New benzo[*b*]chromeno-naphthyridin-7-one and pyrano[2',3':7,8]quino[2,3-*b*]quinoxalin-7-one compounds, process for their preparation and pharmaceutical compositions containing them

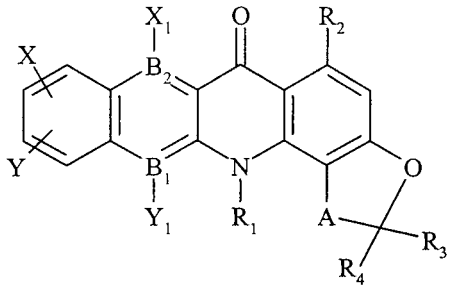
The present invention relates to new benzo[*b*]chromeno-naphthyridin-7-one and pyrano[2',3':7,8]quino[2,3-*b*]quinoxalin-7-one compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the invention are derivatives of acronycin, which is an alkaloid having anti-tumour properties that have been demonstrated in experimental models (*J. Pharm. Sci.*, 1966, 55 (8), 758-768). Despite having a broad spectrum of activity, however, acronycin is not very powerful and is only moderately active. In addition, this product is of low solubility, which limits its bioavailability and thus its use in pharmaceutical compositions administrable by the intravenous route.

Various modifications have been made to that molecule, such as those described in *J. Med. Chem.*, 1996, 39, 4762-4766, EP 1 042 326, EP 1 061 081 or EP 1 297 835, which have enabled significant improvement of the potency, the anti-tumour efficacy and the solubility of those products. Nevertheless, anti-cancer therapeutic requirements call for the constant development of new anti-tumour agents, with the aim of obtaining medicaments that are both more active and better tolerated. More especially, solid tumours pose a major problem for anti-cancer chemotherapy in view of their intrinsic and/or acquired resistance to existing products. It is accordingly of the utmost importance to have access to as broad as possible a range of products that express a strong cytotoxic activity in order to be able to have available the most effective treatments for tumour diseases as a whole.

In addition to the fact that the compounds of the invention are new, they have a surprising *in vitro* and *in vivo* cytotoxic activity superior to that observed hitherto. Thus, the compounds discovered by the Applicant have anti-tumour properties that make them particularly useful in the treatment of cancers. Among the types of cancer that can be treated by the compounds of the present invention, adenocarcinomas and carcinomas, sarcomas, gliomas and leukaemias may be mentioned without implying any limitation.

More especially, the present invention relates to compounds of formula (I) :



(I)

wherein:

- B_1 and B_2, which may be identical or different, each independently of the other represents a carbon atom or a nitrogen atom, with the proviso that at least one of the two groups B_1 or B_2 represents a nitrogen atom,

- X and Y, which may be identical or different, each independently of the other represents one or more groups selected from :
  - the atoms hydrogen and halogen,
  - the groups hydroxy, linear or branched $(C_1\text{-}C_6)$alkoxy, nitro, cyano, linear or branched $(C_1\text{-}C_6)$alkyl, linear or branched $(C_2\text{-}C_6)$alkenyl, linear or branched $(C_1\text{-}C_6)$-polyhaloalkyl, or
  - groups of formula $-NR_aR_b$ wherein :

    R_a and R_b, which may be identical or different, each independently of the other represents a group selected from hydrogen and the groups $-C(O)-CF_3$, $-C(O)-NH_2$ and linear or branched $(C_1\text{-}C_6)$alkyl, optionally substituted by a group $NR'_aR'_b$ wherein :

    R'_a and R'_b, which may be identical or different, each independently of the other represents a group selected from hydrogen and linear or branched $(C_1\text{-}C_6)$alkyl, or R'_a and R'_b, together with the nitrogen atom carrying them, form a monocyclic heterocycle having from 5 to 7 ring members and optionally containing in the ring system a second hetero atom selected from oxygen and nitrogen,

    or R_a and R_b, together with the nitrogen atom carrying them, form a monocyclic heterocycle having from 5 to 7 ring members and optionally containing in the ring system a second hetero atom selected from oxygen and nitrogen,

- X_1 and Y_1, which may be identical or different, each independently of the other represents a group selected from the substituents as defined for X and Y,

it being understood that, when B_1 and/or B_2 represent a nitrogen atom, B_1 and B_2 do not carry substituents Y_1 and X_1 respectively,

- R_1 represents a hydrogen atom or a linear or branched $(C_1\text{-}C_6)$alkyl group,

- R_2 represents a group selected from hydrogen and the groups linear or branched $(C_1\text{-}C_6)$alkyl, $-OR''_a$; $-NR'_aR'_b$; $O-T_a-OR''_a$; $-NR''_a-T_a-NR'_aR'_b$; $-NR''_a-C(O)-T_aH$; $O-C(O)-T_aH$; $-O-T_a-NR'_aR'_b$; $-NR''_a-T_a-OR''_a$; $-NR''_a-T_a-CO_2R''_a$; and $-NR''_a-C(O)-T_a-NR'_aR'_b$,
  wherein:
  * T_a represents a linear or branched $(C_1\text{-}C_6)$alkylene chain,
  * R'_a and R'_b are as defined hereinbefore,
  * R''_a represents a group selected from hydrogen and linear or branched $(C_1\text{-}C_6)$alkyl,

- R_3 and R_4, which may be identical or different, each independently of the other represents a hydrogen atom or a linear or branched $(C_1\text{-}C_6)$alkyl group, or R_3 and R_4, together with the carbon atom carrying them, form a monocyclic ring having from 3 to 6 ring members,

- A represents a group of formula :
  a) $-CH(R_5)-CH(R_6)-$ wherein :

  * *R_5 and R_6,, which may be identical or different, each represents independently of the other a group selected from :*

    1) hydrogen,

    2) the groups OR_c, NR_cR_d, SR_c, wherein :
       - R_c, R_d, which may be identical or different, each independently of the other

represents a group selected from hydrogen, the groups linear or branched (C_1-C_6)alkyl, aryl and aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched,

or the group C(O)–R_e wherein R_e represents a group selected from hydrogen, aryl or $NR'''_aR'''_b$ wherein R'''_a and R'''_b are identical and represent a hydrogen atom or wherein R'''_a and R'''_b, together with the nitrogen atom carrying them, form a monocyclic heterocycle having from 5 to 7 ring members and optionally containing in the ring system a second hetero atom selected from oxygen and nitrogen,

3) W_1–$C(W_2)$–U–V wherein :

α) W_1 represents an oxygen atom, a sulphur atom or NR_c (wherein R_c is as defined hereinbefore),

β) W_2 represents an oxygen atom or a sulphur atom,

γ) U represents a linear or branched (C_1-C_8)alkylene chain or a linear or branched (C_2-C_8)alkenylene chain,

δ) V represents a group selected from :

- hydrogen,
- aryl,
- and the groups OR_c, CO_2R_c, COR_c, $CONR'_aR'_b$, NR_cR_d, $N(R_c)$–$CO_2R'_c$, $N(R_c)$–COR'_c, wherein R'_a, R'_b, R_c and R_d are as defined hereinbefore and R'_c represents a group selected from hydrogen, linear or branched (C_1-C_6)alkyl, aryl, or aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched,

ε) U represents a bond when W_2 does not represent an oxygen atom and when V does not represent a group selected from :

- hydrogen
- aryl and
- NH_2,

4) W_1–$C(W_2)$–W_3–T_1 wherein :

α) W_1 and W_2 are as defined hereinbefore,

β) W_3 represents an oxygen atom, a sulphur atom, or NR_c wherein R_c is as defined hereinbefore,

γ) T_1 represents a group selected from :

- hydrogen,
- linear or branched $(C_1\text{-}C_6)$alkyl,
- linear or branched $(C_2\text{-}C_6)$alkenyl,
- aryl, aryl-$(C_1\text{-}C_6)$alkyl in which the alkyl moiety may be linear or branched, and
- linear or branched $(C_1\text{-}C_6)$alkylene or linear or branched $(C_2\text{-}C_6)$alkenylene chains, each of which is substituted by a group OR_c wherein R_c is as defined hereinbefore or $NR'_aR'_b$ wherein R'_a and R'_b are as defined hereinbefore,

5) $W_1\text{–}S(O)_n\text{–}W_3\text{–}T_1$ wherein :

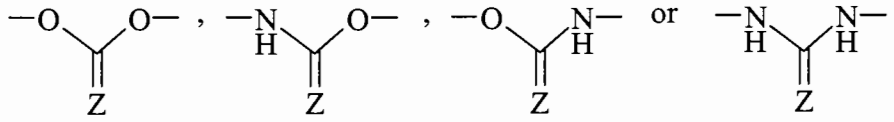
α) W_1, W_3 and T_1 are as defined hereinbefore, and

β) n represents an integer selected from 1 and 2,

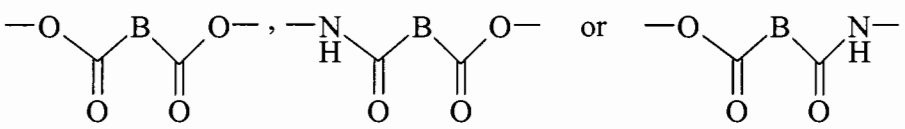
6) $W_1\text{–}S(O)_n\text{–}T_1$ wherein W_1, T_1 and n are as defined hereinbefore, and

7) $C(W_2)\text{–}T_1$ wherein W_2 and T_1 are as defined hereinbefore,

* *or R_5 and R_6, together form :*

1) a group  wherein Z represents an oxygen atom or a sulphur atom,

2) a group–O–$(CH_2)_m$–O– wherein m represents an integer of from 1 to 4 inclusive, or

3) a group  wherein B represents a single bond, a linear or branched $(C_1\text{-}C_6)$alkylene chain or

a linear or branched (C_2-C_6)alkenylene chain,

* *or R_5 and R_6, together with the carbon atoms carrying them, form an oxirane group or an aziridine group*, optionally substituted on the nitrogen atom by a linear or branched (C_1-C_6)alkyl group,

b) –CH=C(R_7)– or –C(R_7)=CH– wherein R_7 represents a group selected from :
- hydrogen,
- and the groups OR"$_a$, W_1–C(W_2)–U–V, W_1–C(W_2)–W_3–T_1, W_1–S(O)$_n$–W_3–T_1, W_1–S(O)$_n$–T_1 and C(W_2)–T_1 wherein R"$_a$, W_1, W_2, U, V, W_3, T_1 and n are as defined hereinbefore,

or

c) –C(O)–CH(R_8)– or – CH(R_8)–C(O)– wherein R_8 represents a group selected from :
- hydrogen,
- linear or branched (C_1-C_6)alkylcarbonyloxy and the groups OR"$_a$ wherein R"$_a$ is as defined hereinbefore,

to their enantiomers, diastereoisomers, N-oxides, and also to addition salts thereof with a pharmaceutically acceptable acid or base,

wherein aryl is understood as a phenyl or naphthyl group optionally containing one or more identical or different substituents selected from linear or branched (C_1-C_6)alkyl, linear or branched (C_2-C_6)alkenyl, hydroxy, halogen, carboxy, nitro, amino, alkylamino or dialkylamino in which the alkyl moieties contain from 1 to 6 carbon atoms and may be linear or branched, linear or branched (C_1-C_6)alkoxy, linear or branched (C_1-C_6)acyl and linear or branched (C_1-C_6)alkylcarbonyloxy,

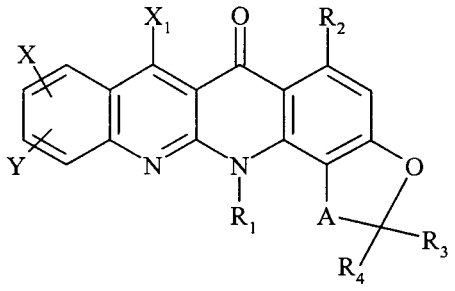
among the monocyclic heterocycles having from 5 to 7 ring members and optionally containing in the ring system a second hetero atom selected from oxygen and nitrogen there may be mentioned, without implying any limitation, the groups pyrrolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, imidazolidinyl, piperidyl, morpholinyl, hexahydropyridazinyl, hexahydropyrimidinyl, piperazinyl, azepanyl, oxazepanyl and diazepanyl,

among the monocyclic rings having from 3 to 6 ring members there may be mentioned, without implying any limitation, the groups cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, camphoric acid, lysine etc..

Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine, etc..

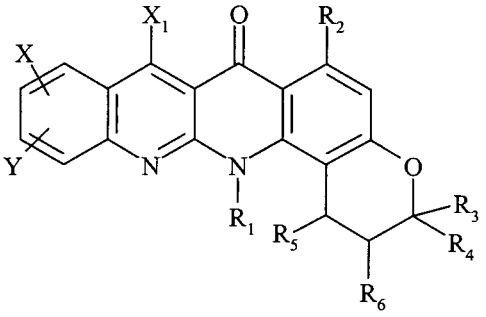
According to an advantageous embodiment of the invention, preferred compounds are those of formula (IA) :



(IA)

wherein X, Y, X_1, R_1, R_2, R_3, R_4 and A are as defined for formula (I).

According to a second advantageous embodiment of the invention, preferred compounds are those of formula (IB) :

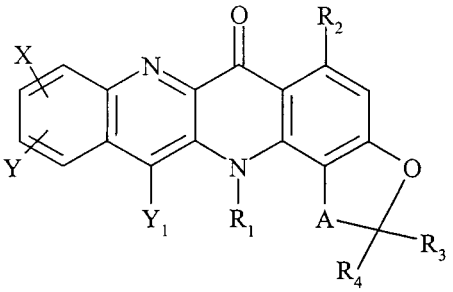


(IB)

wherein X, Y, X_1, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined for formula (I).

According to a third advantageous embodiment of the invention, preferred compounds are

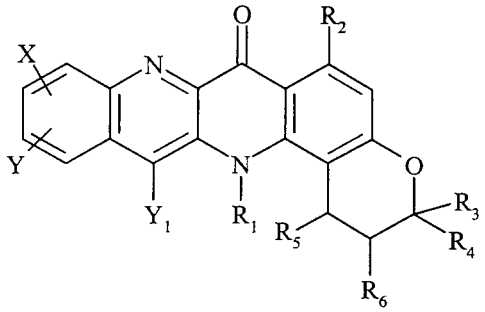
those of formula (IC) :



(IC)

wherein X, Y, Y_1, R_1, R_2, R_3, R_4 and A are as defined for formula (I).

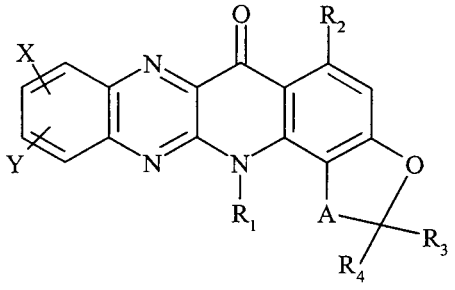
According to a fourth advantageous embodiment of the invention, preferred compounds are those of formula (ID) :



(ID)

wherein X, Y, Y_1, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined for formula (I).

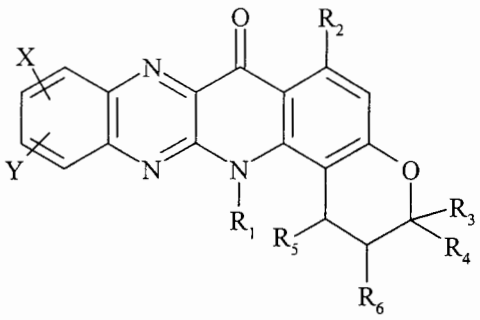
According to a fifth advantageous embodiment of the invention, preferred compounds are those of formula (IE) :



(IE)

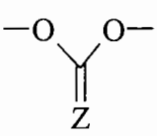
wherein X, Y, R_1, R_2, R_3, R_4 and A are as defined for formula (I).

According to a sixth advantageous embodiment of the invention, preferred compounds are those of formula (IF) :



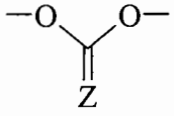
(IF)

wherein X, Y, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined for formula (I).

Preferred compounds of formulae (IB), (ID) and (IF) are those wherein R_5 and R_6 are identical and represent a group of formula $-OR_c$ or W_1-C(W_2)-U-V or wherein R_5 and R_6 together form a group  wherein R_c, W_1, W_2, U, V and Z are as defined for formula (I).

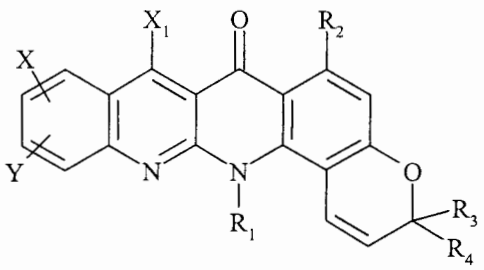
Of particular interest, preferred compounds of formula (IB), (ID) and (IF) are those wherein R_5 and R_6 are identical and represent a group of formula $-OR_c$ wherein R_c represents a hydrogen atom or a linear or branched (C_1-C_6)alkyl group.

Also of particular interest, preferred compounds of formulae (IB), (ID) and (IF) are those wherein R_5 and R_6 are identical and represent a group of formula W_1-C(W_2)-U-V wherein W_1 and W_2 represent an oxygen atom, U represents a linear or branched (C_1-C_6)alkylene chain and V represents a hydrogen atom.

Also of very particular interest, preferred compounds of formulae (IB), (ID) and (IF) are those wherein R_5 and R_6 together form a group 

wherein Z represents an oxygen atom.

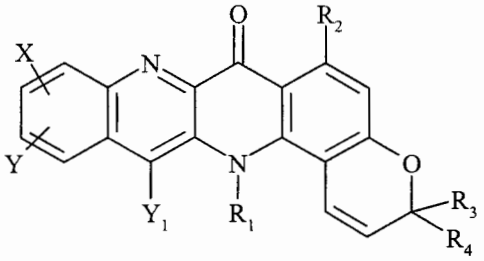
According to a seventh advantageous embodiment of the invention, preferred compounds are those of formula (IG) :



(IG)

wherein X, Y, X_1, R_1, R_2, R_3 and R_4 are as defined for formula (I).

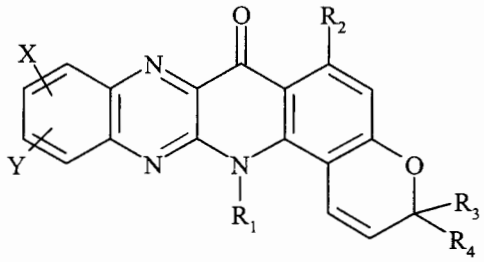
According to an eighth advantageous embodiment of the invention, preferred compounds are those of formula (IH) :



(IH)

wherein X, Y, Y_1, R_1, R_2, R_3 and R_4 are as defined for formula (I).

According to a ninth advantageous embodiment of the invention, preferred compounds are those of formula (IJ) :



(IJ)

wherein X, Y, R_1, R_2, R_3 and R_4 are as defined for formula (I).

Substituents R_3 and R_4 preferred in accordance with the invention are linear or branched (C_1-C_6)alkyl groups.

The substituent R_2 preferred in accordance with the invention is the group –OR"$_a$ wherein R"$_a$ is as defined for formula (I).

Even more especially, the substituent R_2 preferred in accordance with the invention is the group –OR"$_a$ wherein R"$_a$ represents a linear or branched (C_1-C_6)alkyl group, and even

more especially a methyl group.

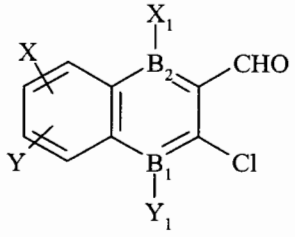
Preferred in accordance with the invention as substituents X, Y, X_1 and Y_1 is hydrogen.

