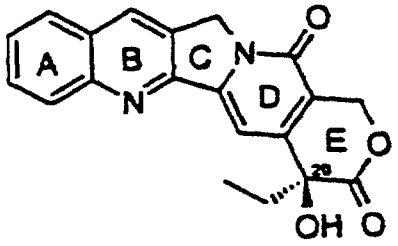
PRODRUG FORMS AND NEW ANALOGUES OF CAMPTOTHECIN, THEIR USE AS MEDICAMENTS

Camptothecin is a natural compound which has been isolated for the first time from the leaves and the bark of the Chinese plant called *camptotheca acuminata* (see Wall et al. J. Amer. Chem. Soc. 88:3888 (1966) Camptothecin is a pentacyclic compound constituted by an indolizino[1,2-b]quinoline fragment (rings A, B, C and D) fused with an α-hydroxylactone with six members (ring E). The carbon in position 20 which carries the α-hydroxy group is asymmetrical and confers a rotatory power on the molecule. The natural form of camptothecin has an absolute "S" configuration as regards the carbon 20 and corresponds to the following formula:



Camptothecin and its analogues have an anti-proliferative activity in several cancerous cell lines, including the cell lines of human tumors of the colon, lung and breast (Suffness, M et al: The Alkaloids Chemistry and Pharmacology, Bross A., ed., Vol. 25, p. 73 (Acedemic Press, 1985)). It is suggested that the anti-proliferative activity of camptothecin is related to its inhibitory activity on DNA topoisomerase I.

Moreover, camptothecin and certain of its analogues are not hydrosoluble, which makes their administration by parenteral route difficult. Hydrosoluble derivatives of camptothecin have been prepared where rings A and B carry salifiable substituents (cf. for example US 4,981,968, US 5,049,668, EP 540,099). However, these products revealed an antitumoral activity which was reduced with respect to that of non-hydrosoluble derivatives. Other hydrosoluble derivatives of camptothecin have also been prepared where the hydroxyl group in position 20 is esterified by an acid carrying a salifiable radical such as for example glycine (cf. US Patent No. 4,943,579 and PCT No. WO 96/02546). These derivatives are designated by a person skilled in the art under the name "prodrug forms" as they are not biologically active in themselves, but only after a first metabolization phase once administered to the patient. The prodrug forms of the α-hydroxylactone analogues of camptothecin have shown a good anti-tumoral effectiveness in animals and clinically, but accompanied by damaging side-

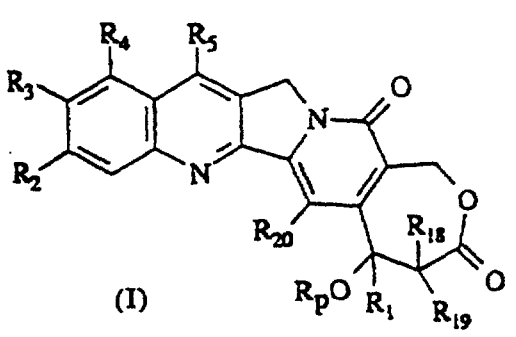
effects such as the appearance of serious diarrhoeas which can put the patient's life in danger. It is therefore necessary to develop hydrosoluble analogues of camptothecin which are more effective and better tolerated.

Furthermore, it has been indicated that α-hydroxylactone was an absolute requirement both for the *in vivo* and *in vitro* activity of campotothecins (Camptothecins: New Anticancer Agents, Putmesil, M et al, ed., p. 27 (CRC Press, 1995); Wall M. et al, Cancer Res. 55:753 (1995); Hertzberg et al, J. Med. Chem. 32:715 (1982) and Crow et al, J. Med. Chem. 35:4160 (1992)). However, the Applicant discovered that β-hydroxylactones with 7 members have a biological activity comparable to or greater than that of α-hydroxylactones (unpublished PCT Application No. FR 96/00980). The present invention relates to new derivatives of this class of analogues of camptothecin, in which a β-hydroxylactone with 7 members replaces the natural α-hydroxylactone of camptothecin. By β-hydroxylactone is meant a lactone comprising an additional carbon atom between the carbon of the carboxyl and the α-carbon carrying the hydroxyl in the α-hydroxylactone.

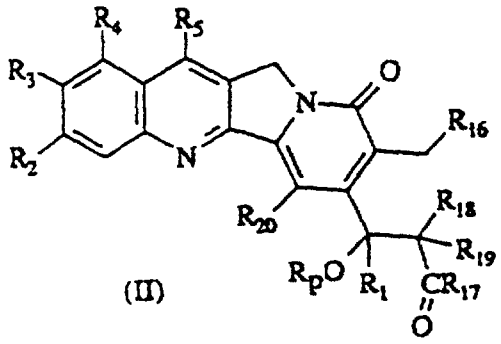
Two solutions were chosen in order to increase the hydrosolubility of the camptothecin analogues: the first consists in grafting an oxazine onto the A ring of the molecule, and the second in designing prodrug forms by acetylating the hydroxy function of the β-hydroxylactone.

More specifically, among this new class of camptothecin analogues, the compounds according to the present invention are either analogues modified by fixation of an oxazine ring on carbons 10 and 11 or prodrug forms in which a β-hydroxylactone replaces the natural α-hydroxylactone of camptothecin. The compounds of the present invention are therefore camptothecin analogue β-hydroxylactones on which an oxazine ring or hydrosoluble prodrugs have been grafted and present a powerful biological activity which is unexpected in the light of the state of the prior art.

A more particular subject of the invention is the compounds of formula (I) and formula (II):



(I)



(II)

in racemic or enantiomeric form or any combinations of these forms, in which

R_1 represents a lower alkyl, a lower alkenyl, a lower alkynyl, a lower haloalkyl, a lower alkoxy lower alkyl or lower alkylthio lower alkyl;

R_2, R_3 and R_4 represent, independently, H, halo, lower halo alkyl, lower alkyl, lower alkenyl, cyano, lower cyano alkyl, nitro, lower nitro alkyl, amido, lower amido alkyl, hydrazino, lower hydrazino alkyl, azido, lower azido alkyl, $(CH_2)_mNR_6R_7$, $(CH_2)_mOR_6$, $(CH_2)_mSR_6$, $(CH_2)_mCO_2R_6$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mC(O)R_8$, $(CH_2)_mOC(O)R_8$, $O(CH_2)_mNR_6R_7$, $OC(O)NR_6R_7$, $OC(O)(CH_2)_mCO_2R_6$ or $(CH_2)_n[N\approx X]$, $OC(O)[N\approx X]$, $(CH2)_mOC(O)[N\approx X]$ (in which $[N\approx X]$, in this invention, represents a heterocyclic group with 4 to 7 members with the nitrogen atom N, which is a member of the heterocyclic group, and X represents the remaining members, which are necessary to complete the heterocylic group, selected from the group constituted by O, S. CH_2, CH, N, NR_9 and COR_{10}), substituted (i.e. substituted between once and four times on the aryl group or the heterocycle) or non substituted aryl or lower aryl alkyl, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl or R_2 and R_3 or R_3 and R_4 form together a chain with 3 or 4 members in which the elements of the chain are selected from the group constituted by CH, CH_2, O, S, N or NR_9;

R_5 represents H, halo, lower halo alkyl, lower alkyl, lower alkoxy, lower alkoxy lower alkyl, lower alkylthio lower alkyl, cycloalkyl, lower cycloalkyl alkyl, cyano, alkyl cyano, lower alkyl sulphonyl lower alkyl, lower hydroxy alkyl, nitro, $(CH_2)_mC(O)R_8$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mNR_6R_7$, $(CH_2)_mN(CH_3)(CH_2)_nNR_6R_7$, $(CH_2)_mOC(O)R_8$, $(CH_2)_mOC(O)NR_6R_7$, $(CH_2)_mS(O)_qR_{11}$, $(CH_2)_mP(O)R_{12}R_{13}$ $(CH_2)_2P(S)R_{12}R_{13}$ or $(CH_2)_n[N\approx X]$, $OC(O)[N\approx X]$, $(CH_2)_mOC(O)[N\approx X]$, substituted (i.e. substituted between once and four times on the aryl or heteroaryl group) or non substituted aryl or

lower alkyl aryl, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl;

R_6 and R_7 represent, independently, H, a lower alkyl, lower hydroxy alkyl, lower alkyl amino lower alkyl, lower amino alkyl, cycloalkyl, lower cycloalkyl alkyl, lower alkenyl, lower alkoxy lower alkyl, lower halo alkyl, or substituted (i.e. substituted between once and four times on the aryl group) or non substituted aryl or lower aryl alkyl, in which the substituent is an lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl;

R_8 represents H, a lower alkyl, lower hydroxy alkyl, amino, lower alkyl amino, lower alkyl amino lower alkyl, lower amino alkyl, cycloalkyl, lower cycloalkyl alkyl, lower alkenyl, lower alkoxy, lower alkoxy lower alkyl, lower halo alkyl, or substituted (i.e. substituted between once and four times on the aryl group) or non substituted aryl or lower aryl alkyl, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl;

R_9 represents H, a lower alkyl, lower halo alkyl, aryl, or aryl substituted by one or more groups chosen from the following radicals: lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkyoxy lower alkyl;

R_{10} represents H, a lower alkyl, lower halo alkyl, lower alkoxy, aryl or aryl substituted (i.e. having one to four substituents on the aryl group) by one or more groups chosen from the following radicals: lower alkyl, lower halo alkyl, lower hydroxy alkyl or lower alkoxy lower alkyl;

R_{11} represents a lower alkyl, aryl, $(CH_2)_mOR_{14}$, $(CH_2)_mSR_{14}$, $(CH_2)_2NR_{14}R_{15}$ or $(CH_2)_m[N{\approx}X]$;

R_{12} and R_{13} represent, independently, a lower alkyl, aryl, lower alkoxy, aryloxy or amino;

R_{14} and R_{15} represent, independently, H, lower alkyl or aryl;

R_{16} represents H or OR_{21};

R_{17} represents OR_6 or NR_6R_7;

R_{18} and R_{19} represent, independently, H, halo, lower alkyl, lower alkoxy or hydroxy;

R_{20} represents H or halo;

R_{21} represents H, a lower alkyl, CHO or C(O) $(CH_2)_mCH_3$;

R_p represents H or an easily cleavable group preferably chosen from the groups corresponding to the formula -C(O)-A-$NR_{22}R_{23}$, in which A represents a linear or branched alkylene radical optionally substituted by a radical chosen from the free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino, mono or dialkylamino radicals, while R_{22} and R_{23}, independently, represent H, a lower alkyl, lower hydroxy alkyl, lower amino alkyl lower alkyl, lower amino alkyl, cycloalkyl, lower cycloalkyl alkyl, lower alkenyl, lower alkoxy lower alkyl, lower halo alkyl, or substituted (i.e., one to four times on the aryl group) or non substituted aryl or lower aryl alkyl, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl;

m is an integer comprised between 0 and 6;

n is 1 or 2; and

q represents an integer from 0 to 2; and [N≈X] represents a heterocyclic group with 4 to 7 members, X representing the chain necessary to complete said heterocyclic group and selected from the group constituted by O, S, CH_2, CH, N, NR_9 and COR_{10};

it being understood that when Rp is a hydrogen atom, R_3 and R_4 together form a chain with 3 or 4 members;

or a pharmaceutically acceptable salt of the latter.

