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New benzo[b]pyrano[3,2-h]acridin-7-one compounds, a process for their preparation and pharmaceutical compositions containing them

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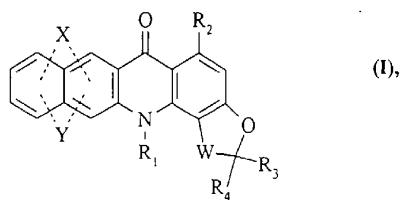
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ABSTRACT

**New benzo[*b*]pyrano[3,2-*h*]acridin-7-one compounds,
a process for their preparation
and pharmaceutical compositions containing them**

Compounds of formula (I) :



wherein :

- X and Y represent a group selected from hydrogen, halogen, mercapto, cyano, nitro, alkyl, trihaloalkyl, trihaloalkylcarbonylamino, -ORa, -NRaRb, -NRa-C(O)-T₁, -O-C(O)-T₁, -O-T₂-NRaRb, -O-T₂-ORa, -NRa-T₂-NRaRb, -NRa-T₂-ORa and -NRa-T₂-CO₂Ra wherein Ra, Rb, T₁, T₂ are as defined in the description, or X and Y together form a methylenedioxy or ethylenedioxy group,
- R₁ represents a hydrogen atom or an alkyl group,
- R₂ represents a group selected from hydrogen, -ORa, -NRaRb, -NRa-C(O)-T₁, -O-C(O)-T₁, -O-T₂-NRaRb, -O-T₂-ORa, -NRa-T₂-NRaRb, -NRa-T₂-ORa and -NRa-T₂-CO₂Ra wherein Ra, Rb, T₁ and T₂ are as defined hereinbefore,
- R₃ and R₄ represent a hydrogen atom or an alkyl group,
- W represents a group of formula -CH(R₅)-CH(R₆)-, -CH=C(R₇)-, -C(R₇)=CH- or -C(O)-CH(R₈)- wherein R₅, R₆, R₇ and R₈ are as defined in the description, their isomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

Medicaments

AUSTRALIA

Patents Act 1990

**COMPLETE SPECIFICATION
STANDARD PATENT**

Application Number:

Lodged:

Invention Title: **NEW BENZO[*b*]PYRANO[3,2-*h*]ACRIDIN-7-ONE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

The following statement is a full description of this invention, including the best method of performing it known to us

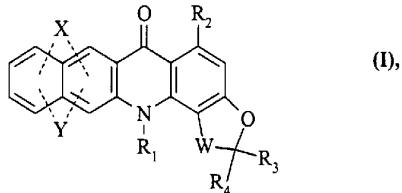
The present invention relates to new benzo[*b*]pyrano[3,2-*h*]acridin-7-one compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the invention are derivatives of acronycine, an alkaloid which has anti-tumour properties that have been demonstrated in experimental models (*J. Pharm. Sci.*, 5 1966, 55 (8), 758-768). However, despite having quite a broad spectrum of activity, acronycine is of low potency and moderate activity. The solubility of the compound is, moreover, low, which limits its bioavailability, as well as its use in pharmaceutical compositions for administration by the intravenous route.

Various modifications have been made to the molecule, for example those described in 10 *J. Med. Chem.*, 1996, 39, 4762-4766 or EP 1 042 326, allowing a significant improvement in the potency, anti-tumour efficacy and solubility of the products. Nevertheless, anti-cancer therapeutic requirements call for the constant development of new anti-tumour agents with the aim of obtaining medicaments that are simultaneously more active and better tolerated. More specifically, solid tumours constitute a major problem for anti-cancer chemotherapy because of their intrinsic and/or acquired resistance to existing 15 compounds. Moreover, certain compounds which are shown to be highly active with respect to certain cell lines are found to be inactive with respect to other cell lines or indeed toxic. It is therefore of prime importance to have access to the widest range of compounds exhibiting powerful cytotoxic activity in order to have available the most effective treatments for the totality of tumour disorders, together with limited secondary 20 effects and the longest desirable action over time.

Besides the fact that the compounds of the invention are new, they have surprising *in vitro* and *in vivo* activity which is greater than that observed hitherto. The compounds discovered by the Applicant accordingly have anti-tumour properties that make them especially useful in the treatment of cancers and, especially, of solid tumours. 25

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



wherein :

- X and Y, which may be the same or different, represent, independently of one another,
- 5 a group selected from :
 - hydrogen and halogen atoms,
 - mercapto, cyano, nitro, linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)-trihaloalkyl and linear or branched trihalo-(C₁-C₆)alkyl-carbonylamino groups,
 - groups of formulae -ORa, -NRaRb, -NRa-C(O)-T₁, -O-C(O)-T₁, -O-T₂-NRaRb,
 - 10 -O-T₂-ORA, -NRa-T₂-NRaRb, -NRa-T₂-ORA and -NRa-T₂-CO₂Ra wherein :
 - * Ra represents a group selected from a hydrogen atom and a linear or branched (C₁-C₆)alkyl group, an aryl group and an aryl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched,
 - * Rb represents a group selected from a hydrogen atom and a linear or branched (C₁-C₆)alkyl group, an aryl group and an aryl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched,
 - 15 or
 - * Ra+Rb, together with the nitrogen atom carrying them, form a monocyclic 5- or 6-membered heterocycle optionally containing in the cyclic system a second hetero atom selected from oxygen and nitrogen,
 - * T₁ represents a group selected from linear or branched (C₁-C₆)alkyl, linear or branched (C₂-C₆)alkenyl, aryl, aryl-(C₁-C₆)alkyl (wherein the alkyl moiety is linear or branched), and a linear or branched (C₁-C₆)alkylene chain substituted by a group selected from -ORA and -NRaRb wherein Ra and Rb are as defined hereinbefore,
 - * T₂ represents a linear or branched (C₁-C₆)alkylene chain,
 - 20 - or X and Y, when they are in adjacent positions, together form a methylenedioxy

group or an ethylenedioxy group,
it being understood that the substituents X and Y may be present on either of the two
adjacent benzene rings,

• R_1 represents a hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

5 • R_2 represents a group selected from a hydrogen atom and linear or branched
(C_1-C_6)alkyl, -ORa, -NRaRb, -NRa-C(O)-T₁, -O-C(O)-T₁, -O-T₂-NRaRb, -O-T₂-
ORa, -NRa-T₂-NRaRb, -NRa-T₂-ORa and -NRa-T₂-CO₂Ra groups, wherein Ra, Rb, T₁ and
T₂ are as defined hereinbefore,

10 • R_3, R_4 , which may be the same or different, represent, independently of one another, a
hydrogen atom or a linear or branched (C_1-C_6)alkyl group,

• W represents a group of formula -CH(R₅)-CH(R₆)-, -CH=C(R₇)-, -C(R₇)=CH- or -C(O)-
CH(R₈)- wherein:

* R_5 and/or R_6 , represent(s) a group selected from -W₁-C(W₂)-W₃-T₁, -W₁-S(O)_n-W₃-T₁
and -W₁-S(O)_n-T₁ wherein:

15 - W₁ represents an oxygen or sulphur atom or a nitrogen atom substituted by a
hydrogen atom or by a linear or branched (C_1-C_6)alkyl group, an aryl group or an aryl-
(C_1-C_6)alkyl group wherein the alkyl moiety is linear or branched,

- W₂ represents an oxygen atom or a sulphur atom,

- W₃ represents an oxygen or sulphur atom or a nitrogen atom substituted by a
20 hydrogen atom or by a linear or branched C_1-C_6 alkyl group, an aryl group or an aryl-
(C_1-C_6)alkyl group wherein the alkyl moiety is linear or branched, a bond when T₁
represents a C_4 alkenyl group,

- T₁ is as defined hereinbefore,

- n represents an integer selected from 1 and 2,

and in the case where only one of the two groups R₅ and R₆ represents a group as defined hereinbefore then the other of the said groups R₅ and R₆ represents a group selected from a hydrogen atom, hydroxy, linear or branched (C₁-C₆)alkoxy, linear or branched (C₁-C₆)alkyl-carbonyloxy, arylcarbonyloxy, aryl-(C₁-C₆)alkyl-carbonyloxy (wherein the alkyl moiety is linear or branched), and amino optionally substituted by one or two, identical or different, linear or branched (C₁-C₆)alkyl groups,

* R₇ represents a group selected from hydroxy, linear or branched (C₁-C₆)alkoxy, -C(W₂)-T₁, -W₁-C(W₂)-W₃-T₁, -W₁-C(W₂)-T₁, -W₁-S(O)_n-W₃-T₁ and -W₁-S(O)_n-T₁ wherein W₁, W₂, W₃, T₁ and n are as defined hereinbefore, or R₇ may have the additional meaning of a hydrogen atom when R₂ represents a group -O-T₂-OR_a and/or when X represents a hydrogen atom and Y, located in the 13-position of the naphthyl system of the pentacyclic skeleton, represents an amino group optionally substituted by one or two identical or different groups selected independently of one another from linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)acyl and linear or branched trihalo-(C₁-C₆)alkyl-carbonyl,

* R₈ represents a linear or branched (C₁-C₆)alkoxy or linear or branched (C₁-C₆)alkyl-carbonyloxy group, or may have the additional meaning of hydroxy when R₂ represents a group -O-T₂-OR_a as defined hereinbefore,

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

Aryl is understood to mean a phenyl or naphthyl group optionally containing one or more, identical or different, substituents selected from hydroxy, halogen, carboxy, nitro, amino, linear or branched (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino wherein each alkyl moiety may be linear or branched, linear or branched (C₁-C₆)alkoxy, linear or branched (C₁-C₆)acyl and

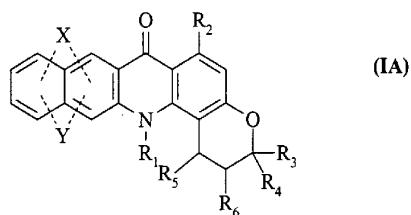
linear or branched (C₁-C₆)alkyl-carbonyloxy.

Isomers are understood to comprise optical isomers, that is to say enantiomers and diastereoisomers.

Among the pharmaceutically acceptable acids there may be mentioned, without implying
5 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
10 any limitation, sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine etc..

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



wherein X, Y, R₁, R₂, R₃, R₄, R₅ and R₆ are as defined for formula (I).

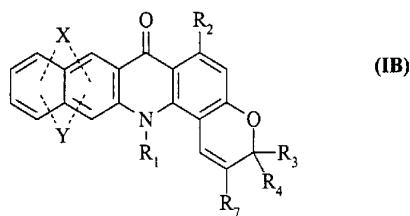
15 Preferred compounds of formula (IA) are compounds wherein R₅ and R₆ are identical and
each represent a group of formula -W₁-C(W₂)-W₃-T₁ or -W₁-S(O)_n-T₁ wherein W₁, W₂,
W₃, T₁ and n are as defined for formula (I).

In especially interesting manner, preferred compounds of formula (IA) are compounds
wherein R₅ and R₆ are identical and each represent a group of formula -W₁-C(W₂)-W₃-T₁
20 wherein W₁ represents an oxygen atom, W₂ represents an oxygen atom, W₃ represents a
nitrogen atom substituted by a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, an

aryl group or an aryl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched and T₁ is as defined for formula (I).

In another especially interesting manner, preferred compounds of formula (IA) are compounds wherein R₅ and R₆ are identical and each represent a group of formula 5 -W₁-S(O)_n-T₁ wherein W₁ represents an oxygen atom, T₁ is as defined for formula (I) and n is equal to 2.

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

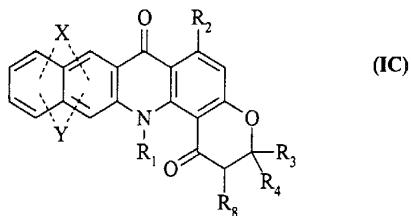


10 wherein X, Y, R₁, R₂, R₃, R₄ and R₇ are as defined for formula (I).

Preferred compounds of formula (IB) are compounds wherein R₇ represents a group selected from -C(W₂)-T₁ and -W₁-C(W₂)-T₁ wherein W₁, W₂ and T₁ are as defined for formula (I).

In especially interesting manner, preferred compounds of formula (IB) are compounds 15 wherein W₁ represents an oxygen atom, W₂ represents an oxygen atom and T₁ represents a linear or branched (C₁-C₆)alkyl group, an aryl group or an aryl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched.

According to a third advantageous embodiment of the invention, preferred compounds are compounds of formula (IC) :

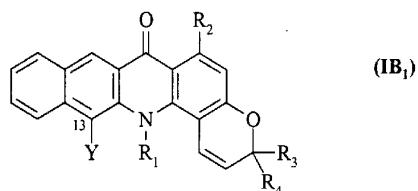


wherein X, Y, R₁, R₂, R₃, R₄ and R₈ are as defined for formula (I).

