_1-C_6 alkylammonium salts,

R24 independently of R21, has the same meanings as R21, or H, CN, $COCH_3$, COOH, $COOR21$, $CONR21R22$, NH_2, $NHCOR21$,

R25 independently of R21, has the same meanings as R21, or H, CN, $COCH_3$, COOH, $COOR21$, $CONR21R22$, NH_2, $NHCOR21$,

R24, R25 together mean C_4-C_8 cycloalkyl,

R3 means H, F, Cl, Br, I, OH, OR31, NO_2, NH_2, NHR31, NR31R32, NHCHO, NHCOR31, NHCOCF3, $CH_{3-m}hal_m$ (with hal = Cl, F, especially F, and m = 1, 2, 3), OCOR31,

R31, 32 independently from each other mean C_1-C_6 alkyl,

R5, R6 independently from each other mean H, C_1-C_{14} alkyl, C_2-C_{14} alkenyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl, cycloalkyl, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y = independently selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH, SR21), or R5 and R6, together with X_1-C-C-X_2, form a ring with 5, 6, or 7 members,

R4, R7, R8 independently from each other mean H, C_1-C_6 alkyl, CO-R41,

R41 independently from R21 has the same meanings as R21,

X1 means O, S, NH, N-C_1-C_8 alkyl, N-cycloalkyl,

X2 means O, S, NH, N-C_1-C_8 alkyl, N-cycloalkyl,

Y1 means O, N-R9, wherein R9 can, independently from R5, adopt the same meanings as R5,

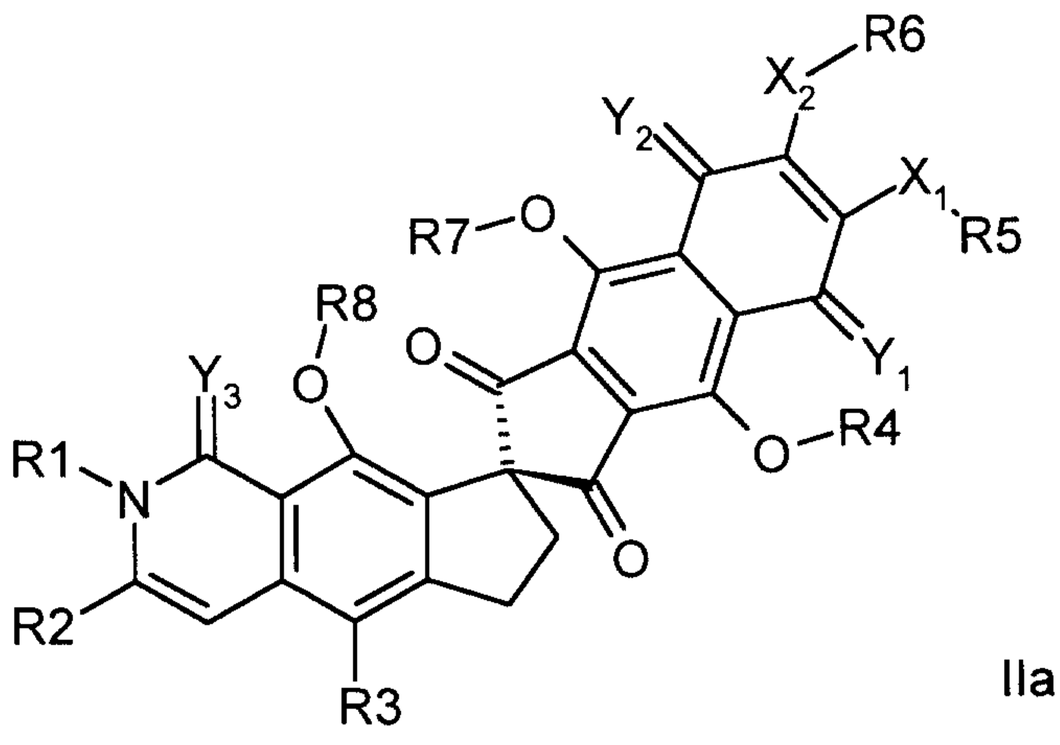
Y2 means O, N-R10, wherein R10 can, independently from R5, adopt the same meanings as R5,

and, if Y1 or Y2 are N-R9 or N-R10, X2-R6 may be H,

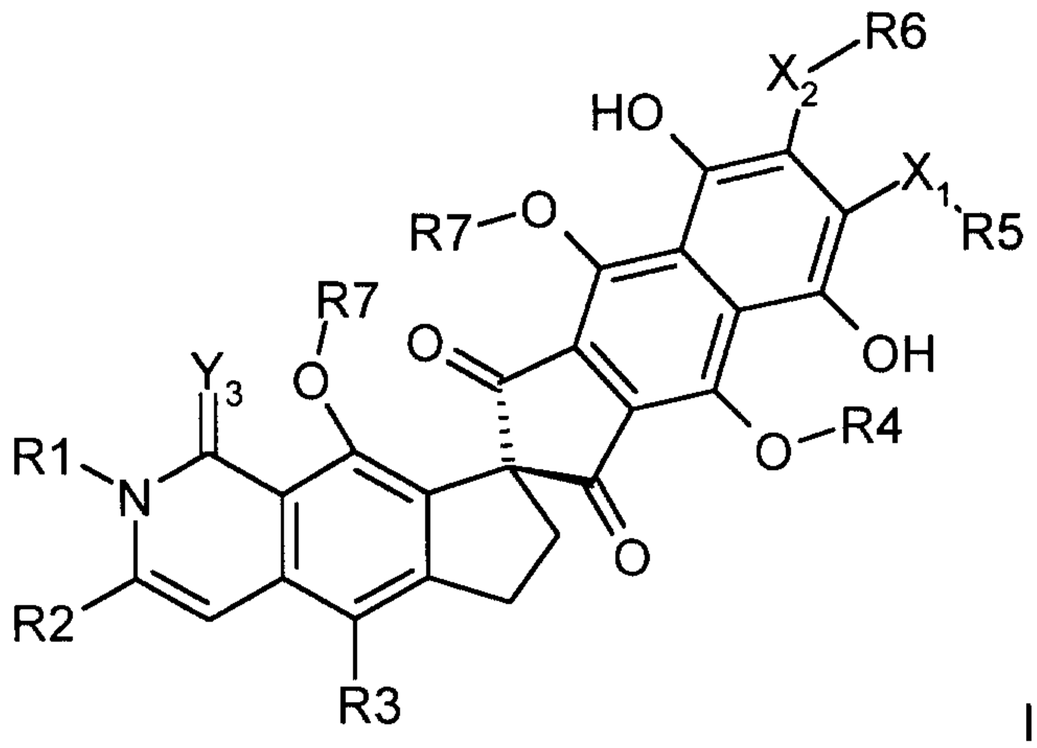
Y3 means O, S, NH,

as well their stereoisomers, tautomers, and their physiologically tolerable salts or inclusion compounds.

Preferred are compounds of Formula IIa or IIb



IIa



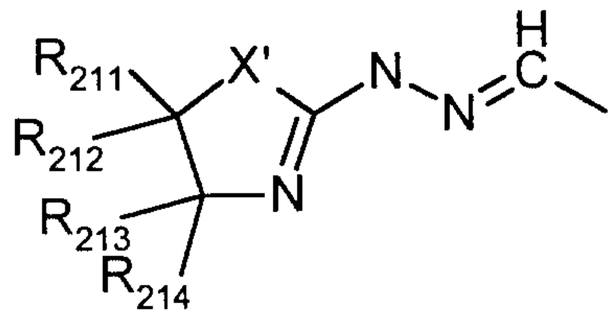
IIb

wherein the meaning of the residues R1-R41, X1, X2, Y1 and Y2 is as described above, their tautomers and their physiologically tolerable salts or inclusion compounds.

The invention also relates to compounds of the Formula Ia, Ib, IIa or IIb, in which the residues R have the above described meanings, and the water solubility of R2 is at least two times higher, preferably at least five timer higher, more preferred at least ten times higher, especially preferred at least fifty time higher, particularly one hundred times higher, or even five hundred times higher than of R2 being CH=CH-CH=CH-CH_3, when all other residues are

maintained. The increase in water solubility is mediated e.g. by introduction of groups which can increasingly form hydrogen bonds and/or are polar and/or ionic. A key intermediate product are compounds with an aldehyde function in R2. Preferred are aldehydes and the thereof derived compounds, in which at least R1 or R3 not equal H, when R4 to R8 are H or alkyl.

Preferred R2 residues are heteroaryl, cycloalkyl, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y = independently selected from each other from the group of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH, SR21), CH_2NHCOR21, CH_2NHCSR21, CH_2S(O)nR21, with n = 0, 1, 2, CH_2SCOR21, CH_2OSO_2-R21, CH(OH)R21, -CH=NOCOR21, -CH=NOCH$_2$CONR21R22, -CH=NOCH(CH_3)CONR21R22, -CH=NOC(CH_3)$_2$CONR21R22, -CH=N-NHCO-R23, -CH=N-NHCO-CH_2NHCOR21, -CH=N-O-CH_2NHCOR21, -CH=N-NHCS-R23, -CH=CR24R25 (trans or cis), CONR21R22, -CH=NR21, -CH=N-NR21R22,



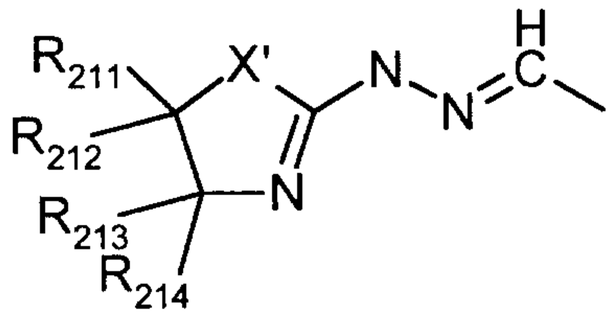
(with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently from each other H or C_1-C_6 alkyl), -CH=N-NHSO$_2$ aryl, -CH=N-NHSO$_2$ heteroaryl.

Furthermore preferred are still compounds as described above, wherein the residues R preferably independently from each other adopt one or more of the following meanings:

R1 means H, C_1-C_5 alkyl, cycloalkyl, especially H,

R2 means C_1-C_5 alkyl, C_1-C_4 alkylaryl, C_2-C_5 alkenyl, heteroaryl, C_1-C_4 alkylheteroaryl, CHF_2, CF_3, polyol side chain, particularly CHOH-CHOH-CHOH-CHOH-CH_3, CHOH-CHOH-CH=CH-CH_3, CH=CH-CHOH-CHOH-CH_3, CH_2Y (Y = F, Cl, Br, I), CH_2NH_2, CH_2NR21R22, CH_2NHCOR23, CH_2NHCSR23, CH_2SH, CH_2S(O)nR21, with n = 0, 1, 2,

$CH_2SCOR21$, particularly CH_2OH, CH_2OR21, CH_2OSO_2-R21, particularly CHO, $CH(OR21)_2$, $CH(SR21)_2$, CN, CH=NOH, CH=NOR21, CH=NOCOR21, CH=N-NHCO-R23, CH=CR24, R25 (trans or cis), particularly COOH (particularly their physiologically tolerable salts), COOR21, CONR21R22, -CH=NR21, -CH=N-NR21R22,



, (with X' = NR215, O, S, and R211, R212, R213, R214, R215 being independently from each other H or C_1-C_6 alkyl), -CH=N-$NHSO_2$ aryl, -CH=N-$NHSO_2$ heteroaryl, CH=N-NHCO-R23,

R21, R22 independently from each other mean C_1-C_6 alkyl, cycloalkyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl,

R23 independently of R21, has the same meanings as R21, or CH_2-pyridinium salts, CH_2-tri-C_1-C_6 alkylammonium salts,

R24 independently of R21, has the same meanings as R21, or H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, NHCOR21,

R25 independently of R21, has the same meanings as R21, or H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, NHCOR21,

R24, R25 together mean C_4-C_8 cycloalkyl,

R3 means F, Cl, Br, I, NO2, NH2, NHCOR31,

R31 independently from each other mean C_1-C_6 alkyl,

R5, R6 independently from each other mean H, C_1-C_{14} alkyl, C_2-C_{14} alkenyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl, cycloalkyl, C_1-C_4 alkylcycloalkyl,

heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y_p$ (with m = 1 to 6, for o = 1, p = 1 to 2m+o; for m = 2 to 6, o = -1, p = 1 to 2m+o; for m = 4 to 6, o = -2, p = 1 to 2m+o; Y = independently selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH, SR21), or R5 and R6, together with X_1-C-C-X_2, form a ring with 5, 6, or 7 members,

R4, R7, R8 independently from each other mean H, C_1-C_6 alkyl, CO-R41,

R41 independently from R21 has the same meanings as R21,

Y3 means O, S, preferably O,

as well their stereoisomers, tautomers, and their physiologically tolerable salts or inclusion compounds.