As it is used here, the term lower with reference to the alkyl, alkylthio and alkoxy groups designates linear or branched saturated aliphatic hydrocarbon groups containing 1 to 6 carbons, such as for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methylthio, ethylthio, methoxy and ethoxy. With reference to the alkenyl or alkynyl groups, the term lower designates groups containing 2 to 6 carbon atoms and one or more double or triple bonds, such as for example, the vinyl, allyl, isopropenyl, pentenyl, hexanyl, ethynyl propenyl, propynyl and butynyl groups. The term cycloalkyl designates a ring with 3 to 7 carbons, such as for example, the cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups. The term aryl designates a mono- di- or tricyclic hydrocarbon compound with at least one aromatic ring, each ring containing a maximum of 7 members, such as for example, phenyl, naphthyl, anthracyl, biphenyl or indenyl. The term halo signifies chloro, bromo, iodo or fluoro. The radicals corresponding to the expressions lower halo alkyl, lower cyano alkyl, lower nitro alkyl, lower amido alkyl, lower hydrazino alkyl, lower azido alkyl, lower aryl alkyl, lower hydroxy alkyl, lower alkoxy lower alkyl, lower alkylthio lower alkyl, and lower alkyl

sulphonyl lower alkyl are substituted, respectively, by one to three halo, cyano, nitro, amido, hydrazino, azido, aryl, hydroxy, lower alkoxy, lower alkylthio or lower sulphonyl groups. The lower alkyl amino radical can contain one or two lower alkyl groups and represent, for example, $NHCH_3$, $NHCH_2CH_3$, $N(CH_3)_2$ or $N(CH_3)(CH_2CH_3)$. The term free, esterified, etherified or salified hydroxy refers to the OH, $OCOR_{26}$, OR_{27} groups and to the alcoholate salt.

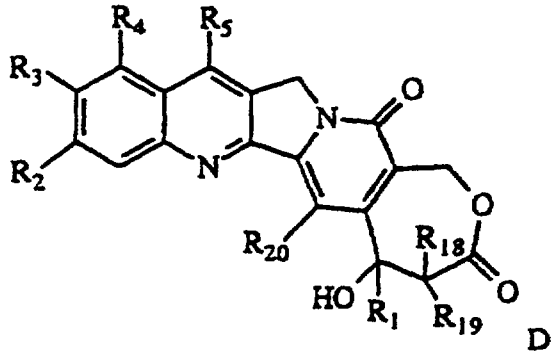
The compounds according to the present invention have two possible enantiomeric forms, i.e. under "R" and "S" configurations. The present invention includes the two enantiomeric forms and any combinations of these forms, including "RS" racemic mixtures. In an effort to simplify matters, when no specific configuration is indicated in the structural formulae, it should be understood that the two enantiomeric forms and their mixtures are represented.

As concerns the prodrug forms of the invention (those for which R_p is not a hydrogen atom), the products of general formula I are preferred.

Examples of substituted camptothecins used as starting products can be found in the American Patents Nos. 4 473 692, 4 604 463, 4 894 956, 5 162 532, 5 395 939, 5 315 007, 5 264 579, 5 258 516, 5 254 690, 5 212 317 and 5 341 745, the PCT Patent Applications Nos. US91/08028, US94/06451, US90/05172, US92/04611, US93/10987, US91/09598, EP94/03058 and EP95/00393 and the European Patent Application Nos. 325 247, 495 432, 321 122 and 540 099.

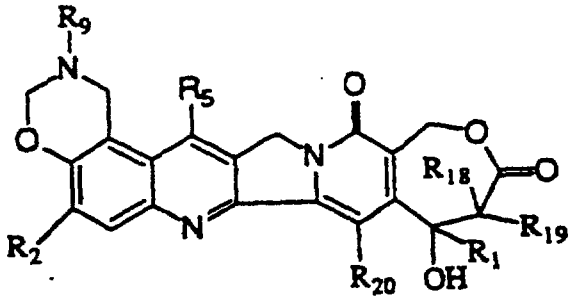
For the compounds comprising an oxazine ring:

- a β-hydroxylactonic compound of general formula D



D

in which R_3 is a hydroxyl radical, R_4 is H and R_1, R_2, R_5, R_{18}, R_{19} and R_{20} have the meaning indicated above is treated with a primary amine, under Mannich's conditions, in order to obtain a β-hydroxylactonic compound of general formula Ia

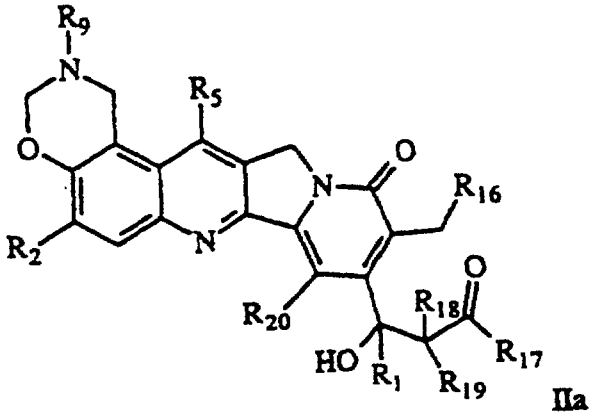


Ia

in which R_1, R_2, R_5, R_9, R_{18}, R_{19} and R_{20} have the meaning indicated above.

This process consists in heating the starting product in the presence of a primary amine such as benzylamine, of formaldehyde in an acid solvent such as acetic acid or propionic acid at a temperature of 30°C to 80°C for a period of 0.5 to 5 hours. Alternatively, a suspension of starting product in acetic acid with a tri-*N*-substituted hexahydrotriazine such as hexahydro-1,3,5-trimethyl triazine, 1,3,5-triethylhexahydro triazine or 1,3,5-tribenzyl hexahydrotriazine can be heated at a temperature of 30°C to 80°C for a period of 0.5 to 5 hours.

- the lactone of general formula Ia is opened optionally in a basic medium in order to produce after neutralization the compound of formula IIa



IIa

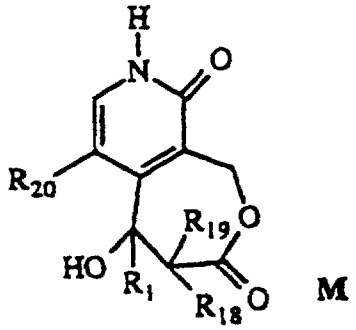
in which R_1, R_2, R_5, R_9, R_{17}, R_{18}, R_{19} and R_{20} have the meaning indicated above; R_{16} represents OR_{21} in which R_{21} represents H or a lower alkyl; and R_{17} represents OR_6 or NHR_6 and R_6 represents H, a lower alkyl, cycloalkyl, lower cycloalkyl alkyl, lower alkenyl, lower alkoxy lower alkyl, or aryl or lower aryl alkyl.

- the said compound of general formula D or Ia is optionally acylated, preferably with a derivative of the C(O)-A-N-$R_{22}R_{23}$ radical as defined above in order to produce the β-hydroxylactonic compound of general formula Ib, i.e. I with R_p different from H (prodrug form of the invention).

- in the same manner as with the lactone Ia, the lactone Ib can be opened in order to produce hydroxyacid IIb.

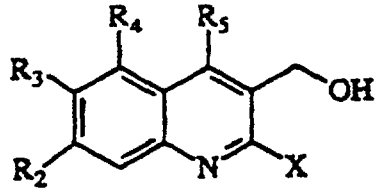
In the above process, the R_2, R_3, R_4 and R_5 groups can be protected if necessary according to standard protection methods (Greene, T., Protective Groups in Organic Synthesis 10-86 (John Wiley & Sons 1981)). If at least one of the R_{22} or R_{23} groups is H, or contains at least one function which is chemically incompatible with the acylation process such as, for example, a primary or secondary amine, it is then necessary to use a protective group which is resistent to acylation conditions. A protective group commonly used for the amines is *tert*-butyloxycarbonyl (BOC). The acylation reaction is then carried out as described above, then the protective group is cleaved, for example by treatment with trifluoroacetic acid in the case of BOC, in order to produce the compound of general formula (I) or (II). Use of protective groups is known to a person skilled in the art (for other examples, reference can be made to Greene, T., Protective Groups in Organic Synthesis, John Wiley & Sons, 1981).