Substituents R₃ and R₄ that are preferred according to the invention are linear or branched (C₁-C₆)alkyl groups.

5 Substituents R₂ that are preferred according to the invention are groups selected from linear or branched (C₁-C₆)alkoxy, -NRaRb, -O-T₂-NRaRb, -O-T₂-ORa, -NRa-T₂-NRaRb and -NRa-T₂-ORa wherein Ra, Rb, T₁ and T₂ are as defined for formula (I).

According to a fourth advantageous embodiment of the invention, preferred compounds are compounds of formula (IB₁) :



10

wherein R₁, R₂, R₃ and R₄ are as defined for formula (IB) and Y represents an amino group optionally substituted by one or two identical or different groups selected independently of one another from linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)acyl and linear or branched trihalo-(C₁-C₆)alkyl-carbonyl.

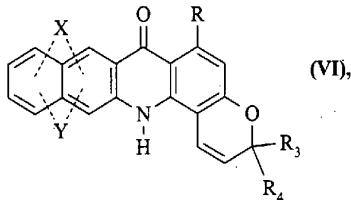
15 In especially advantageous manner, preferred compounds of the invention are:

- (1S,2S)-1-{{(dimethylamino)carbonyl}oxy}-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl dimethylcarbamate,
- (1S,2S)-6-methoxy-3,3,14-trimethyl-2-{{(4-methylphenyl)sulphonyl}oxy}-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-1-yl 4-methylbenzenesulphonate,

- 6-methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3*H*-benzo[*b*]pyrano[3,2-*h*]acridin-2-yl acetate,
- 2-benzoyl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-acridin-7-one
- 5 - 2-butyryl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-acridin-7-one,
- 2-acetyl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-acridin-7-one,
- 6-methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3*H*-benzo[*b*]pyrano[3,2-*h*]acridin-2-yl butyrate,
- 10 - 6-(2-hydroxyethoxy)-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-acridin-7-one,
- 13-amino-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-acridin-7-one,
- 15 - *N*-(6-methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3*H*-benzo[*b*]pyrano[3,2-*h*]-acridin-13-yl)acetamide,
- 6-methoxy-3,3-dimethyl-1,7-dioxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]pyrano[3,2-*h*]-acridin-2-yl acetate.

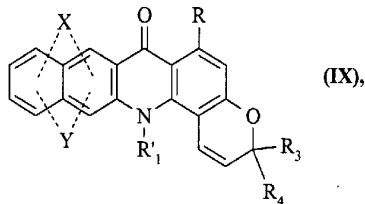
20 The enantiomers, diastereoisomers, N-oxides and addition salts with a pharmaceutically acceptable acid or base of the preferred compounds form an integral part of the invention.

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



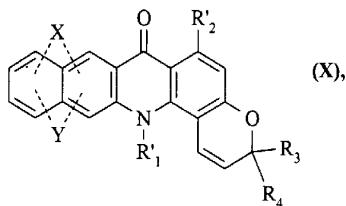
25 wherein X, Y, R, R₃ and R₄ are as defined hereinbefore,

the nitrogen atom of which compound of formula (VI) is optionally substituted, by the action of an alkyl halide or of a dialkyl sulphate in the presence of a deprotonating agent, in an aprotic polar solvent or under phase transfer conditions, yielding the compounds of formula (IX) :



wherein X, Y, R, R₃ and R₄ are as defined hereinbefore and R'₁ represents a linear or branched (C₁-C₆)alkyl group.

10 which compounds of formula (IX) are subjected to the action of an alkylating agent or an acylating agent under customary conditions of organic synthesis to yield the compounds of formula (X) :



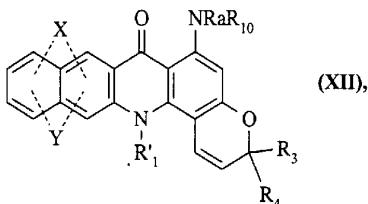
wherein X, Y, R'₁, R₃ and R₄ are as defined hereinbefore and R'₂ represents a group selected from -ORa, -O-C(O)-T₁, -O-T₂-NRaRb and -O-T₂-ORa wherein Ra, Rb, T₁ and T₂ are as defined for formula (I),

15 which compounds of formula (X), in the case where R'₂ represents an alkoxy group, are treated with a compound of formula (XI) :



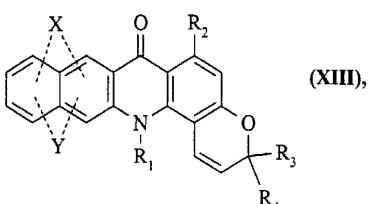
wherein Ra represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, an aryl group or an aryl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched, and R₁₀ represents a group selected from Rb, -C(O)-T₁, -T₂-NRaRb, -T₂-ORa and -T₂-CO₂Ra wherein Ra, Rb, T₁ and T₂ are as defined for formula (I),

to yield the compounds of formula (XII) :



wherein X, Y, R₁, R₃, R₄, Ra and R₁₀ are as defined hereinbefore,

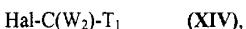
the totality of the compounds of formulae (VI), (IX), (X) and (XII) forming the compounds of formula (XIII) :



wherein X, Y, R₁, R₂, R₃ and R₄ are as defined in the general definition for formula (I),

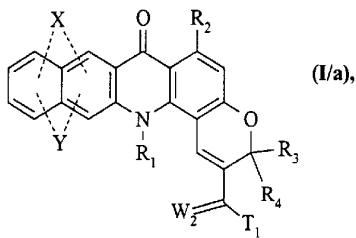
which compounds of formula (XIII) are subjected :

a) \Rightarrow either to the action of a compound of formula (XIV) :



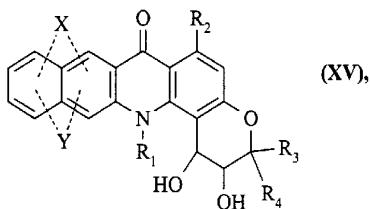
wherein Hal represents a halogen atom and W₂ and T₁ are as defined in the general definition for formula (I),

to yield the compounds of formula (I/a), a particular case of the compounds of formula (I) :



wherein X, Y, R₁, R₂, R₃, R₄, W₂ and T₁ are as defined hereinbefore,

b) \Rightarrow or to the action of an oxidising agent for alkene functions to yield the compounds of formula (XV) :



5

wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

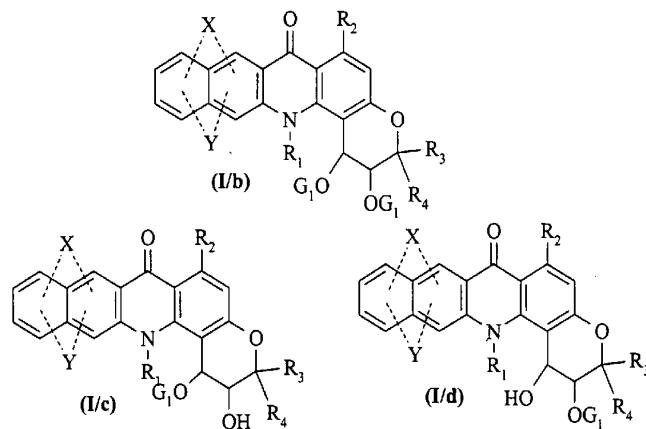
which compounds of formula (XV) are treated with a compound of formula (XVI) :



10 wherein Hal represents a halogen atom and G₁ represents a group selected from -C(W₂)-W₃-T₁, -C(W₂)-T₁, -S(O)_n-W₃-T₁ and -S(O)_n-T₁ wherein W₂, W₃, T₁ and n are as defined for formula (I),

to yield the compounds of formulae (I/b), (I/c) and (I/d), particular cases of the compounds of formula (I) :

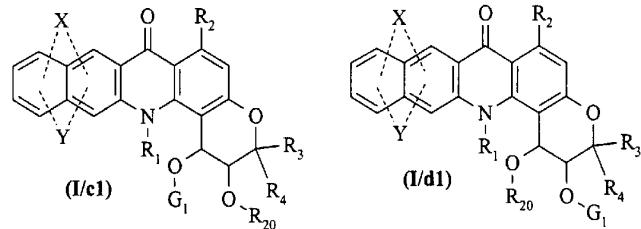
15



wherein X, Y, R_1 , R_2 , R_3 , R_4 and G_1 are as defined hereinbefore,

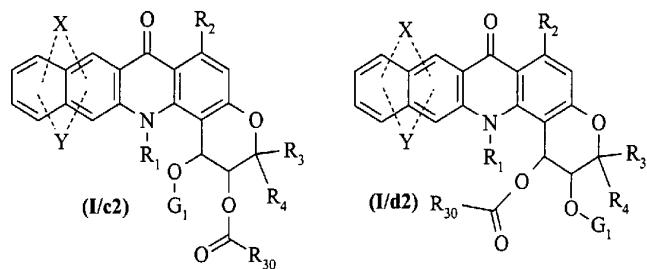
which compounds of formulae (I/c) and/or (I/d) are subjected :

5 ◆ either to the action of an alcohol of formula $R_{20}-OH$, wherein R_{20} represents a linear or branched (C_1-C_6)alkyl group, to yield the compounds of formulae (I/c1) and (I/d1), respectively :



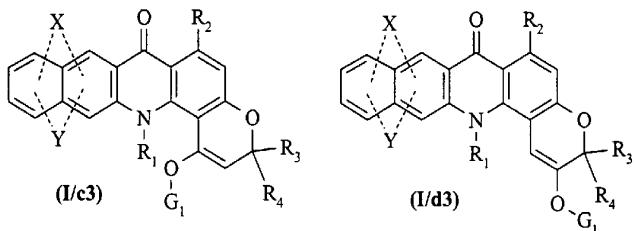
wherein X, Y, R_1 , R_2 , R_3 , R_4 , G_1 and R_{20} are as defined hereinbefore,

10 ◆ or to the action of an anhydride of formula $(R_{30}CO)_2O$, wherein R_{30} represents a linear or branched (C_1-C_6)alkyl group, an aryl group or an aryl- (C_1-C_6) alkyl group wherein the alkyl moiety is linear or branched, to yield the compounds of formulae (I/c2) and (I/d2), respectively :



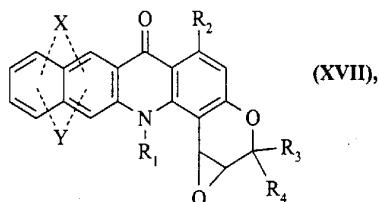
wherein X, Y, R₁, R₂, R₃, R₄, G₁ and R₃₀ are as defined hereinbefore,

❖ or to dehydrating conditions in an acid medium to yield the compounds of formulae (I/c3) and (I/d3), respectively, particular cases of the compounds of formula (I) :



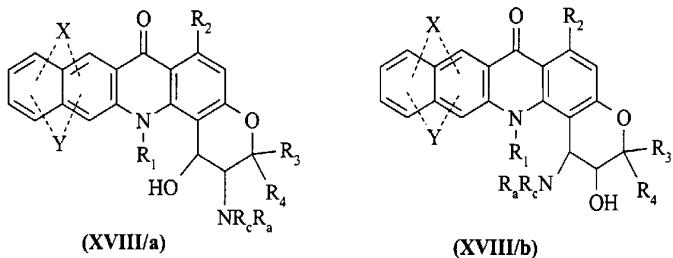
wherein X, Y, R₁, R₂, R₃, R₄ and G₁ are as defined hereinbefore,

c) \Rightarrow or to the action of a peracid or of dimethyl dioxirane to yield the compounds of formula (XVII) :



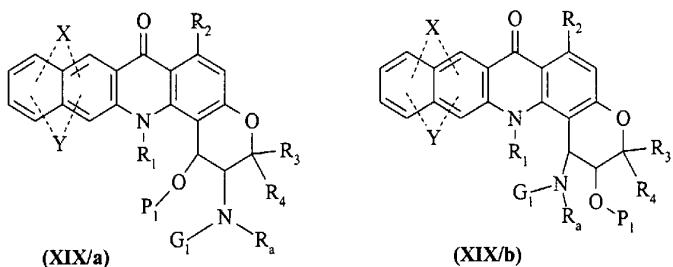
10 wherein X , V , R_1 , R_2 , R_3 and R_4 are as defined hereinbefore.

which compounds of formula (XVII) are treated with ammoniac or with a primary amine to yield the compounds of formulae (XVIII(a)) and/or (XVIII(b)):