Especially preferred are the compounds, their stereo isomers, tautomers, and physiologically tolerable salts or inclusion compounds selected from the group consisting of the compounds of the examples and the compounds demonstrating combinations of the various substituents of the compounds of these examples.

Also preferred are drugs which contain the above compounds of Formula I or II in addition to the usual carriers and adjuvants.

Also preferred are the above mentioned drugs in combination with other agents for tumor treatment.

These compounds according to the invention are used for preparation of drugs for treatment of tumors, particularly such that may be treated by inhibition of the topoisomerases I and/or II. Tumors that can be treated with the substances according to the invention are e.g. leukemia, lung cancer, melanomas, prostate tumors and colon tumors.

Furthermore, the compounds according to the invention are used for preparation of drugs for treatment of neurodermitis, parasites and for immunosuppression.

In the description and the claims the substituents are described by the following definitions:

The term "alkyl" by itself or as part of another substituent means a linear or branched alkyl chain radical of the respectively indicated length, in which optionally a CH_2 group may be substituted by a carbonyl function. Thus, C_{1-4} alkyl may be methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl, 2-butyl, C_{1-6} alkyl, e.g. C_{1-4} alkyl, pentyl, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl, or 3,3-dimethylbutyl.

The term "C_1-C_6 alkylhydroxy" by itself or as part of another substituent means a linear or branched alkyl chain radical of the respectively indicated length, which may be saturated or unsaturated, and which carries an OH group, e.g. hydroxymethyl, hydroxymethyl, 1-hydroxypropyl, 2-hydroxypropyl.

The term "alkenyl" by itself or as part of another substituent means a linear or branched alkyl chain radical with one or more C=C double bonds of the respectively indicated length, several double bonds being preferably conjugated. Thus, C_{2-6} alkenyl may for example be ethenyl, 1-propenyl, 2-propenyl, 2-methyl-2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 1,3-butdienyl, 2,4-butdienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1,3-pentdienyl, 2,4-pentdienyl, 1,4-pentdienyl, 1-hexenyl, 2-hexenyl, 1,3-hediexyl, 4-methyl-1-pentenyl, or 3,3-dimethylbutenyl.

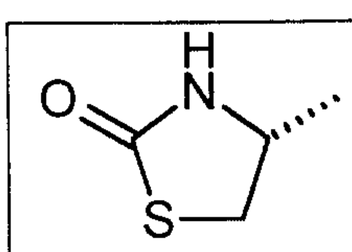
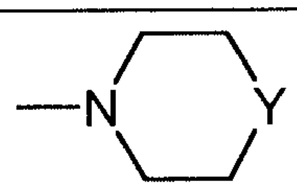
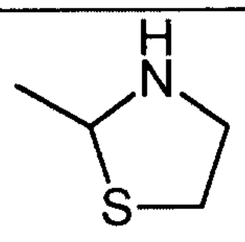
The term "halogen" stands for fluorine, chlorine, bromine, iodine, preferably bromine and chlorine.

The term "NR21R22" stands for a dialkylamino group, wherein the two alkyl groups, together with the N, may also form a ring with 5 or 6 members.

If R5 and R6, together with X_1-C-C-X_2, form a ring with 5, 6 or 7 members, then R5 and R6 together are preferably CH_2, CH_2-CH_2, CH=CH, CH_2-CH_2-CH_2, CH=CH-CH_2, or CH_2-CH=CH.

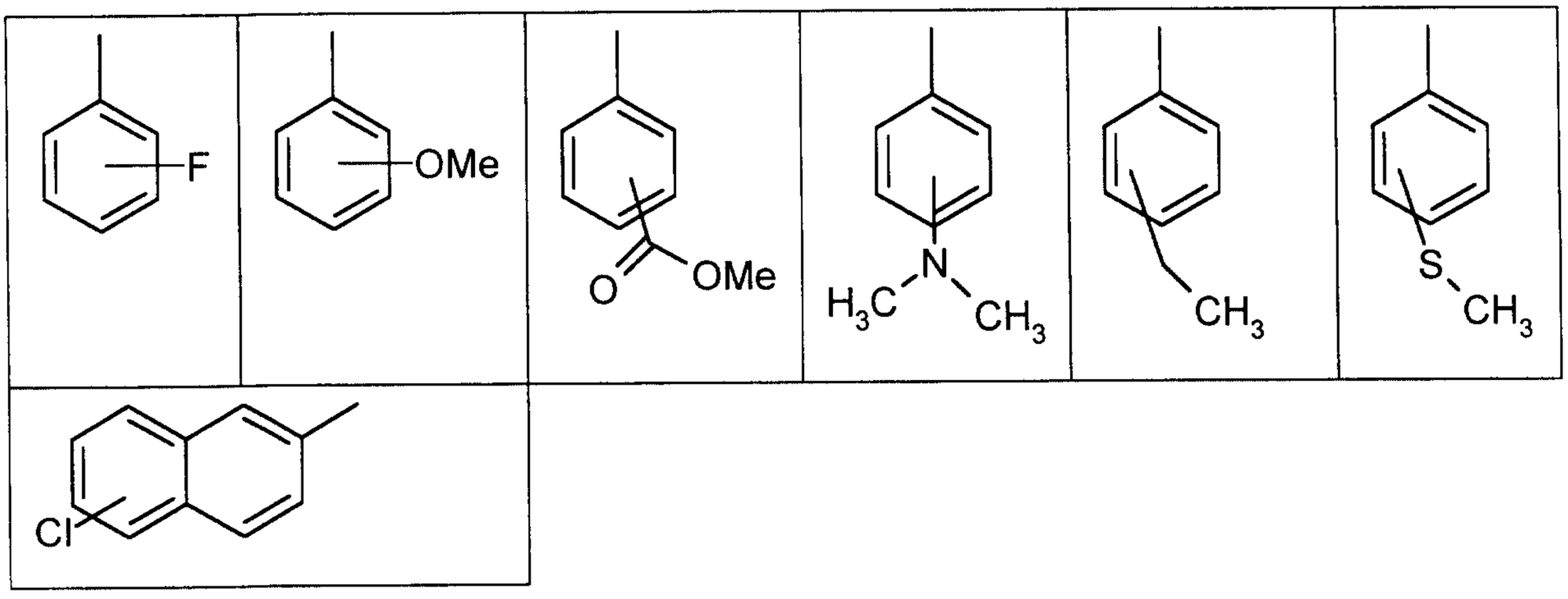
The term "cycloalkyl" by itself or as part of another substituent comprises saturated, cyclic carbohydrate groups with 3 to 8 C atoms, such as e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, cyclohexylmethylene, cycloheptyl or cyclooctyl.

The term "heterocycloalkyl" by itself or as part of another substituent includes cycloalkyl groups, wherein up to two CH_2 groups may be substituted by oxygen, sulfur or nitrogen atoms, and another CH_2 group may be substituted by a carbonyl function, for example pyrrolidine, piperidine, morpholine or

	 Y = CH_2, S, O NH, NC_1-C_6 alkyl	

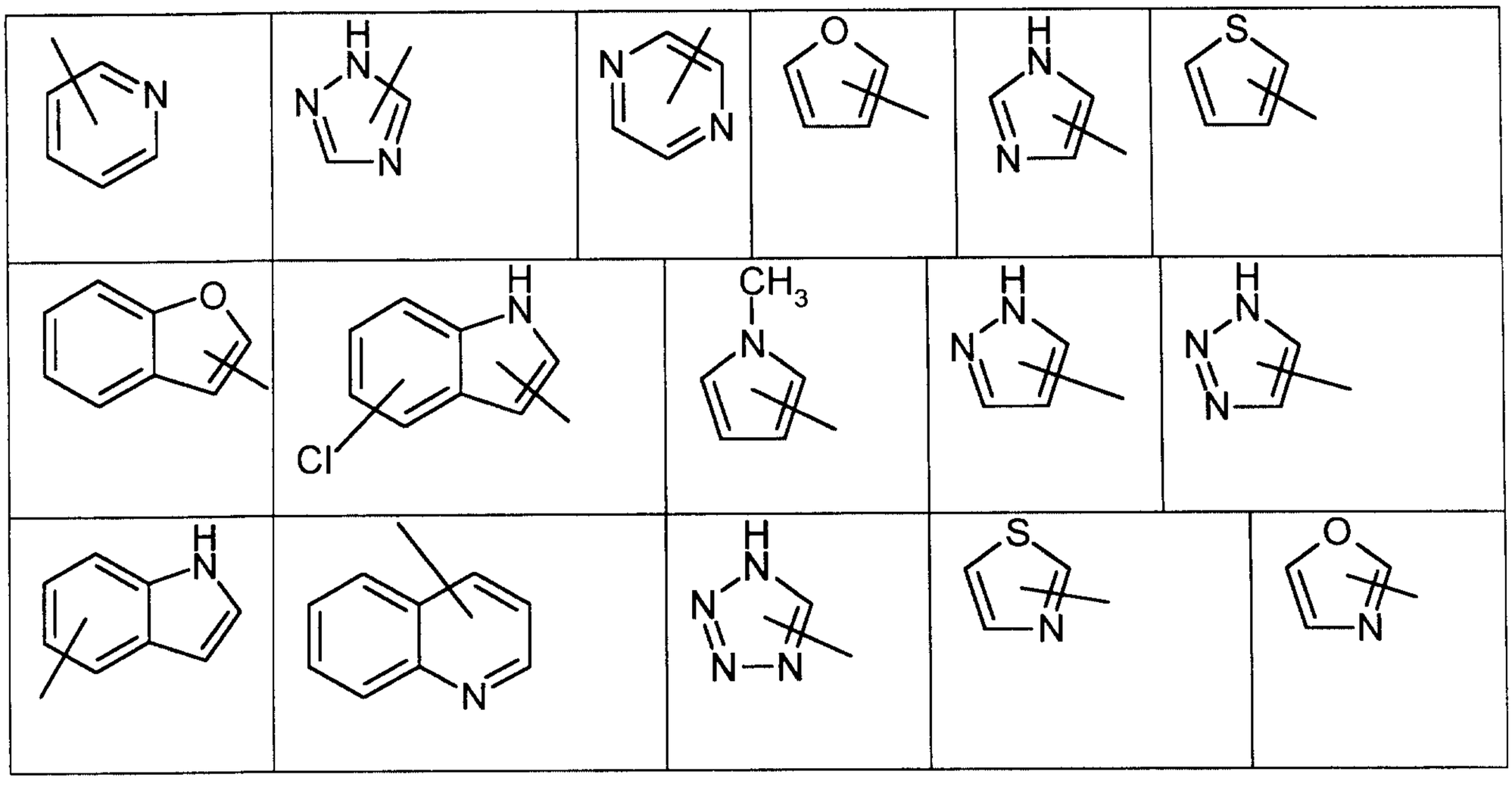
The term "aryl" by itself or as part of another substituent includes aromatic ring systems with up to 3 rings, in which at least 1 ring system is aromatic, and those with up to 3 substituents, preferably up to 1 substituent, wherein the substituents independently from each other can have the meaning C_1-C_6 alkyl, OH, NO_2, CN, CF_3, OR11, SH, SR11, C_1-C_6 alkylhydroxy, C_1-C_6 alkyl-OR11, COOH, COOR11, NH2, NHR11, NR11R12, halogen, wherein the residues R11, R12 independently from each other can mean C_1-C_{10} alkyl, cycloalkyl, C_1-C_4 alkylcycloalkyl.