The compounds of formula D are prepared as follows:
- a compound of general formula M



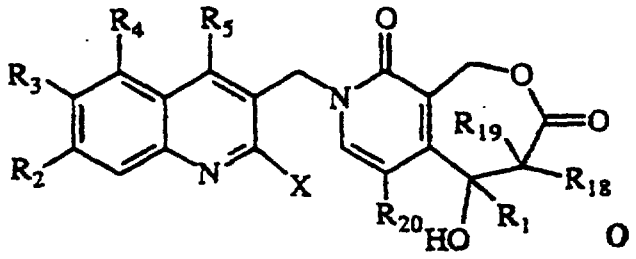
M

in which R_1, R_{18} and R_{19} have the meaning indicated above and R_{20} represents hydrogen or a halogen atom, is coupled with 2-halo-3-quinoline-methanol of general formula N



N

in which R_2, R_3, R_4 and R_5 have the meaning indicated above and X represents a halogen atom, in order to produce the compound of formula O



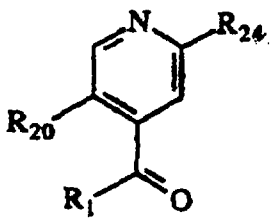
in which R_1, R_2, R_3, R_4, R_5, R_{18}, R_{19}, R_{20} and X have the meaning indicated above;

- then the compound of general formula O is cyclized in order to obtain the compound of general formula D as defined above.

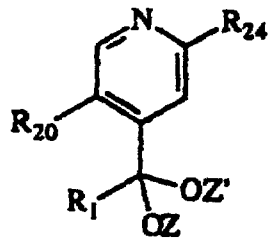
In the above process, the R_1, R_2, R_3 and R_4 groups can be protected if necessary according to standard protection methods (Greene. T., Protective Groups in Organic Synthesis 10-86 (John Wiley & Sons 1981)). The formation of compound O starting from the compounds of general formulae M and N is carried out with a treatment known to a person skilled in the art under the name Mitsunobu's reaction (refer to Mitsunobu, O. et al. *Synthesis*, p.1 (1981)). The hydroxyl function of compound N is displaced by a nucleophile such as compound M or a deprotonated derivative of the latter, by a treatment with a phosphine, for example triphenylphosphine, and an azodicarboxylate derivative, for example diethyl azodicarboxylate, in an aprotic solvent such as, for example, tetrahydrofuran or *N,N*-dimethylformamide. The cyclization of compound O is preferably carried out in the presence of a palladium catalyst (for example palladium diacetate) under basic conditions (provided for example by an alkaline acetate optionally combined with a phase transfer agent, such as, for example, tetrabutylammonium bromide), in an aprotic solvent such as acetonitrile or *N,N*-dimethylformamide, at a temperature comprised between 50°C and 120°C (R. Grigg et al., *Tetrahedron* 46, page 4003 (1990)).

The compounds of general formula M can be prepared according to a process characterized in that

- the carbonyl of a pyridine of general formula



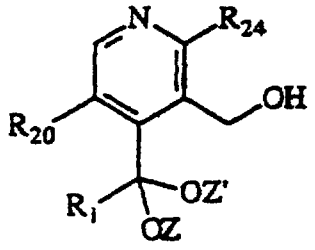
in which R_1 and R_{20} have the meaning indicated above and R_{24} represents a halogen atom or a lower alkoxy, is protected with an acetal function, in order to produce the compound of general formula F



F

in which R_1, R_{20} and R_{24} have the meaning indicated above and the Z and Z' groups represent, independently, a lower alkyl or form together a saturated hydrocarbon chain with 2 to 4 members:

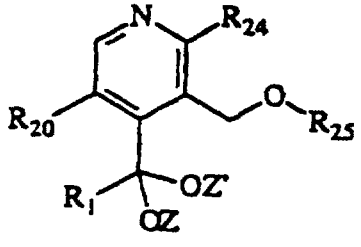
- a hydroxymethyl function is introduced into the compound of general formula F in order to obtain a compound of general formula G



G

in which R_1, R_{20}, R_{24}, Z and Z' have the meaning indicated above,

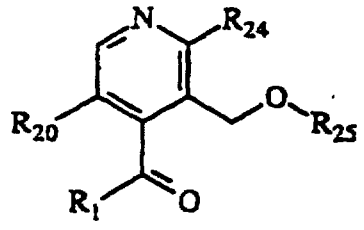
- then the alcohol function of the compound of general formula G is protected in order to produce a compound of general formula H



H

in which R_1, R_{20}, R_{24}, Z and Z' have the meaning indicated above and R_{25} represents a protective group of the alcohol function.

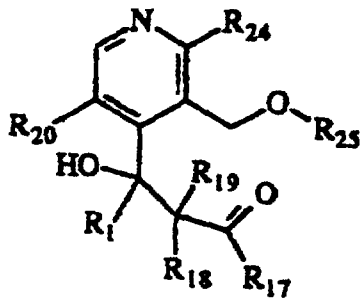
- the acetal of the compound of general formula H is deprotected in order to produce the compound of general formula I'



I'

in which R_1, R_{20}, R_{24} and R_{25} have the meaning indicated above,

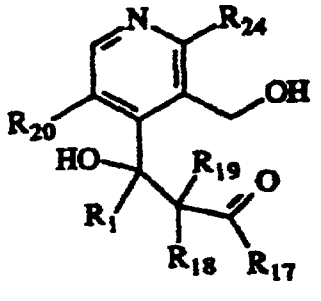
- the compound of formula I' is treated with a functionalized alkylating agent in order to produce a β-hydroxyester of general formula J



J

in which R_1, R_{20}, R_{24} and R_{25} have the meaning indicated above, R_{17}, R_{18} and R_{19} are as defined in general formula II,

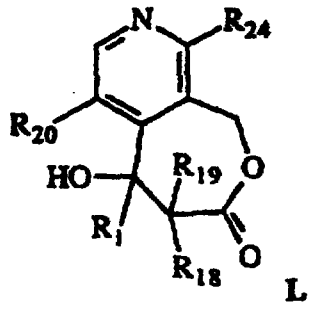
- the protective group R_{25} of the compound of general formula J is cleaved in order to produce a compound of general formula K,



K

in which R_1, R_{18}, R_{19}, R_{20} and R_{24} have the meaning indicated above, and R_{17} represents OR_6 or NHR_6 and R_6 represents H, a lower alkyl, cycloalkyl, lower cycloalkyl alkyl, lower alkenyl, lower alkoxy lower alkyl or aryl or lower aryl alkyl,

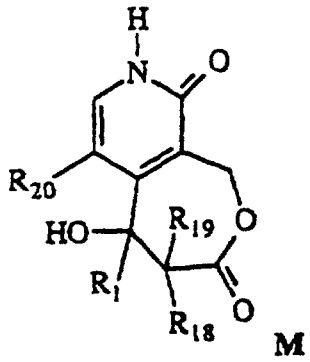
- the compound of general formula K is cyclized into the compound of general formula L



L

in which R_1, R_{18}, R_{19}, R_{20} and R_{24} have the meaning indicated above, and finally

- the R_{24} radical of compound L is converted into carbonyl in order to obtain the compound of general formula M



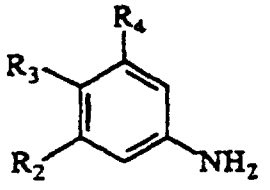
M

in which R_1, R_{18}, R_{19} and R_{20} have the meaning indicated above.

The carbonyl function of a 4-acyl-2-halo pyridine (obtained for example according to Lammattina J.L. *J. Heterocyclic Chem. 20,* p. 553 (1983)) is preferably protected by an acetal function, preferably a cyclic acetal, according to the standard conditions known to a person skilled in the art (Greene. T., Protective Groups in Organic Synthesis 10-86 (John Wiley & Sons 1981)). The intermediate thus obtained is treated with a sodium or potassium alcoholate in an aprotic solvent (for example acetonitrile), or the alcohol from which the alcoholate is derived, at a temperature comprised between 0°C and 100°C in order to produce the compound of general formula F. The latter can be lithiated in position 3 by treatment with an aryl- or alkyl-lithium (for example mesityl-lithium) in an ethereal solvent such as tetrahydrofuran at a temperature comprised between -100°C and 0°C. A formylating electrophile such as *N,N*-dimethylformamide is added to the lithiated intermediate thus obtained, and the aldehyde thus obtained is treated, after hydrolysis, with a reducing agent such as sodium borohydride in order to produce the compound of general formula G. The protection of the alcohol function of compound G is carried out according to the

standard conditions known to a person skilled in the art, in order to obtain a compound of general formula H. Examples of protective groups of the alcohol function include those which form ethers (i.e. methyl, methoxymethyl, tetrahydropyranyl, 2-methoxyethoxy methyl, benzyloxymethyl, t-butyl and benzyl (substituted or non substituted)), and esters (i.e. formate, acetate and isobutyrate). For other examples of protective groups of primary hydroxyl refer to Greene. T., Protective Groups in Organic Synthesis 10-86 (John Wiley & Sons 1981). The deprotection of the compound of general formula H in order to produce the compound of general formula I' is carried out under selective conditions maintaining the integrity of the R_{25} radical, for example, by treatment under acid conditions (for example by trifluoroacetic acid). The selective conditions for the protection and deprotection of functional groups are known to a person skilled in the art (Greene. T., Protective Groups in Organic Synthesis 10-86 (John Wiley & Sons 1981)). The treatment of compound I' with a functionalized alkylating agent in order to produce a β-hydroxy ester of general formula J can be carried out using a lithium enolate or a zinc derivative of a carboxylic ester in an anhydrous aprotic solvent, for example, tetrahydrofuran. The protective group R_{25} of the compound of general formula J is cleaved in order to produce a compound of general formula K under deprotection conditions known to a person skilled in the art. For example, when R_{25} is a benzyl group, an alcoholic solution of the compound of general formula J with a palladium catalyst added to it can be subjected to a hydrogen atmosphere under a pressure of 0.5 to 10 Bar. The cyclization of the compound of general formula K thus obtained can be carried out under acid conditions (for example by treatment with trifluoroacetic acid, or hydrochloric gas dissolved in an anhydrous solvent such as dichloromethane or dioxan) in order to produce a β-hydroxylactonic ring with seven members such as in the compound of general formula L. The compounds of general formula L can be converted into pyridones of general formula M, for example, by treatment with warm hydrochloric acid, or by treatment with trimethylsilyl iodide.