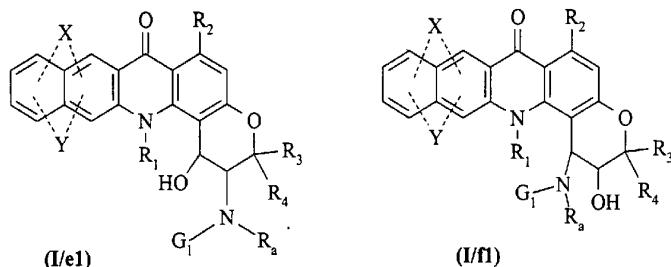
wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore, R_c represents a hydrogen atom and R_d represents a hydrogen atom in the case where the reagent used is ammoniac or represents a group selected from linear or branched (C₁-C₆)alkyl, aryl and aryl-(C₁-C₆)alkyl (wherein the alkyl moiety is linear or branched) in the case where the reagent used is a primary amine,

the alcohol function of which compounds of formulae (XVIII/a) and (XVIII/b) is protected by a protecting group for hydroxy groups, the compounds then being subjected to the action of a compound of formula Hal-G₁ (XVI) as defined hereinbefore to yield the compounds of formulae (XIX/a) and (XIX/b), respectively,



wherein X, Y, R₁, R₂, R₃, R₄, R₅ and G₁ are as defined hereinbefore and P₁ represents a protecting group for hydroxy functions,

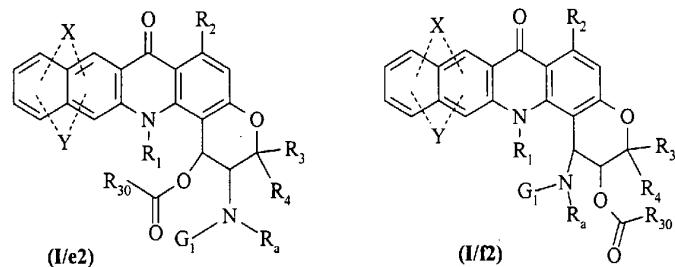
15 the hydroxy group of which compounds of formulae (XIX/a) and (XIX/b) is deprotected to yield the compounds of formulae (I/e1) and (I/f1), respectively, particular cases of the compounds of formula (I) :



wherein X, Y, R₁, R₂, R₃, R₄, R_a and G₁ are as defined hereinbefore,

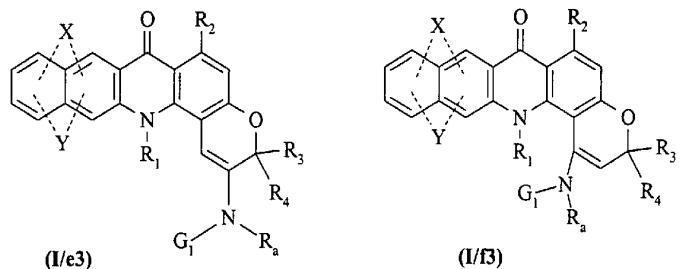
which compounds of formulae (I/e1) and (I/f1) are subjected:

- ❖ either to the action of an anhydride of formula $(R_{30}CO)_2O$, wherein R_{30} represents a linear or branched (C_1-C_6) alkyl group, an aryl group or an aryl- (C_1-C_6) alkyl group wherein the alkyl moiety is linear or branched, to yield the compounds of formulae (I/e2) and (I/f2), respectively, particular cases of the compounds of formula (I) :



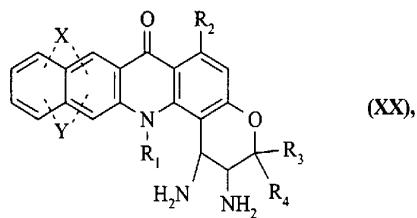
wherein X, Y, R₁, R₂, R₃, R₄, R_a, G₁ and R₃₀ are as defined hereinbefore,

10 ♦ or to dehydrating conditions in an acid medium to yield the compounds of formulae (Ie3) and (If3), respectively, particular cases of the compounds of formula (I) : .



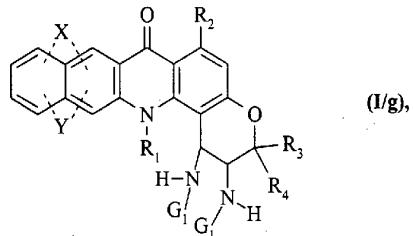
wherein X, Y, R₁, R₂, R₃, R₄, R_a and G₁ are as defined hereinbefore,

5 d) \Rightarrow or to the action of NaN_3 in the presence of hydrogen peroxide, followed by a reduction step using tri-*n*-butyltin hydride, for example, to yield the compounds of formula (XX):



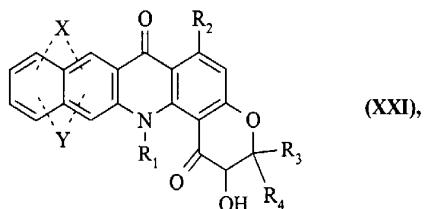
wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

which compounds of formula (XX) are subjected to the action of a compound of formula Hal-G₁ (XVI) as defined hereinbefore to yield the compounds of formula (I/g), a particular case of the compounds of formula (I) :



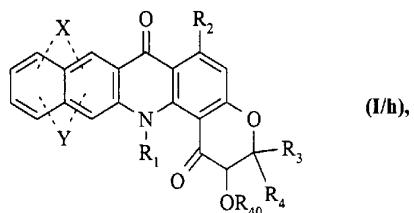
wherein X, Y, R₁, R₂, R₃, R₄ and G₁ are as defined hereinbefore,

e) \Leftrightarrow or to the action of potassium permanganate in a polar medium to yield the compounds of formula (XXI) :



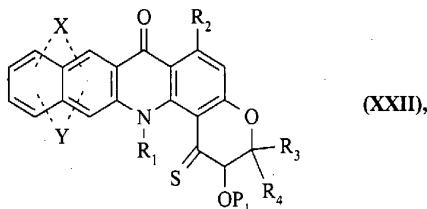
wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

5 which compounds of formula (XXI) are subjected to the action of either an alkylating agent or an acylating agent to yield the compounds of formula (I/h), a particular case of the compounds of formula (I) :



10 wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore and R₄₀ represents a linear or branched (C₁-C₆)alkyl group or a linear or branched (C₁-C₆)acyl group,

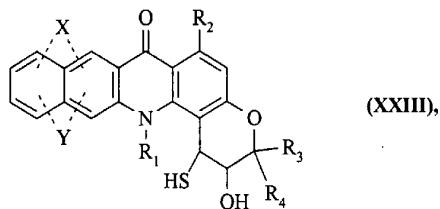
or the hydroxy functions of which compounds of formula (XXI) are protected with a protecting group conventionally used in organic synthesis, the compounds then being subjected to the action of P₂S₅ to yield the compounds of formula (XXII) :



15 wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore and P₁ represents a protecting

group for hydroxy functions,

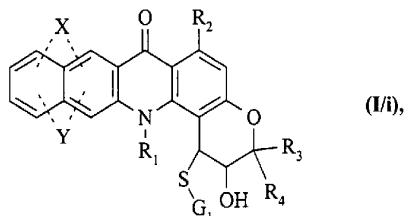
which compounds of formula (XXII) are treated with a reducing agent and then subjected to a reaction for deprotection of the hydroxy function to yield the compounds of formula (XXIII) :



5

wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

which compounds of formula (XXIII) are treated with a compound of formula (XVI) as defined hereinbefore to yield the compounds of formula (I/i), a particular case of the compounds of formula (I) :



10

wherein X, Y, G₁, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

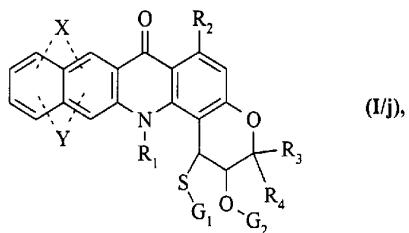
which compounds of formula (I/i) may be subjected to the action of an alkylating agent, an acylating agent or a compound of formula (XVIa) :



15

wherein Hal represents a halogen atom and G'₁ represents a group selected from -C(W₂)-W₃-T₁, -C(W₂)-T₁, -S(O)_n-W₃-T₁ and -S(O)_n-T₁, wherein W₂, W₃, T₁ and n are as defined for formula (I),

to yield the compounds of formula (I/j), a particular case of the compounds of formula (I) :

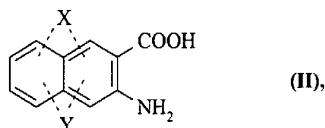


wherein X, Y, G₁, R₁, R₂, R₃ and R₄ are as defined hereinbefore and G₂ represents a group selected from G'₁ as defined hereinbefore, linear or branched (C₁-C₆)alkoxy, linear or branched (C₁-C₆)alkyl-carbonyloxy, arylcarbonyloxy and aryl-(C₁-C₆)alkyl-carbonyloxy (wherein the alkyl moiety is linear or branched),

the compounds of formulae (I/a) to (I/j), (I/c₁) to (I/c₃), (I/d₁) to (I/d₃), (I/e₁) to (I/e₃) and (I/f₁) to (I/f₃) constituting the totality of the compounds of the invention, which are purified, if necessary, according to a conventional purification technique, which may be, if desired, separated into their different isomers according to a conventional separation technique and which are converted, if desired, into their N-oxides and, where appropriate, their addition salts with a pharmaceutically acceptable acid or base.

The compounds of formula (VI) may advantageously be obtained :

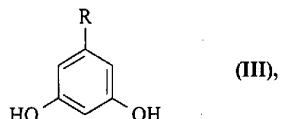
- either starting from 3-amino-2-naphthalenecarboxylic acid compounds (II) :



15

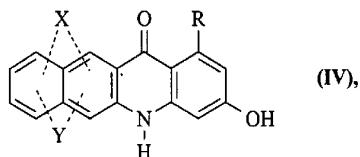
wherein X and Y are as defined for formula (I),

which are reacted with a phloroglucinol compound of formula (III) :



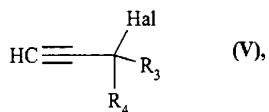
wherein R represents a hydrogen atom, a hydroxy group or a linear or branched (C₁-C₆)alkyl group,

to yield the compounds of formula (IV) :



5 wherein X, Y and R are as defined hereinbefore,

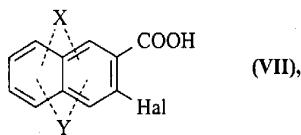
which are then treated under basic conditions in an aprotic solvent with an alkyne of formula (V) :



wherein Hal represents a halogen atom and R₃ and R₄ are as defined for formula (I),

10 to yield the compounds of formula (VI) as defined hereinbefore,

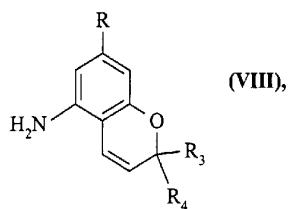
• or starting from 3-halo-2-naphthalenecarboxylic acid compounds of formula (VII) :



wherein X and Y are as defined for formula (I) and Hal represents a halogen atom,

15

which are reacted with an amino-chromene compound of formula (VIII) :

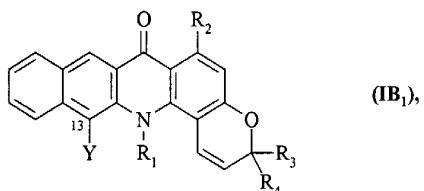


wherein R_3 and R_4 are as defined for formula (I) and R is as defined hereinbefore,

to yield, likewise, the compounds of formula (VI) as defined hereinbefore.

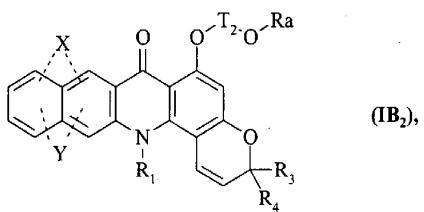
5 The compounds of formula (XIII) are synthesis intermediates that are useful in obtaining the compounds of formula (I). Among those compounds of formula (XIII) there are distinguished :

➤ compounds of formula (IB₁):



10 wherein R₁, R₂, R₃ and R₄ are as defined for formula (IB) and Y represents an amino group optionally substituted by one or two identical or different groups selected independently of one another from linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)acyl and linear or branched trihalo-(C₁-C₆)alkyl-carbonyl,

➤ and compounds of formula (IB₂):



wherein R₁, R₃, R₄, T₂, Ra, X and Y are as defined for formula (I).

Those compounds of formulae (IB₁) and (IB₂) are new and have cytotoxic activity. They are therefore useful in the treatment of cancers.

5 The compounds of formula (XXI) likewise are synthesis intermediates that are useful in obtaining the compounds of formula (I) and, more especially, compounds of formula (IC).

Those compounds of formula (XXI) likewise have cytotoxic activity. Their use as an active ingredient in a pharmaceutical composition makes the latter useful in the treatment of cancers.

10 The compounds of formulae (II), (III), (V), (VII), (VIII), (XI), (XIV) and (XVI) either are commercially available compounds or are obtained according to conventional methods of organic synthesis well known to the person skilled in the art.