Apart from phenyl and 1-naphthyl and 2-naphthyl, preferred aryls are:



The term "heteroaryl" by itself or as part of another substituent includes aromatic ring systems with up to 3 rings and with up to 3 identical or different heteroatoms N, S, O, in which at least 1 ring system is aromatic, and those with up to 3 substituents, preferably up to 1 substituent, wherein the substituents independently from each other can have the meaning C_1-C_6 alkyl, OH, NO_2, CN, CF_3, OR11, SH, SR11, C_1-C_6 alkylhydroxy, C_1-C_6 alkyl-OR11, COOH, COOR11, NH_2, NHR11, NR11R12, halogen, wherein the residues R11 independently from each other can have the above indicated meanings.

Preferred heteroaryls are:



The term "ring system" generally refers to rings with 3, 4, 5, 6, 7, 8, 9, or 10 members. Preferred are rings with 5 and 6 members. Furthermore, ring systems with one or 2 annelated rings are preferred.

The compounds of Formula I may be present as such, or, if they contain acidic or basic groups, in the form of their salts with physiologically tolerable bases or acids. Examples for such acids are: hydrochloric acid, citric acid, trifluoracetic acid, tartaric acid, lactic acid, phosphoric acid, methane sulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid, succinic acid, hydroxysuccinic acid, sulfuric acid, glutaric acid, aspartic acid, pyruvic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid, and acetylglycine. Examples for bases are alkali ions, preferably Na, K, alkaline earth ions, preferably C, Mg, ammonium ions.

The compounds according to the invention may be administered orally in the usual way. The application may also be i.v., i.m., with vapors, or sprays through the nasopharynx.

The dosage depends on age, condition and weight of the patient as well as on the type of application. Usually, the daily dose of the active ingredient per person is between 0.1 µg/kg and 1 g/kg orally. This dosage may be given as 2 to 4 split dosages, or once per day as a slow release form.

The novel compounds may be used in the usual solid or liquid pharmaceutical application forms, e.g. as tablets, film tablets, capsules, powder, granules, coated tablets, solutions, or sprays. These are prepared in the usual way. The agents can be processed with the usual pharmaceutical adjuvants such as tablet binders, fillers, preservatives, disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, retardation agents, antioxidants, and/or propellants (see H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). Usually, the so obtained application forms contain the active ingredient in amounts of 0.1 to 99 percent per weight.

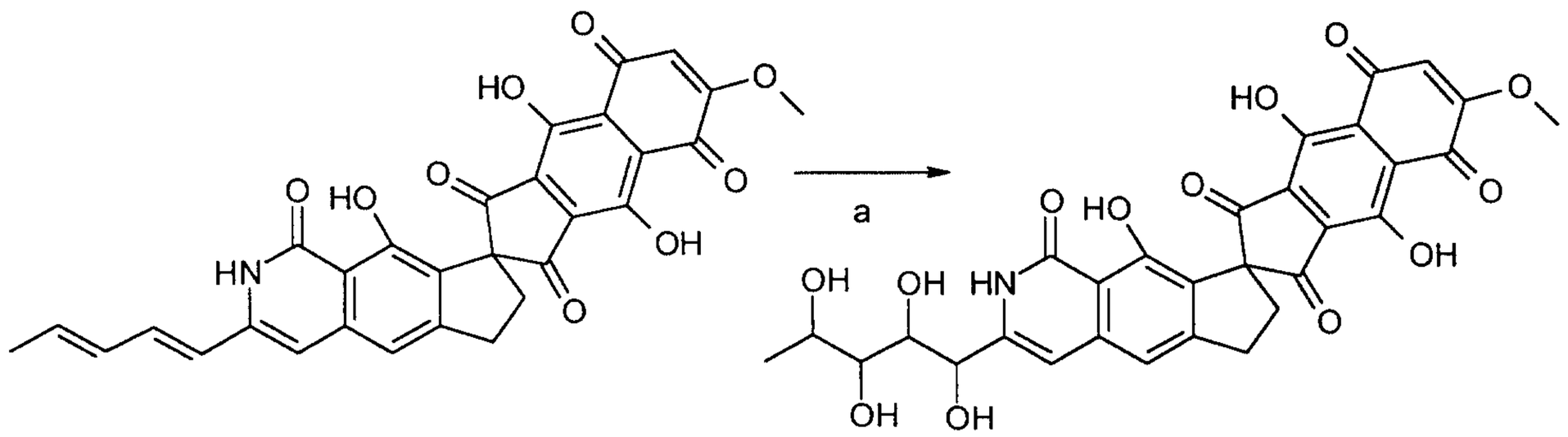
Experimental Part

Fredericamycin A can be prepared by fermentation or fully synthetically according to the known methods. The reduced forms of the Formulas Ib and IIb can be obtained from the appropriate compounds of Formulas Ia and IIa using mild reducing agents.

Preparation of the substances

For the synthesis of water soluble fredericamycin derivatives, fredericamycin (1) was first hydroxylated with osmium(IV)oxide at the diene side chain (see diagram 1).

Diagram 1



Fredericamycin

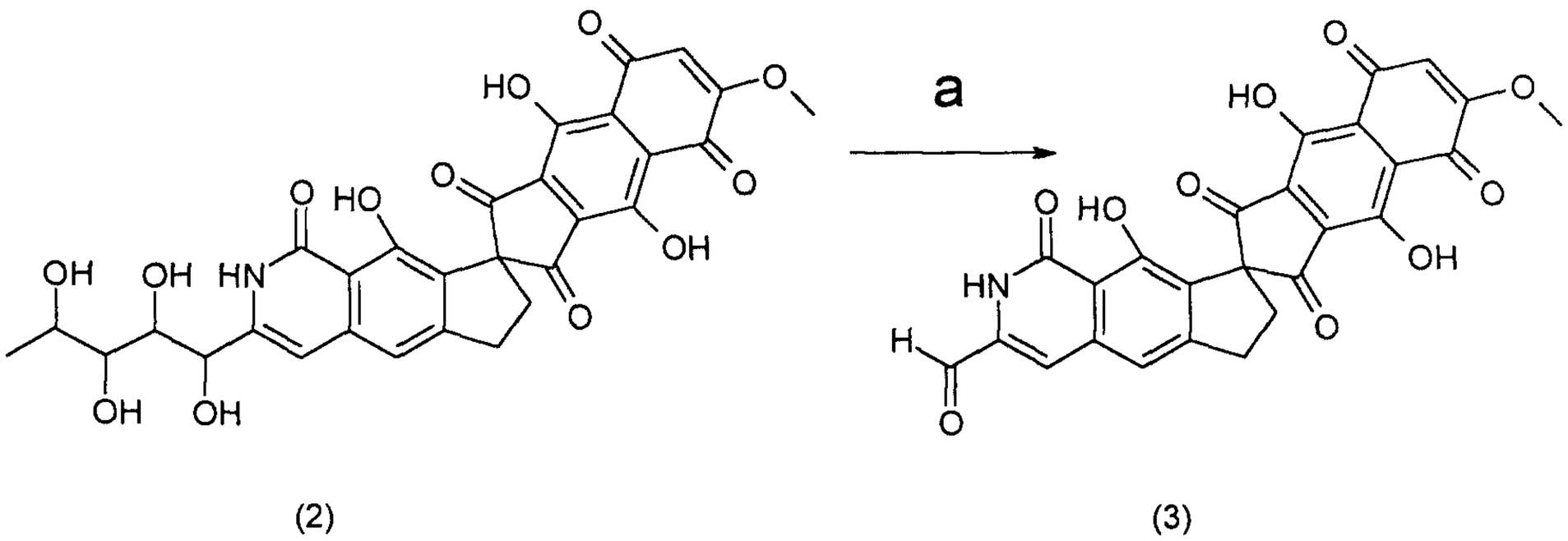
(1)

(2)

a) OsO_4, N-methylmorpholine-N-oxide, CH_2Cl_2, CH_3OH, H_2O

The fredericamyin tetrol (10) also serves as an important intermediate for the synthesis of the herein mentioned fredericamyin derivatives with increased solubility and/or efficacy profile. By iodine cleavage with sodium metaperiodate or carrier-bound periodate, the tetrol side chain can be broken down to the fredericamycin aldehyde (4) with very high yields (see diagram 2).

Diagram 2



a) $NaIO_4$-H_2O-DMF or carrier-bound -IO_4-H_2O-DMF

The fredericamycin aldehyde (3) can be reacted with acylhydrazones, hydroxylamine and O-alkylhydroxylamine to the corresponding hydrazone (see diagram 3) or oxime and oxime ether (see diagram 4). The reaction can be performed at room temperature in solvents such as DMF or pyridine, and is finished after several minutes to hours.