The 2-halo-3-quinoline methanols of general formula N can be obtained starting from the acetanilides of general formula P



P

in which R_2, R_3 and R_4 have the meaning indicated in the general formulae of compounds I and II. In the processes below, the R_2, R_3 and R_4 groups can be protected if necessary according to standard protection methods (Greene. T., Protective Groups in Organic Synthesis 10-86 (John Wiley & Sons 1981)).

The compounds of formula N can therefore be obtained according to the following process: the said anilines of formula P are *N*-acetylated by treatment with an acetylating agent such as, for example, acetic anhydride. The acetanilides thus obtained are treated at a temperature comprised between 50°C and 100°C, preferably 75°C, with a reagent known to a person skilled in the art under the name Vilsmeyer's reagent (obtained by the action of phosphoryl oxychloride on *N,N*-dimethylformamide at a temperature comprised between 0°C and 10°C) in order to produce the corresponding 2-chloro-3-quinolinecarbaldehyde (for example, refer to Meth-Cohn et al. *J. Chem. Soc., Perkin Trans. I* p.1520 (1981); Meth-Cohn et al. *J. Chem. Soc., Perkin Trans. I* p.2509 (1981); and Nakasimhan et al. *J. Am. Chem. Soc., 112* p.4431 (1990)). The chlorine in position 2 of the 2-chloro-3-quinolinecarbaldehydes can be substituted by iodine or bromine by heating the product in an inert solvent such as acetonitrile in the presence of an iodine or bromine salt (for example sodium iodide or tetrabutylammonium bromide). A trace of acid such as concentrated hydrochloric acid may be necessary to catalyze this conversion. The 2-halo-3-quinolinecarbaldehydes are easily reduced to the corresponding 2-halo-3-quinolinemethanols of general formula N, under standard conditions known to a person skilled in the art such as treatment in an alcoholic solvent (for example methanol) with sodium borohydride at a temperature comprised between 0°C and 40°C.

The compounds of formula N can also be obtained according to the following process: the anilines of general formula P as defined above are acylated by reaction with a nitrile (such as chloroacetonitrile or propionitrile) in the presence of boron trichloride and another Lewis acid such as aluminium trichloride, titanium tetrachloride or diethylaluminium chloride in an aprotic solvent or a mixture of aprotic solvents, followed by hydrolysis (*cf.* Sugasawa T. et al. *J. Am. Chem. Soc. 100* p.4842 (1978)). The intermediate thus obtained is then treated with ethylmalonyl chloride in an aprotic solvent such as acetonitrile in the presence of a base such as triethylamine, then treated with an alkaline alcohol, for example, sodium methylate in methanol, in order to produce an ethyl 2-hydroxy-3-quinolinecarboxylate substituted in position 4. This is converted into ethyl 2-chloro-3-quinolinecarboxylate by treatment with phosphoryl oxychloride. When position 4 of the quinoline carries a chloromethyl group, a nucleophile substitution can be carried out by treatment with a secondary amine such

as, for example, dimethylamine, N-methylpiperazine, morpholine or piperidine. The ethyl 2-chloro-3-quinolinecarboxylate is then reduced with diisobutylaluminium hydride in an aprotic solvent such as dichloromethane in order to produce the 2-chloro-3-quinolinemethanol of general formula N. Analogues of intermediate compounds (N) have been described in the literature and in particular in the PCT Application 95/05427.

Certain compounds of the invention can be prepared in the form of pharmaceutically acceptable salts according to the usual methods. Acceptable salts include, by way of example and in a non-limitative fashion, the addition salts with inorganic acids such as hydrochloride, sulphate, phosphate, diphosphate, hydrobromide, and nitrate or with organic acids such as acetate, maleate, fumarate, tartrate, succinate, citrate, lactate, methane sulphonate, p-toluenesulphonate, pamoate, salicylate, oxalate and stearate. The salts formed from bases such as sodium or potassium hydroxide also form part of the field of application of the present invention, when they are useable. For other examples of pharmaceutically acceptable salts one can refer to "Pharmaceutical Salts", J. Pharm. Sci. 66:1 (1977).

The compounds of the present invention possess useful pharmacological properties. Thus the compounds of the present invention have an inhibitory effect on topoisomerase I and/or II and an anti-tumoral activity. The state of the art suggests that the compounds according to the invention have an anti-parasitic and/or anti-viral activity. The compounds according to the present invention can also be used in different therapeutic applications.

There follows in the experimental section below an illustration of the pharmacological properties of the compounds of the invention.

The compounds can inhibit topoisomerase, for example of type I and/or II, in a patient, for example a mammal such as man, by administration to this patient of a therapeutically effective quantity of a compound of formula (I) or (II).

The compounds according to the invention also have an anti-tumoral activity. They can be used for the treatment of tumors, for example tumors expressing a topoisomerase, in a patient by administration to the latter of a therapeutically effective quantity of a compound of formula (I) or (II). Examples of tumors or cancers include cancers of the oesophagus, the stomach, the intestines, the rectum, the oral cavity, the pharynx, the larynx, the lung, the colon, the breast, the cervix uteri, the corpus

endometrium, the ovaries, the prostate, the testicles, the bladder, the kidneys, the liver, the pancreas, the bone, the connective tissues, the skin, the eyes, the brain and the central nervous system, as well as cancer of the thyroid, leukemia, Hodgkin's disease, lymphomas other than those related to Hodgkin, multiple myelomas and others.

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

These properties make the products of formula (I) or (II) suitable for pharmaceutical use. A subject of the present Application is also, as medicaments, the products of formula (I) or (II) as defined above as well as the addition salts with pharmaceutically acceptable mineral or organic acids of said products of formula (I) or (II), as well as the pharmaceutical compositions containing at least one of the medicaments as defined above as active ingredient.

Therefore the invention relates to pharmaceutical compositions containing a compound according to the invention or an addition salt with a pharmaceutically acceptable acid of it, in combination with a pharmaceutically acceptable support according to the chosen administration method (for example oral, intravenous, intraperitoneal, intramuscular, trans-dermic or sub-cutaneous). The pharmaceutical composition (for example therapeutic) can be in the form of a solid, liquid, liposome or lipidic micella.

The pharmaceutical composition can be in solid form, for example, powders, pills, granules, tablets, liposomes, gelatin capsules or suppositories. The pill, tablet or gelatin capsule can be covered in a substance which is capable of protecting the composition from the action of gastric acid or enzymes in the stomach of the subject for a sufficient period of time to allow this composition to pass in a non-digested form into the small intestine of the latter. The compound can also be administered locally, for example, at the same location as the tumor. The compound can also be administered according to a sustained release process (for example a sustained release composition or an infusion pump). The appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, magnesium carbonate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine and wax. The pharmaceutical compositions containing a compound according to the invention can also be presented in liquid form such as, for example, solutions, emulsions, suspensions or a sustained release formulation. The

appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols such as polyethylene glycol, similarly their mixtures, in varied proportions, in water.

A subject of the invention is also the use of the products of formula (I) or (II) as defined above for the preparation of medicaments intended to inhibit topoisomerase and more particularly topoisomerase of type I or type II, medicaments intended for the treatment of tumors, medicaments intended for the treatment of parasitic infections, as well as medicaments intended for the treatment of viral diseases.

The dose of a compound according to the present invention envisaged for the treatment of the diseases or disorders mentioned above, varies according to the administration method, the age and body weight of the subject as well as the state of the latter and it will be decided definitively by the attending doctor or vet. Such a quantity determined by the attending doctor or vet is called here "effective therapeutic quantity".

Unless defined in another manner, all the technical and scientific terms used here have the same meaning as that commonly understood by an ordinary specialist in the field to which the invention belongs. Similarly, all publications, Patent Applications, all Patents and all other references mentioned here are incorporated by way of reference.

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

EXPERIMENTAL PART

Preparation 1 : 5-ethyl-4,5-dihydro-1*H*-oxepino [3',4':6,7]- indolizine [1,2-b] quinoline -3,15 (4*H*,13*H*)-dione

1.a. 4-ethyl-3,4-dihydroxy-1H-pyrano [3',4':6,7] indolizino [1,2-b] quinoline -14 (4*H*,12*H*)-one

Sodium borohydride (14 g, 370 mmol) is added by portions to a suspension of (S)-(+)-camptothecin (14 g, 40 mmol, which can be obtained from different commercial sources such as Aldrich Chemical Co. (Milwaukee, WI)), in methanol (750 ml) and the resultant mixture is heated gently to 55°C in order to obtain a limpid solution which is then agitated for 16 hours at ambient temperature. The solvent is then evaporated off under reduced pressure, the residue is taken up in water (250 ml), neutralized by the

addition of acetic acid (21 ml) and left at rest for 2 hours at 4°C. The resultant suspension is filtered and washed successively with cold water, acetone and diethyl ether, which allows the sought product to be obtained, after drying under reduced pressure, in the form of a white solid m.p. 280°C.

1.b. 8-formyloxymethyl-7-propionylindolizino [1,2-b] quinoline-9 (11*H*)-one

A solution of sodium metaperiodate (14 g, 65 mmol) in water (140 ml) is added dropwise to a suspension of 4-ethyl-3,4-dihydroxy-1H-pyrano [3',4':6,7] indolizine [1,2-b] quinoline -14 (4*H*,12*H*)-one (13.4 g, 38 mmol) in glacial acetic acid (720 ml) and the resultant solution is agitated for one hour at ambient temperature. The reaction mixture is then poured into an ice/water mixture (650 ml) and the resultant suspension is then agitated for half an hour then filtered and washed successively with water, isopropyl alcohol and diethyl ether, which allows the sought product (11.5 g) to be obtained, after drying under reduced pressure, in the form of a pale yellow solid m.p. > 200°C (d).