15 The compounds of formula (I) have especially valuable anti-tumour properties. They have excellent *in vitro* cytotoxicity with respect to cell lines originating from murine and human tumours, by virtue of specific blockage of the cell cycle, and are active *in vivo*, in the mouse, with respect to transplantable murine and human tumours. The characteristic properties of these compounds allow them to be used therapeutically as anti-tumour agents.

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

25 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.

Pharmaceutical compositions according to the invention for parenteral injections especially include aqueous and non-aqueous sterile solutions, dispersions, suspensions or emulsions and also sterile powders for reconstituting injectable solutions or dispersions.

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

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

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

15 Among the inert, non-toxic, pharmaceutically acceptable excipients or carriers there may be mentioned, by way of non-limiting example, diluents, solvents, preservatives, wetting agents, emulsifiers, dispersing agents, binders, swelling agents, disintegrating agents, retardants, lubricants, absorbents, suspending agents, colourants, aromatising agents etc..

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

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

25 The starting materials used are products that are known or that are prepared according to known operating procedures. The various Preparations yield synthesis intermediates that are useful in preparation of the compounds of the invention.

The structures of the compounds described in the Examples and Preparations were determined according to the usual spectrophotometric techniques (infrared, nuclear magnetic resonance, mass spectrometry, ...).

5 The melting points were determined using either a Kofler hot-plate or a hot-plate under a microscope. When the compound is in the form of a salt, the melting point given refers to the salt form of the compound.

Preparation 1 : 6-Methoxy-3,3,14-trimethyl-7,14-dihydro-3H-benzo[b]pyrano-[3,2-h]acridin-7-one

10 Step A : *1,3-Dihydroxy-5,12-dihydro-benzo[b]acridin-12-one*

To a solution of 5 g of 3-amino-2-naphthalenecarboxylic acid in 50 ml of heptan-1-ol there are added 3.5 g of 1,3,5-trihydroxybenzene and 62.5 mg of para-toluenesulphonic acid. The mixture is stirred for 48 hours under reflux using a Dean-Stark apparatus, and the 15 reaction mixture is then concentrated *in vacuo*. The residue is chromatographed over silica gel (eluant : cyclohexane/acetone : 90/10). The isolated product is crystallised from a cyclohexane/acetone mixture, allowing 5.2 g of the expected product to be obtained.

Step B : *6-Hydroxy-3,3-dimethyl-7,14-dihydro-3H-benzo[b]pyrano[3,2-h]acridin-7-one*

20 To a solution of 2 g of the product of Step A in 50 ml of anhydrous dimethylformamide, under an inert atmosphere, there are added 2 g of anhydrous potassium carbonate. 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 held at 65°C for 24 hours and then at 130°C for 1 hour. After cooling, the solution is hydrolysed and then extracted with dichloromethane. The combined organic phases are washed with water and then with 1M 25 potassium hydroxide solution, dried over sodium sulphate and then evaporated. After chromatography over silica gel (cyclohexane/acetone : 90/10), 1.10 g of the expected product are isolated.

Melting point : 225°C

Step C : 6-Methoxy-3,3,14-trimethyl-7,14-dihydro-3H-benzo[*b*]pyrano-[3,2-*h*]acridin-7-one

To a solution of 0.5 g of the product obtained in Step B in 20 ml of anhydrous dimethylformamide there are slowly added, at 0°C, under an inert atmosphere, 0.16 g of sodium hydride and then, after 15 minutes, 0.65 ml of dimethyl sulphate (6 equivalents). After 1 hour, the reaction mixture is hydrolysed using ice and is then extracted with ethyl acetate. After washing the organic phase with aqueous sodium hydroxide solution, it is dried over sodium sulphate and then evaporated *in vacuo*. Chromatography over silica gel (cyclohexane/acetone : 98/2) allows 0.42 g of the expected product to be obtained.

10 *Melting point :* 188°C.

Preparation 2 : (±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3,14-trimethyl-2,3,7,14-tetra-
hydro-1H-benzo[*b*]pyrano[3,2-*h*]acridin-7-one

To a solution of 2 g of the product of Preparation 1 and 0.9 g of 4-methylmorpholine-N-oxide monohydrate in 40 ml of a mixture of tert-butanol/tetrahydrofuran/water (10/3/1) 15 there is added osmium tetroxide in the form of a 2.5 % solution in 3.8 ml of 2-methyl-2-propanol. After 2 days at ambient temperature, 105 ml of saturated NaHSO₃ solution are added, and the mixture is stirred for 1 hour and then extracted with dichloromethane. The combined organic phases are dried over sodium sulphate and concentrated *in vacuo*.
20 Chromatography over silica gel (dichloromethane/methanol : 95/5) allows 1.3 g of the expected product to be isolated.

Melting point : 194°C.

Preparation 3 : 6-(Diethylaminopropylamino)-3,3,14-trimethyl-7,14-dihydro-3H-
benzo[*b*]pyrano[3,2-*h*]acridin-7-one

25 To 0.15 g of the product of Preparation 1 there are added 4 ml of N,N-diethylpropylenediamine. After reacting for 5 days at 70°C under an inert atmosphere, the reaction mixture is evaporated under reduced pressure. The residue obtained is

chromatographed over silica gel (cyclohexane/ethyl acetate : 80/20), allowing the expected product to be isolated.

Mass spectrum : (DIC/NH₃) : m/z : 470 (M+H)⁺

Preparation 4 : 6-[(2-Morpholin-4-yl)ethylamino]-3,3,14-trimethyl-7,14-dihydro-3*H*-5
benzo[*b*]pyrano[3,2-*h*]acridin-7-one

The procedure is as in Preparation 3, using 4-(2-aminoethyl)-morpholine as reagent.

Mass spectrum : (DIC/NH₃) : m/z : 470 (M+H)⁺

Preparation 5 : (±)-*cis*-1,2-Dihydroxy-6-(diethylaminopropylamino)-3,3,14-trimethyl-2,3,7,14-tetrahydro-1*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one

10 The procedure is as in Preparation 2, using the compound of Preparation 3 as substrate.

Preparation 6 : (±)-1-Amino-2-hydroxy-6-methoxy-3,3,14-trimethyl-2,3,7,14-tetrahydro-1*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one

Step A : (±)-1-Azido-2-hydroxy-6-methoxy-3,3,14-trimethyl-2,3,7,14-tetrahydro-1*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one

15 To a solution of 0.15 g of the compound of Preparation 2 and 0.5 g of NaN₃ in 6 ml of chloroform there are slowly added, at ambient temperature, 3 ml of trifluoroacetic acid. After stirring for 12 hours, 1 equivalent of NaN₃ is added and the reaction mixture is held at ambient temperature for a further 12 hours. The reaction mixture is then washed with water and then with saturated NaCl solution and is dried over sodium sulphate. 20 Chromatography over silica gel (dichloromethane/methanol : 95/5) allows the expected product to be isolated.

Step B : (±)-1-Amino-2-hydroxy-6-methoxy-3,3,14-trimethyl-2,3,7,14-tetrahydro-1*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one

5 A solution containing 0.2 g of the compound obtained in Step A and 0.09 g of Pd/C in 5 ml of ethanol is stirred at ambient temperature under an H₂ atmosphere for 48 hours. The catalyst is then filtered off and the filtrate is concentrated *in vacuo*. The residue is chromatographed over silica (dichloromethane/methanol : 95/5), allowing the desired product to be isolated.

Preparation 7 : 6-(Dimethylaminoethoxy)-3,3,14-trimethyl-7,14-dihydro-3H-benzo-[b]pyrano[3,2-h]acridin-7-one

Step A : 6-Hydroxy-3,3,14-trimethyl-7,14-dihydro-3H-benzo[b]pyrano[3,2-h]acridin-7-one

10 The product is obtained according to the procedure of Preparation 1, using only 1.5 equivalents of sodium hydride and 2 equivalents of dimethyl sulphate.

Melting point : 138 °C.

Step B : 6-(Dimethylaminoethoxy)-3,3,14-trimethyl-7,14-dihydro-3H-benzo[b]-pyrano[3,2-h]acridin-7-one

15 To a solution, under nitrogen, of 0.2 g of the compound obtained in Step A in 20 ml of dimethylformamide, there are added 1 equivalent of sodium hydride and 1 equivalent of 2-dimethylaminoethyl chloride hydrochloride. After 48 hours at 70°C, the reaction mixture is cooled; it is then poured onto 80 ml of ice-cold water and extracted with dichloromethane. After washing and drying over MgSO₄, the solution is evaporated under reduced pressure.

20 Chromatography over silica gel (ethyl acetate/cyclohexane : 80/20) allows the expected product to be isolated.

Mass spectrum : (DIC/NH₃) : m/z : 429 (M+H)⁺

Preparation 8 : 1,2-Diamino-6-methoxy-3,3,14-trimethyl-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-7-one

25 Chromatography over silica gel allows isolation of this co-product, which forms during

synthesis of the compound of Preparation 6.

Example 1 : 6-(2-Hydroxyethoxy)-3,3,14-trimethyl-3,14-dihydro-7H-benzo[b]-pyrano[3,2-h]acridin-7-one

5 A solution of 500 mg of the compound of Preparation 1 in 5 ml of dichloroethane in the presence of 36 mg of AlCl_3 is heated at 70°C for 3 hours. The reaction mixture is then poured onto 10 % HCl solution and extracted with dichloromethane. After conventional treatment of the organic phases and evaporation thereof under reduced pressure, chromatography of the residue over silica gel (dichloromethane/methanol : gradient from 0.2 to 10 %) allows the expected product to be isolated.

10 *Melting point* : 230°C

Example 2 : 2-Butyryl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7H-benzo[b]-pyrano[3,2-h]acridin-7-one

15 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 Preparation 1 in 2 ml of dichloromethane at 0°C . The reaction mixture is stirred for 4 hours at ambient temperature and is then poured onto 10 % HCl solution. After conventional treatment of the organic phases and evaporation thereof under reduced pressure, chromatography of the residue over silica gel (dichloromethane/methanol : gradient from 0.1 to 6 %) allows the expected product to be isolated.

20 *Melting point* : 302°C

Example 3 : 2-Benzoyl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7H-benzo[b]-pyrano[3,2-h]acridin-7-one

The product is obtained according to the procedure of Example 2, using benzoyl chloride as reagent.

25 *Melting point* : 319°C

Example 4 : 2-Acetyl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7H-benzo[b]-pyrano[3,2-h]acridin-7-one

The product is obtained according to the procedure of Example 2, using acetyl chloride as reagent.

5 *Melting point* : 277°C

Example 5 : 2-Butyryl-6-(diethylaminopropylamino)-3,3,14-trimethyl-3,14-dihydro-7H-benzo[b]pyrano[3,2-h] acridin-7-one

The product is obtained according to the procedure of Example 2, using the compound of Preparation 3 as substrate.

10 **Example 6 : 2-Butyryl-6-[(2-morpholin-4-yl)ethylamino]-3,3,14-trimethyl-3,14-dihydro-7H-benzo[b]pyrano[3,2-h]acridin-7-one**

The product is obtained according to the procedure of Example 2, using the compound of Preparation 4 as substrate.

15 **Example 7 : (±)-cis-1,2-Dipentenoyloxy-6-methoxy-3,3,14-trimethyl-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-7-one**

A solution of 1.48 mmol of the compound of Preparation 2 in 15 ml of anhydrous pyridine is added to 14.8 mmol of pentenoyl chloride. The reaction mixture is stirred at ambient temperature for 6 hours and is then extracted with dichloromethane. The combined organic phases are dried over magnesium sulphate, filtered and then evaporated under reduced pressure. Chromatography of the residue over silica gel (dichloromethane/methanol : gradient from 0.2 to 2 %) allows the expected product to be isolated.

20 *Melting point* : 152°C

25 **Example 8 : (±)-cis-1-Hydroxy-6-methoxy-2-pentenoyloxy-3,3,14-trimethyl-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-7-one**

The co-product is isolated during chromatography of the compound of Example 7 over silica gel.

Melting point : 194°C

Example 9 : 6-Methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3H-benzo[b]pyrano-

5 **[3,2-h]acridin-2-yl butyrate**

Step 1 : *(±)-cis-1-Hydroxy-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl butyrate*

To a solution of 0.74 mmol of the compound of Preparation 2 in 7 ml of anhydrous pyridine in the presence of 4-dimethylaminopyridine there are added 2 equivalents of butyryl chloride. The reaction mixture is stirred at ambient temperature. After 72 hours, 10 5 equivalents of butyryl chloride are added and the mixture is stirred for 72 hours and then evaporated to dryness. Chromatography over silica gel allows the expected product to be isolated.