Diagram 3

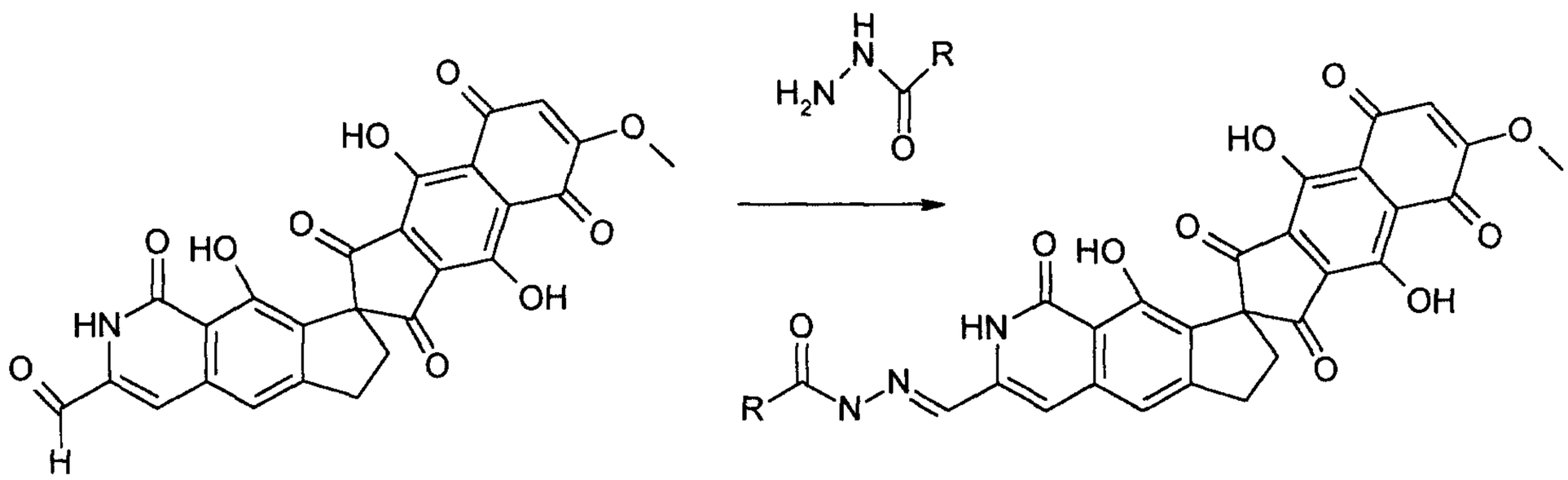
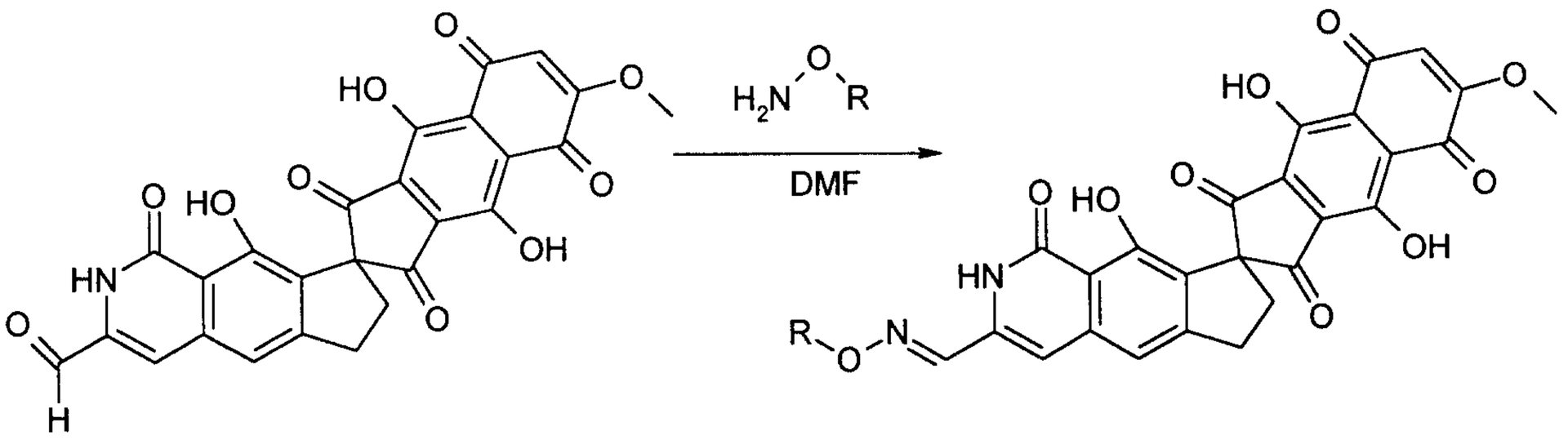


Diagram 4



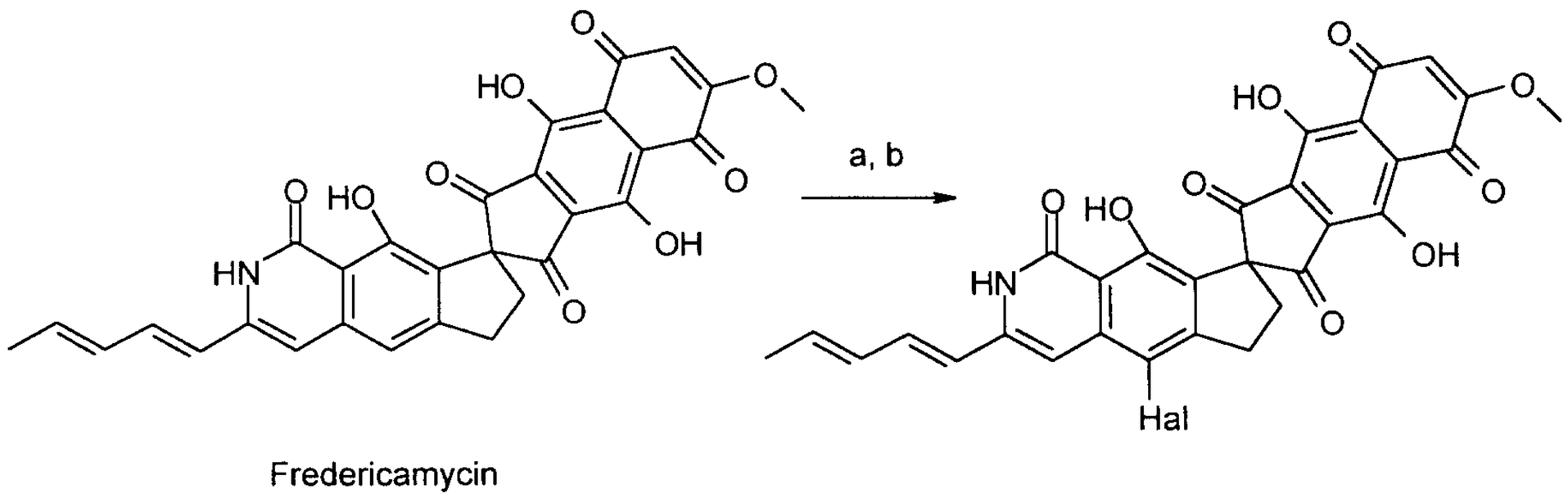
(3)

Halogen-substituted fredericamycin derivatives R=I, Br, Cl, F

Fredericamycin (1) can be reacted with halogenization agents such as N-bromosuccinimide (NBS) and N-iodosuccinimide (NIS) to the substituted 5-bromo- or 5 iodofredericamyin derivatives (4) and (5) with good yields (diagram 5).

The corresponding fluorine compound is also accessible.

Diagram 5

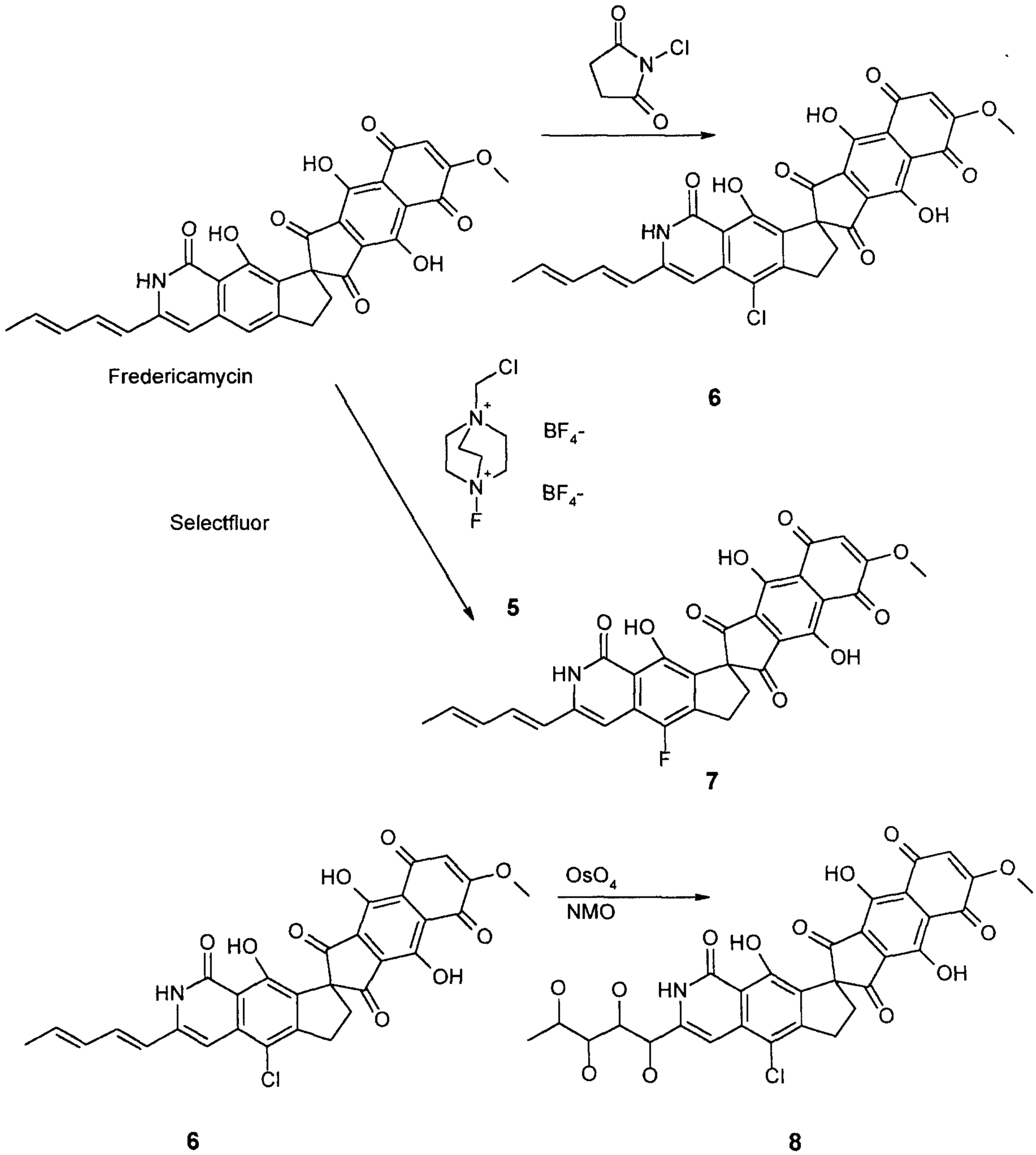


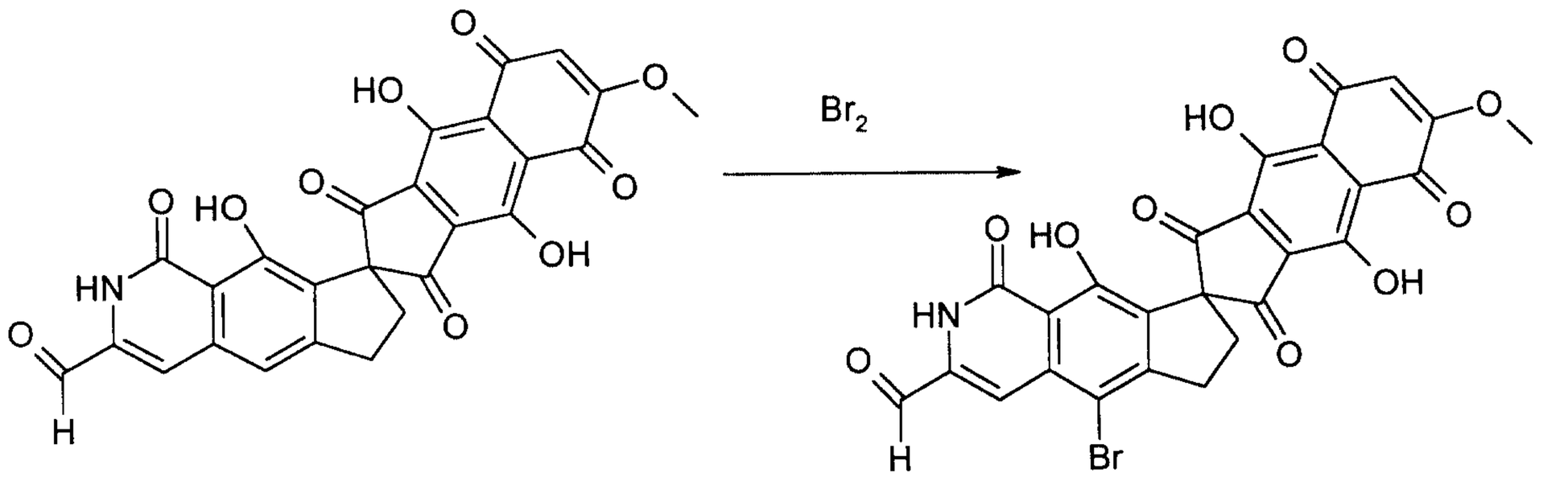
Fredericamycin

Hal: Br (4), I (5)

a) N-bromosuccinimide, DMF, 0°C;

b) N-iodosuccinimide, DMF, 0°C;