1.c. *tert*-butyl β-ethyl-β-hydroxy-β-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate

A suspension of zinc (6.5 g, 100 mmol) stirred with a magnetic stirrer in anhydrous diethyl ether (50 ml) under argon, is activated by the dropwise addition of chlorotrimethylsilane (0.75 ml, 5.7 mmol). Stirring is continued for 15 minutes at ambient temperature then the reaction medium is heated to reflux. The heating bath is then removed and tert-butyl bromoacetate (15 ml, 100 mmol) is added dropwise at a rate which ensures reflux is maintained. The external heating is put back and heating is continued for one hour. The resultant ethereal solution of Reformatsky's reagent is left to cool down to ambient temperature then transferred using a cannula into a suspension of 8-formyloxymethyl-7-propionylindolizino [1,2-*b*] quinoline-9 (11*H*)-one (1.6 g, 4.7 mmol) in anhydrous tetrhydrofuran (40 ml) under argon. The reaction mixture is agitated under reflux for one hour, then left to cool down to ambient temperature and the reaction is stopped by the addition of saturated ammonium chloride (100 ml) and extraction is carried out with chloroform (3 x 100 ml). The combined chloroformic extracts are dried over sodium sulphate, evaporated and the residue is purified by chromatography on a silica gel column (1-2% $MeOH/CH_2Cl_2$), which allows 0.64 g of sought product (31%) to be obtained in the form of a pale yellow solid, m.p. 146-149°C.

NMR-^{1}H ($CDCl_3$): 0.93 (t, 3H); 1.37 (s, 9H); 1.99 (m, 2H); 2.97 (dd, 2H); 3.5 (se, 1H); 5.10 (s, 2H); 5.24 (s, 2H); 7.40 (s,1H); 7.59 (t, 1H); 7.83 (t, 1H); 7.90 (d, 1H); 8.20 (d, 1H); 8.34 (s, 1H).

NMR-^{13}C ($CDCl_3$): 8.18; 27.90; 34.59; 45.34; 49.91; 58.55; 77.39; 82.42; 100.52; 127.67; 127.97; 128.10; 128.64; 129.44; 129.79; 130.42; 130.99; 142.86; 148.69; 152.75; 155.16; 162.38; 172.24.
IR (KBr): 764; 1016; 1157; 1580; 1651; 1726.

1.d. 5-ethyl-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7]-indolizine [1,2-*b*] quinoline-3,15 (4*H*, 13*H*)-dione

tert-butyl β-ethyl-β-hydroxy-β-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate (1.45 g, 3.32 mmol) is dissolved in anhydrous dichloromethane (25 ml) and treated with a saturated solution of hydrogen chloride in dichloromethane (100 ml). The resultant mixture is maintained at -20°C for 16 hours. The precipitate is filtered, washed with methanol and dried under reduced pressure, which allows 662 mg (55%) of sought product to be obtained in the form of a yellow solid, m.p. > 300°C.
NMR-^{1}H (DMSO): 0.90 (t, 3H); 1.20 (q, 2H); 3.27 (dd, 2H); 5.29 (s, 2H); 5.49 (dd, 2H); 7.42 (s, 1H); 7.73 (t, 1H); 7.90 (t, 1H); 8.16 (t, 2H); 8.71 (s, 1H).
NMR-^{13}C (DMSO): 8.45; 36.48; 42.54; 50.68; 61.44; 73.34; 99.78; 122.71; 127.83; 128.15; 128.75; 129.08; 130.07; 130.61; 131.81; 144.66; 148.04; 152.80; 155.91; 159.26; 172.08.
IR (KBr): 761; 1127; 1204; 1285; 1580; 1653; 1757.

<u>Preparation 2</u> : resolution of 5-ethyl-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7]-indolizine [1,2-*b*] quinoline-3,15 (4*H*, 13*H*)-dione

A mixture of β-ethyl-β-hydroxy-(8-hydroxymethylindolizino-[1,2-*b*] quinoline-9-(11*H*-one-7-yl)-propionic acid (19.5 g, 51 mmol) and L-(-)-α-methylbenzylamine (12.12 g, 100 mmol) in absolute ethanol (1 l) is heated to boiling, followed by filtering while warm and leaving at rest for 68 hours. The precipitate is filtered and washed with ethanol and ether to produce 9.8 g of a white solid. Analysis by high pressure liquid chromatography on the chiral stationary phase ("Chiral HPLC" on Chiral-AGP column (Chromtech, Stockholm, Sweden) 100 x 4 mm, eluant 2% acetonitrile in 10 mM phosphate buffer at pH 6.9, peaks eluting at 4.5 and 7.5 min) reveals two peaks integrating respectively 24% and 76% of the total area of the two peaks. The solid is taken up in 93% ethanol (350 ml) under reflux, then left at rest for 48 hours. The precipitate is filtered out then washed with ethanol and ether in order to obtain 4.8 g of a white solid which produces two peaks integrating respectively 9% and 91% of the total area of the two peaks using chiral HPLC. The solid is taken up in 50% ethanol (48 ml) under reflux then left at rest for 48 hours. The precipitate is filtered out then washed with ethanol and ether in order to produce 2.7 g of a white solid which

produces two peaks integrating respectively 3% and 97% of the total area of the two peaks using chiral HPLC. The solid is taken up in 50% ethanol (22 ml) under reflux then left at rest for 48 hours. The precipitate is filtered out then washed with ethanol and ether in order to produce 1.6 g of a white solid which produces two peaks integrating respectively 1% and 99% of the total area of the two peaks using chiral LC. The resultant salt, diastereoisomerically enriched, taken up in distilled water (20 ml), is treated with acetic acid (0.35 ml, 6.4 mmol) for 15 minutes. The precipitate obtained is filtered out, washed with water, with acetone and with ether, then dried under vacuum at 80°C in order to obtain 1.1 g of a white solid. The latter is taken up in absolute ethanol (55 ml) with concentrated hydrochloric acid (11.5 N, 11 ml) added to it in order to obtain a yellow solution which is maintained under agitation at ambient temperature for 68 hours. The precipitate thus obtained is filtered out and washed with water, with ethanol and with ether, then dried under vacuum at 80°C in order to obtain 770 mg of 5-ethyl-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7]-indolizine [1,2-*b*] quinoline-3,15 (4*H*, 13*H*)-dione which is enantiomerically enriched. Analysis by chiral HPLC (Chiral-AGP column, eluted with a 2 to 5% gradient of acetonitrile in 10 mM phosphate bufffer at pH 6.9, peaks eluting at 15 and 20 minutes) reveals an enantiomeric excess of 98%. The procedure described above is carried out again replacing the L-(-)-α-methylbenzylamine with D-(+)- α-methylbenzylamine. In this way the other enantiomer of 5-ethyl-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7]-indolizine [1,2-*b*] quinoline-3,15 (4*H*, 13*H*)-dione is obtained.

Preparation 3 : 5,12-diethyl-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7]-indolizino [1,2-*b*] quinoline-3,15 (4*H*,13*H*)-dione

This compound is prepared in a similar manner to Example 1, except that in stage 1.a., 7-ethyl camptothecin (Sawada et al., Chem. Pharm. Bull. 39:2574 (1991)) is used instead of camptothecin. The sought compound is obtained in the form of a vivid yellow solid, m.p. > 270°C.

NMR-^{1}H (DMSO): 0.92 (t, 3H); 1.39 (t, 3H); 1.93 (q, 2H); 3.08 (d, 2H); 3.25 (q, 2H); 3.51 (d, 2H); 5.32 (s, 2H); 5.52 (dd, 2H); 7.42 (s, 1H); 7.76 (t, 1H); 7.89 (t, 1H); 8.18 (d, 1H); 8.32 (d, 1H).

NMR-^{13}C (DMSO): 8.46; 14.15; 22.42; 36.50; 42.54; 49.95; 61.45; 73.35; 99.68; 122.61; 124.27; 126.76; 127.70; 128.27; 129.92; 130.18; 145.17; 145.82; 148.57; 152.15; 155.89; 159.; 172.08.

Preparation 4 : 5-ethyl-9,10-difluoro-4,5-dihydro-5-hydroxy-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione

4.a. 2-ethyl-2-(2-methoxy-4-pyridyl)-1,3-dioxolane

The water is distilled in an azeotropic manner (overnight) with a Dean Stark apparatus from a mixture of 2-chloro-4-propionylpyridine (10 g, 59 mmol) obtained as in Lamattina, J.L. *J.Heterocyclic Chem. 20*, p. 553 (1983), ethylene glycol (20 ml) and *p*-toluenesulphonic acid (250 mg) in toluene (150 ml). The solvent is then eliminated under reduced pressure, the acid is neutralized with saturated aqueous sodium bicarbonate (100 ml) and the product is extracted with ether. The combined ethereal extracts are washed with brine, dried over sodium sulphate and evaporated, which produces 13.3 g (96%) of crude product protected by the carbonyl group which is heated to reflux with 3 equivalents of sodium methoxide in acetonitrile until the end of the reaction (checked by thin layer chromatography: SiO_2, *tert*-butyl methyl oxide /hexane (TBMO/HX) 50/50). The acetonitrile solution is then filtered and evaporated. The residue is taken up in ether, washed with water and with brine, dried over sodium sulphate and evaporated, which produces a brown oil which is distilled (70-75°C, 0.04 mbar); 10.7 g (overall yield 81%) of product (F) is collected in the form of a limpid oil.