Melting point : 197°C

15 Step 2 : *6-Methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3H-benzo[b]pyrano-[3,2-h]acridin-2-yl butyrate*

To a solution of 0.29 mmol of the compound obtained in Step 1 in 6 ml of dichloromethane there are added 4 drops of 10 % HCl solution. The reaction mixture is stirred at ambient temperature for 3 days and is then dried and evaporated under reduced pressure. 20 Chromatography of the residue over silica gel (dichloromethane/methanol : gradient from 0.2 to 5 %) allows the expected product to be isolated.

Melting point : 180°C

Example 10 : 6-Methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3H-benzo[b]pyrano-

25 **[3,2-h]acridin-2-yl acetate**

Step 1 : *(±)-cis-1-Hydroxy-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl acetate*

The product is obtained according to the procedure of Step 1 of Example 9, using acetyl chloride as reagent.

Step 2 : 6-Methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3H-benzo[*b*]pyrano-[3,2-*h*]acridin-2-yl acetate

5 The product is obtained according to the procedure of Step 2 of Example 9, using the compound obtained in Step 1 above as substrate.

Melting point : 165°C

10 **Example 11 : (1S,2S)-1-[(Dimethylamino)carbonyl]oxy-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[*b*]pyrano[3,2-*h*]acridin-2-yl dimethylcarbamate**

In a flask, 0.698 mmol of potassium hydride is washed three times with hexane and then cooled to -10°C, and a solution of 0.123 mmol of the compound of Preparation 2 in 4 ml of anhydrous tetrahydrofuran is added. After the dropwise addition of 0.327 mmol of *N,N*-dimethylcarbamoyl chloride at -10°C, stirring is carried out for 3 hours 30 minutes at ambient temperature. The reaction is stopped by adding 50 ml of ethyl acetate and 10 ml of saturated NaHCO₃ solution in order to obtain a pH of 8. The organic phase is washed with water and dried over magnesium sulphate. After evaporation under reduced pressure and crystallisation from ethyl acetate, the expected product is isolated.

Melting point : 173°C

20 **Example 12 : (1S,2S)-6-Methoxy-3,3,14-trimethyl-2-[(4-methylphenyl)sulphonyl]oxy-7-oxo-2,3,7,14-tetrahydro-1H-benzo[*b*]pyrano[3,2-*h*]acridin-1-yl 4-methylbenzenesulfonate**

The product is obtained according to the procedure of Example 11, using tosyl chloride as reagent.

Example 13 : (1S,2S)-6-{{[3-(Diethylamino)propyl]amino}-1-{{(dimethylamino)-carbonyloxy}-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl dimethylcarbamate

5 The product is obtained according to the procedure of Example 11, Steps 1 to 2, using the product of Preparation 5 as substrate.

Example 14 : (1S,2S)-1-{{(Dimethylamino)carbonyl}amino}-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl dimethylcarbamate

10 The product is obtained according to the procedure of Example 11, Steps 1 to 2, using the product of Preparation 6 as substrate.

Example 15 : N'-(1S,2S)-1-{{(Dimethylamino)carbothioyl}amino}-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl)-N,N-dimethylthiourea

15 The product is obtained according to the procedure of Example 11, Steps 1 to 2, using the product of Preparation 8 as substrate and dimethylthiocarbamoyl chloride as reagent.

Example 16 : 6-[2-(Dimethylamino)ethoxy]-3,3,14-trimethyl-7-oxo-7,14-dihydro-3H-benzo[b]pyrano[3,2-h]acridin-2-yl butyrate

The product is obtained according to the procedure of Steps 1 to 2 of Example 9, using the compound of Preparation 7 as substrate in Step 1.

20 **Example 17 : 13-Amino-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7H-benzo[b]-pyrano[3,2-h]acridin-7-one**

Step 1 : 3-Acetamido-4-nitro-2-naphthalenecarboxylic acid

5 A solution of 5 g of 3-amino-2-naphthalenecarboxylic acid in 40 ml of acetic anhydride is stirred at ambient temperature for 30 minutes and then 5 ml of nitric acid are added dropwise. The reaction mixture is then stirred in an ice bath for 7 days and is then poured onto ice. The precipitate formed is filtered off, washed with water and then dried and rinsed with 40 ml of methanol, allowing the expected product to be isolated after drying.

Melting point : 235°C

Step 2 : 3-Amino-4-nitro-2-naphthalenecarboxylic acid

10 A solution of 1 g of the compound obtained in Step 1 in 18 ml of hydrochloric acid is refluxed for 4 hours and then poured onto ice. The precipitate formed is filtered off, washed with water until the pH is 5-6 and then dried, allowing the expected product to be isolated.

Melting point : 238°C

Step 3 : 3-Chloro-4-nitro-2-naphthalenecarboxylic acid

15 1.2 g of sodium nitrite are slowly added to 13 ml of concentrated sulphuric acid; the temperature is brought to 70°C until the sodium nitrite has dissolved completely; the solution is then cooled to 20°C.

20 A solution of 3 g of the compound obtained in Step 2 above in 27 ml of acetic acid is cautiously added to the reaction mixture. The solution is then heated at 40°C for 30 minutes and is then cooled in an ice bath.

A solution of cuprous chloride (3.3 g) in 30 ml of concentrated hydrochloric acid is cooled in an ice bath and the solution of the diazoic compound previously obtained is slowly added. The temperature of the reaction mixture is then brought to 80°C and the reaction mixture is stirred until the evolution of gas has ceased.

25 Water is added to the reaction mixture, whilst cooling the latter in an ice bath. The precipitate formed is filtered off, carefully rinsed with water and dried. Crystallisation from dichloromethane allows the expected product to be obtained.

Melting point : 246°C

Step 4 : 3-[*(2,2-Dimethyl-7-methoxy-2H-chromen-5-yl)amino*]-4-nitro-2-naphthalene-carboxylic acid

To 3.3 g of 5-amino-7-methoxy-2,2-dimethylchromene there are added 3 g of the compound obtained in Step 3 above, 3.4 g of potassium acetate, 375 mg of Cu(OAc)₂.H₂O and 120 ml of 2-propanol containing 3.8 ml of triethylamine. The solution is refluxed for 5 days and is then evaporated under reduced pressure. The residue is taken up in a 1/1 mixture of dichloromethane and 1N aqueous HCl solution. After extraction of the aqueous phase, the combined organic phases are treated in customary manner. Chromatography over silica gel (dichloromethane/methanol : gradient from 0.1 to 1 %) allows the expected product to be isolated.

10 Melting point : 165°C

Step 5 : 6-Methoxy-3,3-dimethyl-13-nitro-3,14-dihydro-7H-benzo[*b*]pyrano[3,2-*h*]-acridin-7-one

15 772 mg of the compound obtained in Step 4 are dissolved in 45 ml of anhydrous dichloromethane, and 3 ml of trifluoroacetic anhydride are added. After stirring for 5 minutes at ambient temperature, the reaction mixture is evaporated. The residue is taken up in a mixture of dichloromethane and saturated NaHCO₃ solution. After extraction of the aqueous phase with dichloromethane, the combined organic phases are treated in conventional manner and then distilled, allowing the expected product to be isolated.

20 Melting point : >350°C

Step 6 : 6-Methoxy-3,3,14-trimethyl-13-nitro-3,14-dihydro-7H-benzo[*b*]pyrano-[3,2-*h*]acridin-7-one

To a solution of 300 mg of the compound obtained in Step 5 in 30 ml of 25 dimethylformamide there are added 1.48 g of sodium hydride and then 1.8 ml of iodomethane. The reaction mixture is refluxed, under argon, for 3 days, and is then slowly hydrolysed by the addition of ice. The precipitate formed is filtered off and then dried and is chromatographed over silica gel (dichloromethane/methanol : gradient from 0.1 to

0.5 %), allowing the expected product to be isolated.

Melting point : 283°C

Step 7 : 13-Amino-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7H-benzo[b]pyrano-[3,2-h]acridin-7-one

5 To 178 mg of the compound obtained in Step 6 above in 10 ml of acetic acid and 1 ml of water there are added 621 mg of zinc wool. The reaction mixture is stirred at ambient temperature for 2.5 hours and is then filtered. The filtrate is made alkaline using 10 % aqueous ammonium hydroxide solution; the precipitate formed is then separated off by filtration. The crude residue is purified by chromatography over silica gel (dichloromethane/methanol : gradient from 0.1 to 0.5 %), allowing the expected product to be isolated.

10

Melting point : 157°C

Example 18 : 2,2,2-Trifluoro-N-(6-methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3H-benzo[b]pyrano[3,2-h]acridin-13-yl)acetamide

15 A solution of 0.039 mmol of the compound obtained in Example 17 in 7 ml of anhydrous pyridine, under argon, is stirred at -20°C, and 0.15 mmol of trifluoroacetic anhydride is added. The reaction mixture is stirred for 6 hours at -20°C and is then diluted with 15 ml of methanol and concentrated under reduced pressure. Chromatography of the residue over 20 silica gel (dichloromethane/methanol : 99.9/0.1) allows the expected product to be isolated.

Example 19 : N-(6-Methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3H-benzo[b]pyrano[3,2-h]acridin-13-yl)acetamide

The product is obtained according to the procedure of Example 18, using acetic anhydride as reagent.

25 Example 20 : 6-Methoxy-3,3,14-trimethyl-1,7-dioxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl acetate

Step 1 : 2-Hydroxy-6-methoxy-3,3,14-trimethyl-2,3-dihydro-1H-benzo[b]pyrano-[3,2-h]acridine-1,7(14H)-dione

A suspension of 1.28 g of KMnO_4 in 15 ml of water is added dropwise, over 30 minutes, to a solution of 0.5 g of the product of Preparation 1 dissolved in 25 ml of acetone. The reaction mixture is stirred at ambient temperature for 8 hours and is then extracted with 2-butanone. The organic phase is treated in conventional manner and chromatography of the residue over silica gel (dichloromethane/methanol : 98/2) allows the expected product to be isolated.

Melting point : 272°C

10 Step 2 : 6-Methoxy-3,3,14-trimethyl-1,7-dioxo-2,3,7,14-tetrahydro-1H-benzo-[b]pyrano[3,2-h]acridin-2-yl acetate

The product is obtained according to the procedure of Step 1 of Example 9, using acetic anhydride as reagent.

Melting point : 206°C

15 **Example 21 : 6-Methoxy-3,3,14-trimethyl-1,7-dioxo-2,3,7,14-tetrahydro-1H-benzo-[b]pyrano[3,2-h]acridin-2-yl propionate**

The product is obtained according to the procedure of Example 20, using propionic anhydride as reagent in Step 2.

Melting point : 218°C

20 **Example 22 : 6-Methoxy-3,3-dimethyl-1,7-dioxo-2,3,7,14-tetrahydro-1H-benzo-[b]pyrano[3,2-h]acridin-2-yl acetate**

Step 1 : 3-[*(8-Methoxy-2,2-dimethyl-2H-chromen-5-yl)amino*]-2-naphthoic acid

A solution containing 1.2 mmol of 3-bromonaphthalene-2-carboxylic acid, 1.19 mmol of 7-methoxy-2,2-dimethyl-2H-1-benzopyran-5-ylamine, 2.38 mmol of potassium acetate,

10 mg of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and 1.19 mmol of triethylamine in 17 ml of 2-propanol is refluxed for 24 hours and then concentrated under reduced pressure. The residue obtained is taken up in a 2/1 mixture of dichloromethane/1N HCl. The aqueous phase is extracted with dichloromethane and the combined organic phases are then treated in conventional manner. Chromatography of the residue over silica gel (dichloromethane) allows the expected product to be isolated.

Step 2 : 6-Methoxy-3,3-dimethyl-3,14-dihydro-7H-benzo[*b*]pyrano[3,2-*h*]acridin-7-one

10 To a solution containing 1.94 mmol of the compound obtained in Step 1 in 20 ml of anhydrous dichloromethane, maintained at 0°C under argon, there are added 9.71 mmol of trifluoroacetic anhydride. After reacting for 3 days at ambient temperature, the reaction mixture is concentrated under reduced pressure. The residue is taken up in a mixture of dichloromethane and aqueous NaHCO_3 solution. After extraction with dichloromethane, the combined organic phases are treated in conventional manner. Chromatography of the residue over silica gel (dichloromethane) allows the expected product to be isolated, the latter being subsequently recrystallised from ethyl ether.

Melting point : 278°C

Step 3 : 2-Hydroxy-6-methoxy-3,3-dimethyl-2,3-dihydro-1H-benzo[*b*]pyrano[3,2-*h*]acridine-1,7(14H)-dione

20 To a solution of 1.33 mmol of the compound obtained in Step 2 in 30 ml of a 10/3/1 mixture of *tert*-butanol/tetrahydrofuran/water there are added osmium tetroxide in the form of a 2.5 % solution in 0.67 ml of 2-methyl-2-propanol and 1.35 mmol of 4-methylmorpholine-N-oxide monohydrate. After stirring for two days at ambient temperature, NaHSO_3 solution is added. After stirring for one hour, the reaction mixture is extracted with dichloromethane. The organic phase is dried, filtered and then evaporated under reduced pressure. Chromatography of the residue over silica gel (dichloromethane/methanol : 98/2) allows the expected product to be isolated.