Especially advantageously, preferred compounds of the invention are the following :

- (±)-*cis*-1,2-dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]-chromeno[6,5-*g*][1,8]naphthyridin-7-one,
- (±)-*cis*-1,2-diacetoxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]-chromeno[6,5-*g*][1,8]naphthyridin-7-one,
- (±)-*cis*-7-methoxy-4,4,15-trimethyl-15,15c-dihydro-4*H*-benzo[*b*][1,3]dioxolo-[4',5':3,4]chromeno[6,5-*g*][1,8]naphthyridine-2,8(3a*H*)-dione,

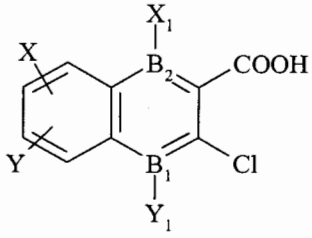
The enantiomers, diastereoisomers, N-oxides and addition salts with a pharmaceutically acceptable acid or base of the preferred compounds of the invention form an integral part of the invention.

The present invention relates also to a process for the preparation of compounds of formula (I), which is characterised in that there is used as starting material a compound of formula (II) :



(II)

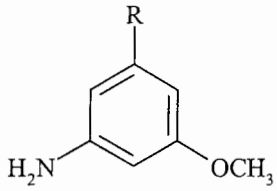
wherein X, Y, X_1, Y_1, B_1 and B_2 are as defined for formula (I),
which compounds of formula (II) are placed in the presence of pyridinium dichromate to yield compounds of formula (III) :



(III)

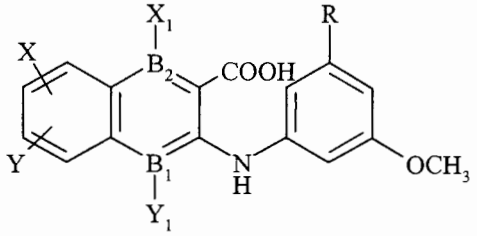
wherein X, Y, X_1, Y_1, B_1 and B_2 are as defined for formula (I),
which compounds of formula (III) are treated in basic and anhydrous medium with a

compound of formula (IV) :



(IV)

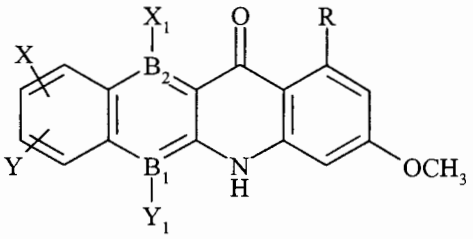
wherein R represents a hydrogen atom, a hydroxy group, a linear or branched (C_1-C_6)alkyl group or a linear or branched (C_1-C_6)alkoxy group to yield compounds of formula (V) :



(V)

wherein X, Y, X_1, Y_1, B_1, B_2 and R are as defined for formula (I),

which compounds of formula (V) are placed in the presence of polyphosphoric acid to yield compounds of formula (VI) :

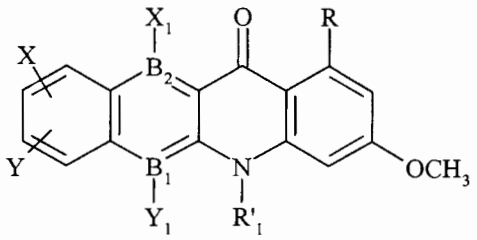


(VI)

wherein X, Y, X_1, Y_1, B_1, B_2 and R are as defined hereinbefore,

of which compounds of formula (VI) :

a) the nitrogen atom is substituted by the action of an alkyl halide or of a dialkyl sulphate in the presence of a deprotonation agent, in a polar aprotic solvent, to yield compounds of formula (VII):

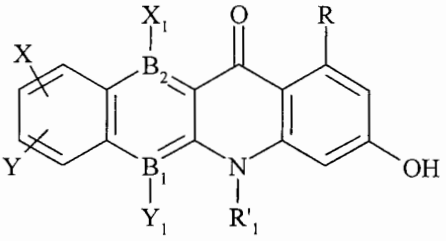


(VII)

wherein R'_1 represents a linear or branched (C_1-C_6)alkyl group and X, Y, X_1, Y_1, B_1, B_2 and R are as defined hereinbefore,

which compounds of formula (VII) are treated with a solution of hydrobromic acid in

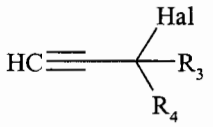
acetic acid to yield compounds of formula (VIII) :



(VIII)

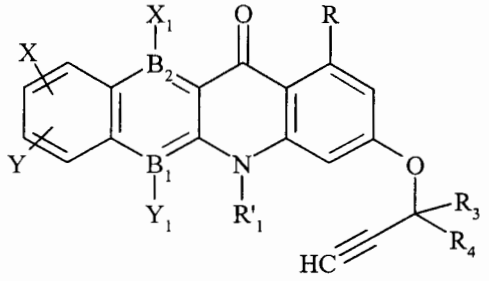
wherein X, Y, X_1, Y_1, B_1, B_2, R and R'_1 are as defined hereinbefore,

which compounds of formula (VIII) are then treated under basic conditions, in an anhydrous aprotic solvent, with an alkyne of formula (IX) :



(IX)

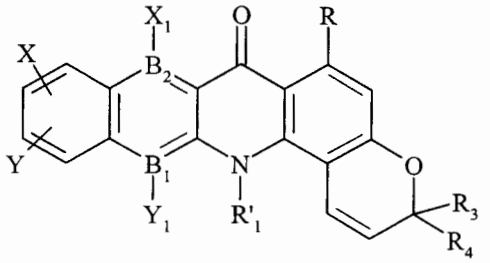
wherein Hal represents a halogen atom and R_3 and R_4 are as defined for formula (I) to yield compounds of formula (X) :



(X)

wherein X, Y, X_1, Y_1, B_1, B_2, R, R'_1, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (X) are refluxed in anhydrous dimethylformamide to yield compounds of formula (I/a), a particular case of the compounds of formula (I) :

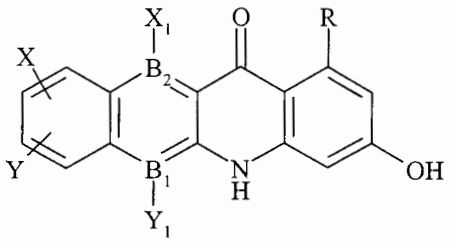


(I/a)

wherein X, Y, X_1, Y_1, B_1, B_2, R, R'_1, R_3 and R_4 are as defined hereinbefore,

or which compounds of formula (VI)

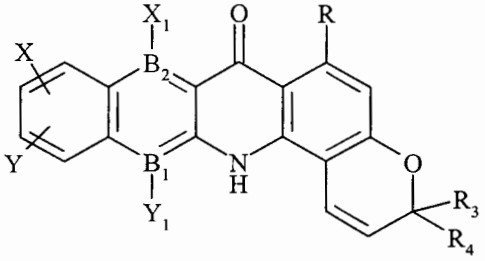
b) are subjected to the same conditions as the compounds of formula (VII) to yield compounds of formula (XI) :



(XI)

wherein X, Y, X_1, Y_1, B_1, B_2 and R are as defined hereinbefore,

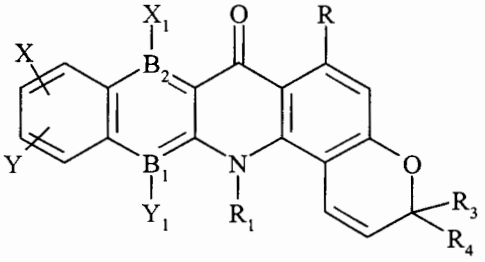
which compounds of formula (XI) are subjected in succession to the same conditions as the compounds of formula (VIII) and (X) to yield compounds of formula (I/b), a particular case of the compounds of formula (I) :



(I/b)

wherein X, Y, X_1, Y_1, B_1, B_2, R, R_3 and R_4 are as defined hereinbefore,

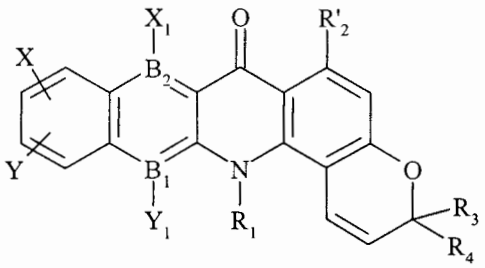
the totality of the compounds (I/a) and (I/b) constituting the compounds of formula (I/c), a particular case of the compounds of formula (I) :



(I/c)

wherein R_1 is as defined for formula (I) and X, Y, X_1, Y_1, B_1, B_2, R, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (I/c) are, if desired, subjected to the action of an alkylating agent or an acylating agent to yield compounds of formula (I/d), a particular case of the compounds of formula (I) :



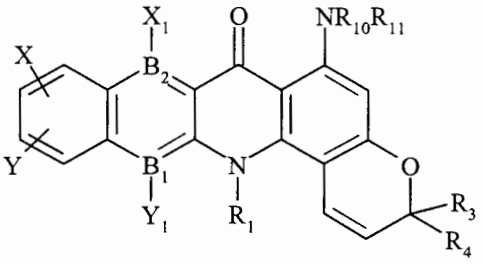
(I/d)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_3 and R_4 are as defined hereinbefore, and R'_2 represents a group selected from $-OR''_{a1}$, $O\text{-}T_a\text{-}OR''_a$, $-O\text{-}C(O)\text{-}T_aH$ and $-O\text{-}T_a\text{-}NR'_aR'_b$ wherein R'_a, R'_b, R''_a and T_a are as defined for formula (I) and R''_{a1} represents a linear or branched $(C_1\text{-}C_6)$alkyl group,

which compounds of formula (I/d) are, if desired, treated, when R'_2 represents a group $-OR''_{a1}$ wherein R''_{a1} is as defined hereinbefore, with a compound of formula (XII) :

$$HNR_{10}R_{11} \qquad (XII)$$

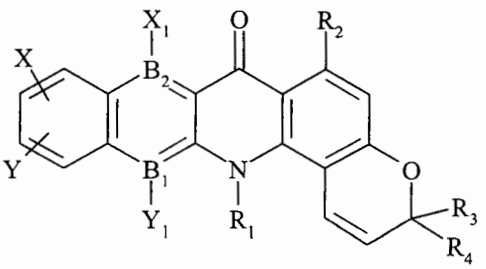
wherein R_{10} represents a group selected from R'_a and R''_a, and R_{11} represents a group selected from R'_b, $-T_a-NR'_aR'_b$, $-C(O)-T_aH$, $-T_a-OR''_a$, $-T_a-CO_2R''_a$ and $-C(O)-T_a-NR'_aR'_b$ wherein R'_a, R'_b, R''_a and T_a are as defined hereinbefore, to yield compounds of formula (I/e), a particular case of the compounds of formula (I) :



(I/e)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_3, R_4, R_{10} and R_{11} are as defined hereinbefore,

the totality of the compounds of formulae (I/c), (I/d) and (I/e) constituting the compounds of formula (I/f), a particular case of the compounds of formula (I) :

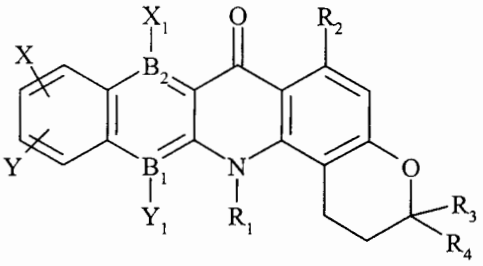


(I/f)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined for formula (I),

which compounds of formula (I/f) may be subjected,

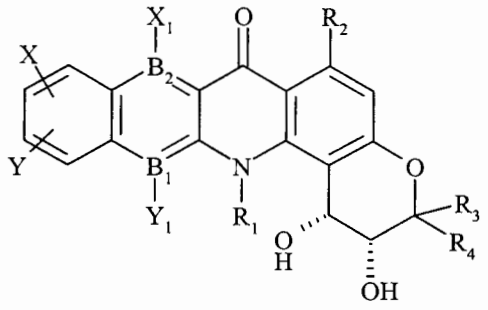
a) either to the action of a reducing agent to yield compounds of formula (I/g), a particular case of the compounds of formula (I) :



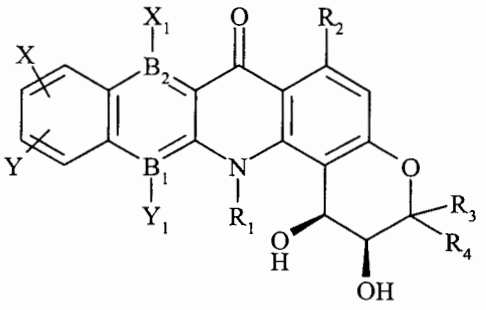
(I/g)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

b) or to the action of osmium tetroxide in polar medium, and in the presence of 4-methylmorpholine-N-oxide, to yield compounds of formulae (I/h_1) and (I/h_2), a particular case of the compounds of formula (I) :



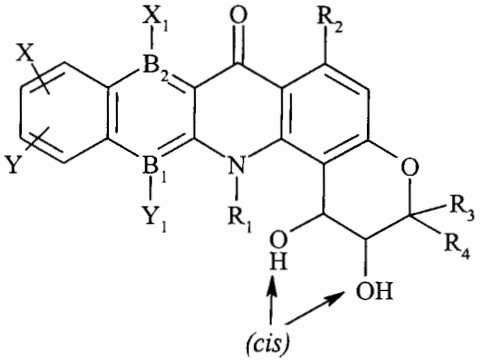
(I/h_1)



(I/h_2)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

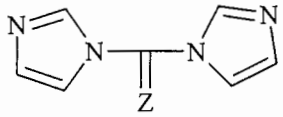
the totality of the compounds of formulae (I/h_1) and (I/h_2) constituting the *cis*–diol compounds of formula (*cis*–I/h), a particular case of the compounds of formula (I) :



(*cis* - I/h)

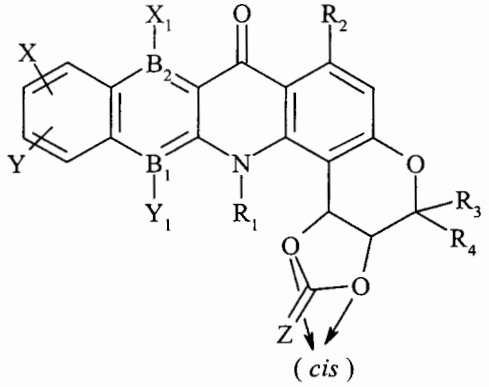
wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

which *cis*–diol compounds of formula (*cis*–I/h) are optionally subjected to the action of a compound of formula (XIII) :



(XIII)

wherein Z is as defined for formula (I) to yield compounds of formula (*cis*–I/i), a particular case of the compounds of formula (I) :

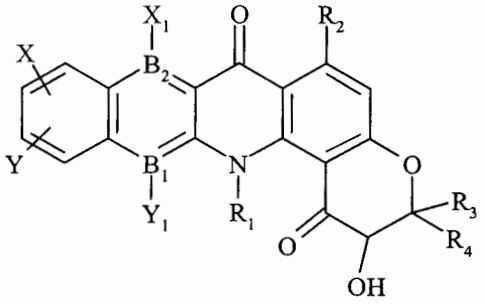


(*cis*-I/i)

(*cis*)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

c) or to the action of potassium permanganate in polar medium to yield compounds of formula (I/j), a particular case of the compounds of formula (I) :

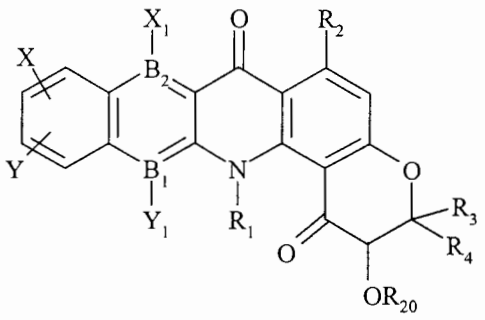


(I/j)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

<u>which compounds of formula (I/j) may be subjected</u> :

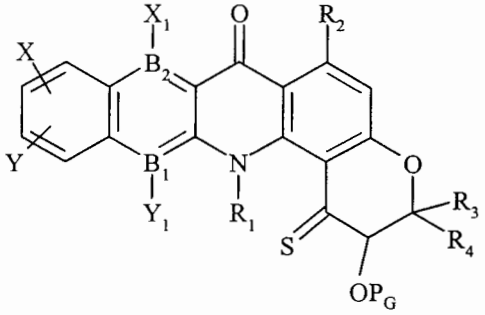
α) either to the action of an alkylating agent or an acylating agent to yield compounds of formula (I/k), a particular case of the compounds of formula (I) :



(I/k)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore, and R_{20} represents a group selected from linear or branched (C_1-C_6)alkyl and linear or branched (C_1-C_6)alkylcarbonyl,

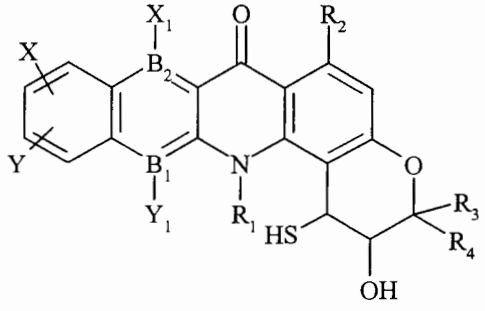
β) or to the action of a protecting group P_G for the hydroxy function then to the action of P_2S_5 to yield compounds of formula (XIV) :



(XIV)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and P_G are as defined hereinbefore,

which compounds of formula (XIV) are treated with a reducing agent, then subjected to a reaction for deprotection of the hydroxy function, to yield compounds of formula (I/l), a particular case of the compounds of formula (I) :



(I/l)

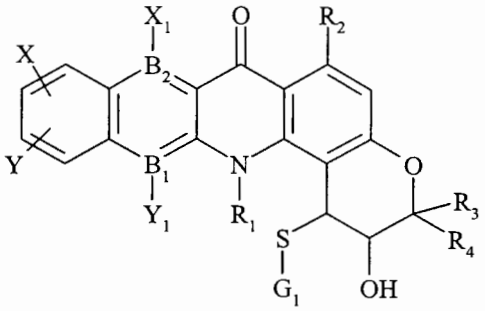
wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (I/l) are, if desired, subjected to the action of a compound of

formula (XV) :

$$Hal - G_1 \qquad (XV)$$

wherein Hal represents a halogen atom and G_1 represents a group selected from $-R_c$, $-C(W_2)-U-V$, $-C(W_2)-W_3-T_1$, $-S(O)_n-W_3-T_1$ and $-S(O)_n-T_1$ wherein R_c, W_2, W_3, U, V, T_1 and n are as defined for formula (I) to yield compounds of formula (I/m), a particular case of the compounds of formula (I) :



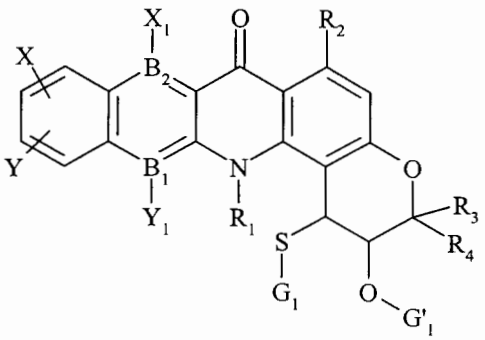
(I/m)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G_1 are as defined hereinbefore,

which compounds of formula (I/m) may be subjected to the action of a compound of formula (XVI) :

$$Hal - G'_1 \qquad (XVI)$$

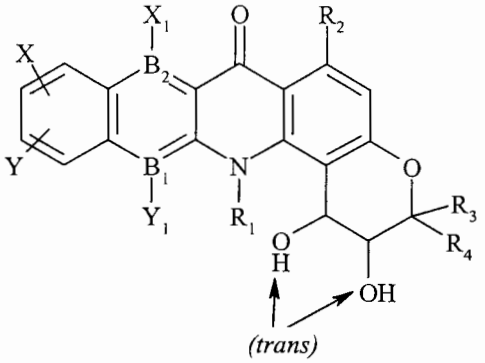
wherein Hal is as defined hereinbefore and G'_1 represents a group selected from $-R_c$, $-C(W_2)-U-V$, $-C(W_2)-W_3-T_1$, $-S(O)_n-W_3-T_1$ and $-S(O)_n-T_1$ wherein R_c, W_2, W_3, U, V, T_1 and n are as defined for formula (I), to yield compounds of formula (I/n), a particular case of the compounds of formula (I) :