4.b. 2-ethyl-2-(3-hydroxymethyl-2-methoxy-4-pyridyl)-1,3-dioxolane

tert-butyllithium (1.7 M in pentane, 100 ml, 170 mmol) is added dropwise using a cannula to a solution of bromomesitylene (13 ml, 85 mmol) in anhydrous tetrahydrofuran (300 ml) at -78°C and under argon. The resultant white precipitate is agitated at -78°C for one hour then 2-ethyl-2-(2-methoxy-4-pyridyl)-1,3-dioxolane (10 g, 44.8 mmol) is added and the reaction mixture is agitated for 15 minutes at -78°C, for one hour at 0°C and for one hour at ambient temperature. After again cooling down to -78°C, anhydrous N,N-dimethylformamide (100 mmol) is added and the reaction mixture is left to heat up to ambient temperature then agitated for 16 hours, after which analysis by thin layer chromatography (SiO_2, TBMO/HX: 50/50) reveals the complete consumption of the starting product. The reaction is stopped with saturated ammonium chloride and the reaction mixture is extracted with diethyl ether (200 ml, 50 ml, 50 ml). The combined extracts are dried over sodium sulphate and evaporated, which produces a yellow oil which is purified by column chromatography (SiO_2, TBMO/HX: 0/100 to 5/95 to elute the mestylene derivatives then 20/80 to 50/50 to elute the product) in order to obtain the intermediate aldehyde (7 g). The aldehyde is dissolved in methanol (100 ml) and treated with sodium borohydride (5 g, 132 mmol) and the resultant mixture is agitated until complete consumption of the

intermediate aldehyde (approximately 1 hour) with analytical control by thin layer chromatography. The solvent is then evaporated off, the residue is taken up in ether, washed with water and with brine, dried and the solvent is evaporated off. Column chromatography (SiO_2, TBMO/HX: 10/90 to 50/50) of the residue produces 7 g (overall yield 62%) of product (G) in the form of a yellow oil.

4.c. 2-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-2-ethyl-1,3-dioxolane

A solution of 2-ethyl-2-(3-hydroxymethyl-2-methoxy-4-pyridyl)-1,3-dioxolane (7 g, 30 mmol) and benzyl chloride (5 ml, 45 mmol) in anhydrous tetrahydrofuran (50 ml) is added dropwise to a suspension of sodium hydride (80% in mineral oil, 1.85 g, 61 mmol) in anhydrous tetrahydrofuran (100 ml) and the reaction mixture is maintained under reflux for 16 hours. The reaction mixture is then left to cool down to ambient temperature, the reaction is stopped with water (50 ml) and the reaction mixture is concentrated under reduced pressure. The residue is dissolved in diethyl ether (150 ml) and washed with water and with brine, dried and evaporated. Purification by column chromatography (SiO_2, TBMO/HX: 5/95 to 20/80) produced the product protected by the benzyl (H), 9 g, (87%) in the form of a limpid oil.

4.d. 1-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-propane-1-one

2-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-2-ethyl-1,3-dioxolane (9 g, 27 mmol) is treated with trifluoroacetic acid (10 ml) and water (5 ml) at a bath temperature of 120°C for 3 hours. The reaction mixture is concentrated under reduced pressure and the residual traces of acids are neutralized by the addition of saturated aqueous sodium bicarbonate. Extraction is carried out with ether followed by column chromatography (SiO_2, TBMO/HX: 10/90) produces 5.5 g (70%) of product (I).

4.e. *tert*-butyl β-ethyl-β-hydroxy-β-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-propionate

tert-butyl bromoacetate (13 ml, 80 mmol) is added dropwise to a zinc suspension (5.3 g, 80 mmol activated with 6*N* HCl over 10 seconds, then washed successively with water until a neutral pH is achieved, with acetone and with diethyl ether) in anhydrous tetrahydrofuran (60 ml) under reflux. The reaction medium is maintained under reflux for another 10 minutes after the addition is terminated. Then, a solution of 1-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-propane-1-one (5.8 g, 20 mmol) in anhydrous tetrahydrofuran (20 ml) is added and the reaction mixture is agitated under reflux for another hour. The reaction is stopped at 0°C with saturated aqueous ammonium chloride (100 ml) and the reaction mixture is extracted with diethyl ether. The

combined extracts are dried over sodium sulphate and evaporated, which produces a yellow oil which is purified by column chromatography (SiO_2, TBMO/HX: 5/95 to 10/90) in order to obtain the *tert*-butyl ester (J) (7 g, 95%) in the form of a limpid oil.

4.f. *tert*-butyl β-ethyl-β-hydroxy-β-(3-hydroxymethyl-2-methoxy-4-pyridyl)-propionate

tert-butyl β-ethyl-β-hydroxy-β-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-propionate (1 g, 2.5 mmol) is subjected to hydrogenolysis at atmospheric pressure and at ambient temperature using 5% palladium on carbon as catalyst (50 mg) and absolute ethanol as solvent (10 ml). Once the reaction has terminated (6 hours), the catalyst is separated by filtration and the solvent is evaporated off, which leaves 0.7 g (90%) of product (K) of a sufficient purity for a subsequent synthetic use.

4.g. 5-ethyl-1,5-dihydro-5-hydroxy-9-methoxy-oxepino[3,4-c] pyridine-3(4*H*)-one

tert-butyl β-ethyl-β-hydroxy-β-(3-hydroxymethyl-2-methoxy-4-pyridyl)-propionate (8.8 g, 28 mmol) is treated with trifluoroacetic acid (30 ml) for 3 hours at ambient temperature. The volatile components are evaporated off and the residue is purified by column chromatography (SiO_2, CH_2Cl_2/MeOH: 100/0 to 98/2), which produces a limpid oil which, after treatment with toluene, produces 5.9 g of product (L) (89%) in the form of white crystals, m.p. 97-98°C.

4.h. 5-ethyl-1,5-dihydro-5-hydroxy-oxepino[3,4-c] pyridine-3,9(4*H*,8*H*)-dione

5-ethyl-1,5-dihydro-5-hydroxy-9-methoxy-oxepino[3,4-c] pyridine-3(4*H*)-one (0.5 g, 2.1 mmol) is heated under reflux for 9 hours in 1*N* hydrochloric acid (20 ml). The reaction mixture is concentrated under reduced pressure and the residue is again dried by the addition and evaporation of toluene twice, then left overnight under reduced pressure in the presence of phosphorus pentoxide. The resultant oil is dissolved in anhydrous acetonitrile (5 ml) and agitated under argon for 24 hours. The precipitate is filtered out and dried, which produces 0.23 g (49%) of a white solid (M), m.p. 118-119°C.

4.i. 2-chloro-6,7-difluoro-3-quinoline-methanol

The procedure described by Meth-Cohn and collaborators, J. Chem. Soc. Perkin Trans. I, p. 1520 (1981); Meth-Cohn, J. Chem. Soc. Perkin Trans. I, p. 2509 (1981) is used. 3,4-difluoroacetanilide (38 g, 22 mmol) is added to the Vilsmeyer reagent obtained by the dropwise addition of phosphoryl oxychloride (103 ml, 1.1 mol) to

anhydrous dimethylformamide (34 ml, 44 mmol), cooled down with a water/ice bath and agitated for 0.5 hours under an argon atmosphere. The resultant mixture is heated at 70°C for 16 hours. After cooling down to ambient temperature, the reaction mixture is added to a mixture of ice and water (400 ml) which is maintained under agitation for 2 hours, then filtered and washed successively with water, with ethanol and with ether in order to produce 9 g of 2-chloro-6,7-difluoroquinoline-3-carbaldehyde in the form of a yellow solid, m.p. 222-224°C. This intermediate is treated with sodium borohydride (2 g, 52 mmol) in methanol (400 ml) at ambient temperature for 0.5 hours then the excess reagent is destroyed by the addition of acetic acid (2 ml). The solvent is eliminated under reduced pressure, the residue is put into solution in ethyl acetate and washed successively with dilute sodium bicarbonate, with water and with a saturated aqueous solution of sodium chloride. The organic phase is dried over sodium sulphate, filtered and concentrated. The resultant solid is recrystallized from 1,2-dichloroethane in order to produce 8 g of 2-chloro-6,7-difluoro-3-quinoline-methanol in the form of a beige solid.

4.j. 5-ethyl-8-(2-chloro-6,7-difluoro-3-quinolinemethyl)-1,5-dihydro-5-hydroxy-oxepino[3,4-c] pyridine-3,9(4*H*,8*H*)-dione

Diethyl azodicarboxylate (570 µl, 3.6 mmol) is added dropwise over 5 minutes to a solution of 5-ethyl-1,5-dihydro-5-hydroxy-oxepino[3,4-c] pyridine-3,9(4*H*,8*H*)-dione (400 mg, 1.79 mmol), the compound obtained in the preceding stage 4.i. (770 mg, 2.23 mmol) and triphenylphosphine (934 mg, 3.58 mmol) in anhydrous N,N-dimethylformamide (45 ml) and the resultant mixture is agitated under argon at ambient temperature for 16 hours. The reaction mixture is then concentrated under reduced pressure and the residue is dissolved in ether (100 ml). The resultant solution is washed with brine (4 x 50 ml), dried over sodium sulphate and evaporated. The residue is purified by column chromatography (SiO_2, CH_2Cl_2/MeOH: 99/1 to 98/2), which produces 650 mg (66%) of product (O) in the form of a white solid, m.p. 165-167°C.

4.k. 5-ethyl-9,10-difluoro-4,5-dihydro-5-hydroxy-1*H*-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15 (4*H*,13*H*)-dione

5-ethyl-8-(2-chloro-6,7-difluoro-3-quinolinemethyl)-1,5-dihydro-5-hydroxy-oxepino [3,4-c] pyridine-3,9(4*H*,8*H*)-dione (600 mg, 1.1 mmol), tetrabutyl-ammonium bromide (352 mg, 1.1 mmol), sodium acetate (359 mg, 4.4 mmol) and palladium II acetate (98 mg, 0.43 mmol) are dissolved in anhydrous acetonitrile (40 ml) and heated at 90°C under argon for 16 hours. After cooling down to ambient temperature, a white precipitate is separated from the reddish solution. This precipitate is filtered out and

dried under reduced pressure. The crude product is suspended in water, filtered and dried under reduced pressure over phosphorus pentoxide which produces 250 mg of sought compound in the form of a beige solid, m.p. > 250°C.