Melting point : 230°C

Step 4 : 6-Methoxy-3,3-dimethyl-1,7-dioxo-2,3,7,14-tetrahydro-1H-benzo-[b]pyrano[3,2-h]acridin-2-yl acetate

The product is obtained according to the procedure of Step 2 of Example 20, using an excess of acetic anhydride.

5 Melting point : 206°C

Example 23 : (±)-cis-1-{{(Diethylamino)carbonyl}oxy}-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl diethylcarbamate

10

The product is obtained according to the procedure of Example 11, using *N,N*-diethylcarbamoyl chloride as reagent.

Melting point : 193°C

15

Example 24 : (±)-cis-1-{{(Diisopropylamino)carbonyl}oxy}-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl diisopropylcarbamate

20

The product is obtained according to the procedure of Example 11, using *N,N*-diisopropylcarbamoyl chloride as reagent.

Melting point : 149.5°C

25

Example 25 : (±)-cis-1-{{(Dibutylamino)carbonyl}oxy}-6-methoxy-3,3,14-trimethyl-7-oxo-2,3,7,14-tetrahydro-1H-benzo[b]pyrano[3,2-h]acridin-2-yl dibutylcarbamate

30

The product is obtained according to the procedure of Example 11, using *N,N*-dibutylcarbamoyl chloride as reagent.

Melting point : 138°C

Example 26 : 6-Methoxy-3,3-dimethyl-1,7-dioxo-2,3,7,14-tetrahydro-1H-benzo-[b]pyran[3,2-h]acridin-2-yl propionate

5 To a previously cooled solution of anhydrous pyridine (1.5 ml) and an excess of propionic anhydride there is added 0.26 mmol of the compound obtained in Step 3 of Example 22. The reaction mixture is stirred at ambient temperature, protected from light, for 24 hours and is then poured onto ice-cold water (10 ml). The precipitate obtained is filtered off, washed with water and dried under a phosphoric vacuum. Chromatography of the residue over silica gel (dichloromethane) allows the expected product to be isolated.

10 *Melting point* : 231°C

PHARMACOLOGICAL STUDY OF COMPOUNDS OF THE INVENTION

EXAMPLE 27 : *In vitro* activity

15 Murine leukaemia L1210 was used *in vitro*. The cells are cultured in RPMI 1640 complete culture medium containing 10 % foetal 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 exposed to the cytotoxic compounds for 4 doubling periods, or 48 hours. The number of viable cells is then quantified by means of a colorimetric assay, the Microculture Tetrazolium Assay (J. Carmichael *et al.*, *Cancer Res.*, **47**, 936-942, (1987)). The results are expressed as IC₅₀, the concentration of cytotoxic agent which 20 inhibits the proliferation of the treated cells by 50 %.

By way of illustration, the compounds of Examples 11 and 7 exhibit an IC₅₀ of 0.78 µM and 0.52 µM, respectively, thereby demonstrating their greater activity than the reference compound (acronycine).

25 **EXAMPLE 28 : *In vitro* activity**

1- Anti-tumour activity with respect to P388 leukaemia

30 Line P388 (murine leukaemia) was supplied by the National Cancer Institute (Frederick, USA). The tumour cells (10⁶ cells) were inoculated on day 0 into the peritoneal cavity of female B6D2F1 mice (Iffa Credo, France). Six mice weighing from 18 to 20 g were used

in each test group. The products were administered by the intravenous route on day 1.

The anti-tumour activity is expressed as % T/C :

$$\% \text{ T/C (mouse)} = \frac{\text{Median survival time of the treated animals}}{\text{Median survival time of the control animals}} \times 100$$

The compounds of the present invention are very active in this model, having a T/C of
5 > 150 %, whereas acronycine is only marginally active.

2- Anti-tumour activity with respect to C38 adenocarcinoma of the colon

Tumour fragments of C38 adenocarcinoma of the colon weighing approximately 30 mg were implanted under the skin of B6D2F1 mice (Iffa Credo, France) on day 0.

10 After growth of the tumour, the mice were divided into control (18 animals) and treated (6 or 7 animals) groups, which were homogeneous with respect to tumour size. The products were administered by the i.v. route once per week for 3 weeks (on days 10, 17 and 24), at their Maximum Tolerated Dose (MTD), MTD/2 and MTD/4.

15 The tumours were measured twice a week and the tumour volumes were calculated according to the following formula : volume (mm³) = length (mm) x breadth (mm²) / 2.

The anti-tumour activity is expressed as % T/C :

$$\% \text{ T/C} = \frac{\text{median Vt/V0 of the treated animals}}{\text{median Vt/V0 of the control animals}} \times 100$$

V0 and Vt being the initial volume of the tumour and its volume at measurement time t, respectively.

20 The optimum dose is the dose giving the lowest T/C value without toxicity (early death or weight loss greater than 20 %).

By way of example, the compounds of Examples 7 and 11 exhibit an anti-tumour activity of 30 % for an optimum dose of 12.5 mg/kg and 41 % for an optimum dose of 25 mg/kg, 25 respectively, whereas acronycine exhibits an anti-tumour activity of 27 % for an optimum dose of 100 mg/kg, thereby demonstrating their strong therapeutic potential.

EXAMPLE 29 : Pharmaceutical composition : injectable solution

Compound of Example 11 10 mg

Distilled water for injectable preparations 25 ml

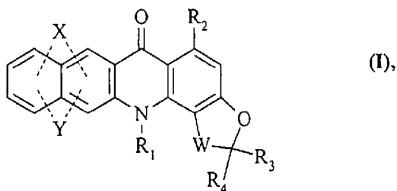
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Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

CLAIMS

I. Compounds of formula (I) :



5 wherein :

- X and Y, which may be the same or different, represent, independently of one another, a group selected from :

- hydrogen and halogen atoms,
- mercapto, cyano, nitro, linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)-trihaloalkyl and linear or branched trihalo-(C₁-C₆)alkyl-carbonylamino groups,
- groups of formulae -ORA, -NRaRb, -NRa-C(O)-T₁, -O-C(O)-T₁, -O-T₂-NRaRb, -O-T₂-ORA, -NRa-T₂-NRaRb, -NRa-T₂-ORA and -NRa-T₂-CO₂Ra wherein :

10 * Ra represents a group selected from a hydrogen atom and a linear or branched (C₁-C₆)alkyl group, an aryl group and an aryl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched,

15 * Rb represents a group selected from a hydrogen atom and a linear or branched (C₁-C₆)alkyl group, an aryl group and an aryl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched,

or

20 * Ra+Rb, together with the nitrogen atom carrying them, form a monocyclic 5- or 6-membered heterocycle optionally containing in the cyclic system a second hetero atom selected from oxygen and nitrogen,

* T₁ represents a group selected from linear or branched (C₁-C₆)alkyl, linear or branched (C₂-C₆)alkenyl, aryl, aryl-(C₁-C₆)alkyl (wherein the alkyl moiety is linear or

branched), and a linear or branched (C_1 - C_6)alkylene chain substituted by a group selected from -ORa and -NRaRb wherein Ra and Rb are as defined hereinbefore,

* T_2 represents a linear or branched (C_1 - C_6)alkylene chain,
- or X and Y, when they are in adjacent positions, together form a methylenedioxy group or an ethylenedioxy group,

5 it being understood that the substituents X and Y may be present on either of the two adjacent benzene rings,

- R_1 represents a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group,
- R_2 represents a group selected from a hydrogen atom and linear or branched (C_1 - C_6)alkyl, -ORa, -NRaRb, -NRa-C(O)- T_1 , -O-C(O)- T_1 , -O- T_2 -NRaRb, -O- T_2 -ORa, -NRa- T_2 -NRaRb, -NRa- T_2 -ORa and -NRa- T_2 -CO₂Ra groups, wherein Ra, Rb, T_1 and T_2 are as defined hereinbefore,
- R_3 , R_4 , which may be the same or different, represent, independently of one another, a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group,
- 15 • W represents a group of formula -CH(R_5)-CH(R_6)-, -CH=C(R_7)-, -C(R_7)=CH- or -C(O)-CH(R_8)- wherein :
 - * R_5 and/or R_6 , represent(s) a group selected from -W₁-C(W₂)-W₃- T_1 , -W₁-S(O)_n-W₃- T_1 and -W₁-S(O)_n- T_1 wherein :
 - W₁ represents an oxygen or sulphur atom or a nitrogen atom substituted by a hydrogen atom or by a linear or branched (C_1 - C_6)alkyl group, an aryl group or an aryl- (C_1 - C_6)alkyl group wherein the alkyl moiety is linear or branched,
 - W₂ represents an oxygen atom or a sulphur atom,
 - W₃ represents an oxygen or sulphur atom or a nitrogen atom substituted by a hydrogen atom or by a linear or branched C_1 - C_6 alkyl group, an aryl group or an aryl- (C_1 - C_6)alkyl group wherein the alkyl moiety is linear or branched, a bond when T_1 represents C_4 alkanyl group,
 - T_1 is as defined hereinbefore,
 - n represents an integer selected from 1 and 2,

and in the case where only one of the two groups R₅ and R₆ represents a group as defined hereinbefore then the other of the said groups R₅ or R₆ represents a group selected from a hydrogen atom, hydroxy, linear or branched (C₁-C₆)alkoxy, linear or branched (C₁-C₆)alkyl-carbonyloxy, arylcarbonyloxy, aryl-(C₁-C₆)alkyl-carbonyloxy (wherein the alkyl moiety is linear or branched), and amino optionally substituted by one or two, identical or different, linear or branched (C₁-C₆)alkyl groups,

* R₇ represents a group selected from hydroxy, linear or branched (C₁-C₆)alkoxy, -C(W₂)-T₁, -W₁-C(W₂)-W₃-T₁, -W₁-C(W₂)-T₁, -W₁-S(O)_n-W₃-T₁ and -W₁-S(O)_n-T₁ wherein W₁, W₂, W₃, T₁ and n are as defined hereinbefore, or R₇ may have the additional meaning of a hydrogen atom when R₂ represents a group -O-T₂-OR_a and/or when X represents a hydrogen atom and Y, located in the 13-position of the naphthyl system of the pentacyclic skeleton, represents an amino group optionally substituted by one or two identical or different groups selected independently of one another from linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)acyl and linear or branched trihalo-(C₁-C₆)alkyl-carbonyl,

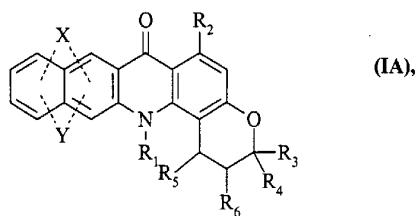
* R₈ represents a linear or branched (C₁-C₆)alkoxy or linear or branched (C₁-C₆)alkyl-carbonyloxy group, or may have the additional meaning of hydroxy when R₂ represents a group -O-T₂-OR_a as defined hereinbefore,

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

aryl being understood to mean a phenyl or naphthyl group optionally containing one or

more, identical or different, substituents selected from hydroxy, halogen, carboxy, nitro, amino, linear or branched (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino wherein each alkyl moiety may be linear or branched, linear or branched (C₁-C₆)alkoxy, linear or branched (C₁-C₆)acyl and linear or branched (C₁-C₆)alkyl-carbonyloxy,
5 and isomers being understood to comprise optical isomers.

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



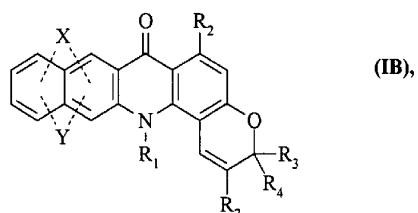
10 wherein X, Y, R₁, R₂, R₃, R₄, R₅ and R₆ are as defined for formula (I), their enantiomers, diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

15 3. Compounds of formula (I) according to claim 2, characterised in that they represent compounds of formula (IA) wherein R₅ and R₆ are identical and each represent a group of formula -W₁-C(W₂)-W₃-T₁ or -W₁-S(O)_n-T₁ wherein W₁, W₂, W₃, T₁ and n are as defined for formula (I), their enantiomers, diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

20 4. Compounds of formula (I) according to any one of claims 1 to 3, characterised in that they represent compounds of formula (IA) wherein R₅ and R₆ are identical and each represent a group of formula -W₁-C(W₂)-W₃-T₁ wherein W₁ represents an oxygen atom, W₂ represents an oxygen atom, W₃ represents a nitrogen atom substituted by a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, an aryl group or an aryl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched and T₁ is as defined for formula (I), their enantiomers, diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

5. Compounds of formula (I) according to any one of claims 1 to 3, characterised in that
they represent compounds of formula (IA) wherein R₅ and R₆ are identical and each
represent a group of formula -W₁-S(O)_n-T₁ wherein W₁ represents an oxygen atom, T₁ is as
defined for formula (I) and n is 2, their enantiomers, diastereoisomers and N-oxides, and
addition salts thereof with a pharmaceutically acceptable acid or base.