(I/n)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G_1 and G'_1 are as defined hereinbefore,

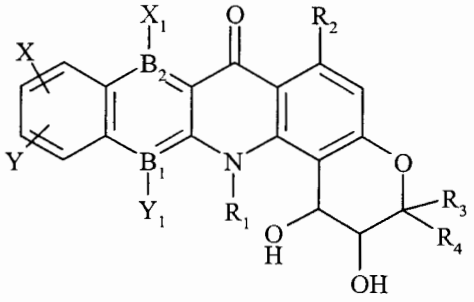
γ) or to reducing conditions in the presence of $NaBH_4$ to yield compounds of formula (I/o), a particular case of the compounds of formula (I) :



(I/o)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

the totality of the compounds of formulae (*cis*–I/h) and (I/o) constituting the compounds of formula (I/p),

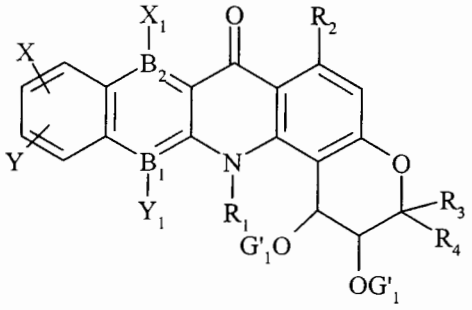


(I/p)

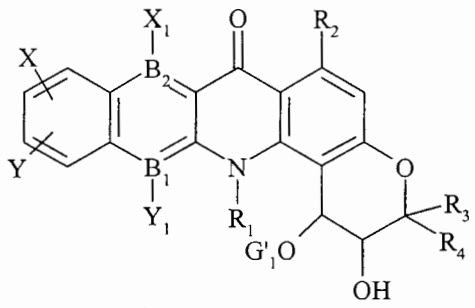
wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

<u>which compounds of formula (I/p) may be subjected</u> :

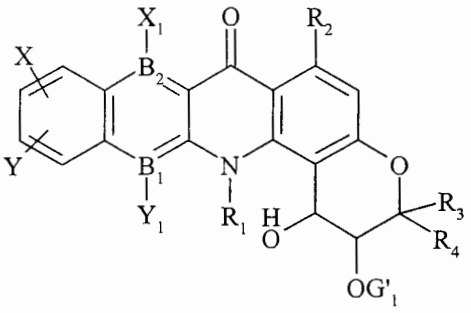
α) either to the action of a compound of formula (XVI) as defined hereinbefore to yield compounds of formulae (I/q_1), (I/q_2) and (I/q_3), particular cases of the compounds of formula (I) :



(I/q_1)



(I/q_2)

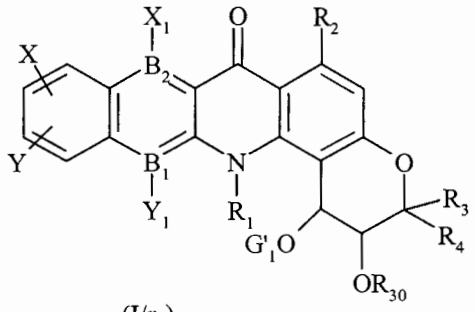


(I/q_3)

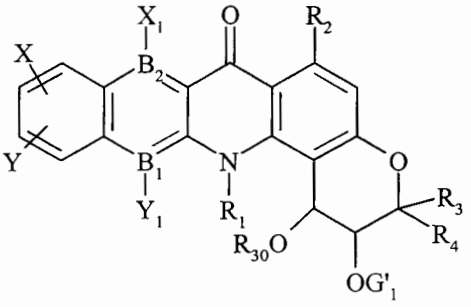
wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G'_1 are as defined hereinbefore,

which compounds of formulae (I/q_2) and (I/q_3) are, if desired, subjected :

1) either to the action of an alcohol of formula R_{30}-OH wherein R_{30} represents a linear or branched $(C_1$-$C_6)$alkyl group to yield, respectively, compounds of formulae (I/r_2) and (I/r_3), particular cases of the compounds of formula (I) :



(I/r_2)



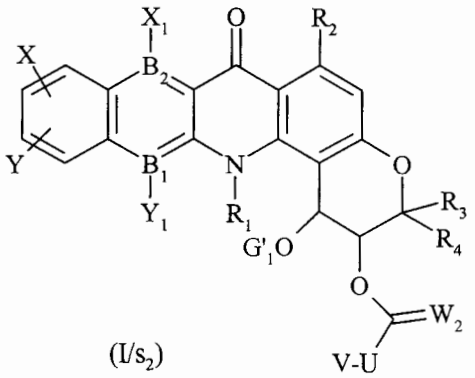
(I/r_3)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G'_1 and R_{30} are as defined hereinbefore,

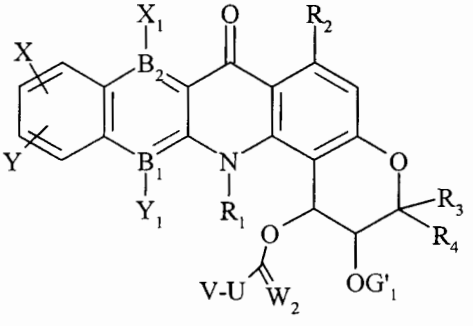
2) or to the action of an anhydride of formula (XVII) :

$$[V\text{-}U\text{-}C(W_2)]_2O \qquad (XVII)$$

wherein W_2, U and V are as defined for formula (I) to yield compounds of formulae (I/s_2) and (I/s_3), particular cases of the compounds of formula (I) :



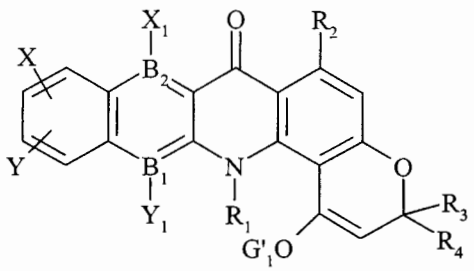
(I/s_2)



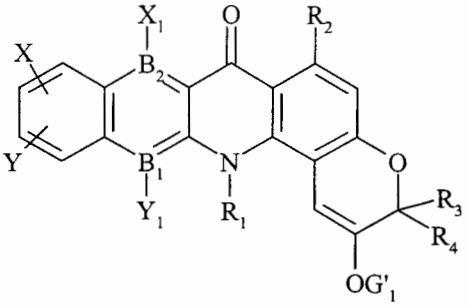
(I/s_3)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G'_1, W_2, U and V are as defined hereinbefore,

3) or to dehydration conditions in acid medium to yield compounds of formulae (I/t_2) and (I/t_3), particular cases of the compounds of formula (I) :



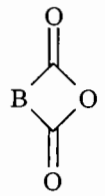
(I/t_2)



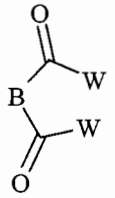
(I/t_3)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G'_1 are as defined hereinbefore,

β) or to the action of a compound of formula (XVIII) or (XIX)

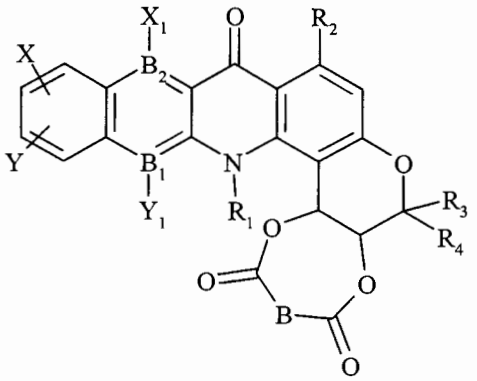


(XVIII)



(XIX)

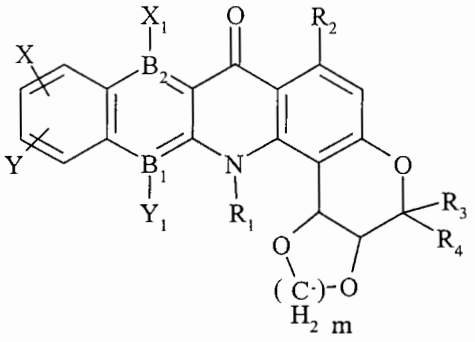
wherein B is as defined for formula (I) and W represents a halogen atom or a hydroxyl group to yield compounds of formula (I/u), a particular case of the compounds of formula (I) :



(I/u)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and B are as defined hereinbefore,

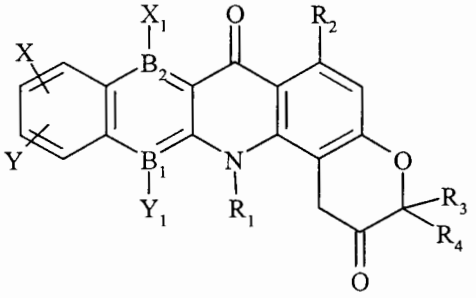
γ) or to the action of a linear (C_1-C_6)alkyl dihalide to yield compounds of formula (I/v), a particular case of the compounds of formula (I) :



(I/v)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore and m is as defined for formula (I),

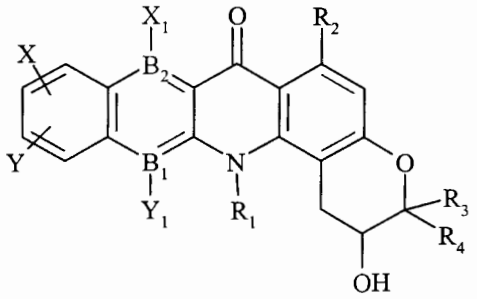
ε) or to dehydration conditions in acid medium to yield compounds of formula (I/w), a particular case of the compounds of formula (I) :



(I/w)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

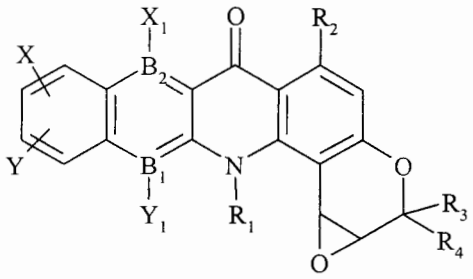
which compounds of formula (I/w) are, if desired, reduced in the presence of $NaBH_4$ to yield compounds of formula (I/x), a particular case of the compounds of formula (I) :



(I/x)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

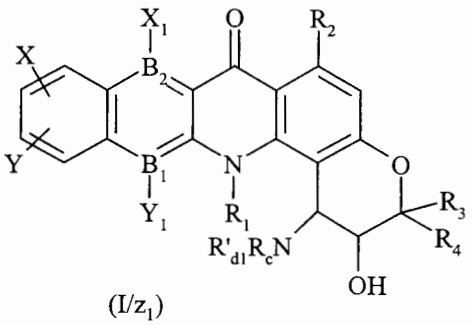
d) or to the action of a peracid or of dimethyl dioxirane to yield compounds of formula (I/y), a particular case of the compounds of formula (I) :



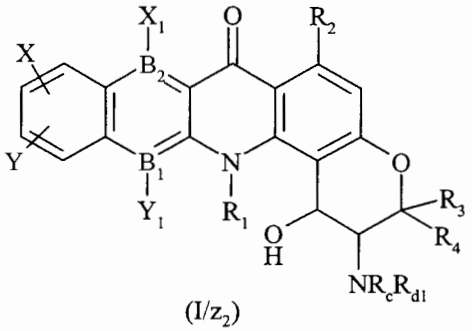
(I/y)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (I/y) are, if desired, treated with ammonia or a primary or secondary amine to yield compounds of formulae (I/z_1) and (I/z_2), particular cases of the compounds of formula (I) :



(I/z_1)

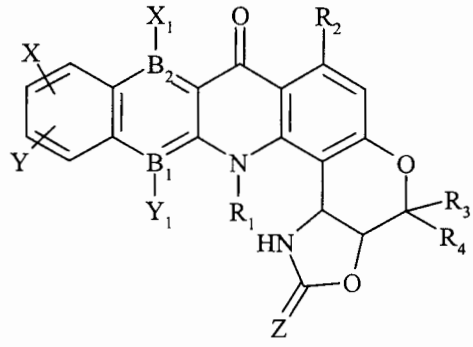


(I/z_2)

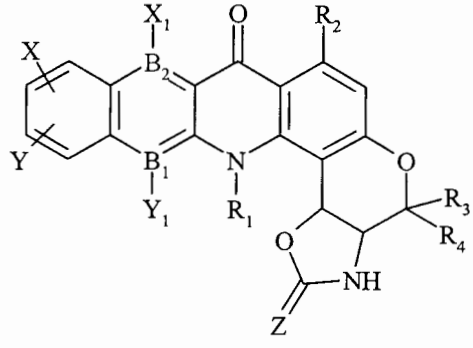
wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore, R_c is as defined for formula (I) and R_{d1} represents a group selected from R_d, $-C(W_2)$-U-V, $-C(W_2)$-W_3-T_1, $-S(O)_n$-W_3-T_1 and $-S(O)_n$-T_1 wherein R_d, W_2, W_3, U, V and T_1 are as defined hereinbefore,

<u>which compounds of formulae (I/z_1) and (I/z_2) may be subjected</u>

α) either, when R_c and R_{d1} represent a hydrogen atom, to the action of a compound of formula (XIII) as defined hereinbefore to yield compounds of formulae (I/aa_1) and (I/aa_2), particular cases of the compounds of formula (I) :



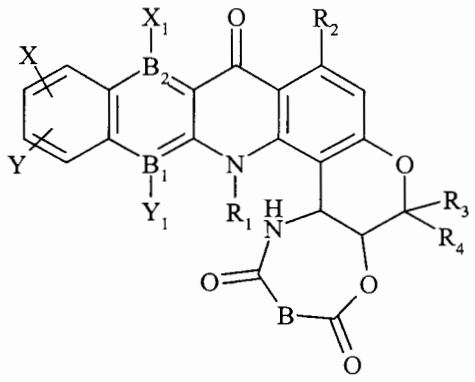
(I/aa_1)



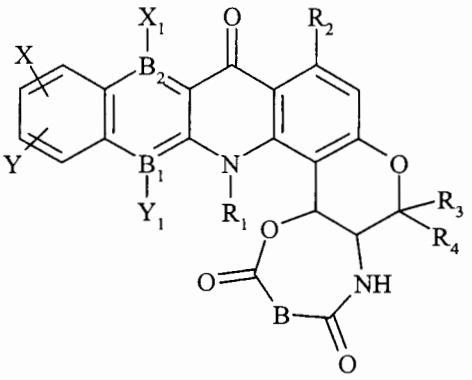
(I/aa_2)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and Z are as defined hereinbefore,

β) or to the action of a compound of formula (XIX) as defined hereinbefore to yield compounds of formulae (I/ab_1) and (I/ab_2), particular cases of the compounds of formula (I) :



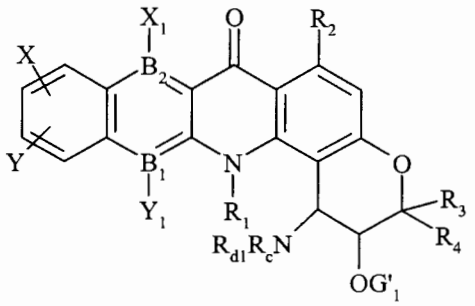
(I/ab_1)



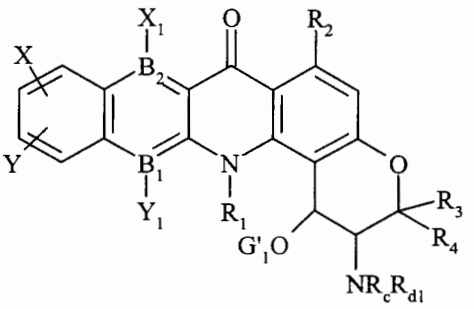
(I/ab_2)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and B are as defined hereinbefore,

γ) or to the action of a compound of formula (XVI) as defined hereinbefore to yield compounds of formulae (I/ac_1) and (I/ac_2), particular cases of the compounds of formula (I) :



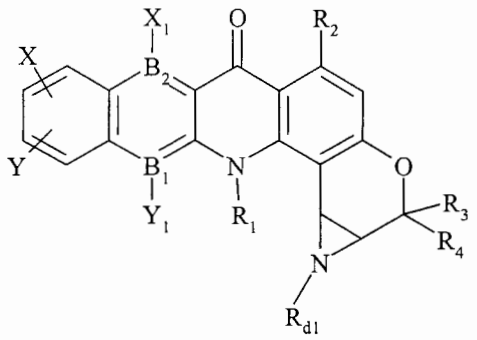
(I/ac_1)



(I/ac_2)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, R_c, R_{d1} and G'_1 are as defined hereinbefore,

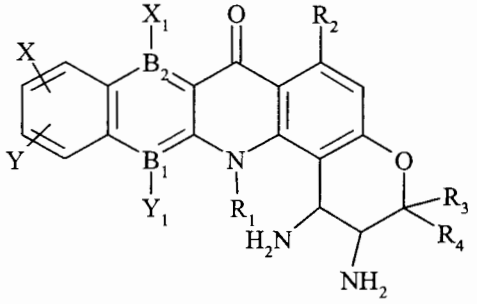
δ) or to the action of triphenylphosphine dibromide in the presence of triethylamine to yield compounds of formula (I/ad), a particular case of the compounds of formula (I) :



(I/ad)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and R_{d1} are as defined hereinbefore,

ε) or to the action of NaN_3 in the presence of hydrogen peroxide, followed by a reduction step, to yield compounds of formula (I/ae), a particular case of the compounds of formula (I) :

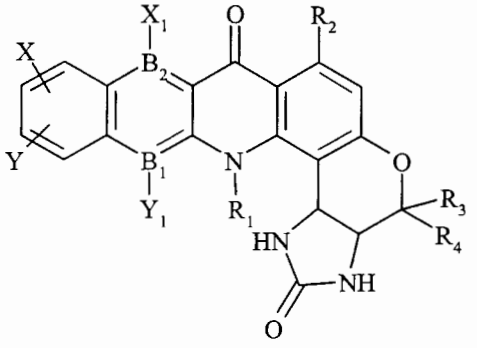


(I/ae)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (I/ae) are, if desired, subjected

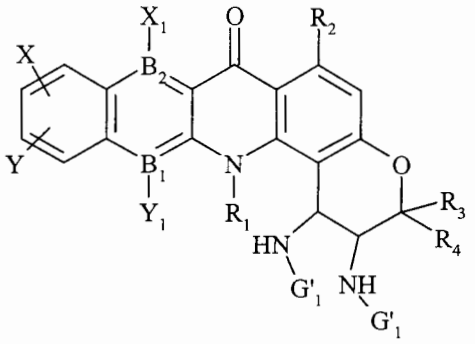
1) either to the action of carbon dioxide in the presence of diphenyl phosphite to yield compounds of formula (I/af), a particular case of the compounds of formula (I) :



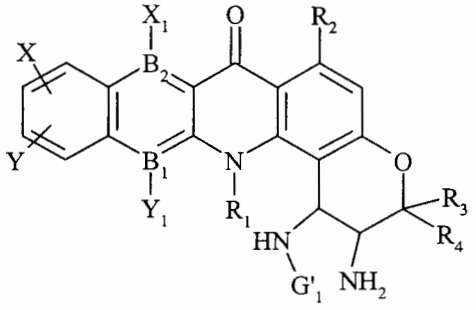
(I/af)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