NMR-^{1}H (DMSO): 0.91 (t, 3H); 1.87 (m, 2H); 3.08 (d, 1H); 3.51 (d, 1H); 4.45 (s, 4H); 5.19 (s, 2H); 5.47 (dd, 2H); 6.02 (se, 1H); 7.33 (s, 1H); 7.54 (s,1H); 7.55 (s, 1H); 8.43 (s, 1H).

NMR-^{13}C (DMSO): 8.43; 36.47; 42.54; 50.52; 61.43; 64.43 (2C); 73.31; 99.07; 112.27; 113.14; 122.00; 124.24; 128.18; 129.74; 144.59; 145.01; 145.33; 147.63; 150.88; 155.88; 159.23; 172.07.

Preparation 5 : 5-ethyl-4,5-dihydro-5,10-dihydroxy-1*H*-oxepino [3',4':6,7]indolizino[1,2-b]quinoline-3,15 (4*H*,13*H*)-dione

10-benzyloxy-5-ethyl-4,5-dihydro-5-hydroxy-1H-oxepino[3',4':6,7]-indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione (370 mg, 0.79 mmol) is treated with hydrogen at atmospheric pressure and at ambient temperature using 10% palladium on carbon as catalyst (60 mg) and trifluoroacetic acid as solvent (15 ml). Once the reaction is terminated (16 hours), dichloromethane (50 ml) and methanol (50 ml) are added to the reaction mixture, the catalyst is filtered out and the volatile components are evaporated off under reduced pressure, which allows the crude sought product to be obtained containing traces of trifluoroacetic acid. These traces are eliminated by co-distillation with 1,4-dioxan. The product is obtained in the form of an orange solid, m.p. 150°C (d), of a sufficient purity for a subsequent synthetic use.

NMR-^{1}H (DMSO): 0.89 (t, 3H); 1.85 (q, 2H); 3.02 (d, 1H); 3.45 (d, 1H); 5.19 (s, 2H); 5.37 (d, 1H); 5.50 (d, 1H); 5.98 (se, 1H); 7.26 (s 1H); 7.31 (s, 1H); 7.40 (d, 1H); 8.00 (d, 1H); 8.42 (s, 1H); 10.32 (s, 1H).

NMR-^{13}C (DMSO): 8.47; 36.50; 42.61; 50.57; 61.46; 73.35; 98.84; 109.02; 121.83; 123.18; 129.50; 129.85; 130.12; 130.80; 143.39; 145.10; 149.69; 155.97; 156.82; 159.30; 172.11.

Preparation 6 : 5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methoxy-1*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

This compound is obtained from 3-fluoro-4-methoxyaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. Yellow solid, m.p. > 250°C.

NMR-^{1}H (DMSO): 0.89 (t, 3H); 1.85 (q, 2H); 3.08 (d, 1H); 3.49 (d, 1H); 4.00 (s, 3H); 5.25 (s, 2H); 5.39 (d, 1H); 5.51 (d,1H); 6.00 (s, 1H); 7.32 (s, 1H); 7.72 (d, 1H); 7.91 (d, 1H); 8.58 (s, 1H).

NMR-^{13}C (DMSO): 8.43; 36.48; 42.51; 50.68; 56.60; 61.42; 73.29; 99.25; 108.68; 113.52; 122.23; 126.33; 129.99; 130.30; 143.79; 144.70; 148.42; 151.18; 153.19; 155.81; 159.20; 172.06.
IR (KBr): 1259; 1503; 1602; 1737.

Preparation 7 : 9-chloro-5-ethyl-4,5-dihydro-5-hydroxy-10-methyl-1*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

This compound is obtained from 3-chloro-4-methoxyaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. Yellow solid, m.p. > 250°C.
NMR-^{1}H (DMSO): 0.85 (t, 3H); 1.85 (q, 2H); 2.55 (s, 3H); 3.07 (d, 1H); 3.45 (d, 1H); 5.25 (s, 2H); 5.39 (d, 1H); 5.51 (d, 1H); 6.05 (s, 1H); 7.39 (s, 1H); 8.10 (s, 1H); 8.20 (s, 1H); 8.60 (s, 1H).
NMR-^{13}C (DMSO): 8.43; 20.20; 36.47; 42.49; 50.67; 61.41; 73.28; 99.87; 122.82; 126.98; 127.99; 129.60; 130.53; 131.08; 135.64; 136.56; 144.39; 147.11; 153.10; 155.85; 159.18; 172.03.
IR (KBr): 1208; 1479; 1606; 1656; 1724.

Preparation 8 : 8-ethyl-2,3,8,9-tetrahydro-8-hydroxy-10H,12H-[1,4]dioxino [2,3-*g*] oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-10,13 (15*H*)-dione

This compound is obtained from 3,4-ethylenedioxyaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. Yellow solid, m.p. > 250°C.
NMR-^{1}H (DMSO): 0.85 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.47 (d, 1H); 5.25 (s, 2H); 5.39 (d, 1H); 5.51 (d, 1H); 6.05 (s, 1H); 7.39 (s, 1H); 8.15 (q, 1H); 8.25 (q, 1H); 8.68 (s, 1H).
NMR-^{13}C (DMSO): 8.41; 36.45; 42.48; 50.68; 61.40; 73.25; 99.92; 114.44; 115.42; 115.58; 122.96; 125.52; 130.56; 131.46; 144.21; 145.25; 142.36; 153.41; 155.85; 159.15; 172.00.
IR (KBr): 1266; 1512; 1581; 1618; 1751.

Preparation 9 : 7-ethyl-7,8-dihydro-7-hydroxy-9*H*,11*H*-[1,3]dioxolo [4,5-*g*] oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-9,12 (14*H*)-dione

This compound is obtained from 3,4-methylenedioxyaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. Cream solid, m.p. > 250°C.
NMR-^{1}H (DMSO): 0.85 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.45 (d, 1H); 5.20 (s, 2H); 5.39 (d, 1H); 5.51 (d, 1H); 6.00 (s, 1H); 6.30 (s, 2H); 7.30 (s, 1H); 7.49 (d, 2H); 8.45 (s, 1H).

NMR-^{13}C (DMSO): 8.43; 36.49; 42.56; 50.58; 61.42; 73.31; 98.87; 102.75; 103.33; 104.92; 121.76; 125.74; 128.59; 130.33; 145.08; 146.69; 148.78; 150.19; 151.49; 155.90; 159.24; 172.08.
IR (KBr): 1248; 1459; 1606;1731.

Preparation 10 : 9-chloro-5-ethyl-4,5-dihydro-5-hydroxy-10-methoxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

This compound is obtained from 3-chloro-4-methoxyaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. White solid, m.p. > 250°C.
NMR-^{1}H (DMSO): 0.85 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.45 (d, 1H); 4.01 (s, 3H); 5.22 (s, 2H); 5.39 (d, 1H); 5.51 (d, 1H); 6.02 (s, 1H); 7.31 (s, 1H); 7.68 (s, 1H); 8.20 (s, 1H); 8.55 (s, 1H).
NMR-^{13}C (DMSO): 8.22; 36.27; 42.30; 50.48; 56.69; 61.23; 73.08; 99.16; 107.44; 122.16; 127.12; 128.12; 129.25; 130.02; 130.53; 143.29; 144.37; 151.12; 153.29; 155.71; 158.98; 171.84.
IR (KBr): 1056; 1256; 1483; 1592; 1657; 1747.

Preparation 11 : 5-ethyl-4,5-dihydro-5-hydroxy-10-methoxy-1*H*- oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

This compound is obtained from 4-methoxyaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. Yellow solid, m.p. > 250°C.
NMR-^{1}H (DMSO): 0.85 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.45 (d, 1H); 3.95 (s, 3H); 5.28 (s, 2H); 5.40 (d, 1H); 5.51 (d, 1H); 6.00 (s, 1H); 7.38 (s, 1H); 7.51 (d, 2H); 8.07 (d, 1H); 8.55 (s, 1H).
NMR-^{13}C (DMSO): 8.45; 36.48; 42.51; 50.64; 55.92; 61.42; 73.33; 99.01; 106.49; 122.02; 123.19; 129.59; 130.20; 130.43; 144.17; 144.94; 150.40; 155.92; 158.31; 159.26; 172.07.
IR (KBr): 1251; 1604; 1655; 1735.

Preparation 12 : 9,11-dichloro-5-ethyl-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

This compound is obtained from 3,5-dichloroaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. Yellow solid, m.p. > 250°C.
NMR-^{1}H (DMSO): 0.85 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.45 (d, 1H); 5.30 (s, 2H); 5.41 (d, 1H); 5.55 (d, 1H); 6.08 (s, 1H); 7.41 (s, 1H); 8.05 (s, 1H); 8.21 (s, 1H); 8.91 (s, 1H).

NMR-^{13}C (DMSO): 8.39; 36.45; 42.51; 51.03; 61.39; 73.25; 100.62; 123.55; 124.63; 127.60; 128.08; 128.56; 132.06; 132.19; 134.53; 143.77; 148.80; 154.88; 155.82; 159.13; 171.98.
IR (KBr): 1064; 1275; 1586; 1651; 1743.

Preparation 13 : 5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

This compound is obtained from 3-fluoro-4-methylaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. Yellow solid, m.p. > 250°C.
NMR-^{1}H (DMSO): 0.89 (t, 3H); 1.85 (q, 2H); 2.49 (s, 3H); 3.08 (d, 1H); 3.49 (d, 1H); 5.21 (s, 2H); 5.39 (d, 1H); 5.51 (d,1H); 6.05 (s, 1H); 7.39 (s, 1H); 7.87 (d, 1H); 8.05 (d, 1H); 8.61 (s, 1H).
NMR-^{13}C (DMSO): 8.40; 15.14; 36.45; 42.52; 50.60; 61.41; 73.28; 99.71; 112.00; 122.66; 125.38; 127.66; 129.59; 130.28; 144.49; 147.88; 152.88; 155.85; 159.18; 162.25; 172.02.
IR (KBr): 1054; 1580; 1651; 1760.