Fredericamycin
6
Selectfluor
5
7
6
8

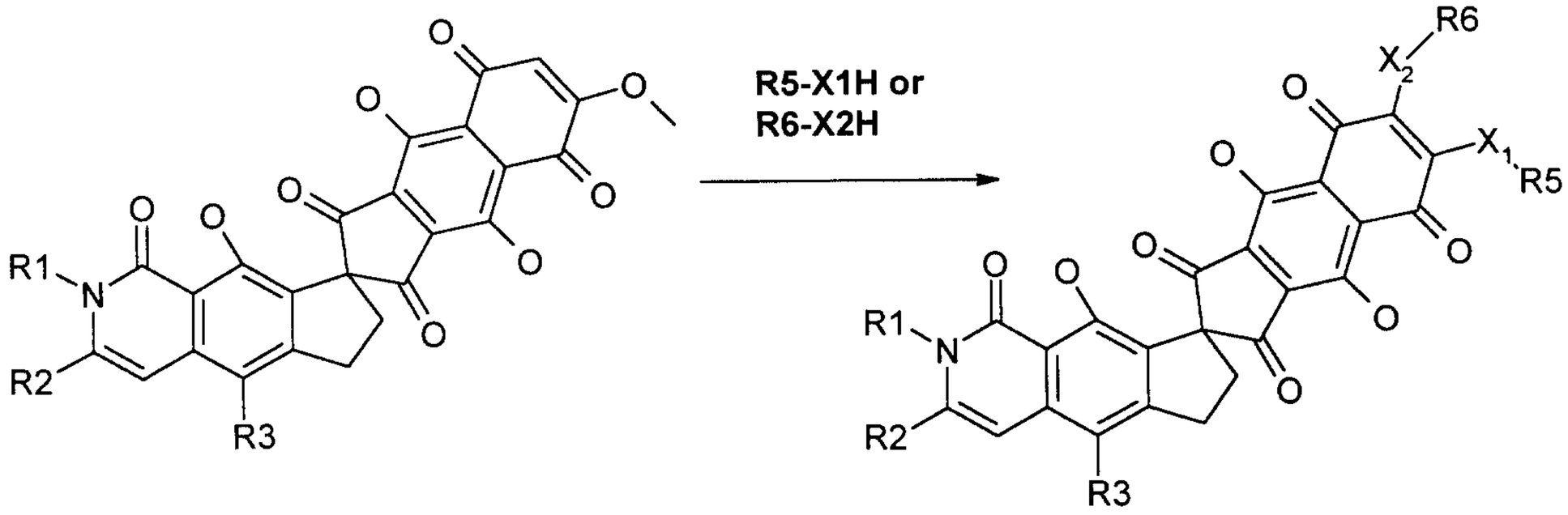


Fredericamycinaldehyde 3

9

The here named fredericamycin derivatives may then be converted into the claimed compounds by reactions with the corresponding S or N nuclophiles. Diagram 6.

Diagram 6



The substitutions of Y1 and/or Y2 equaling N-R5 are accessible over corresponding primary amines HN-R5.

Synthesis examples:

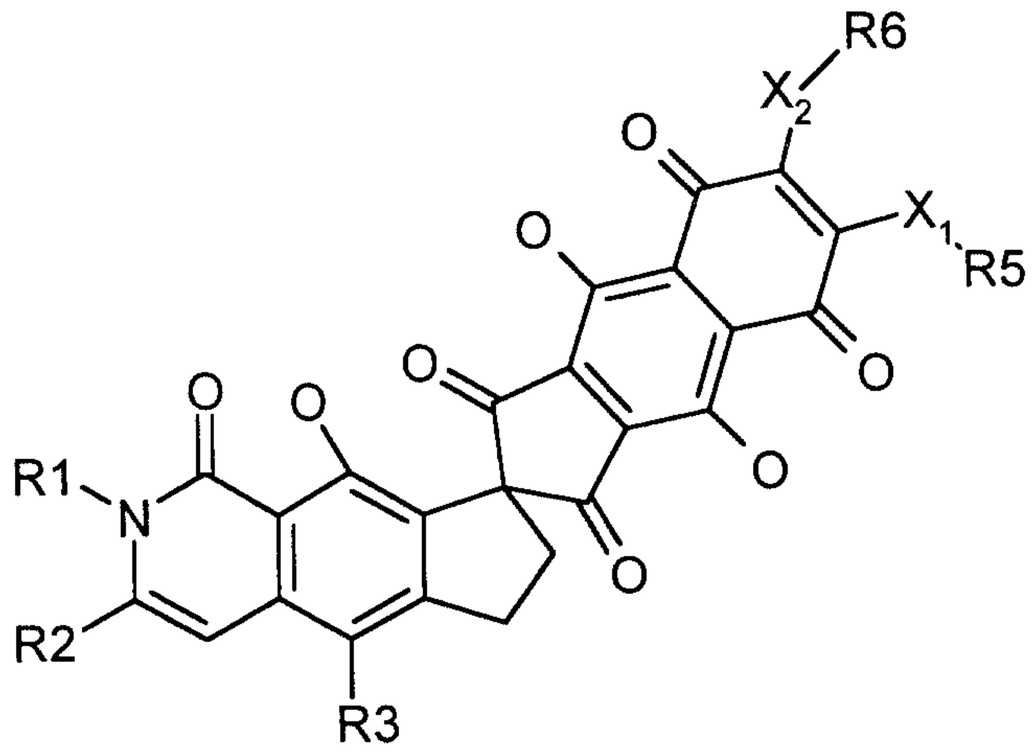


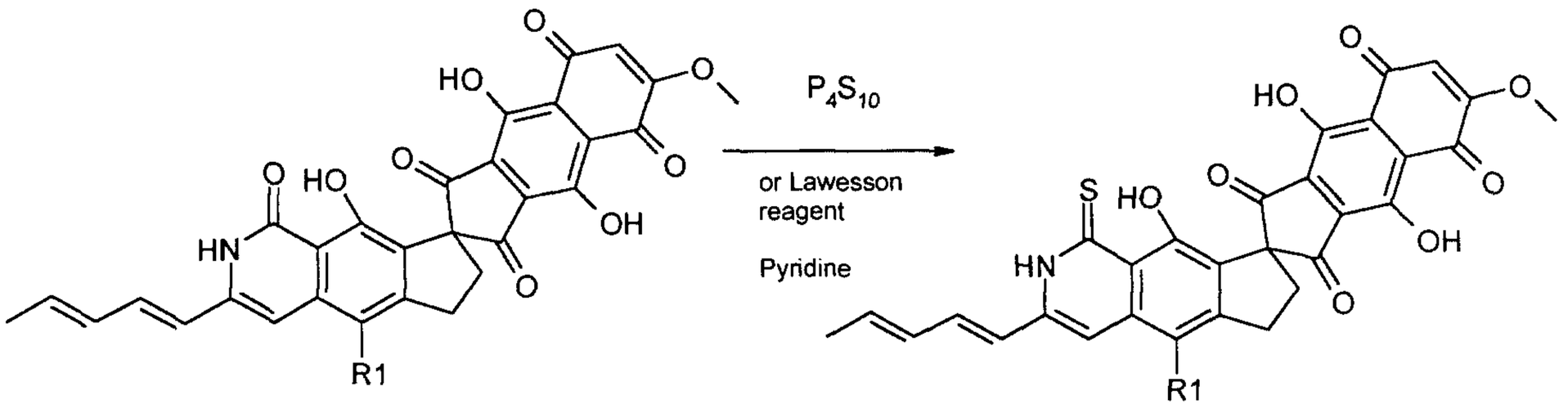
Table 1:

R3	X1-R5	X2-R6	Example
H	OMe	SCH2COOEt	1
H	OH	SCH2CH2NEt2	2
H	OMe	SCH2CH2OH	3
H	OMe	SCH2CH2Net2	4
Cl	OMe	SCH2Ph	5
H	OMe	OH	6

Preparation of thioanalogoues of fredericamycin derivatives

By sulfurization of fredericamycin or its derivatives with Lawesson reagent or P_4S_{10} in pyridine, the derivatives analogous to thiopyridone are accessible (see diagram 7, therein demonstrated with fredericamycin A).

Diagram 7



R1: H,

Biological activity against 12 cancer cell lines:

LCL (H460/lung), MACL (MCF7, breast), LXFL (529L, lung), LXFA (629L, lung), MEXF (462NL, melanoma), MEXF (514L, melanoma), MAXF (401NL, breast), RXF (944L, renal), RXF (486L, renal), UXF (1138L, uterus), PRXF (PC3M, prostate), PRXF (22RV1).

Efficacy (IC70), averaged over all cell lines in µg/ml with 5 test concentrations.

Table 7

Example/Reference	**IC70 µg/ml**
Adriamycin	0.0210
Cisplatin	37.1020
Fredericamycin	0.2790
3	0.1340

Examples

Example 1

(8S)-4',9,9'-trihydroxy-6'-methoxy-7-ethylthioaceto-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1'-3',5',8'(2H)-pentone

Ten (10) mg (18.6 µmol) fredericamycin are dissolved under argon in 1 mL DMF, and then 2.5 µl (22.3 µmol) mercaptoacetic acid ethyl ester is added at room temperature. After 24 h, a

uniform new product has formed according to HPLC (RP18, acetonitril/water). The reaction mixture is concentrated in the high vacuum until dry.

Red crystal mass. Yield: 12 mg (98 %). M/e = 558.9 (M+H), λ_{max}: 510 nm.

Example 2

(8S)-4',9,9'-trihydroxy-6'-methoxy-7(2-diethylaminoethylmercapto)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1'-3',5',8'(2H)-pentone

Ten (10) mg (18.6 µmol) fredericamycin are dissolved under argon in 1 mL DMF, and then 3.8 mg (22.3 µmol) 2-diethylaminoethanthiol.HCl is added at room temperature. After 23 h, another 3.17 mg 2-diethylaminoethanthiol.HCl is added. After a total reaction time of 45 h, the reaction mixture is concentrated in the high vacuum until dry, and the residue is chromatographed using preparative HPLC (RP18, acetonitril/water).

Red crystal mass. Yield: 4 mg (33%). M/e = 657.5 (M+H), λ_{max}: 486 nm.

Example 3

(8S)-4',9,9'-trihydroxy-6'-methoxy-7(2-hydroxyethylmercapto)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1'-3',5',8'(2H)-pentone

Ten (10) mg (18.6 µmol) fredericamycin are dissolved under argon in 1 mL DMF, and then 1.6 µl (22.3 µmol) mercaptoethanol is added at room temperature. After 20 h, a uniform new product has formed according to HPLC (RP18, acetonitril/water). The reaction mixture is concentrated in the high vacuum until dry.