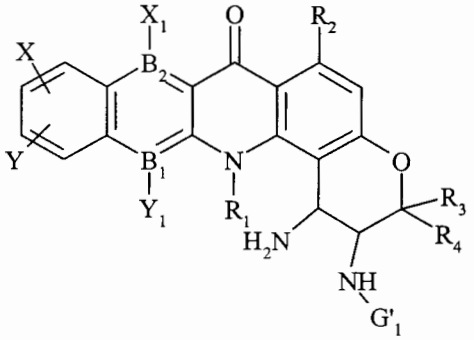
2) or to the action of a compound of formula (XVI) as defined hereinbefore to yield compounds of formulae (I/ag_1), (I/ag_2) and (I/ag_3), a particular case of the compounds of formula (I) :



(I/ag_1)



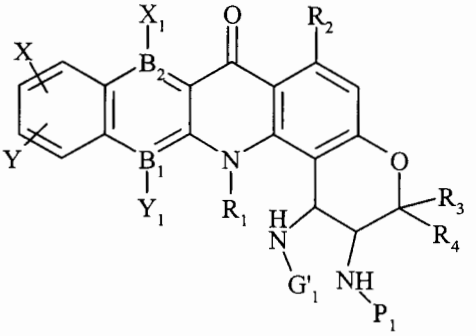
(I/ag_2)



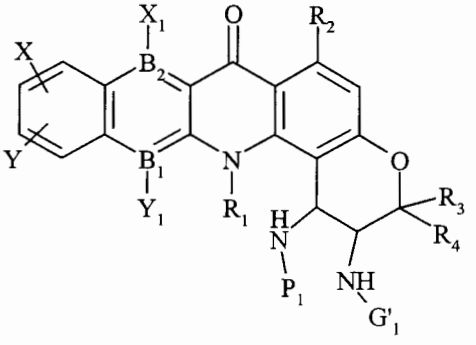
(I/ag_3)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G'_1 are as defined hereinbefore,

the primary amine function of which compounds of formulae (I/ag_2) and (I/ag_3) is protected by a group for the protection of primary amine groups to yield compounds of formulae (XX/a) and (XX/b),



(XX/a)



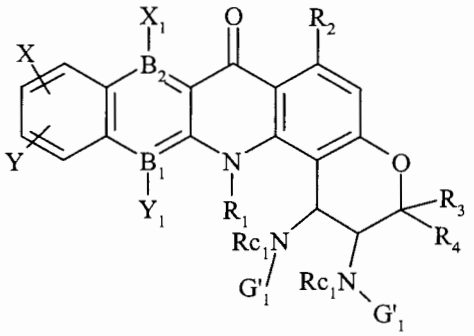
(XX/b)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G'_1 are as defined hereinbefore and P_1 represents a protecting group for primary amine functions,

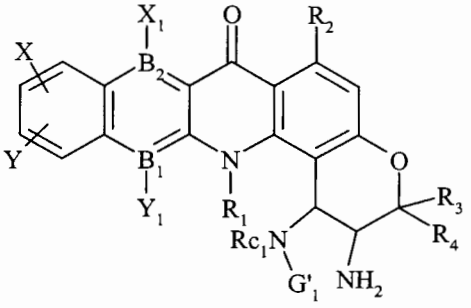
which compounds of formulae (I/ag_1) and (XX/a) and (XX/b) are, if desired, subjected to the action of a compound of formula (XXI) :

$$R_{c1}–Hal \qquad (XXI)$$

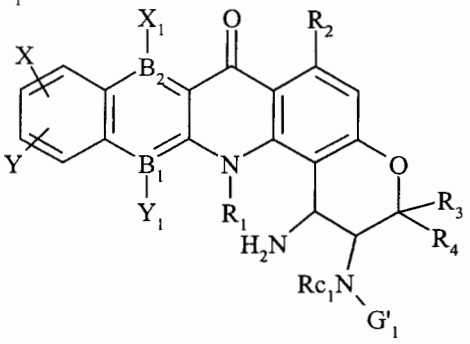
wherein Hal represents a halogen and R_{c1} represents a group selected from linear or branched (C_1-C_6)alkyl, aryl and aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, and then subjected, in the case of compounds of formulae (XX/a) and (XX/b), to conditions for the deprotection of the primary amine function, to yield compounds of formulae (I/ah_1), (I/ah_2) and (I/ah_3), particular cases of the compounds of formula (I) :



(I/ah_1)



(I/ah_2)



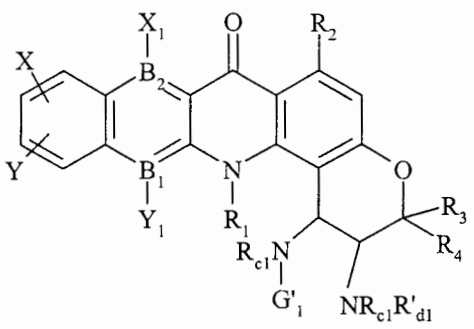
(I/ah_3)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G'_1 and R_{c1} are as defined hereinbefore,

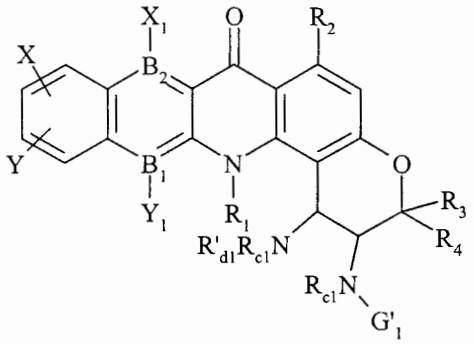
which compounds of formulae (I/ah_2) and (I/ah_3) are, if desired, subjected in succession to the action of a compound of formula (XXI) as defined hereinbefore and then to the action of a compound of formula (XXII) :

$$R_{d'1}–Hal \qquad (XXII)$$

wherein Hal is as defined hereinbefore and $R_{d'1}$ may have the same definitions as R_{c1}, to yield compounds of formulae (I/ai_2) and (I/ai_3), particular cases of the compounds of formula (I) :



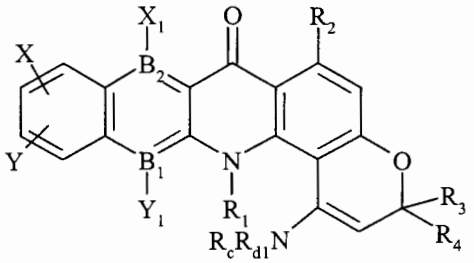
(I/ai$_2$)



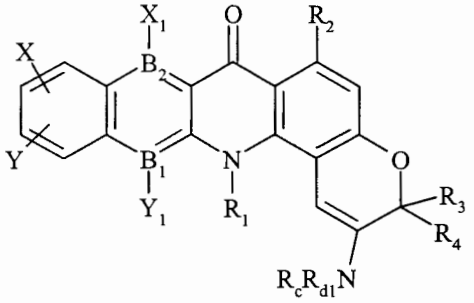
(I/ai$_3$)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G'_1, R_{c1} and R_{d1} are as defined hereinbefore,

ϕ) or to dehydration conditions in acid medium to yield compounds of formulae (I/aj$_2$) and (I/aj$_3$), particular cases of the compounds of formula (I) :



(I/aj$_2$)



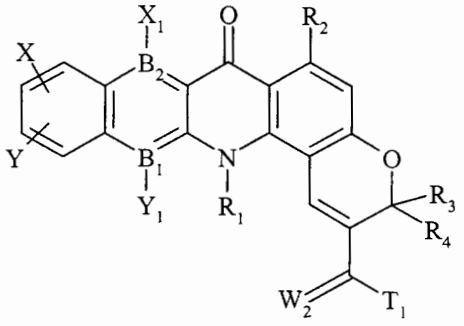
(I/aj$_3$)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, R_c and R_{d1} are as defined hereinbefore,

e) or to the action of a compound of formula (XXIII) :

$$Hal–C(W_2)–T_1 \qquad (XXIII)$$

wherein Hal represents a halogen atom and W_2 and T_1 are as defined for formula (I) to yield compounds of formula (I/aj), a particular case of the compounds of formula (I) :



(I/aj)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, W_2 and T_1 are as defined hereinbefore,

the compounds (I/a) to (I/aj) constituting the totality of the compounds of the invention, which, if necessary, are purified according to a conventional purification technique, if desired may be separated into their different isomers according to a conventional separation technique and, if desired, are converted into their N-oxides and optionally into addition salts with a pharmaceutically acceptable acid or base.

The compounds of formulae (II), (IV), (IX), (XII), (XIII), (XV), (XVI), (XVII), (XVIII), (XIX), (XXI) and (XXII) are either commercial products or are obtained according to conventional methods of organic synthesis well known to the person skilled in the art.

The compounds of formula (I) have anti-tumour properties of particular interest. They have an excellent cytotoxicity *in vitro* in relation to cell lines originating from murine and human tumours, owing to a specific blockade of the cell cycle, and are active *in vivo* in mice in relation to transplantable murine and human tumours. The characteristic properties of the compounds enable them to be used therapeutically as anti-tumour agents.

The present invention relates also to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), its enantiomers, diastereoisomers, N-oxides or an addition salt thereof with a pharmaceutically acceptable acid or base, on its own or in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, intravaginal, rectal, nasal, perlingual, buccal, ocular or respiratory administration.

The pharmaceutical compositions according to the invention for parenteral injections include especially sterile solutions, which may be aqueous or non-aqueous, dispersions, suspensions or emulsions and also sterile powders for the reconstitution of injectable solutions or dispersions.

The pharmaceutical compositions according to the invention for solid oral administration include especially tablets or dragées, sublingual tablets, sachets, gelatin capsules and granules, and those for liquid oral, nasal, buccal or ocular administration include especially emulsions, solutions, suspensions, drops, syrups and aerosols.

The pharmaceutical compositions for rectal or vaginal administration are preferably suppositories, and those for per- or trans-cutaneous administration include especially powders, aerosols, creams, ointments, gels and patches.

The pharmaceutical compositions mentioned above illustrate the invention but do not limit it in any way.

Among the pharmaceutically acceptable, inert, non-toxic excipients or carriers there may be mentioned, by way of example and without implying any limitation, diluents, solvents, preservatives, wetting agents, emulsifiers, dispersing agents, binders, swelling agents, disintegrators, retardants, lubricants, absorbents, suspending agents, colorants, flavourings etc.

The useful dosage varies according to the age and weight of the patient, the route of administration, the pharmaceutical composition employed, the nature and severity of the disease, and the administration of any associated treatments, and ranges from 0.1 mg to 1000 mg in one or more administrations per day.

The Examples which follow illustrate the invention but do not limit it in any way.

The starting materials used are known products or products prepared according to known procedures. The various preparations result in synthesis intermediates for use in the preparation of the compounds of the invention.

The structure of the compounds described in the Examples and in the Preparations were determined according to customary spectrophotometric techniques (infra-red, nuclear

magnetic resonance, mass spectrometry, ...).

The melting points were determined using a Kofler hot plate, or a hot plate under a microscope. When the compound is to be found in salt form, the melting point corresponds to that of the salt product.

PREPARATION 1 : 2-Chloro-3-quinolinecarboxylic acid

5 g of 2-chloro-3-quinolinecarboxaldehyde are dissolved in 200 ml of anhydrous dimethylformamide. 96 g of pyridinium dichromate are added in small portions at ambient temperature, a calcium chloride guard is mounted on the flask and the mixture is stirred magnetically for 24 hours. The reaction mixture is diluted with 1 litre of water and extracted with dichloromethane. The combined organic solutions are evaporated to dryness under reduced pressure, in the cold, using a vane pump. Chromatography on silica gel (dichloromethane and then dichloromethane with a methanol gradient of from 0.1 to 2 %) allows 1.53 g of the expected product to be isolated.

Mass spectrum (DIC/NH_3) : m/z = 208 $(M+H)^+$.

Melting point : 275°C

PREPARATION 2 : 8-[(1,1-Dimethyl-2-propynyl)oxy]-10-hydroxy-6-methyl-dibenzo[*b*,*g*][1,8]naphthyridin-11-(6*H*)-one

Step A : 2-(3,5-Dimethoxyanilino)-3-quinolinecarboxylic acid

A sample of 5 g of the compound of Preparation 1 and 4.93 g of 3,5-dimethoxyaniline are refluxed in 180 ml of anhydrous dimethylformamide in the presence of 5.165 g of anhydrous potassium carbonate and 0.92 g of powdered copper. The reaction mixture is heated at 155°C for 48 hours under argon. The reaction mixture is evaporated to dryness and the residue is extracted several times with a 1M sodium hydroxide solution. The solution is filtered and then acidified to a pH of 6 using concentrated hydrochloric acid. The precipitate formed is filtered off, washed well with water and dried in air. Chromatography on silica gel (dichloromethane and then dichloromethane with a methanol

gradient of from 0.1 to 2 %) allows 2.98 g of the expected product to be isolated.

Mass spectrum (ESI-MS) : 347 $(M+Na)^+$, 325 $(M+H)^+$.

Melting point : 215°C

Step B : 8,10-Dimethoxydibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one

A mixture of 5.6 g of the compound of the above Step A and 121.8 g of polyphosphoric acid is heated at a temperature of 100°C for 2 hours. The reaction mixture is poured onto ice and then rendered alkaline to a pH of 6-7 using an aqueous 30 % sodium hydroxide solution. The precipitate formed is filtered off, washed with water and dried in air. Chromatography on silica gel (dichloromethane and then dichloromethane with a methanol gradient of from 0.1 to 2 %) allows 4.84 g of the expected product to be isolated.

Mass spectrum (DIC/NH_3) : m/z = 307 $(M+H)^+$.

Melting point : 279°C

Step C : 8,10-Dimethoxy-6-methyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one

3.89 g of anhydrous potassium hydroxide in powder form are added to a solution of 4.5 g of the compound of the above Step B in 250 ml of anhydrous acetone. The reaction mixture is refluxed for 15 min. at a temperature of 57°C under argon, and then 10 ml of iodomethane are added three times at intervals of 2 hours. The reaction mixture is refluxed for 3 days. The solvent is evaporated off under reduced pressure. The residue is extracted with water and then filtered. Chromatography on silica gel (dichloromethane and then dichloromethane with a methanol gradient of from 0.1 to 0.5 %) allows 3.09 g of the expected product to be isolated.

Mass spectrum (DIC/NH_3) : m/z = 321 $(M+H)^+$.

Melting point : 282°C

Step D : 8,10-Dihydroxy-6-methyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one

A sample of 3 g of the compound of the above Step C is dissolved in 150 ml of hydrobromic acid (48 % in H_2O) and then 50 ml of acetic acid are added. The whole is

refluxed for 3 days at 110°C. The reaction mixture is poured onto ice and the precipitate formed is filtered off, washed with water and dried in air. Chromatography on silica gel (dichloromethane and then dichloromethane with a methanol gradient of from 0.1 to 2 %) allows 2.35 g of the expected product to be isolated.

Mass spectrum (DIC/NH_3) : m/z = 293 $(M+H)^+$.

Melting point : 322°C

Step E : 8-[(1,1-Dimethyl-2-propynyl)oxy]-10-hydroxy-6-methyldibenzo[*b*,*g*][1,8]-naphthyridin-11-(6*H*)-one

A solution of 200 ml of anhydrous dimethylformamide containing 2 g of the compound of the above Step D, 5 g of 3-chloro-3-methyl-1-butyne, 3 g of anhydrous potassium carbonate and 3 g of anhydrous potassium iodide is refluxed for 4 days at 70°C under nitrogen. The reaction mixture is then poured onto ice and the precipitate is filtered off and washed with water. The aqueous phase is extracted with dichloromethane (4 x 50 ml). The combined organic phases are dried over anhydrous sodium sulphate, filtered and evaporated to dryness. Chromatography on silica gel (dichloromethane and then a gradient of dichloromethane in methanol of from 0.1 % to 0.4 %) allows 972.8 mg of the expected product to be isolated.

Mass spectrum (DIC/NH_3) : m/z = 359 $(M+H)^+$.

Melting point : 218°C

PREPARATION 3 : 8-[(1,1-Dimethyl-2-propynyl)oxy]-6-methyldibenzo[*b*,*g*][1,8]-naphthyridin-11(6*H*)-one

The product is obtained in accordance with the procedure of Preparation 2 using 3-methoxyaniline instead of 3,5-dimethoxyaniline.

PREPARATION 4 : 7,9-Dihydroxydibenzo[*b*,*g*][1,5]naphthyridin-6(11*H*)-one

3.5 g of 1,3,5-trihydroxybenzene and 62.5 mg of paratoluenesulphonic acid are added to a solution of 5 g of ethyl 3-amino-2-quinolinecarboxylate in 50 ml of heptan-1-ol. The

mixture is stirred for 48 hours at reflux using a Dean Stark apparatus and then the reaction mixture is concentrated *in vacuo*. Chromatography on silica gel (cyclohexane/acetone : 90/10) allows 5.2 g of the expected product to be isolated.

PREPARATION 5 : 3-[(1,1-Dimethyl-2-propynyl)oxy]-1-hydroxy-5-methylquino-[2,3-*b*]quinoxalin-12(5*H*)-one

The product is obtained in accordance with the procedure of Preparation 2 using 3-chloro-2-quinoxalinecarboxylic acid instead of 2-chloro-3-quinolinecarboxylic acid.

EXAMPLE 1 : 6-Hydroxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo-[*b*]chromeno-[6,5-*g*][1,8]naphthyridin-7-one

A solution of 500 mg of the compound of Preparation 2 in 170 ml of anhydrous dimethylformamide is maintained at reflux at 130°C for 2 days under nitrogen. The reaction mixture is evaporated under reduced pressure. Chromatography on silica gel (dichloromethane and then dichloromethane with a methanol gradient of from 0.1 to 0.3 %) allows 248.86 mg of the expected product to be isolated.

Mass spectrum (DIC/NH_3) : m/z = 359 $(M+H)^+$.

Melting point : 278°C

EXAMPLE 2 : 6-Methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]chromeno-[6,5-*g*][1,8]naphthyridin-7-one

840 mg of sodium hydride (50 % in liquid paraffin) are added in small portions to a solution, maintained under argon at ambient temperature, of 200 mg of the compound of Example 1 in 40 ml of anhydrous dimethylformamide. The resulting mixture is stirred at ambient temperature and under an inert atmosphere for 15 minutes and then 1.8 ml of iodomethane are added. The reaction mixture is refluxed at 52°C for 3 hours under argon. Ice is then cautiously added and the precipitate formed is filtered off and dried in air. Chromatography on silica gel (dichloromethane and then dichloromethane with a methanol gradient of from 0.1 to 0.5 %) allows 180.26 mg of the expected product to be isolated.

Mass spectrum (DIC/NH_3) : m/z = 373 $(M+H)^+$.

Melting point : 270°C

EXAMPLE 3 : (±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-7-one

A mixture of 500 mg of the compound of Example 2, of osmium tetroxide (2.5 %) dissolved in 3.9 ml of 2-methyl-2-propanol and of 626 mg of 4-methylmorpholine *N*-oxide monohydrate is dissolved in 40 ml of a mixture of 55 ml of *t*-BuOH-THF-H_2O (10:3:1). The reaction mixture is stirred at ambient temperature for 3 days. A saturated solution of 55 ml of $NaHSO_3$ is then added. After stirring for one hour, the reaction mixture is extracted with water and dichloromethane. The combined organic phases, dried over anhydrous sodium sulphate, are filtered and evaporated to dryness under reduced pressure. Chromatography on silica gel (dichloromethane and then a gradient of methanol in dichloromethane of from 0.1 to 2 %) allows 314.29 mg of the expected product to be isolated.