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

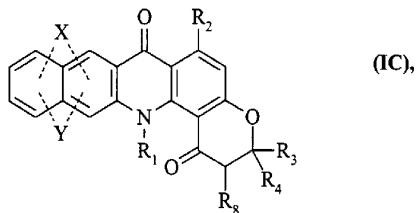


wherein X, Y, R₁, R₂, R₃, R₄ and R₇ are as defined for formula (I), their enantiomers, diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

7. Compounds of formula (I) according to either claim 1 or claim 6, characterised in that they represent compounds of formula (IB) wherein R₇ represents a group selected from -C(W₂)-T₁ and -W₁-C(W₂)-T₁ wherein W₁, W₂ and T₁ are as defined for formula (I), their enantiomers, diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

8. Compounds of formula (I) according to claim 7, characterised in that they represent compounds of formula (IB) wherein W_1 represents an oxygen atom, W_2 represents an oxygen atom and T_1 represents a linear or branched (C_1 - C_6)alkyl group, an aryl group or an aryl- $(C_1$ - C_6)alkyl group wherein the alkyl moiety is linear or branched, their enantiomers, diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

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

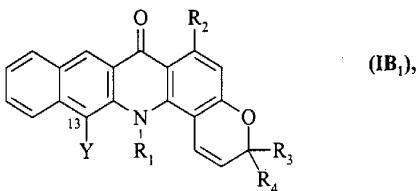


wherein X, Y, R₁, R₂, R₃, R₄ and R₈ are as defined for formula (I), their enantiomers, 5 diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

10. Compounds of formula (I) according to any one of claims 1 to 9, characterised in that R₃ and R₄, which may be the same or different, represent a linear or branched (C₁-C₆)alkyl group, their enantiomers, diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

11. Compounds of formula (I) according to any one of claims 1 to 9, characterised in that R₂ represents a group selected from linear or branched (C₁-C₆)alkoxy, -NRaRb, -O-T₂-NRaRb, -O-T₂-ORa, -NRa-T₂-NRaRb and -NRa-T₂-ORa wherein Ra, Rb, T₁ and T₂ are as defined for formula (I), their enantiomers, diastereoisomers and N-oxides, and 15 addition salts thereof with a pharmaceutically acceptable acid or base.

12. Compounds of formula (I) according to claim 1, characterised in that they represent compounds of formula (IB₁) :



wherein R₁, R₂, R₃ and R₄ are as defined for formula (IB) and Y represents an amino group 20 optionally substituted by one or two identical or different groups selected independently of

one another from linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)acyl and linear or branched trihalo-(C₁-C₆)alkyl-carbonyl, their enantiomers, diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

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

5 - (1*S*,2*S*)-1-{[(dimethylamino)carbonyl]oxy}-6-methoxy-3,3,14-trimethyl-7-oxo-
2,3,7,14-tetrahydro-1*H*-benzo[*b*]pyrano[3,2-*h*]acridin-2-yl dimethylcarbamate
- and (1*S*,2*S*)-6-methoxy-3,3,14-trimethyl-2-{[(4-methylphenyl)sulphonyl]oxy}-7-
oxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]pyrano[3,2-*h*]acridin-1-yl 4-methylbenzenesulfon-
ate,

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

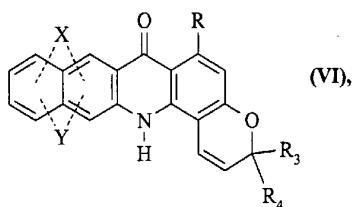
14. Compounds of formula (I) according to claim 1, which are :

15 - 6-methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3*H*-benzo[*b*]pyrano[3,2-*h*]acridin-
2-yl acetate,
- 2-benzoyl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-
acridin-7-one,
- 2-butyryl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-
acridin-7-one,
- 2-acetyl-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-
acridin-7-one,
- 6-methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3*H*-benzo[*b*]pyrano[3,2-*h*]acridin-
2-yl butyrate,
- 6-(2-hydroxyethoxy)-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-
acridin-7-one,
- 13-amino-6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]pyrano[3,2-*h*]-
acridin-7-one
- and *N*-(6-methoxy-3,3,14-trimethyl-7-oxo-7,14-dihydro-3*H*-benzo[*b*]pyrano[3,2-*h*]-
acridin-13-yl)acetamide,

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

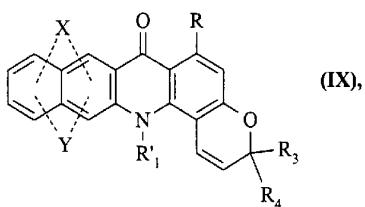
15. Compound of formula (I) according to claim 1, which is 6-methoxy-3,3-dimethyl-1,7-dioxo-2,3,7,14-tetrahydro-1*H*-benzo[*b*]pyrano[3,2-*h*]acridin-2-yl acetate, its enantiomers, diastereoisomers and N-oxides, and addition salts thereof with a pharmaceutically acceptable acid or base.

5 16. Process for the preparation of compounds of formula (I), characterised in that there is used as starting material a compound of formula (VI) :



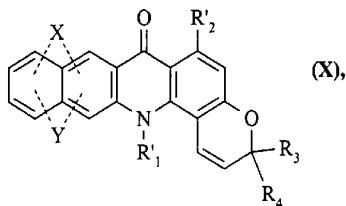
wherein X, Y, R, R₃ and R₄ are as defined hereinbefore,

10 the nitrogen atom of which compound of formula (VI) is optionally substituted, by the action of an alkyl halide or of a dialkyl sulphate in the presence of a deprotonating agent, in an aprotic polar solvent or under phase transfer conditions, to yield the compounds of formula (IX) :



15 wherein X, Y, R, R₃ and R₄ are as defined hereinbefore and R'1 represents a linear or branched (C₁-C₆)alkyl group,

which compounds of formula (IX) are subjected to the action of an alkylating agent or an acylating agent under customary conditions of organic synthesis to yield the compounds of formula (X) :



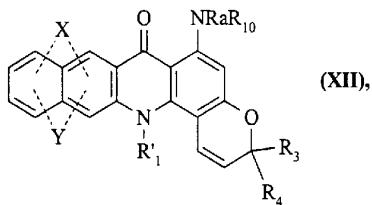
wherein X, Y, R'1, R3 and R4 are as defined hereinbefore and R'2 represents a group selected from -ORa, -O-C(O)-T1, -O-T2-NRaRb and -O-T2-ORa wherein Ra, Rb, T1 and T2 are as defined for formula (I),

5 which compounds of formula (X), in the case where R'2 represents an alkoxy group, are treated with a compound of formula (XI) :



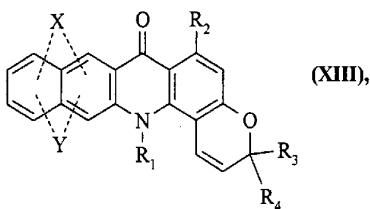
10 wherein Ra represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, an aryl group or an aryl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched, and R₁₀ represents a group selected from Rb, -C(O)-T₁, -T₂-NRaRb, -T₂-ORa and -T₂-CO₂Ra wherein Ra, Rb, T₁ and T₂ are as defined for formula (I),

to yield the compounds of formula (XII) :



wherein X, Y, R'1, R3, R4, Ra and R₁₀ are as defined hereinbefore,

15 the totality of the compounds of formulae (VI), (IX), (X) and (XII) forming the compounds of formula (XIII) :



wherein X, Y, R₁, R₂, R₃ and R₄ are as defined in the general definition for formula (I),

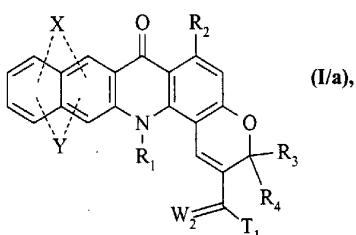
which compounds of formula (XIII) are subjected :

b) \Rightarrow either to the action of a compound of formula (XIV) :



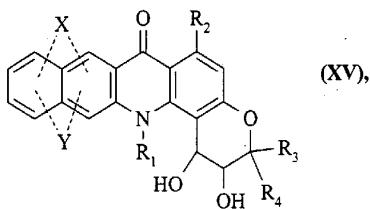
wherein Hal represents a halogen atom and W₂ and T₁ are as defined in the general definition for formula (I),

to yield the compounds of formula (I/a), a particular case of the compounds of formula (I) :



10 wherein X, Y, R₁, R₂, R₃, R₄, W₂ and T₁ are as defined hereinbefore,

b) \Rightarrow or to the action of an oxidising agent for alkene functions to yield the compounds of formula (XV) :



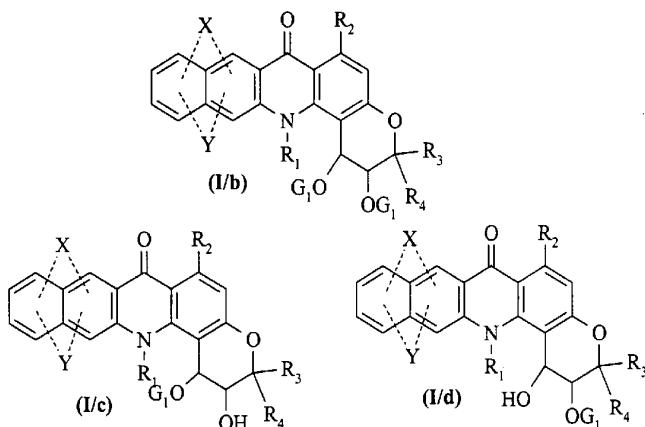
wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

which compounds of formula (XV) are treated with a compound of formula (XVI) :



wherein Hal represents a halogen atom and G₁ represents a group selected from -C(W₂)-W₃-T₁, -C(W₂)-T₁, -S(O)_n-W₃-T₁ and -S(O)_n-T₁ wherein W₂, W₃, T₁ and n are as defined for formula (I),

to yield the compounds of formulae (I/b), (I/c) and (I/d), particular cases of the compounds of formula (I) :

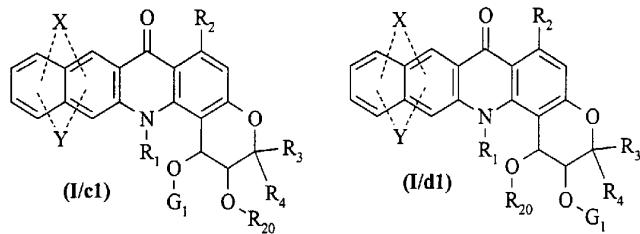


10

wherein X, Y, R₁, R₂, R₃, R₄ and G₁ are as defined hereinbefore,

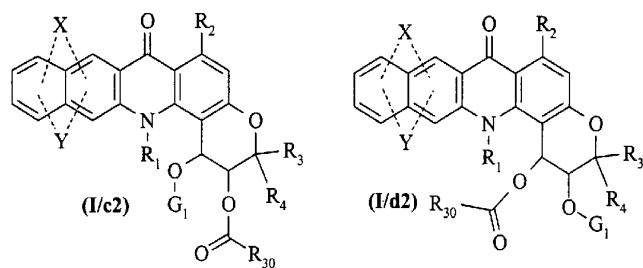
which compounds of formulae (I/c) and/or (I/d) are subjected :

15 ♦ either to the action of an alcohol of formula R₂₀-OH, wherein R₂₀ represents a linear or branched (C₁-C₆)alkyl group, to yield the compounds of formulae (I/c1) and (I/d1), respectively :



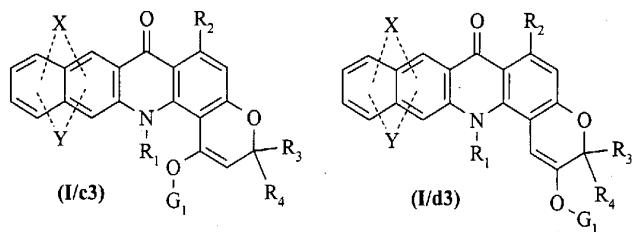
wherein X , Y , R_1 , R_2 , R_3 , R_4 , G_1 and R_{20} are as defined hereinbefore,