Red crystal mass. Yield: 11 mg (99%). M/e = 617.4 (M+H), λ_{max}: 486 nm.

Example 4

(8S)-4',9,9'-trihydroxy-6'-methoxy-7-(2-diethylaminoethylmercapto)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1'-3',5',8'(2H)-pentone

Ten (10) mg (18.6 µmol) fredericamycin are dissolved under argon in 1 mL DMF, and then 3.8 mg (22.3 µmol) 2-diethylaminoethanthiol.HCl is added at room temperature. After 6 h,

another 1.9 mg 2-diethylaminoethanthiol.HCl is added. After 23 h, another 1.9 mg 2-diethylaminoethanthiol.HCl is added. After a total reaction time of 30 h, the reaction mixture is concentrated in the high vacuum until dry, and the residue is chromatographed using preparative HPLC (RP18, acetonitril/water).

Red crystal mass. Yield: 10 mg (80%). M/e = 671.4 (M+H), λ_{max}: 486 nm.

Example 5

(8S)-4',9,9'-trihydroxy-6'-methoxy-7-(benzylmercapto)-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1'-3',5',8'(2H)-pentone

Five (5.0) mg (8.71 µmol) 5-chlorofredericamycin are dissolved under argon in 1 mL DMF, and then 1.23 µl (10.45 µmol) benzylmercapto is added at room temperature. After 6 h, another 1.9 mg 2-diethylaminoethanthiol.HCl is added. After 4 h, the reaction mixture is concentrated in the high vacuum until dry.

Red crystal mass. Yield: 6 mg (99%). M/e = 695.9 (M+H), λ_{max}: 504 nm.

Example 6

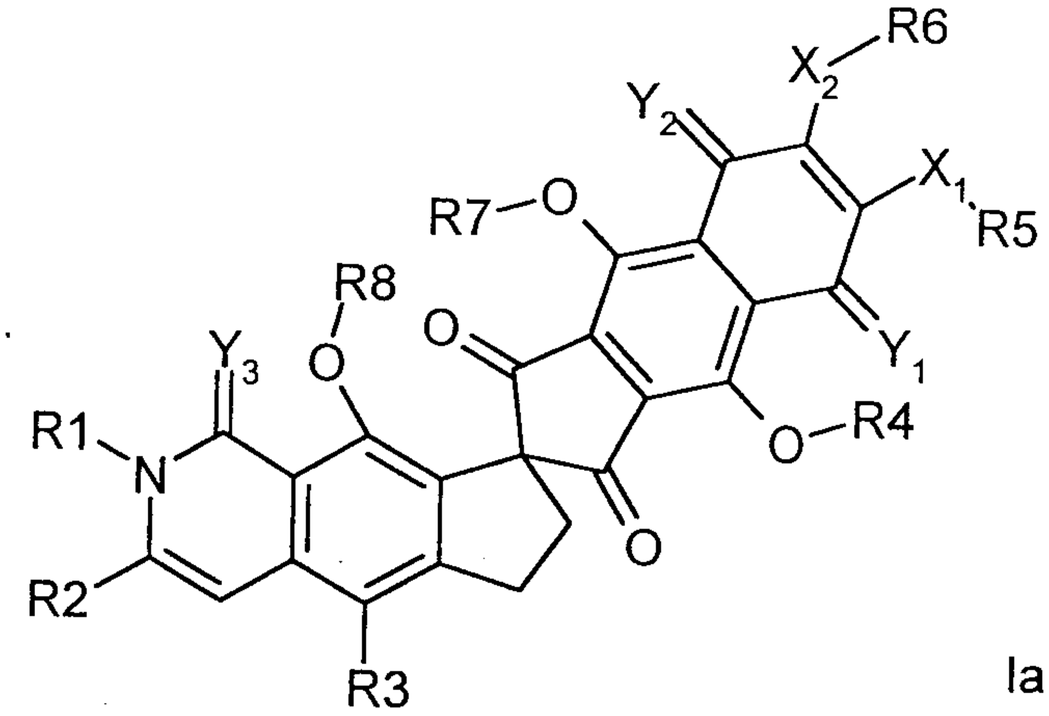
(8S)-4',9,9'-trihydroxy-6'-methoxy-7-hydroxy-3-[(1E,3E)-penta-1,3-dienyl]-6,7-dihydrospiro[cyclopenta[g]isoquinoline-8,2'-cyclopenta[b]-naphthalene]-1,1'-3',5',8'(2H)-pentone

Ten (10) mg (18.6 µmol) fredericamycin are dissolved under argon in 1 mL DMF, and then 2.5 mg (22.3 µmol) 2-aminoethanthiol.HCl is added at room temperature. After 26 h, another 2.1 mg 2-aminoethanthiol.HCl and some trifluoracetic acid is added. After a total reaction time of 72 h, the reaction mixture is concentrated in the high vacuum until dry, and the residue is chromatographed using preparative HPLC (RP18, acetonitril/water).

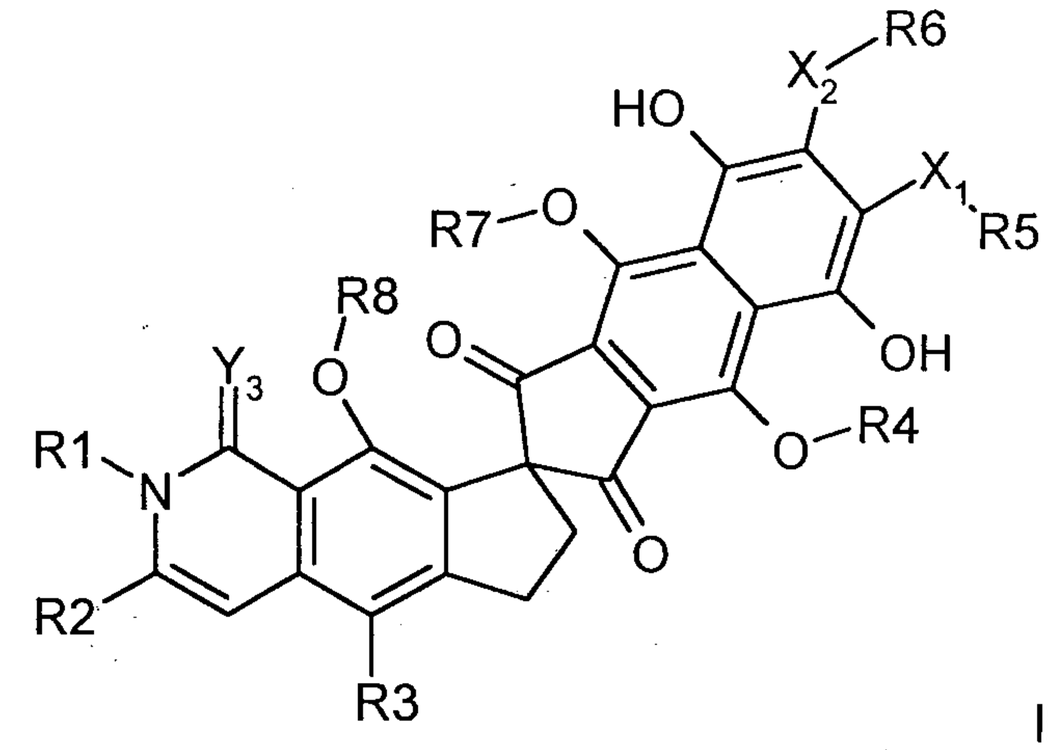
Red crystal mass. Yield: 9 mg (87%). M/e = 554.5 (M-H), λ_{max}: 372 nm.

CLAIMS

1. A compound according to the general formula Ia or Ib:



Ia



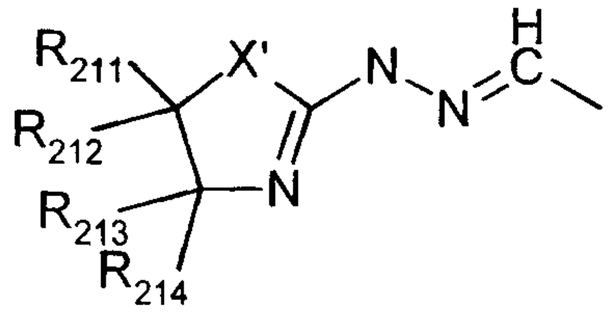
Ib

wherein in each,

R1 is H, C_1-C_6 alkyl, cycloalkyl, or C_1-C_4 alkylcycloalkyl;

R2 is C_1-C_{14} alkyl, C_2-C_{14} alkenyl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkyl heteroaryl, cycloalkyl, C_1-C_4 alkyl-cycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y_p$, $CH_2NHCOR21$, $CH_2NHCSR21$, $CH_2S(O)nR21$, with n=0, 1, 2, $CH_2SCOR21$, CH_2OSO_2—R21, CHO, CH=NOH, CH(OH)R21, —CH=NOR21, —CH=NOCOR21, —CH=NOCH$_2$CONR21R22, —CH=NOCH(CH_3)CONR21R22, —CH=NOC(CH_3)$_2$CONR21 R22, —CH=N—NHCO—R23, —CH=N—NHCO—CH_2NHCOR21, —CH=N—O—

CH_2NHCOR_{21}, —CH=N—NHCS—R23, —CH=CR24R25 (trans or cis),
COOH, COOR21, CONR21R22, —CH=NR21, —CH=N—NR21R22,



—CH=N—$NHSO_2$ aryl, or —CH=N—$NHSO_2$ heteroaryl;
wherein, m is 1 to 6, o is 1, p is 1 to 2m+o;
m is 2 to 6, o is −1, p is 1 to 2m+o; or
m is 4 to 6, o is −2, p is 1 to 2m+o; and
Y independently from each other is selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH and SR21; and
wherein X′ is NR215, O, or S; and R211, R212, R213, R214, and R215 are independently from each other H or C_1-C_6 alkyl;
R21, R22 are independently from each other C_1-C_{14} alkyl, C_1-C_{14} alkanoyl, C_1-C_6 alkylhydroxy, C_1-C_6 alkylamino, C_1-C_6 alkylamino-C_1-C_6 alkyl, C_1-C_6 alkylamino-di-C_1-C_6 alkyl, cycloalkyl, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, aryl, aryloyl, C_1-C_4 alkylaryl, heteroaryl, heteroaryloyl, C_1-C_4 alkylheteroaryl, cycloalkanoyl, C_1-C_4 alkanoylcycloalkyl, heterocycloalkanoyl, C_1-C_4 alkanoylheterocycloalkyl, C_1-C_4 alkanoylaryl, C_1-C_4 alkanoylheteroaryl, or mono- and di-sugar linked through a C atom which would carry an OH group in the sugar, wherein the sugars are independently from each other selected from the group consisting of glucuronic acid and its stereo isomers at all optical C-atoms, aldopentoses, and aldohexoses, including their desoxy compounds;

R23 independently of R21, is R21, CH_2-pyridinium salts, or CH_2-tri-C_1-C_6 alkylammonium salts;

R24 independently of R21, is R21, H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH2, or NHCOR21;

R25 independently of R21, is R21, H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, or NHCOR21; or

R24, R25 together are C_4-C_8 cycloalkyl;

R3 is H, F, Cl, Br, I, OH, OR31, NO_2, NH_2, NHR31, NR31R32, NHCHO, NHCOR31, NHCOCF3, $CH_{3-m}hal_m$ or OCOR31, wherein hal is Cl or F and m is 1, 2 or 3;