Mass spectrum (DIC/NH_3) : m/z = 407 $(M+H)^+$

Melting point : 298°C

EXAMPLE 4 : (±)-*cis*-1,2-Diacetoxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-7-one

200 mg of the compound of Example 3 are added to a previously cooled mixture of 45 ml of anhydrous pyridine, 11 ml of acetic anhydride and 4-dimethylamino-pyridine. The reaction mixture is stirred at ambient temperature for 1 day, with the exclusion of light. The mixture is then poured onto ice, and the precipitate formed is filtered off and washed with water. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried over anhydrous sodium sulphate, filtered, and then evaporated to dryness under reduced pressure. Chromatography on silica gel (dichloromethane and then a gradient of methanol in dichloromethane of from 0.1 to 0.8 %) allow 223 mg of the expected product to be isolated.

Mass spectrum (DIC/NH_3) : m/z = 491 $(M+H)^+$

Melting point : 244°C

EXAMPLE 5 : (±)-*cis*-7-Methoxy-4,4,15-trimethyl-15,15c-dihydro-4*H*-benzo[*b*][1,3]-dioxolo[4',5':3,4]chromeno[6,5-*g*][1,8]naphthyridin-2,8[3a*H*]-dione

635.62 mg of *N,N'*-carbonyldiimidazole are added to a solution of 200 mg of the compound of Example 3 in 90 ml of 2-butanone. The reaction mixture is refluxed for 4 days under argon and then, after cooling, diluted with an aqueous 5 % Na_2CO_3 solution (15 ml) and extracted with ethyl acetate. The organic solutions are combined, dried over anhydrous sodium sulphate, filtered and then evaporated to dryness under reduced pressure. Chromatography on silica gel (dichloromethane and then a gradient of methanol in dichloromethane of from 0.1 to 1.5 %) allow 78 mg of the expected product to be isolated.

Mass spectrum (ESI-MS) : *m/z* = 433 $(M+H)^+$

Melting point : 234°C

EXAMPLE 6 : (±)-*cis*-1-{[(Dimethylamino)carbonyl]oxy}-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]chromeno[6,5-*g*]-[1,8]naphthyridin-2-yl dimethylcarbamate

At -10°C, add a solution of 0.123 mmol of the compound of Example 3 in 4 ml of anhydrous tetrahydrofuran to 0.698 mmol of potassium hydride washed with hexane. After dropwise addition, at -10°C, of 0.327 mmol of N,N-dimethylcarbamoyl chloride, stirring is maintained for 3 hours 30 minutes at ambient temperature. After the addition of 50 ml of ethyl acetate and 10 ml of a saturated $NaHCO_3$ solution, the organic phase is washed with water and dried over magnesium sulphate and then evaporated under reduced pressure to yield the expected product.

EXAMPLE 7 : (±)-*cis*-6-Methoxy-3,3,14-trimethyl-2-{[(4-methylphenyl)sulphonyl]-oxy}-7-oxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]chromeno[6,5-*g*][1,8]-naphthyridin-1-yl 4-methylbenzenesulphonate

The product is obtained according to the procedure of Example 6 using tosyl chloride instead of N,N-dimethylcarbamoyl chloride.

EXAMPLE 8 : (±)-*cis*-4-{[1-(Acetyloxy)-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-2-yl]oxy}-4-oxobutanoic acid

1.1 equivalents of succinic anhydride and 1 mg of dimethylaminopyridine are added to a solution of 0.5 mmol of the compound of Example 3 in 3 ml of anhydrous pyridine. Stir for 2 days and in darkness at ambient temperature, then add 25 ml of acetic anhydride and stir for a further 48 hours before concentrating under reduced pressure. Chromatography on silica gel (dichloromethane/acetic acid : 99/1) allows the expected product to be isolated.

EXAMPLE 9 : (±)-*cis*-5-{[(1-(Acetyloxy)-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-2-yl]oxy}-5-oxopentanoic acid

The product is obtained according to the procedure of Example 8 using glutaric anhydride instead of succinic anhydride.

EXAMPLE 10 : (±)-*cis*-1-(Acetyloxy)-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-2-yl [(tert-butoxycarbonyl)amino]acetate

Slowly add 0.6 mmol of dicyclohexylcarbodiimide to a solution, at 0°C, of 0.5 mmol of the compound of Example 3 and 0.5 mmol of 2-[(*tert*-butoxycarbonyl)amino]acetic acid in 10 ml of dimethylformamide. The reaction mixture is maintained at 0°C for 5 hours and then at ambient temperature for 16 hours. After filtration and evaporation under reduced pressure, the residue is dissolved in 2 ml of anhydrous pyridine, 2 ml of acetic anhydride are added, and stirring is carried out for 48 hours at ambient temperature in darkness. After concentration of the reaction mixture under reduced pressure, chromatography of the residue on silica gel (dichloromethane) allows the expected product to be isolated.

EXAMPLE 11 : (±)-*cis*-1-(Acetyloxy)-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-2-yl aminoacetate

Add 0.14 µl of iodotrimethylsilane to a solution, at ambient temperature, of 0.1 mmol of the compound of Example 10 in 1 ml of chloroform. The reaction mixture is stirred for 5 min. at ambient temperature and then evaporated to dryness under reduced pressure. Chromatography on silica gel (dichloromethane/methanol : 85/15) allows the expected product to be isolated.

EXAMPLE 12 : 2-Butyryl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]-chromeno[6,5-*g*][1,8]naphthyridin-7-one

A mixture of 0.81 mmol of butyryl chloride and 0.673 mmol of $AlCl_3$ in 2 ml of anhydrous dichloromethane is added in small portions to 0.135 mmol of the product of Example 2 in 2 ml of dichloromethane at 0°C. The reaction mixture is stirred for 4 hours at ambient temperature and then poured into a 10 % solution of HCl. Following conventional treatment of the organic phases, and evaporation thereof under reduced pressure, chromatography of the residue on silica gel (dichloromethane/methanol gradient) allows the expected product to be isolated.

EXAMPLE 13 : (±)-*cis* 1-Hydroxy-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-2-yl butyrate

Add 2 equivalents of butyryl chloride to a solution of 0.74 mmol of the compound of Example 3 in 7 ml of anhydrous pyridine in the presence of 4-dimethylaminopyridine. Stir at ambient temperature for 72 hours and then add 5 equivalents of butyryl chloride and stir again for 72 hours and then evaporate to dryness. Chromatography on silica gel allows the expected product to be isolated.

EXAMPLE 14 : 6-Methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-2-yl butyrate

Add 4 drops of a 10 % solution of HCl to a solution of 0.29 mmol of the compound of Example 13 in 6 ml of dichloromethane. The reaction mixture is stirred for 3 days at ambient temperature and then dried and concentrated under reduced pressure. Chromatography of the residue on silica gel (dichloromethane/methanol gradient) allows the expected product to be isolated.

EXAMPLE 15 : 2-Hydroxy-6-methoxy-3,3,14-trimethyl-2,3-dihydro-1*H*-benzo[*b*]-chromeno[6,5-*g*][1,8]naphthyridin-1,7(14*H*)-dione

Over the course of 30 minutes, add a suspension of 1.28 g of $KMnO_4$ in 15 ml of water dropwise to a solution of 0.5 g of the product of Example 2 dissolved in 25 ml of acetone. The reaction mixture is stirred at ambient temperature for 8 hours and then, following conventional extraction and treatment, the expected product is isolated by chromatography of the residue on silica gel (dichloromethane/methanol : 98/2).

EXAMPLE 16 : 6-Methoxy-3,3,14-trimethyl-1,7-dioxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-2-yl acetate

The product is obtained according to the procedure of Example 13 starting from the compound of Example 15 and using acetic anhydride instead of butyryl chloride.

EXAMPLE 17 : 3,3,14-Trimethyl-3,14-dihydro-7*H*-benzo[*b*]chromeno[6,5-*g*][1,8]-naphthyridin-7-one

The product is obtained according to the procedure of Example 1 using the compound of Preparation 3 instead of the compound of Preparation 2.

EXAMPLE 18 : (±)-*cis*-1,2-Dihydroxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-7-one

The product is obtained according to the procedure of Example 3 using the compound of Example 17 instead of the compound of Example 2.

EXAMPLE 19 : (±)-*cis*-1,2-(Diacetoxy)-3,3,14-trimethyl-7-oxo-1,2,3,14-tetrahydro-7*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-7-one

The product is obtained according to the procedure of Example 4 using the compound of Example 18 instead of the compound of Example 3.

EXAMPLE 20 : 6-Hydroxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*b*]chromeno-[5,6-*g*][1,5]naphthyridin-7-one

2 g of anhydrous potassium carbonate are added to a solution of 2 g of the product of Preparation 4 in 50 ml of anhydrous dimethylformamide under an inert atmosphere.
After stirring for 15 minutes at 65°C, 2.4 g of anhydrous potassium iodide and 4.4 g of 3-chloro-3-methyl-1-butyne are added and the reaction mixture is maintained at 65°C for 24 hours and then at 130°C for 1 hour 30 minutes. After cooling, the solution is hydrolysed and then extracted with dichloromethane. The combined organic phases are washed with water and then with a 1M potassium hydroxide solution, dried over sodium sulphate and subsequently evaporated. Chromatography on silica gel (cyclohexane/acetone : 90/10) allows the expected product to be isolated.

EXAMPLE 21 : 6-Methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]chromeno-[5,6-*g*][1,5]naphthyridin-7-one

The product is obtained according to the procedure of Example 2 using the compound of Example 20.

EXAMPLE 22 : (±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]chromeno[5,6-*g*][1,5]naphthyridin-7-one

The product is obtained according to the procedure of Example 3 using the compound of Example 21.

EXAMPLE 23 : (±)-*cis*-1,2-Diacetyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]chromeno[5,6-*g*][1,5]naphthyridin-7-one

The product is obtained according to the procedure of Example 4 using the compound of Example 22.

EXAMPLE 24 : 6-Hydroxy-3,3,14-trimethyl-3,14-dihydro-7*H*-pyrano[2',3':7,8]quino-[2,3-*b*]quinoxalin-7-one

The product is obtained according to the procedure of Example 1 using the compound of Preparation 5 instead of the compound of Preparation 2.

EXAMPLE 25 : 6-Methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-pyrano[2',3':7,8]quino-[2,3-*b*]quinoxalin-7-one

The product is obtained according to the procedure of Example 2 using the compound of Example 24.

EXAMPLE 26 : (±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-pyrano[2',3':7,8]quino[2,3-*b*]quinoxalin-7-one

The product is obtained according to the procedure of Example 3 using the compound of Example 25.

EXAMPLE 27 : (±)-*cis*-1,2-Diacetoxy-6-methoxy-3,3,14-trimethyl-1,2,3,4-tetrahydro-7*H*-pyrano[2',3':7,8]quino[2,3-*b*]quinoxalin-7-one

The product is obtained according to the procedure of Example 4 using the compound of Example 26.

EXAMPLE 28 : (±)-*cis*-7-Methoxy-4,4,15-trimethyl-15,15c-dihydro-4*H*-[1,3]dioxolo-[4"5":4',5']pyrano[2',3':7,8]quino[2,3-*b*]quinoxaline-2,8(3a*H*)-dione

The product is obtained according to the procedure of Example 5 using the compound of Example 26.

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

EXAMPLE 29 : *In vitro* cytotoxicity

Two cell lines were used :

- 1 murine leukaemia, L1210,
- 1 human epidermoid carcinoma : KB-3-1

The cells are cultured in RPMI 1640 complete culture medium comprising 10 % fœtal calf serum, 2 mM glutamine, 50 units/ml of penicillin, 50 µg/ml of streptomycin and 10 mM Hepes, pH 7.4. The cells are distributed on microplates and are exposed to the cytotoxic compounds. The cells are then incubated for 2 days (L1210) or 4 days (KB-3-1) in an incubator at 37°C in the presence of 5 % CO_2. The number of viable cells is then quantified by a colorimetric assay, the tetrazolium microculture assay (Cancer Res. 1987, 47, 939-942).

The results are expressed as IC_{50}, the concentration of cytotoxic compound that inhibits the proliferation of the treated cells by 50 %. By way of example, the compound of Example 4 exhibits, respectively, an IC_{50} of 0.32 µM in respect of L1210 and of 0.037 µM in respect of KB-3-1.

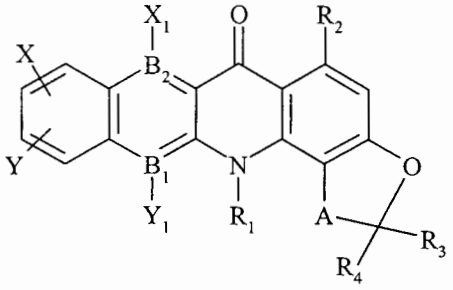
EXAMPLE 30 : Pharmaceutical composition: injectable solution

Compound of Example 4 ..... 10 mg

Distilled water for injectable preparations..... 25 ml

CLAIMS

1. Compounds of formula (I) :



(I)

wherein:

- B_1 and B_2, which may be identical or different, each independently of the other represents a carbon atom or a nitrogen atom, with the proviso that at least one of the two groups B_1 or B_2 represents a nitrogen atom,

- X and Y, which may be identical or different, each independently of the other represents one or more groups selected from :
  - the atoms hydrogen and halogen,
  - the groups hydroxy, linear or branched (C_1-C_6)alkoxy, nitro, cyano, linear or branched (C_1-C_6)alkyl, linear or branched (C_2-C_6)alkenyl, linear or branched (C_1-C_6)-polyhaloalkyl, or
  - groups of formula $-NR_aR_b$ wherein :

    R_a and R_b, which may be identical or different, each independently of the other represents a group selected from hydrogen and the groups $-C(O)-CF_3$, $-C(O)-NH_2$ and linear or branched (C_1-C_6)alkyl, optionally substituted by a group $NR'_aR'_b$ wherein :

    R'_a and R'_b, which may be identical or different, each independently of the other represents a group selected from hydrogen and linear or branched (C_1-C_6)alkyl, or R'_a and R'_b, together with the nitrogen atom carrying them, form a monocyclic heterocycle having from 5 to 7 ring members and optionally containing in the ring system a second hetero atom selected from oxygen and nitrogen,

    or R_a and R_b, together with the nitrogen atom carrying them, form a monocyclic

heterocycle having from 5 to 7 ring members and optionally containing in the ring system a second hetero atom selected from oxygen and nitrogen,

- X_1 and Y_1, which may be identical or different, each independently of the other represents a group selected from the substituents as defined for X and Y,

it being understood that, when B_1 and/or B_2 represent a nitrogen atom, B_1 and B_2 do not carry substituents Y_1 and X_1 respectively,

- R_1 represents a hydrogen atom or a linear or branched $(C_1\text{-}C_6)$alkyl group,

- R_2 represents a group selected from hydrogen and the groups linear or branched $(C_1\text{-}C_6)$alkyl, $-OR''_a$; $-NR'_aR'_b$; $O-T_a-OR''_a$; $-NR''_a-T_a-NR'_aR'_b$; $-NR''_a-C(O)-T_aH$; $O-C(O)-T_aH$; $-O-T_a-NR'_aR'_b$; $-NR''_a-T_a-OR''_a$; $-NR''_a-T_a-CO_2R''_a$; and $-NR''_a-C(O)-T_a-NR'_aR'_b$,
  wherein:
  * T_a represents a linear or branched $(C_1\text{-}C_6)$alkylene chain,
  * R'_a and R'_b are as defined hereinbefore,
  * R''_a represents a group selected from hydrogen and linear or branched $(C_1\text{-}C_6)$alkyl,

- R_3 and R_4, which may be identical or different, each independently of the other represents a hydrogen atom or a linear or branched $(C_1\text{-}C_6)$alkyl group, or R_3 and R_4, together with the carbon atom carrying them, form a monocyclic ring having from 3 to 6 ring members,

- A represents a group of formula :
  a) $-CH(R_5)-CH(R_6)-$ wherein :

  * *R_5 and R_6,, which may be identical or different, each represents independently of the other a group selected from :*

  1) hydrogen,

2) the groups OR_c, NR_cR_d, SR_c, wherein :

- R_c, R_d, which may be identical or different, each independently of the other represents a group selected from hydrogen, the groups linear or branched (C_1-C_6)alkyl, aryl and aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched,

  or the group $C(O)–R_e$ wherein R_e represents a group selected from hydrogen, aryl or $NR'''_aR'''_b$ wherein R'''_a and R'''_b are identical and represent a hydrogen atom or wherein R'''_a and R'''_b, together with the nitrogen atom carrying them, form a monocyclic heterocycle having from 5 to 7 ring members and optionally containing in the ring system a second hetero atom selected from oxygen and nitrogen,

3) $W_1–C(W_2)–U–V$ wherein :

α) W_1 represents an oxygen atom, a sulphur atom or NR_c (wherein R_c is as defined hereinbefore),

β) W_2 represents an oxygen atom or a sulphur atom,

γ) U represents a linear or branched (C_1-C_8)alkylene chain or a linear or branched (C_2-C_8)alkenylene chain,

δ) V represents a group selected from :

- hydrogen,
- aryl,
- and the groups OR_c, CO_2R_c, COR_c, $CONR'_aR'_b$, NR_cR_d, $N(R_c)–CO_2R'_c$, $N(R_c)–COR'_c$, wherein R'_a, R'_b, R_c and R_d are as defined hereinbefore and R'_c represents a group selected from hydrogen, linear or branched (C_1-C_6)alkyl, aryl, or aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched,

ε) U represents a bond when W_2 does not represent an oxygen atom and when V does not represent a group selected from :

- hydrogen
- aryl and
- NH_2,

4) W_1–$C(W_2)$–W_3–T_1 wherein :

α) W_1 and W_2 are as defined hereinbefore,

β) W_3 represents an oxygen atom, a sulphur atom, or NR_c wherein R_c is as defined hereinbefore,

γ) T_1 represents a group selected from :

- hydrogen,
- linear or branched $(C_1$-$C_6)$alkyl,
- linear or branched $(C_2$-$C_6)$alkenyl,
- aryl, aryl-$(C_1$-$C_6)$alkyl in which the alkyl moiety may be linear or branched, and
- linear or branched $(C_1$-$C_6)$alkylene or linear or branched $(C_2$-$C_6)$alkenylene chains, each of which is substituted by a group OR_c wherein R_c is as defined hereinbefore or $NR'_aR'_b$ wherein R'_a and R'_b are as defined hereinbefore,

5) W_1–$S(O)_n$–W_3–T_1 wherein :

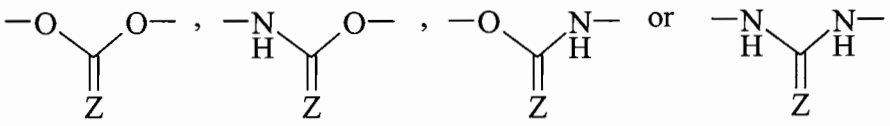
α) W_1, W_3 and T_1 are as defined hereinbefore, and

β) n represents an integer selected from 1 and 2,

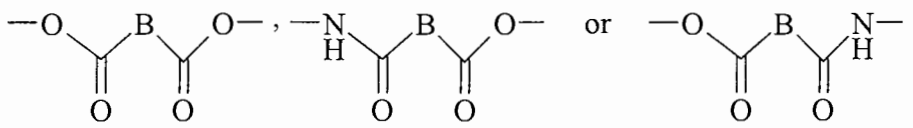
6) W_1–$S(O)_n$–T_1 wherein W_1, T_1 and n are as defined hereinbefore, and

7) $C(W_2)$–T_1 wherein W_2 and T_1 are as defined hereinbefore,

* *or R_5 and R_6, together form :*

1) a group  wherein Z represents an oxygen atom or a sulphur atom,

2) a group–O–$(CH_2)_m$–O– wherein m represents an integer of from 1 to 4 inclusive, or