5 \diamond or to the action of an anhydride of formula $(R_{30}CO)_2O$, wherein R_{30} represents a linear or branched (C_1-C_6) alkyl group, an aryl group or an aryl- (C_1-C_6) alkyl group wherein the alkyl moiety is linear or branched, to yield the compounds of formulae (I/c2) and (I/d2), respectively :



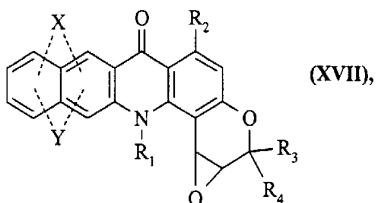
wherein X , Y , R_1 , R_2 , R_3 , R_4 , G_1 and R_{30} are as defined hereinbefore,

10 \diamond or to dehydrating conditions in an acid medium to yield the compounds of formulae (I/c3) and (I/d3), respectively, particular cases of the compounds of formula (I) :



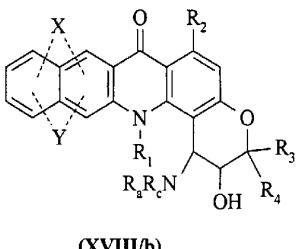
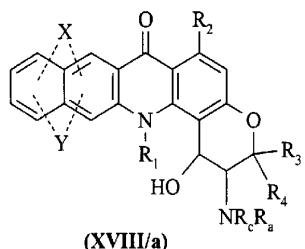
wherein X , Y , R_1 , R_2 , R_3 , R_4 and G_1 are as defined hereinbefore,

c) \Leftrightarrow or to the action of a peracid or of dimethyl dioxirane to yield the compounds of formula (XVII) :



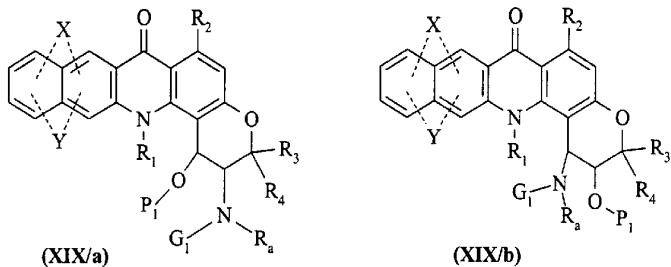
wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

5 which compounds of formula (XVII) are treated with ammoniac or with a primary amine to yield the compounds of formulae (XVIII/a) and/or (XVIII/b) :



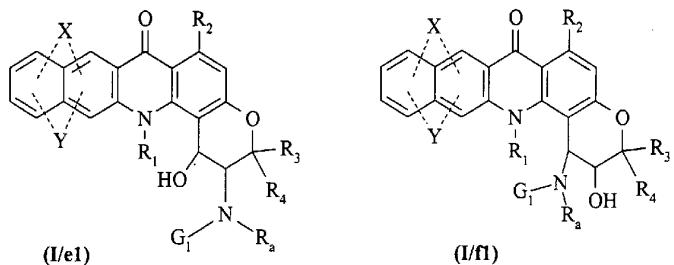
wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore, R_c represents a hydrogen atom and R_a represents a hydrogen atom in the case where the reagent used is ammoniac or 10 represents a group selected from linear or branched (C₁-C₆)alkyl, aryl and aryl-(C₁-C₆)alkyl (wherein the alkyl moiety is linear or branched) in the case where the reagent used is a primary amine,

15 the alcohol function of which compounds of formulae (XVIII/a) and (XVIII/b) is protected by a protecting group for hydroxy groups, the compounds then being subjected to the action of a compound of formula Hal-G₁ (XVI) as defined hereinbefore to yield the compounds of formulae (XIX/a) and (XIX/b), respectively,



wherein X, Y, R₁, R₂, R₃, R₄, R₅ and G₁ are as defined hereinbefore and P₁ represents a protecting group for hydroxy functions,

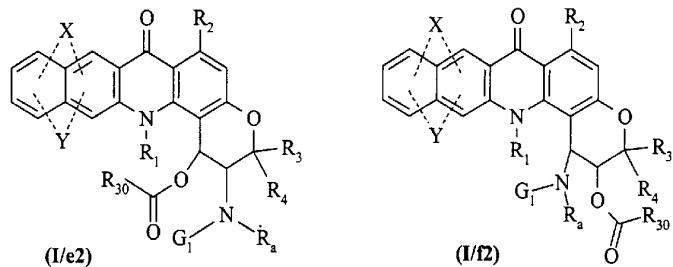
5 the hydroxy group of which compounds of formulae (XIX/a) and (XIX/b) is deprotected to
yield the compounds of formulae (I/e1) and (I/f1), respectively, particular cases of the
compounds of formula (I) :



wherein X, Y, R₁, R₂, R₃, R₄, R_a and G₁ are as defined hereinbefore,

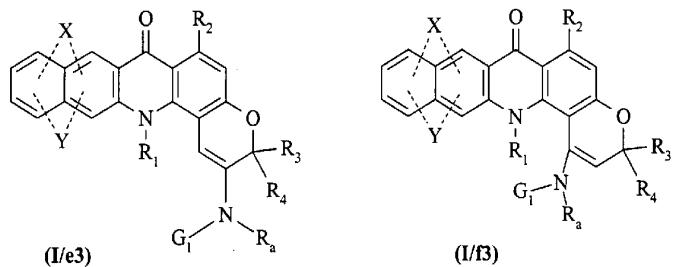
10 which compounds of formulae (I/e1) and (I/f1) are subjected:

- ❖ either to the action of an anhydride of formula $(R_{30}CO)_2O$, wherein R_{30} represents a linear or branched (C_1-C_6) alkyl group, an aryl group or an aryl- (C_1-C_6) alkyl group wherein the alkyl moiety is linear or branched, to yield the compounds of formulae (I/e2) and (I/f2), respectively, particular cases of the compounds of formula (I) :



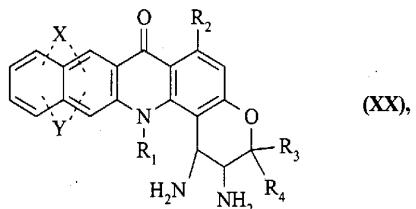
wherein X, Y, R₁, R₂, R₃, R₄, R_a, G₁ and R₃₀ are as defined hereinbefore,

❖ or to dehydrating conditions in an acid medium to yield the compounds of formulae (I/e3) and (I/f3), respectively, particular cases of the compounds of formula (I) :



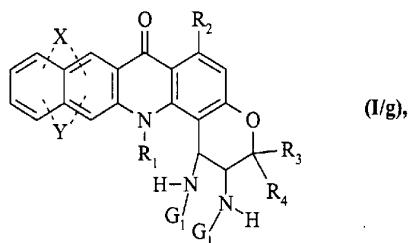
wherein X, Y, R₁, R₂, R₃, R₄, R_a and G₁ are as defined hereinbefore,

10 d) \Leftrightarrow or to the action of NaN_3 in the presence of hydrogen peroxide, followed by a reduction step using tri-*n*-butyltin hydride, for example, to yield the compounds of formula (XX) :



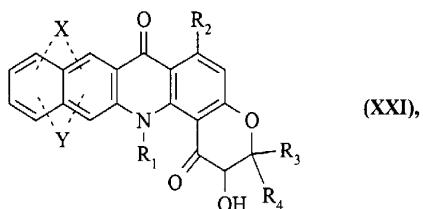
wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

which compounds of formula (XX) are subjected to the action of a compound of formula Hal-G₁ (XVI) as defined hereinbefore to yield the compounds of formula (I/g), a particular case of the compounds of formula (I) :



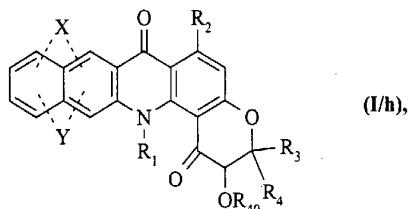
5 wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

e) ⇔ or to the action of potassium permanganate in a polar medium to yield the compounds of formula (XXI) :



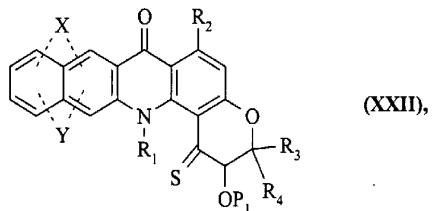
wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

10 which compounds of formula (XXI) are subjected to the action of either an alkylating agent or an acylating agent to yield the compounds of formula (I/h), a particular case of the compounds of formula (I) :



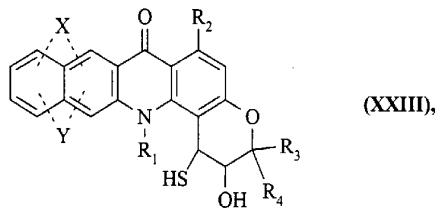
15 wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore and R₄₀ represents a linear or branched (C₁-C₆)alkyl group or a linear or branched (C₁-C₆)acyl group,

or the hydroxy functions of which compounds of formula (XXI) are protected with a protecting group conventionally used in organic synthesis, the compounds then being subjected to the action of P_2S_5 to yield the compounds of formula (XXII) :



5 wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore and P₁ represents a protecting group for hydroxy functions,

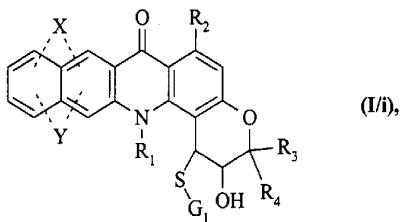
which compounds of formula (XXII) are treated with a reducing agent and then subjected to a reaction for deprotection of the hydroxy function to yield the compounds of formula (XXIII) :



10

wherein X, Y, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

which compounds of formula (XXIII) are treated with a compound of formula (XVI) as defined hereinbefore to yield the compounds of formula (I/i), a particular case of the compounds of formula (I) :



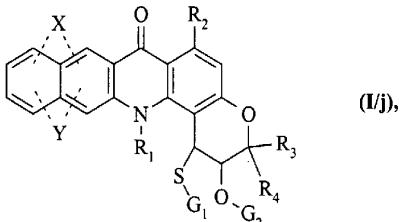
wherein X, Y, G₁, R₁, R₂, R₃ and R₄ are as defined hereinbefore,

which compounds of formula (I/i) may be subjected to the action of an alkylating agent, an acylating agent or a compound of formula (XVIa) :



wherein Hal represents a halogen atom and G'₁ represents a group selected from -C(W₂)-W₃-T₁, -C(W₂)-T₁, -S(O)_n-W₃-T₁ and -S(O)_n-T₁, wherein W₂, W₃, T₁ and n are as defined for formula (I),

to yield the compounds of formula (I/j), a particular case of the compounds of formula (I) :



10

wherein X, Y, G₁, R₁, R₂, R₃ and R₄ are as defined hereinbefore and G₂ represents a group selected from G'₁ as defined hereinbefore, linear or branched (C₁-C₆)alkoxy, linear or branched (C₁-C₆)alkyl-carbonyloxy, arylcarbonyloxy and aryl-(C₁-C₆)alkyl-carbonyloxy (wherein the alkyl moiety is linear or branched),

15

the compounds of formulae (I/a) to (I/j), (I/c₁) to (I/c₃), (I/d₁) to (I/d₃), (I/e₁) to (I/e₃) and (I/f₁) to (I/f₃) constituting the totality of the compounds of the invention, which are purified, if necessary, according to a conventional purification technique, which may be, if desired, separated into their different isomers according to a conventional separation technique and which are converted, if desired, into their N-oxides and, where appropriate,

their addition salts with a pharmaceutically acceptable acid or base.

17. Pharmaceutical compositions comprising as active ingredient at least one compound according to any one of claims 1 to 15, alone or in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

18. Pharmaceutical compositions according to claim 17 comprising at least one active ingredient according to any one of claims 1 to 15 for use as a medicament in the treatment of cancers.

19. Pharmaceutical compositions comprising as active ingredient at least one compound of formula (XXI) as described in claim 16, alone or in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

20. Pharmaceutical composition according to claim 19 comprising as active ingredient 2-hydroxy-6-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*b*]pyrano[3,2-*h*]acridine-1,7(14*H*)-dione, alone or in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

21. Pharmaceutical composition according to either claim 19 or claim 20 for use as a medicament in the treatment of cancers.

22. Compounds according to claim 1, substantially as hereinbefore described with reference to the Examples.

23. Process according to claim 16, substantially as hereinbefore described with reference to the Examples.

24. Pharmaceutical composition according to claim 17, substantially as hereinbefore described with reference to the Examples.

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25. A method of treatment of cancers, wherein a subject in need of such treatment is administered an efficacious amount of a compound as claimed in any one of claims 1 to 15, or a pharmaceutical composition as claimed in any one of claims 17 to 21.
26. Use of a compound of any one of claims 1 to 15 for the manufacture of a medicament for the treatment of cancers.

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