R31, 32 independently from each other are C_1-C_6 alkyl;

R5, R6 Independently from each other are H, C_1-C_{14} alkyl, C_2-C_{14} alkenyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl, cycloalkyl, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_4 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y_p$, or R5 and R6, together with X_1—C—C—X_2, form a ring with 5, 6, or 7 members,

wherein, m is 1 to 6, o is 1, p is 1 to 2m+o;

m is 2 to 6, o is −1, p is 1 to 2m+o; or

m is 4 to 6, o is −2, p is 1 to 2m+o; and

Y independently from each other is selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NR21R22, SH and SR21;

R4, R7, R8 independently from each other are H, C_1-C_6 alkyl, CO—R41;

R41 independently from R21 is R21;

X1 is O, S, NH, N—C_1-C_8 alkyl, or N-cycloalkyl;

X2 is O, S, NH, N—C_1-C_8 alkyl, or N-cycloalkyl;

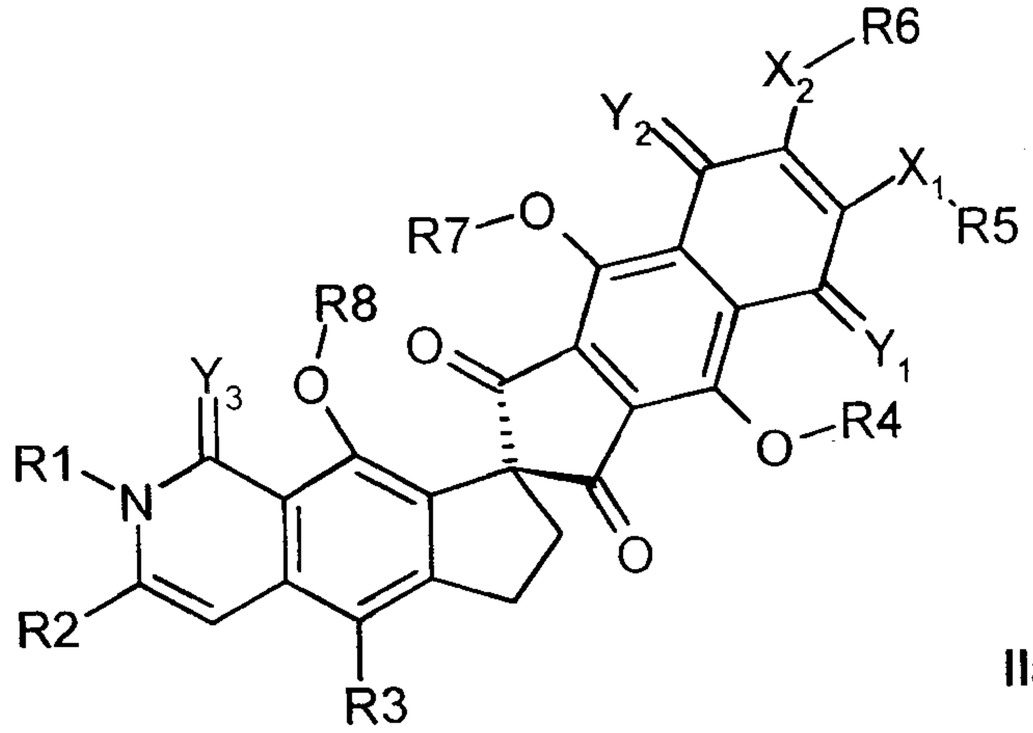
Y1 is O, or N—R9, wherein R9, independently from R5, is R5;

Y2 is O, or N—R10, wherein R10, independently from R5, is R5; and, if Y1 or Y2 are N—R9 or N—R10, X2—R6 may be H;

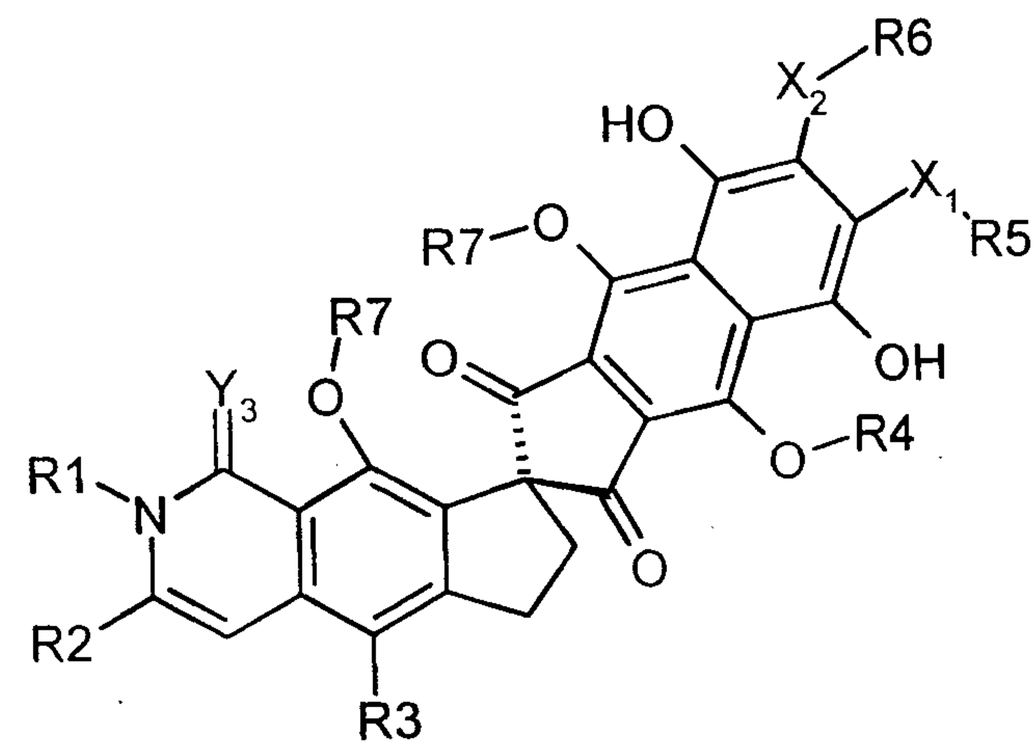
Y3 is O, S, or NH;

or a stereoisomer, tautomer or physiologically tolerable salt thereof.

2. The compound according to claim 1, wherein Formula Ia or Ib adopt the stereochemistry of Formula IIa or IIb:



IIa



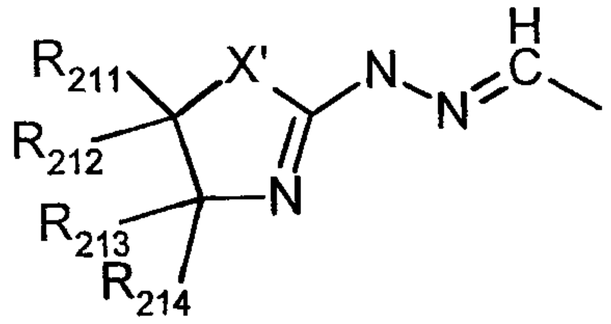
IIb

3. The compound according to claim 1, wherein

R1 is H, C_1-C_5 alkyl, or cycloalkyl;

R2 is C_1-C_5 alkyl, C_1-C_4 alkylaryl, C_2-C_5 alkenyl, heteroaryl, C_1-C_4 alkylheteroaryl, CHF_2, CF_3, polyol side chain, CHOH—CHOH—CHOH—CHOH—CH_3, CHOH—CHOH—CH=CH—CH_3, CH=CH—CHOH—CHOH—CH_3, CH_2Y , CH_2NH_2, $CH_2NR21R22$, $CH_2NHCOR23$, $CH_2NHCSR23$, CH_2SH, $CH_2S(O)nR21$, $CH_2SCOR21$, CH_2OH, CH_2OR21, CH_2OSO_2—R21, CHO, $CH(OR21)_2$, $CH(SR21)_2$, CN, CH=NOH, CH=NOR21, CH=NOCOR21,

CH=N—NHCO—R23, CH=CR24, R25 (trans or cis), COOH, COOR21, CONR21R22, —CH=NR21, —CH=N—NR21R22,



—CH=N—$NHSO_2$ aryl, —CH=N—$NHSO_2$ heteroaryl, or CHN—NHCO—R23,

wherein Y is F, Cl, Br or I; and

wherein X' is NR215, O, or S; and R211, R212, R213, R214, and R215 are independently from each other H or C_1-C_6 alkyl;

R21, R22 independently from each other are C_1-C_6 alkyl, cycloalkyl, aryl, C_1-C_4 alkylaryl, heteroaryl, or C_1-C_4 alkylheteroaryl;

R23 independently of R21, is R21, a CH_2-pyridinium salt, or a CH_2-tri-C_1-C_6 alkylammonium, salt;

R24 independently of R21, is R21, or H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, or NHCOR21;

R25 independently of R21, is R21, or H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, or NHCOR2; or

R24, R25 together are C_4-C_8 cycloalkyl;

R3 is F, Cl, Br, I, NO_2, NH_2, or NHCOR31;

R31 independently from each other is C_1-C_6 alkyl;

R5, R6 independently from each other are H, C_1-C_{14} alkyl, C_2-C_{14} alkenyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl, cycloalkyl, C_1-C_4

alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y_p$, or R5 and R6, together with X_1—C—C—X_2, form a ring with 5, 6, or 7 members,

wherein, m is 1 to 6, o is 1, p is 1 to 2m+o;

m is 2 to 6, o is −1, p is 1 to 2m+o; or

m is 4 to 6, o is −2, p is 1 to 2m+o; and

Y independently from each other is selected from the group consisting of halogen, OH, OR21,

NH_2, NHR21, NR21R22, SH and SR21;

R4, R7, R8 independently from each other are H, C_1-C_6 alkyl, or CO—R41;

R41 independently from R21, is R21;

Y3 is O or S;

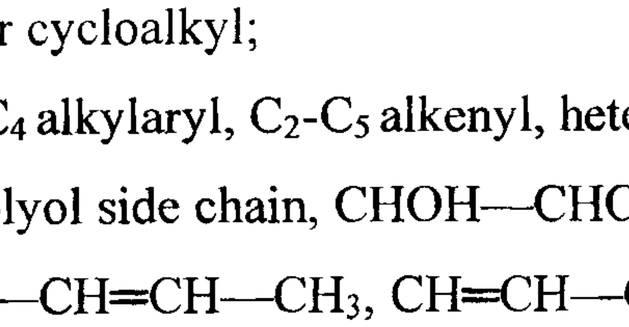
or a stereoisomer, tautomer or physiologically tolerable salt thereof.