3) a group  wherein B represents a single bond, a linear or branched (C_1-C_6)alkylene chain or a linear or branched (C_2-C_6)alkenylene chain,

* *or R_5 and R_6, together with the carbon atoms carrying them, form an oxirane group or an aziridine group*, optionally substituted on the nitrogen atom by a linear or branched (C_1-C_6)alkyl group,

b) –CH=C(R_7)– or –C(R_7)=CH– wherein R_7 represents a group selected from :

- hydrogen,
- and the groups OR"$_a$, W_1–C(W_2)–U–V, W_1–C(W_2)–W_3–T_1, W_1–S(O)$_n$–W_3–T_1, W_1–S(O)$_n$–T_1 and C(W_2)–T_1 wherein R"$_a$, W_1, W_2, U, V, W_3, T_1 and n are as defined hereinbefore,

or

c) –C(O)–CH(R_8)– or – CH(R_8)–C(O)– wherein R_8 represents a group selected from :

- hydrogen,
- linear or branched (C_1-C_6)alkylcarbonyloxy and the groups OR"$_a$ wherein R"$_a$ is as defined hereinbefore,

their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base,

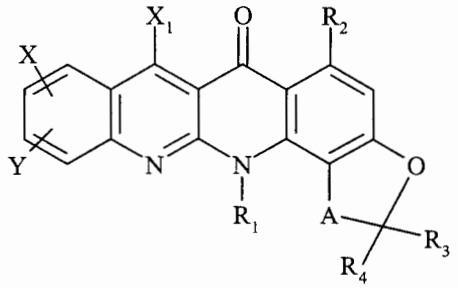
wherein aryl is understood as a phenyl or naphthyl group optionally containing one or more identical or different substituents selected from linear or branched (C_1-C_6)alkyl, linear or branched (C_2-C_6)alkenyl, hydroxy, halogen, carboxy, nitro, amino, alkylamino or dialkylamino in which the alkyl moieties contain from 1 to 6 carbon atoms and may be linear or branched, linear or branched (C_1-C_6)alkoxy, linear or branched (C_1-C_6)acyl and linear or branched (C_1-C_6)alkylcarbonyloxy,

among the monocyclic heterocycles having from 5 to 7 ring members and optionally containing in the ring system a second hetero atom selected from oxygen and nitrogen

there may be mentioned, without implying any limitation, the groups pyrrolidinyl, isoxazolidinyl, oxazolidinyl, pyrazolidinyl, imidazolidinyl, piperidyl, morpholinyl, hexahydropyridazinyl, hexahydropyrimidinyl, piperazinyl, azepanyl, oxazepanyl and diazepanyl,

among the monocyclic rings having from 3 to 6 ring members there may be mentioned, without implying any limitation, the groups cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

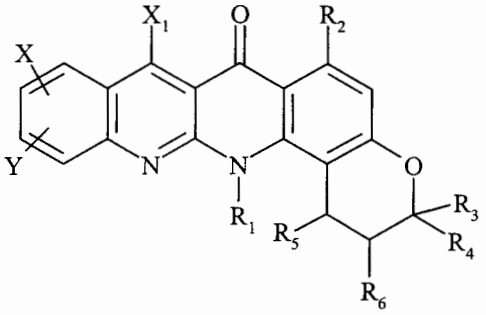
2. Compounds of formula (I) according to claim 1, characterised in that they are compounds of formula (IA) :



(IA)

wherein X, Y, X_1, R_1, R_2, R_3, R_4 and A are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

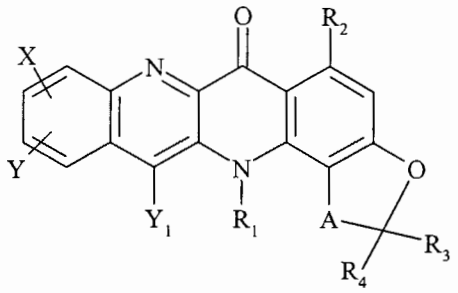
3. Compounds of formula (I) according to claim 1 or claim 2, characterised in that they are compounds of formula (IB) :



(IB)

wherein X, Y, X_1, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

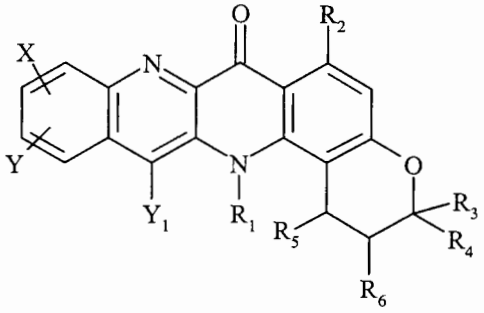
4. Compounds of formula (I) according to claim 1, characterised in that they are compounds of formula (IC) :



(IC)

wherein X, Y, Y_1, R_1, R_2, R_3, R_4 and A are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

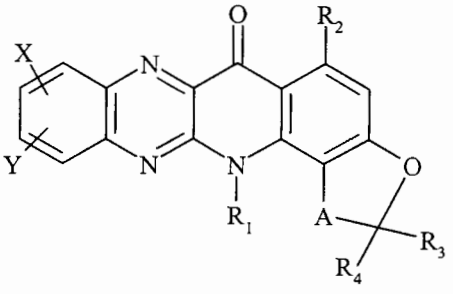
5. Compounds of formula (I) according to claim 1 or claim 4, characterised in that they are compounds of formula (ID) :



(ID)

wherein X, Y, Y_1, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

6. Compounds of formula (I) according to claim 1, characterised in that they are compounds of formula (IE) :

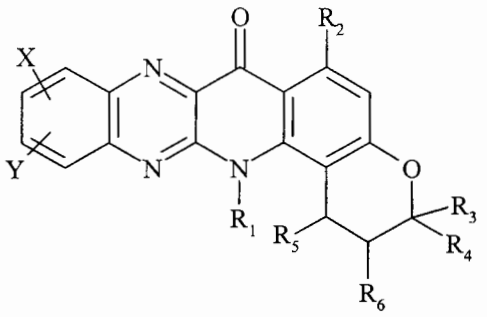


(IE)

wherein X, Y, R_1, R_2, R_3, R_4 and A are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically

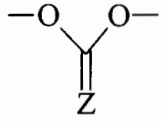
acceptable acid or base.

7. Compounds of formula (I) according to claim 1 or claim 6, characterised in that they are compounds of formula (IF) :



(IF)

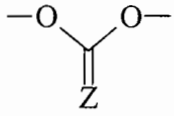
wherein X, Y, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

8. Compounds of formula (I) according to claim 1, characterised in that they are compounds of formulae (IB), (ID) and (IF) wherein R_5 and R_6 are identical and represent a group of formula $-OR_c$ or W_1-C(W_2)-U-V or wherein R_5 and R_6 together form a group  wherein R_c, W_1, W_2, U, V and Z are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

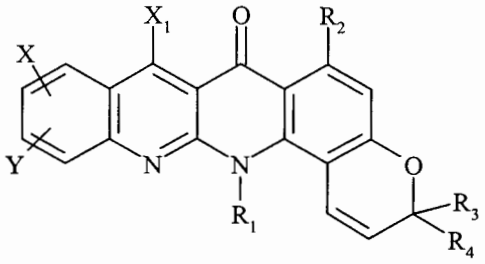
9. Compounds of formula (I) according to claim 1 or claim 8, characterised in that they are compounds of formulae (IB), (ID) and (IF) wherein R_5 and R_6 are identical and represent a group of formula $-OR_c$ wherein R_c represents a hydrogen atom or a linear or branched (C_1-C_6)alkyl group, their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

10. Compounds of formula (I) according to claim 1 or claim 8, characterised in that they are compounds of formulae (IB), (ID) and (IF) wherein R_5 and R_6 are identical and represent a group of formula W_1-C(W_2)-U-V wherein W_1 and W_2 represent an oxygen atom, U represents a linear or branched (C_1-C_6)alkylene chain and V represents a

hydrogen atom, their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

11. Compounds of formula (I) according to claim 1 or claim 8, characterised in that they are compounds of formulae (IB), (ID) and (IF) wherein R_5 and R_6 together form a group  wherein Z represents an oxygen atom, their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

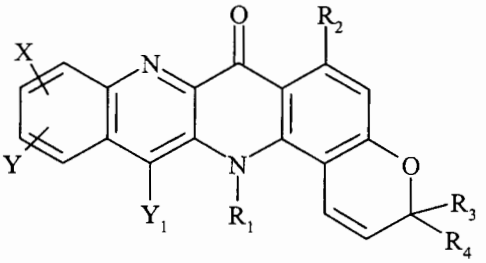
12. Compounds of formula (I) according to claim 1 or claim 2, characterised in that they are compounds of formula (IG) :



(IG)

wherein X, Y, X_1, R_1, R_2, R_3 and R_4 are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

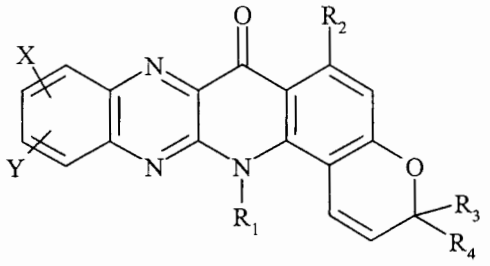
13. Compounds of formula (I) according to claim 1 or claim 4, characterised in that they are compounds of formula (IH) :



(IH)

wherein X, Y, Y_1, R_1, R_2, R_3 and R_4 are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

14. Compounds of formula (I) according to claim 1 or claim 6, characterised in that they are compounds of formula (IJ) :



(IJ)

wherein X, Y, R_1, R_2, R_3 and R_4 are as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

15. Compounds of formula (I) according to any one of claims 1 to 14, characterised in that R_3 and R_4 represent a linear or branched $(C_1\text{-}C_6)$alkyl group, their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

16. Compounds of formula (I) according to any one of claims 1 to 14, characterised in that R_2 represents a group $-OR"_a$ wherein $R"_a$ is as defined for formula (I), their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

17. Compounds of formula (I) according to any one of claims 1 to 14 and 16, characterised in that R_2 represents as group $-OR"_a$ wherein $R"_a$ represents a linear or branched $(C_1\text{-}C_6)$alkyl group, and even more especially a methyl group, their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

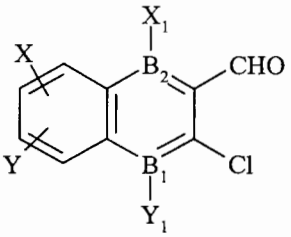
18. Compounds of formula (I) according to any one of claims 1 to 14, characterised in that X, Y, X_1 and Y_1 represent a hydrogen atom, their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

19. Compounds of formula (I) according to claim 1 which are :

- (±)-*cis*-1,2-dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]-chromeno[6,5-*g*][1,8]naphthyridin-7-one,
- (±)-*cis*-1,2-diacetoxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]-chromeno[6,5-*g*][1,8]naphthyridin-7-one,
- (±)-*cis*-7-methoxy-4,4,15-trimethyl-15,15c-dihydro-4*H*-benzo[*b*][1,3]dioxolo-[4',5':3,4]chromeno[6,5-*g*][1,8]naphthyridine-2,8(3a*H*)-dione,

their enantiomers, diastereoisomers, N-oxides, and also addition salts thereof with a pharmaceutically acceptable acid or base.

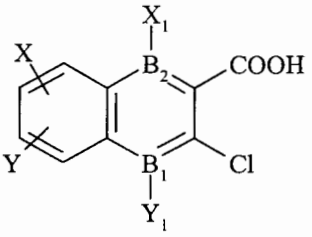
20. Process for the preparation of compounds of formula (I) according to claim 1, characterised in that there is used as starting material a compound of formula (II) :



(II)

wherein X, Y, X_1, Y_1, B_1 and B_2 are as defined for formula (I),

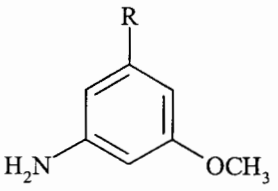
which compounds of formula (II) are placed in the presence of pyridinium dichromate to yield compounds of formula (III) :



(III)

wherein X, Y, X_1, Y_1, B_1 and B_2 are as defined for formula (I),

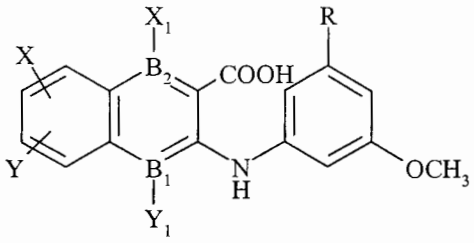
which compounds of formula (III) are treated in basic and anhydrous medium with a compound of formula (IV) :



(IV)

wherein R represents a hydrogen atom, a hydroxy group, a linear or branched (C_1-C_6)alkyl

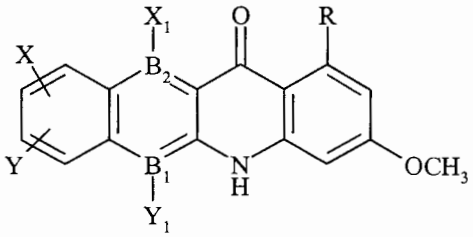
group or a linear or branched (C_1-C_6)alkoxy group to yield compounds of formula (V) :



(V)

wherein X, Y, X_1, Y_1, B_1, B_2 and R are as defined for formula (I),

which compounds of formula (V) are placed in the presence of polyphosphoric acid to yield compounds of formula (VI) :

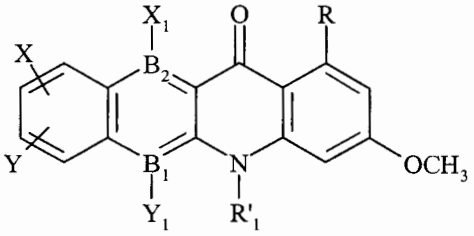


(VI)

wherein X, Y, X_1, Y_1, B_1, B_2 and R are as defined hereinbefore,

of which compounds of formula (VI) :

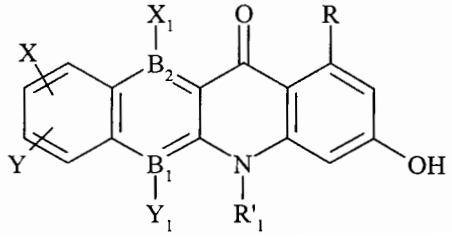
a) the nitrogen atom is substituted by the action of an alkyl halide or of a dialkyl sulphate in the presence of a deprotonation agent, in a polar aprotic solvent, to yield compounds of formula (VII) :



(VII)

wherein R'_1 represents a linear or branched (C_1-C_6)alkyl group and X, Y, X_1, Y_1, B_1, B_2 and R are as defined hereinbefore,

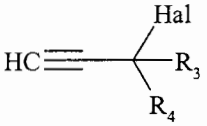
which compounds of formula (VII) are treated with a solution of hydrobromic acid in acetic acid to yield compounds of formula (VIII) :



(VIII)

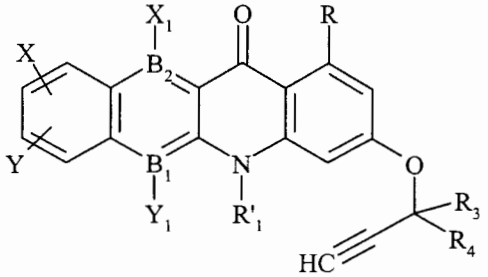
wherein X, Y, X_1, Y_1, B_1, B_2, R and R'_1 are as defined hereinbefore,

which compounds of formula (VIII) are then treated under basic conditions, in an anhydrous aprotic solvent, with an alkyne of formula (IX) :



(IX)

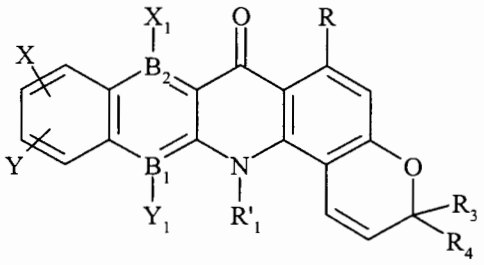
wherein Hal represents a halogen atom and R_3 and R_4 are as defined for formula (I) to yield compounds of formula (X) :



(X)

wherein X, Y, X_1, Y_1, B_1, B_2, R, R'_1, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (X) are refluxed in anhydrous dimethylformamide to yield compounds of formula (I/a), a particular case of the compounds of formula (I) :

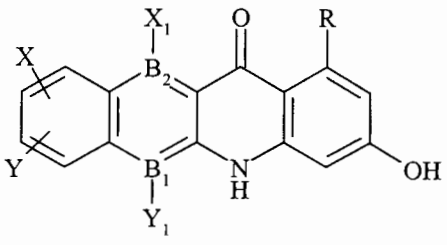


(I/a)

wherein X, Y, X_1, Y_1, B_1, B_2, R, R'_1, R_3 and R_4 are as defined hereinbefore,

or which compounds of formula (VI)

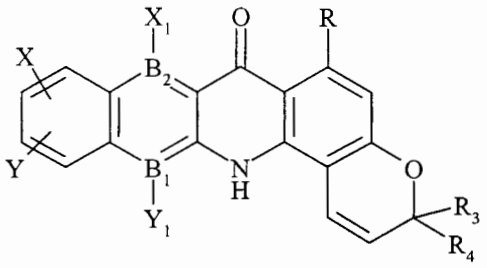
b) are subjected to the same conditions as the compounds of formula (VII) to yield compounds of formula (XI) :



(XI)

wherein X, Y, X_1, Y_1, B_1, B_2 and R are as defined hereinbefore,

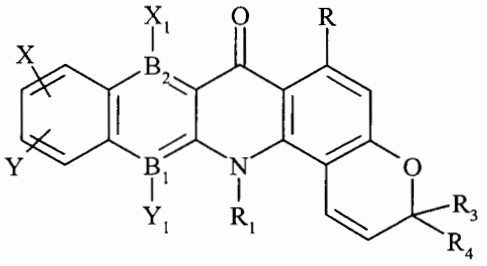
which compounds of formula (XI) are subjected in succession to the same conditions as the compounds of formula (VIII) and (X) to yield compounds of formula (I/b), a particular case of the compounds of formula (I) :



(I/b)

wherein X, Y, X_1, Y_1, B_1, B_2, R, R_3 and R_4 are as defined hereinbefore,

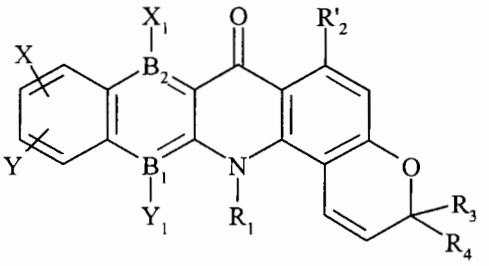
the totality of the compounds (I/a) and (I/b) constituting the compounds of formula (I/c), a particular case of the compounds of formula (I) :



(I/c)

wherein R_1 is as defined for formula (I) and X, Y, X_1, Y_1, B_1, B_2, R, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (I/c) are, if desired, subjected to the action of an alkylating agent or an acylating agent to yield compounds of formula (I/d), a particular case of the compounds of formula (I) :



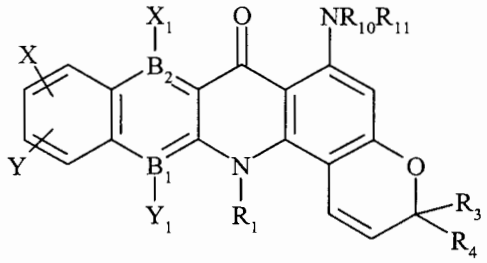
(I/d)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_3 and R_4 are as defined hereinbefore, and R'_2 represents a group selected from $-OR''_{a1}$, $O-T_a-OR''_a$, $-O-C(O)-T_aH$ and $-O-T_a-NR'_aR'_b$ wherein R'_a, R'_b, R''_a and T_a are as defined for formula (I) and R''_{a1} represents a linear or branched (C_1-C_6)alkyl group,

which compounds of formula (I/d) are treated, when R'_2 represents a group $-OR"_{a1}$ wherein $R"_{a1}$ is as defined hereinbefore, with a compound of formula (XII) :

$$HNR_{10}R_{11} \qquad (XII)$$

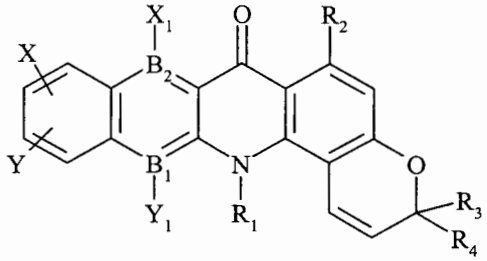
wherein R_{10} represents a group selected from R'_a and $R"_a$, and R_{11} represents a group selected from R'_b, $-T_a-NR'_aR'_b$, $-C(O)-T_aH$, $-T_a-OR"_a$, $-T_a-CO_2R"_a$ and $-C(O)-T_a-NR'_aR'_b$ wherein R'_a, R'_b, $R"_a$ and T_a are as defined hereinbefore, to yield compounds of formula (I/e), a particular case of the compounds of formula (I) :



(I/e)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_3, R_4, R_{10} and R_{11} are as defined hereinbefore,

the totality of the compounds of formulae (I/c), (I/d) and (I/e) constituting the compounds of formula (I/f), a particular case of the compounds of formula (I) :

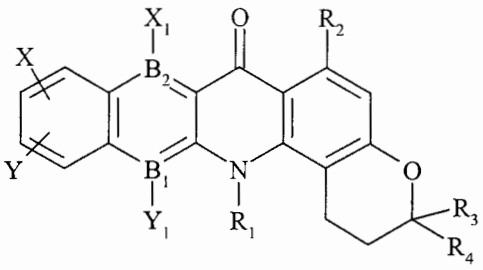


(I/f)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined for formula (I),

which compounds of formula (I/f) may be subjected,

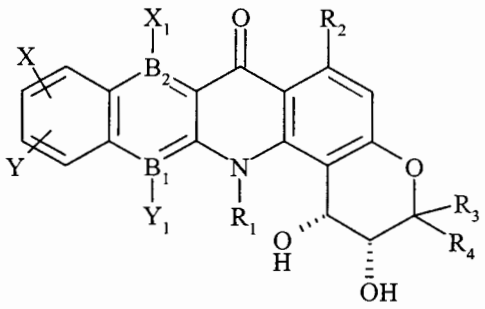
a) either to the action of a reducing agent to yield compounds of formula (I/g), a particular case of the compounds of formula (I) :



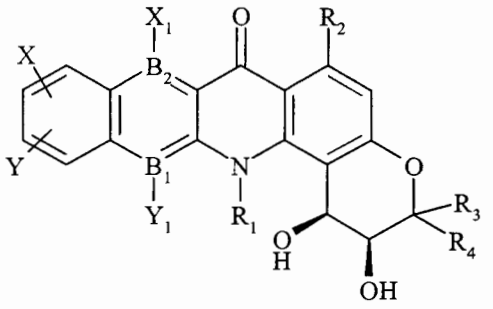
(I/g)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

b) or to the action of osmium tetroxide in polar medium, and in the presence of 4-methylmorpholine-N-oxide, to yield compounds of formulae (I/h_1) and (I/h_2), a particular case of the compounds of formula (I) :



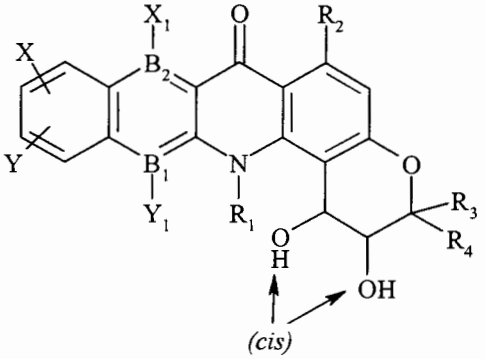
(I/h_1)



(I/h_2)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

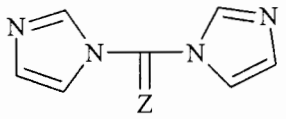
the totality of the compounds of formulae (I/h_1) and (I/h_2) constituting the *cis*–diol compounds of formula (*cis*–I/h), a particular case of the compounds of formula (I) :



(*cis* - I/h)

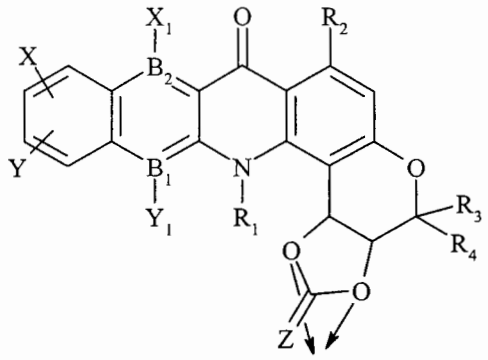
wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

which *cis*–diol compounds of formula (*cis*–I/h) are optionally subjected to the action of a compound of formula (XIII) :



(XIII)

wherein Z is as defined for formula (I) to yield compounds of formula (*cis*–I/i), a particular case of the compounds of formula (I) :

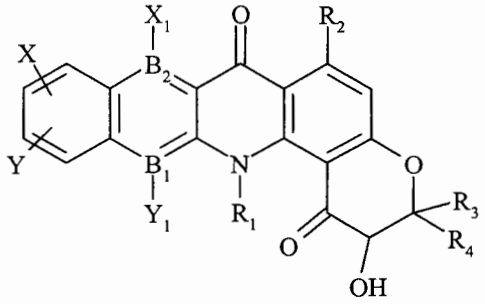


(*cis*-I/i)

(*cis*)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

c) or to the action of potassium permanganate in polar medium to yield compounds of formula (I/j), a particular case of the compounds of formula (I) :

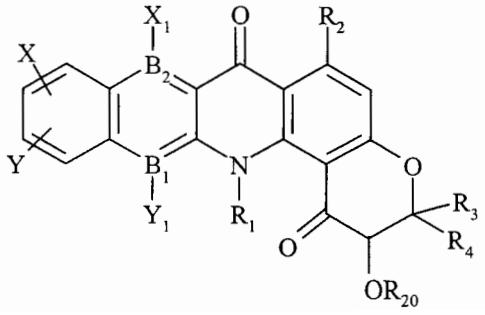


(I/j)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

<u>which compounds of formula (I/j) may be subjected</u> :

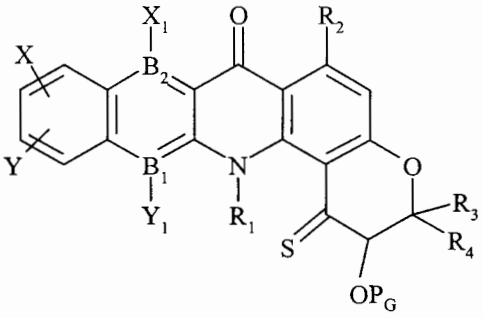
α) either to the action of an alkylating agent or an acylating agent to yield compounds of formula (I/k), a particular case of the compounds of formula (I) :



(I/k)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore, and R_{20} represents a group selected from linear or branched $(C_1\text{-}C_6)$alkyl and linear or branched $(C_1\text{-}C_6)$alkylcarbonyl,

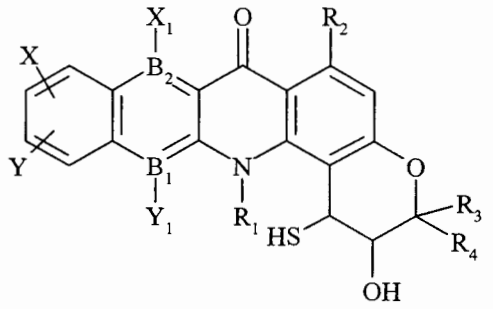
β) or to the action of a protecting group P_G for the hydroxy function then to the action of P_2S_5 to yield compounds of formula (XIV) :



(XIV)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and P_G are as defined hereinbefore,

which compounds of formula (XIV) are treated with a reducing agent, then subjected to a reaction for deprotection of the hydroxy function, to yield compounds of formula (I/l), a particular case of the compounds of formula (I) :



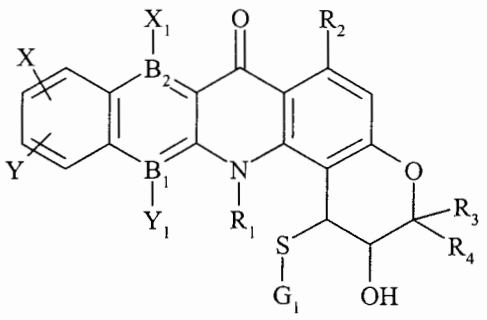
(I/l)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (I/l) are, if desired, subjected to the action of a compound of formula (XV) :

$$Hal - G_1 \qquad (XV)$$

wherein Hal represents a halogen atom and G_1 represents a group selected from $-R_c$, $-C(W_2)\text{-}U\text{-}V$, $-C(W_2)\text{-}W_3\text{-}T_1$, $-S(O)_n\text{-}W_3\text{-}T_1$ and $-S(O)_n\text{-}T_1$ wherein R_c, W_2, W_3, U, V, T_1 and n are as defined for formula (I) to yield compounds of formula (I/m), a particular case of the compounds of formula (I) :



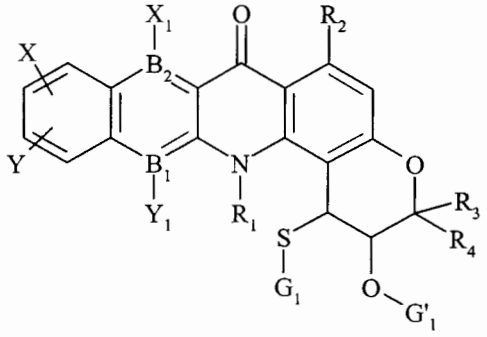
(I/m)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G_1 are as defined hereinbefore,

which compounds of formula (I/m) may be subjected to the action of a compound of formula (XVI) :

$$Hal - G'_1 \qquad (XVI)$$

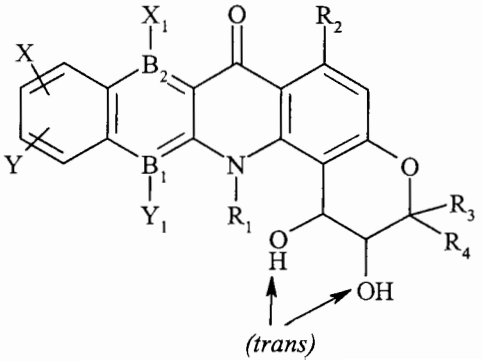
wherein Hal is as defined hereinbefore and G'_1 represents a group selected from $-R_c$, $-C(W_2)-U-V$, $-C(W_2)-W_3-T_1$, $-S(O)_n-W_3-T_1$ and $-S(O)_n-T_1$ wherein R_c, W_2, W_3, U, V, T_1 and n are as defined for formula (I), to yield compounds of formula (I/n), a particular case of the compounds of formula (I) :



(I/n)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G_1 and G'_1 are as defined hereinbefore,

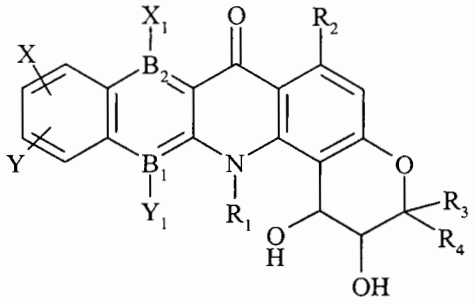
γ) or to reducing conditions in the presence of $NaBH_4$ to yield compounds of formula (I/o), a particular case of the compounds of formula (I) :



(I/o)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

the totality of the compounds of formulae (*cis*–I/h) and (I/o) constituting the compounds of formula (I/p),

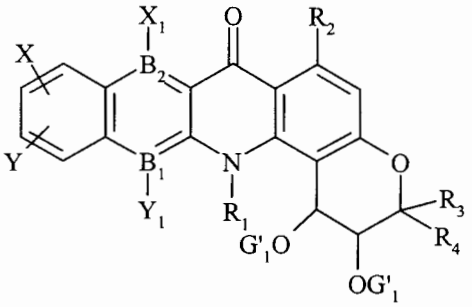


(I/p)

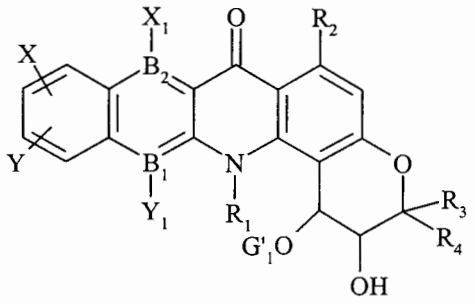
wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

<u>which compounds of formula (I/p) may be subjected</u> :

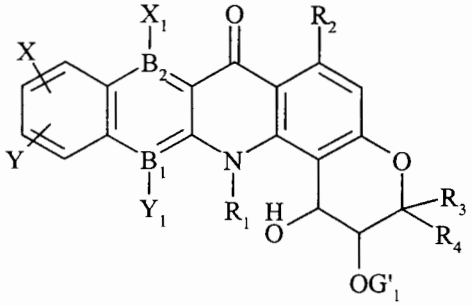
α) either to the action of a compound of formula (XVI) as defined hereinbefore to yield compounds of formulae (I/q_1), (I/q_2) and (I/q_3), particular cases of the compounds of formula (I) :



(I/q_1)



(I/q_2)

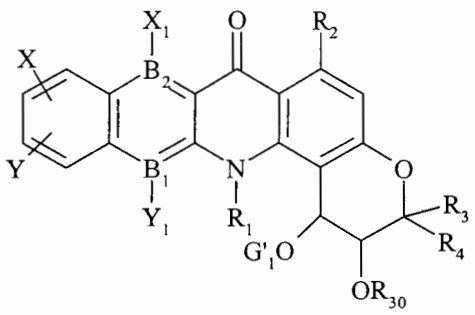


(I/q_3)

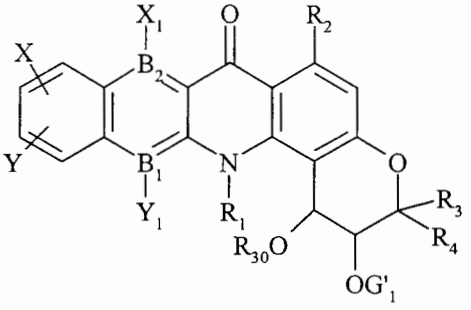
wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G'_1 are as defined hereinbefore,

<u>which compounds of formulae (I/q_2) and (I/q_3) are, if desired, subjected</u> :

1) either to the action of an alcohol of formula R_{30}-OH wherein R_{30} represents a linear or branched (C_1-C_6)alkyl group to yield, respectively, compounds of formulae (I/r_2) and (I/r_3), particular cases of the compounds of formula (I) :



(I/r_2)



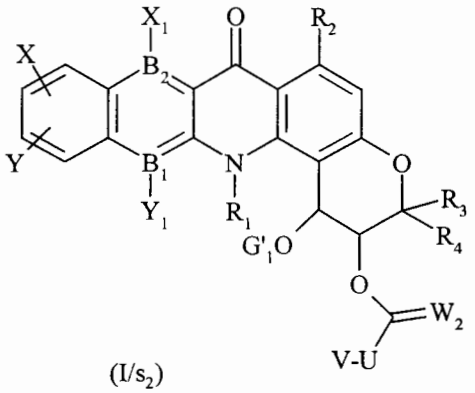
(I/r_3)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G'_1 and R_{30} are as defined hereinbefore,

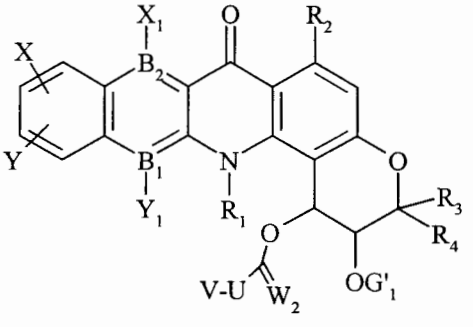
2) or to the action of an anhydride of formula (XVII) :

$$[V\text{-}U\text{-}C(W_2)]_2O \qquad (XVII)$$

wherein W_2, U and V are as defined for formula (I) to yield compounds of formulae (I/s_2) and (I/s_3), particular cases of the compounds of formula (I) :



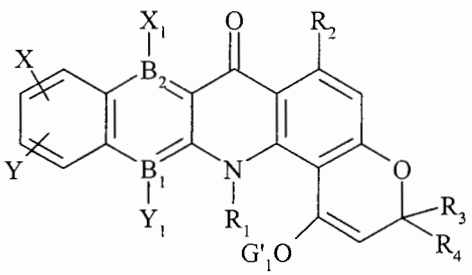
(I/s_2)



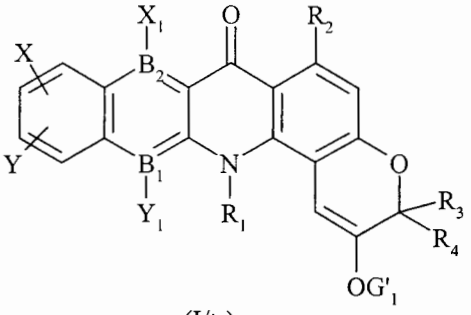
(I/s_3)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G'_1, W_2, U and V are as defined hereinbefore,

3) or to dehydration conditions in acid medium to yield compounds of formulae (I/t_2) and (I/t_3), particular cases of the compounds of formula (I) :



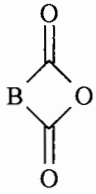
(I/t_2)



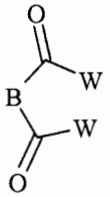
(I/t_3)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G'_1 are as defined hereinbefore,

β) or to the action of a compound of formula (XVIII) or (XIX)

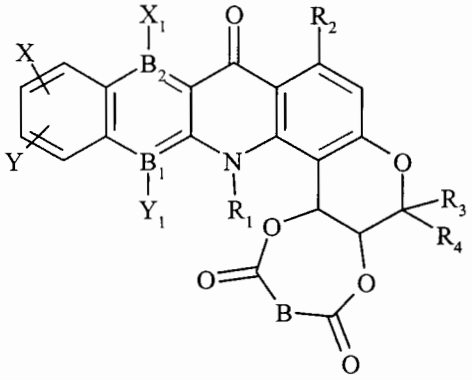


(XVIII)



(XIX)

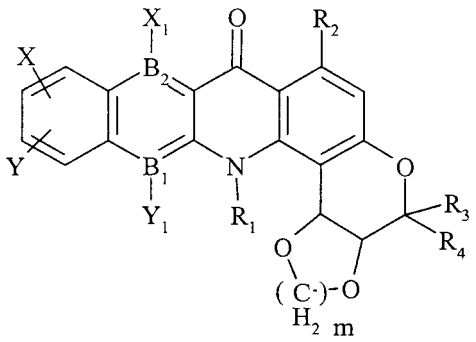
wherein B is as defined for formula (I) and W represents a halogen atom or a hydroxyl group to yield compounds of formula (I/u), a particular case of the compounds of formula (I) :



(I/u)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and B are as defined hereinbefore,

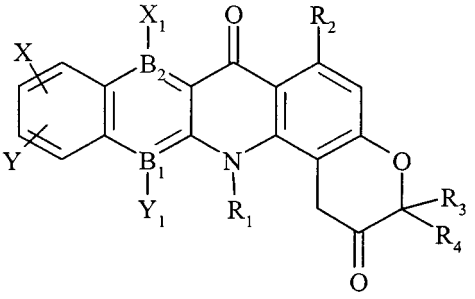
γ) or to the action of a linear (C_1-C_6)alkyl dihalide to yield compounds of formula (I/v), a particular case of the compounds of formula (I) :