4. The compounds according to claim 1 in the form of their inclusion compounds with cyclodextrin.

5. The compound according to claim 2 wherein

R1 is H, C_1-C_5 alkyl, or cycloalkyl;

R2 is C_1-C_5 alkyl, C_1-C_4 alkylaryl, C_2-C_5 alkenyl, heteroaryl, C_1-C_4 alkylheteroaryl, CHF_2, CF_3, polyol side chain, CHOH—CHOH—CHOH—CHOH—CH_3, CHOH—CHOH—CH=CH—CH_3, CH=CH—CHOH—CHOH—CH_3, CH_2Y , CH_2NH_2, $CH_2NR21R22$, $CH_2NHCOR23$, $CH_2NHCSR23$, CH_2SH, $CH_2S(O)nR21$, $CH_2SCOR21$, CH_2OH, CH_2OR21, CH_2OSO_2—R21, CHO, $CH(OR21)_2$, $CH(SR21)_2$, CN, CH=NOH, CH=NOR21, CH=NOCOR21, CH=N—NHCO—R23, CH=CR24, R25 (trans or cis), COOH, COOR21, CONR21R22, —CH=NR21, —CH=N—NR21R22,



—CH=N—$NHSO_2$ aryl, —CH=N—$NHSO_2$ heteroaryl, CH=N—NHCO—R23,

wherein Y is F, Cl, Br or I;

n is 0, 1 or 2; and

wherein X′ is NR215, O, or S; and R211, R212, R213, R214, and R215 are independently from

each other H or C_1-C_6 alkyl;

R21, R22 independently from each other are C_1-C_6 alkyl, cycloalkyl, aryl, C_1-C_4 alkylaryl, heteroaryl, or C_1-C_4 alkylheteroaryl;

R23 independently of R21, is R21, a CH_2-pyridinium salt, or a CH_2-tri-C_1-C_6 alkylammonium salt;

R24 independently of R21, is R21, H, CN, $COOH_3$, COOH, COOR21, CONR21R22, NH_2, or NHCOR21;

R25 independently of R21, is R21, H, CN, $COCH_3$, COOH, COOR21, CONR21R22, NH_2, or NHCOR21; or

R24, R25 together are C_4-C_8 cycloalkyl;

R3 is F, Cl, Br, I, NO_2, NH_2, or NHCOR31;

R31 independently from each other is C_1-C_6 alkyl;

R5, R6 independently from each other are H, C_1-C_{14} alkyl, C_2-C_{14} alkenyl, aryl, C_1-C_4 alkylaryl, heteroaryl, C_1-C_4 alkylheteroaryl, cycloalkyl, C_1-C_4 alkylcycloalkyl, heterocycloalkyl, C_1-C_4 alkylheterocycloalkyl, $C_mH_{2m+o-p}Y_p$ or R5 and R6, together with X_1—C—C—X_2, form a ring with 5, 6, or 7 members,

wherein, m is 1 to 6, o is 1, p is 1 to 2m+o;

m is 2 to 6, o is −1, p is 1 to 2m+o; or

m is 4 to 6, o is −2, p is 1 to 2m+o; and

Y independently from each other is selected from the group consisting of halogen, OH, OR21, NH_2, NHR21, NHR21, NR22, SH and SR21;

R4, R7, R8 independently from each other are H, C_1-C_6 alkyl, or CO—R41;

R41 independently from R21 is R21;

Y3 is O or S;

or a stereoisomer, tautomer or physiologically tolerable salt thereof.

6. The use for treating a tumor selected from the group consisting of lung, renal, prostate, uterine, melanoma and breast tumors of the compound of claim 1.

7. The use of claim 6 wherein said tumor is a lung tumor.

8. The use of claim 6 wherein said tumor is a renal tumor.

9. The use of claim 6 wherein said tumor is a prostate tumor.

10. The use of claim 6 wherein said tumor is a uterine tumor.

11. The use of claim 6 wherein said tumor is a melanoma.

12. The use of claim 6 wherein said tumor is a breast tumor.

13. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or adjuvant.

14. The use for treating a tumor selected from the group consisting of lung, renal, prostate, uterine, melanoma and breast tumors of the compound of claim 2.

15. The use of claim 14 wherein said tumor is a lung tumor.

16. The use of claim 14 wherein said tumor is a renal tumor.

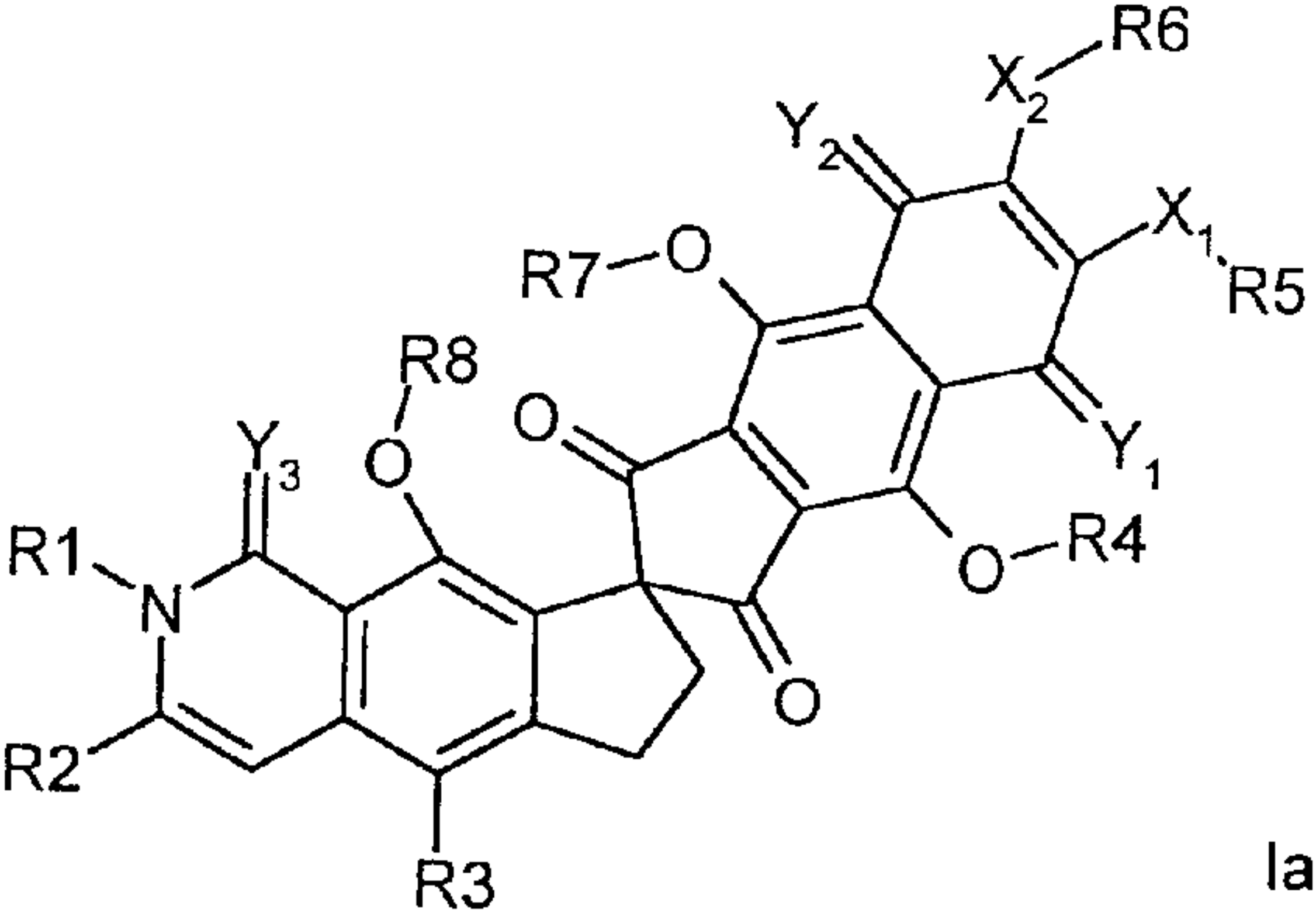
17. The use of claim 14 wherein said tumor is a prostate tumor.

18. The use of claim 14 wherein said tumor is a uterine tumor.

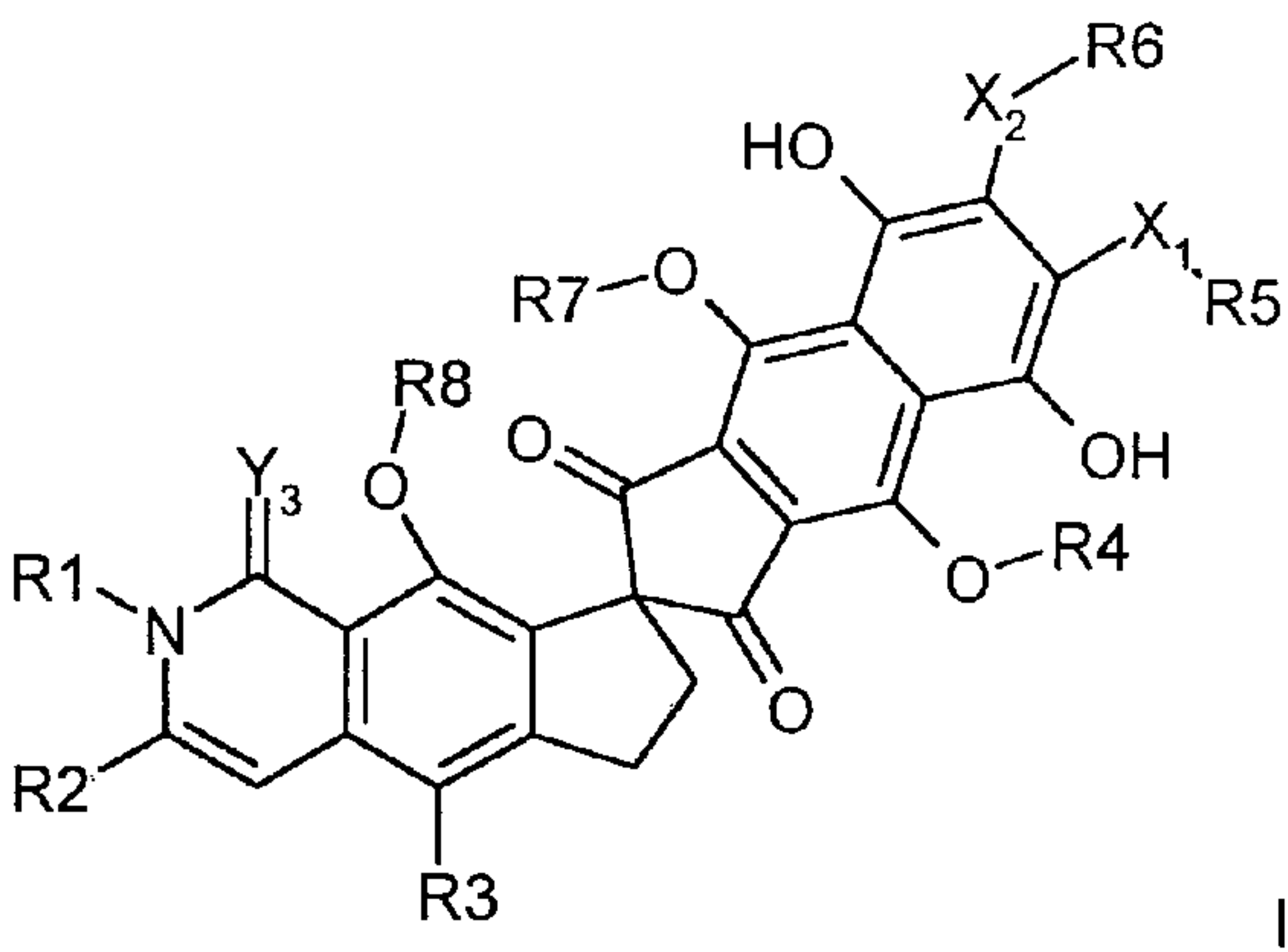
19. The use of claim 14 wherein said tumor is a melanoma.

20. The use of claim 14 wherein said tumor is a breast tumor.

21. A pharmaceutical composition comprising the compound of claim 2 and a pharmaceutically acceptable carrier or adjuvant.


R6
X2
Y2
X1
R5
R7
O
R8
O
Y3
O
Y1
R1
N
O
R4
O
R2
R3

Ia


R6
X2
HO
X1
R5
R7
O
R8
O
OH
Y3
O
R4
R1
N
O
R2
R3

Ib