(I/v)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore and m is as defined for formula (I),

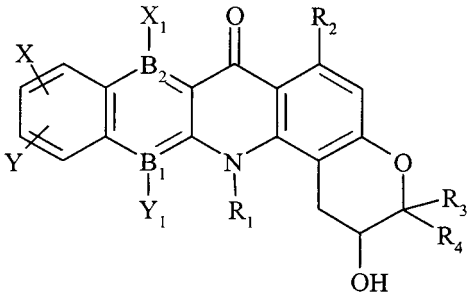
ε) or to dehydration conditions in acid medium to yield compounds of formula (I/w), a particular case of the compounds of formula (I) :



(I/w)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

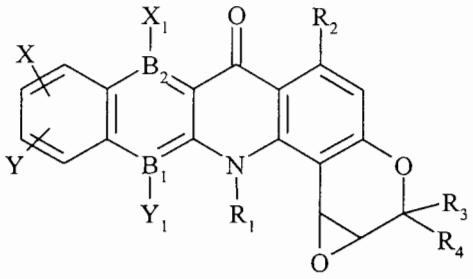
which compounds of formula (I/w) are, if desired, reduced in the presence of $NaBH_4$ to yield compounds of formula (I/x), a particular case of the compounds of formula (I) :



(I/x)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

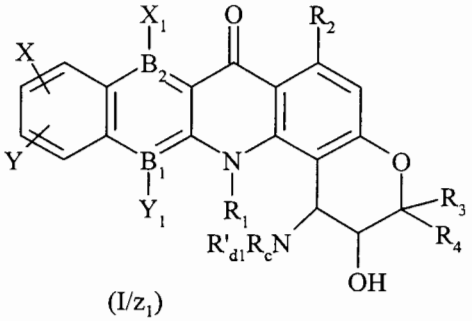
d) or to the action of a peracid or of dimethyl dioxirane to yield compounds of formula (I/y), a particular case of the compounds of formula (I) :



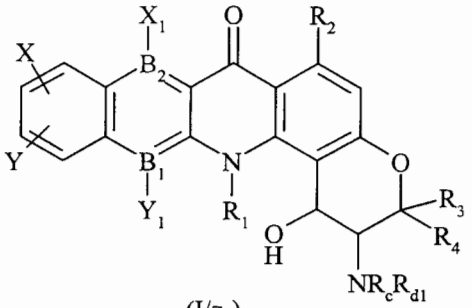
(I/y)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (I/y) are, if desired, treated with ammonia or a primary or secondary amine to yield compounds of formulae (I/z_1) and (I/z_2), particular cases of the compounds of formula (I) :



(I/z_1)

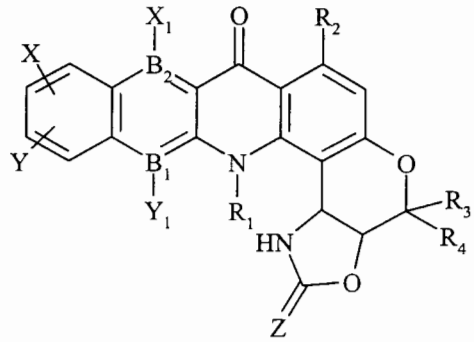


(I/z_2)

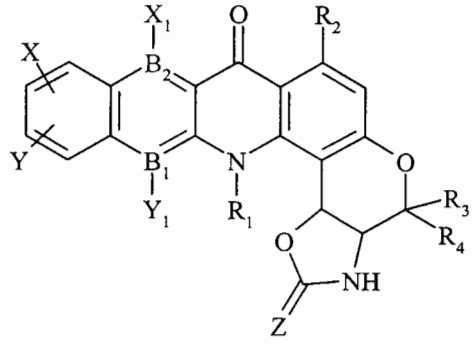
wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore, R_c is as defined for formula (I) and R_{d1} represents a group selected from R_d, $-C(W_2)-U-V$, $-C(W_2)-W_3-T_1$, $-S(O)_n-W_3-T_1$ and $-S(O)_n-T_1$ wherein R_d, W_2, W_3, U, V and T_1 are as defined hereinbefore,

<u>which compounds of formulae (I/z_1) and (I/z_2) may be subjected</u>

α) either, when R_c and Rd_1 represent a hydrogen atom, to the action of a compound of formula (XIII) as defined hereinbefore to yield compounds of formulae (I/aa_1) and (I/aa_2), particular cases of the compounds of formula (I) :



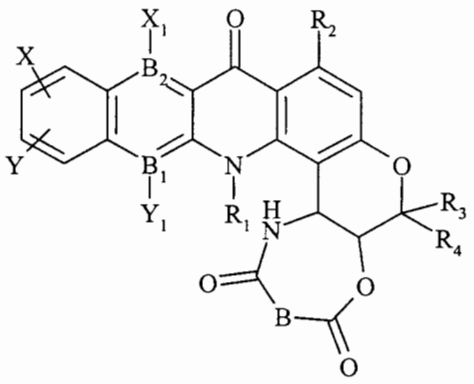
(I/aa_1)



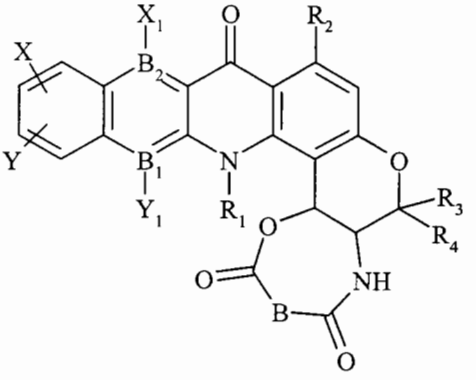
(I/aa_2)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and Z are as defined hereinbefore,

β) or to the action of a compound of formula (XIX) as defined hereinbefore to yield compounds of formulae (I/ab_1) and (I/ab_2), particular cases of the compounds of formula (I) :



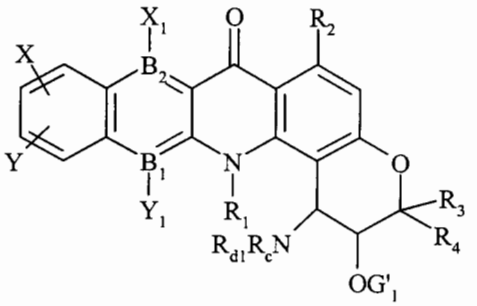
(I/ab_1)



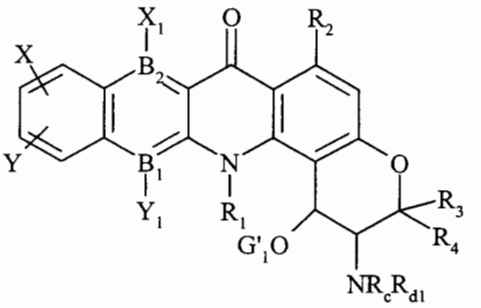
(I/ab_2)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and B are as defined hereinbefore,

γ) or to the action of a compound of formula (XVI) as defined hereinbefore to yield compounds of formulae (I/ac_1) and (I/ac_2), particular cases of the compounds of formula (I) :



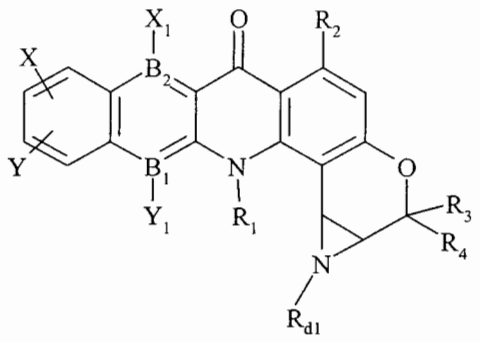
(I/ac_1)



(I/ac_2)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, R_c, R_{d1} and G'_1 are as defined hereinbefore,

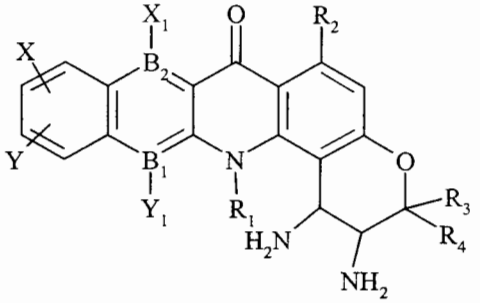
δ) or to the action of triphenylphosphine dibromide in the presence of triethylamine to yield compounds of formula (I/ad), a particular case of the compounds of formula (I) :



(I/ad)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and R_{d1} are as defined hereinbefore,

ε) or to the action of NaN_3 in the presence of hydrogen peroxide, followed by a reduction step, to yield compounds of formula (I/ae), a particular case of the compounds of formula (I) :

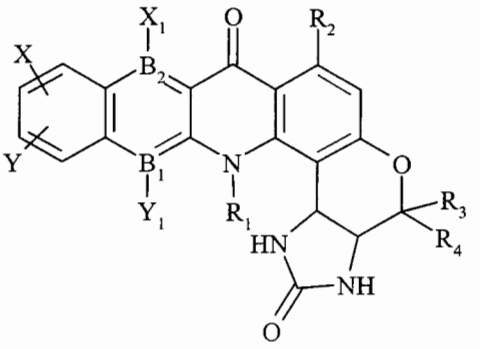


(I/ae)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

which compounds of formula (I/ae) are, if desired, subjected

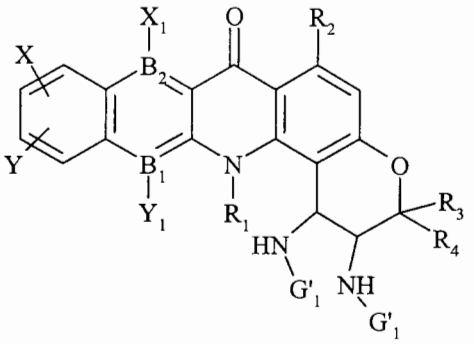
1) either to the action of carbon dioxide in the presence of diphenyl phosphite to yield compounds of formula (I/af), a particular case of the compounds of formula (I) :



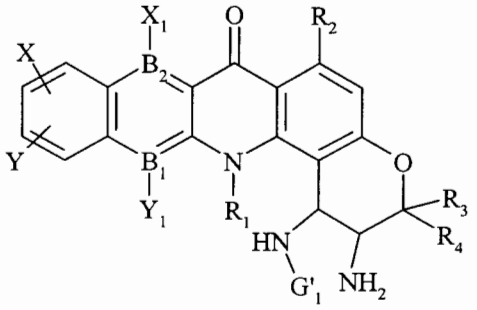
(I/af)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

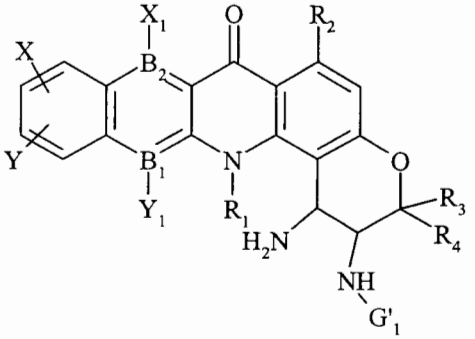
2) or to the action of a compound of formula (XVI) as defined hereinbefore to yield compounds of formulae (I/ag_1), (I/ag_2) and (I/ag_3), a particular case of the compounds of formula (I) :



(I/ag_1)



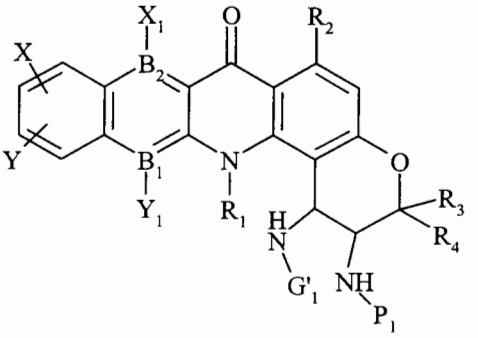
(I/ag_2)



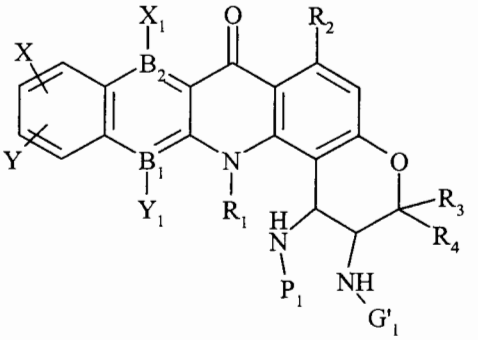
(I/ag_3)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G'_1 are as defined hereinbefore,

the primary amine function of which compounds of formulae (I/ag_2) and (I/ag_3) is protected by a group for the protection of primary amine groups to yield compounds of formulae (XX/a) and (XX/b),



(XX/a)



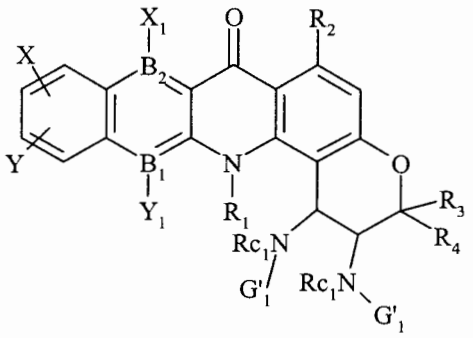
(XX/b)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4 and G'_1 are as defined hereinbefore and P_1 represents a protecting group for primary amine functions,

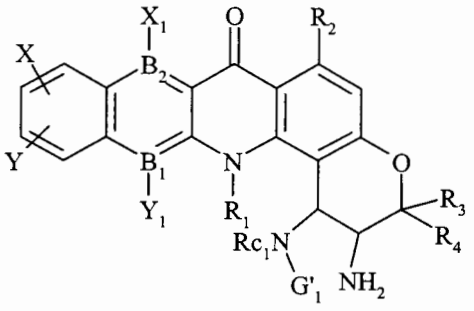
which compounds of formulae (I/ag$_1$) and (XX/a) and (XX/b) are, if desired, subjected to the action of a compound of formula (XXI) :

$$R_{c1}\text{–Hal} \qquad \text{(XXI)}$$

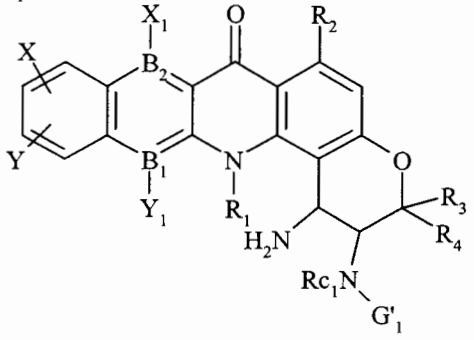
wherein Hal represents a halogen and R_{c1} represents a group selected from linear or branched (C_1-C_6)alkyl, aryl and aryl-(C_1-C_6)alkyl in which the alkyl moiety may be linear or branched, and then subjected, in the case of compounds of formulae (XX/a) and (XX/b), to conditions for the deprotection of the primary amine function, to yield compounds of formulae (I/ah$_1$), (I/ah$_2$) and (I/ah$_3$), particular cases of the compounds of formula (I) :



(I/ah$_1$)



(I/ah$_2$)



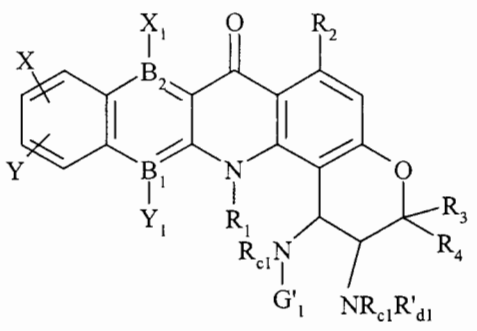
(I/ah$_3$)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G'$_1$ and R_{c1} are as defined hereinbefore,

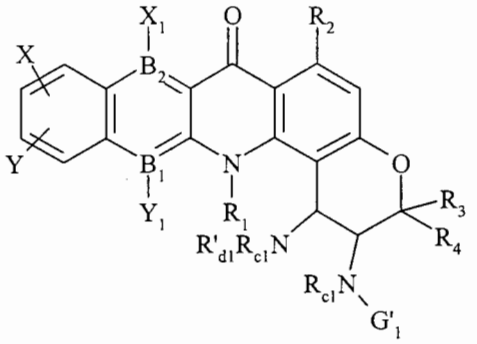
which compounds of formulae (I/ah$_2$) and (I/ah$_3$) are, if desired, subjected in succession to the action of a compound of formula (XXI) as defined hereinbefore and then to the action of a compound of formula (XXII) :

$$R_{d'1}\text{–Hal} \qquad \text{(XXII)}$$

wherein Hal is as defined hereinbefore and $R_{d'1}$ may have the same definitions as R_{c1}, to yield compounds of formulae (I/ai$_2$) and (I/ai$_3$), particular cases of the compounds of formula (I) :



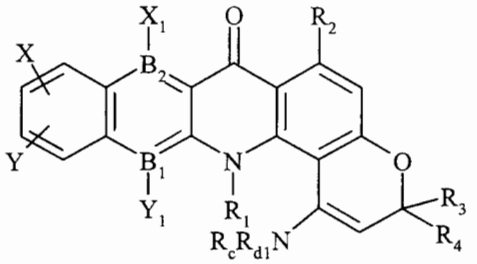
(I/ai$_2$)



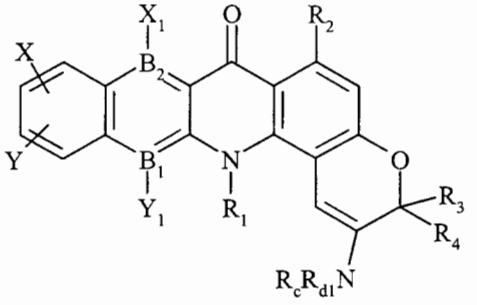
(I/ai$_3$)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, G'_1, R_{c1} and R_{d1} are as defined hereinbefore,

ϕ) or to dehydration conditions in acid medium to yield compounds of formulae (I/aj$_2$) and (I/aj$_3$), particular cases of the compounds of formula (I) :



(I/aj$_2$)



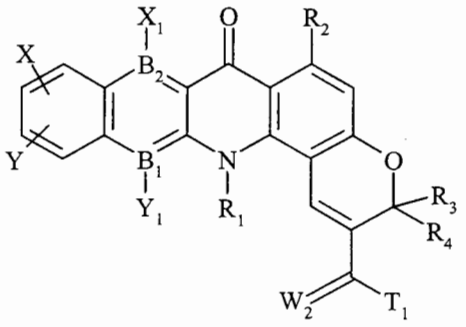
(I/aj$_3$)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, R_c and R_d are as defined hereinbefore,

e) or to the action of a compound of formula (XXIII) :

$$Hal–C(W_2)–T_1 \qquad (XXIII)$$

wherein Hal represents a halogen atom and W_2 and T_1 are as defined for formula (I) to yield compounds of formula (I/aj), a particular case of the compounds of formula (I) :



(I/aj)

wherein X, Y, X_1, Y_1, B_1, B_2, R_1, R_2, R_3, R_4, W_2 and T_1 are as defined hereinbefore,

the compounds (I/a) to (I/aj) constituting the totality of the compounds of the invention, which, if necessary, are purified according to a conventional purification technique, if desired may be separated into their different isomers according to a conventional separation technique and, if desired, are converted into their N-oxides and optionally into addition salts with a pharmaceutically acceptable acid or base.

21. Pharmaceutical compositions comprising as active ingredient at least one compound according to any one of claims 1 to 19 in combination with one or more pharmaceutically acceptable, inert, non-toxic excipients or carriers.

22. Pharmaceutical compositions according to claim 21 containing at least one active ingredient according to any one of claims 1 to 19 for use as medicaments in the treatment of cancers.