Preparation 14 : 5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

This compound is obtained from 4-fluoroaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. White solid, m.p. > 250°C.
NMR-^{1}H (DMSO): 0.85 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.45 (d, 1H); 5.29 (s, 2H); 5.39 (d, 1H); 5.55 (d, 1H); 6.30 (s, 1H); 7.39 (s, 1H); 7.80 (q, 1H); 7.99 (q, 1H); 8.23 (q, 1H);8.68 (s, 1H).
NMR-^{13}C (DMSO): 8.40; 36.46; 42.48; 50.66; 61.41; 73.31; 99.68; 111.83; 122.75; 128.93; 130.93; 131.22; 131.93; 144.46; 145.27; 152.60; 155.89; 159.21; 172.04.
IR (KBr) : 1209; 1589; 1659; 1739.

Preparation 15 : 10-chloro-5-ethyl-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

This compound is obtained from 4-chloroaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. Yellow solid, m.p. > 250°C.
NMR-^{1}H (DMSO) : 0.85 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.47 (d, 1H); 5.25 (s, 2H); 5.39 (d, 1H); 5.51 (d, 1H); 6.05 (s, 1H); 7.39 (s, 1H); 7.89 (d, 1H); 8.19 (d, 1H); 8.29 (s, 1H); 8.67 (s, 1H).
NMR-^{13}C (DMSO): 8.40; 36.46; 42.47; 50.70; 61.42; 73.31; 100.00; 122.96; 127.31; 127.42; 128.87; 131.11; 132.12; 144.34; 146.53; 153.38; 155.88; 159.20; 172.04.

IR (KBr): 1069; 1483; 1606; 1741.

Preparation 16 : 9-chloro-5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

This compound is obtained from 4-chloro-3-fluoroaniline according to the method illustrated by stages 4i, 4j and 4k of Preparation 4. Yellow solid, m.p. > 250°C.
NMR-^{1}H (DMSO): 0.85 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.45 (d, 1H); 5.25 (s, 2H); 5.39 (d, 1H); 5.51 (d, 1H); 6.05 (s, 1H); 7.40 (s, 1H); 8.20 (d, 1H); 8.40 (d, 1H); 8.68 (s, 1H).
NMR-^{13}C (DMSO): 8.38; 36.47; 42.58; 50.71; 61.40; 73.26; 99.99; 113.59; 123.09; 124.28; 127.74; 130.64; 131.31; 144.13; 145.08; 153.57; 154.13; 155.84; 156.61; 159.14; 172.00.
IR (KBr): 1488; 1583; 1655; 1743.

Preparation 17 : 5,12-diethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methoxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

17.a. 5-fluoro-4-methoxy-2-propionylaniline

(This product is obtained according to Sugasawa T; Toyoda T; Adachi M; Sasakura K, *J. Am. Chem. Soc.*, 100 (1978), p.4842-4852). Boron trichloride (1M in heptane, 156 ml, 156 mmol) is added dropwise, under an argon atmosphere at 0°C to a solution of 3-fluoro-4-methoxy-aniline (20 g, 142 mmol) in anhydrous dichloromethane (200 ml). The pink suspension thus obtained is maintained under agitation for 5 minutes, then propionitrile (33 ml, 420 mmol) is added dropwise followed by aluminium trichloride (20.8 g, 156 mmol) in small portions. The reaction medium is heated under reflux for 3 hours, cooled down to 0°C, hydrolyzed by cautiously adding 2N hydrochloric acid (100 ml), then heated at reflux for 45 minutes. After cooling down to 0°C a precipitate is obtained which is filtered out, washed with dichloromethane, then taken up in water (300 ml). The aqueous phase is basified to an alkaline pH, extracted with dichloromethane then ethyl acetate. The organic phase is dried ($MgSO_4$) then evaporated to produce a crude product which is purified by column chromatography (SiO_2, AcOEt/Hpt: 1/99 to 20/80). 15.3 g of a yellow solid is obtained.
NMR-^{1}H ($CDCl_3$): 1.20 (t, 3H); 2.92 (q, 2H); 3.83 (s, 3H); 6.2 (s, 2H); 6.40 (d, 2H); 7.32 (d, 2H).
IR (KBr): 857; 1148; 1240; 1561; 1583; 1662.

17.b. Ethyl 4-ethyl-7-fluoro-2-hydroxy-6-methoxy-3-quinolinecarboxylate

A solution of ethylmalonyl chloride (12.9 ml, 100 mmol) in anhydrous acetonitrile (30 ml) is added dropwise, under argon and at 0°C to a solution of 5-fluoro-4-methoxy-2-propionylaniline (15.3 g, 77.5 mmol) and triethylamine (13.9 ml, 100 mmol) in anhydrous acetonitrile (110 ml). The reaction medium is left to return to ambient temperature, a solution of sodium ethylate (obtained by 1.8 g, 78 mmol of sodium in 80 ml of ethanol) is cannulated dropwise and under argon, then the reaction medium is left under agitation for 12 hours at ambient temperature. The reaction mixture is poured into ice-cooled water (100 ml) and agitation is carried out for two hours, then the precipitate is filtered out and washed with water, with ethanol and with ether. 19.4 g of a white solid is obtained.

NMR-^{1}H (DMSO): 1.25 (m, 6H); 2.78 (q, 2H); 3.92 (s, 3H); 4.30 (q, 2H); 7.15 (d, 2H); 7.40 (d, 2H); 11.93 (s, 1H).

IR (KBr): 786; 1083; 1410; 1521; 1644; 1725.

17.c. Ethyl 2-chloro-4-ethyl-7-fluoro-6-methoxy-3-quinolinecarboxylate

A suspension of ethyl 4-ethyl-7-fluoro-2-hydroxy-6-methoxy-3-quinolinecarboxylate (19.4 g, 0.066 mol) in phosphoryl chloride (243 ml) is heated at reflux for 6 hours. The phosphoryl chloride is distilled off. The reaction mixture is decanted into ice-cooled water, then taken up in dichloromethane to solubilize. The organic phase is washed with water, then with a saturated solution of sodium chloride. The organic phase is dried over magnesium sulphate and the solvent is evaporated off. The residue is suspended in ether and the non-converted starting product (4 g) is filtered out. The filtrate is evaporated and the residue is purified by column chromatography (SiO_2, AcOEt/Hpt: 5/95 to 20/80). 10.9 g of a white solid is obtained.

NMR-^{1}H (DMSO): 1.30 (t, 3H); 1.39 (t, 3H); 3.08 (q, 2H); 4.09 (s, 3H); 4.49 (q, 2H); 7.64 (d, 2H); 7.86 (d, 2H).

IR (KBr): 865; 1016; 1082; 1190; 1224; 1253; 1272; 1508; 1571; 1732.

17.d. 2-chloro-4-ethyl-7-fluoro-6-methoxy-3-quinolinemethanol

A solution of ethyl 2-chloro-4-ethyl-7-fluoro-6-methoxy-3-quinolinecarboxylate (10.8 g, 35 mmol) in anhydrous dichloromethane (200 ml) is treated dropwise at ambient temperature under an inert atmosphere with diisobutylaluminium hydride (1M in dichloromethane, 65 ml, 65 mmol), then heated at 40°C for 4 hours. After cooling down to 0°C, a 20% aqueous solution of Rochelle salt (105 ml) and dichloromethane (200 ml) are added cautiously and the reaction mixture is maintained under agitation

for 1 hour, followed by decanting and washing three times with water. The organic phase is dried over magnesium sulphate and the solvent is evaporated off. The residue is purified by column chromatography (SiO_2, AcOEt/Hpt: 5/95 to 50/50). 6 g of a white solid is obtained.

NMR-^{1}H (DMSO): 1.28 (t, 3H); 3.25 (q, 2H); 4.04 (s, 3H); 4.77 (d, 2H); 5.27 (t, 1H); 7.55 (d, 2H); 7.73 (d, 2H).

IR (KBr): 840; 864; 1023; 1232; 1267; 1317; 1444; 1511; 1569.

17.e. 5,12-diethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methoxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

2-chloro-4-ethyl-7-fluoro-6-methoxy-3-quinolinemethanol is coupled with compound (M) as described in stage 4.j. of Preparation 4. The resultant coupled product is cyclized according to the procedure described in stage 4.k. A yellow solid is obtained, m.p. > 275°C.

NMR-^{1}H (CF3COOD): 1.07 (m, 3H); 1.62 (m, 3H); 2.27 (m,2H); 3.44 (d, 1H); 3.54 (m, 2H); 3.91 (d, 1H); 4.25 (s, 3H); 5.60 (d, 1H); 5.74 (s, 2H); 5.98 (d, 1H); 7.85 (m, 1H); 8.16 (m, 1H); 8.31 (s, 1H).

NMR-^{13}C (CF3COOD): 9.03; 14.20; 26.68; 38.77; 43.98; 53.79; 58.27; 64.73; 77.93; 106.85; 109.24; 110.15; 128.99; 129.20; 131.61; 137.32; 141.23; 144.13; 154.79; 158.32; 160.25; 160.81; 179.30.

IR (KBr): 1013; 1068; 1265; 1466; 1514; 1601; 1655; 1748.

<u>Preparation 18</u>: 5-ethyl- 4,5-dihydro-5-hydroxy-12-methyl-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione

The procedure described in Examples 17.b., 17.c and 17.d. is applied to 2-acetylaniline in order to produce 2-chloro-4-methyl-3-quinolinemethanol. The latter is coupled with compound (M) as described in stage 4.j. of Preparation 4. The resultant coupled product is cyclized according to the procedure described in stage 4.k. A yellow solid is obtained, m.p. > 260°C.

NMR 1H (DMSO): 0.87 (t, 3H); 1.87 (q, 2H); 2.78 (s, 3H); 2.80 (d, 1H); 3.55 (d, 1H); 5.27 (s, 2H); 5.42 (d, 1H); 5.52 (d, 1H); 6.04 (s, 1H); 7.39 (s, 1H); 7.75 (t, 1H); 7.88 (t, 1H); 8.13 (d, 1H); 8.25 (d, 1H).

NMR-^{13}C (DMSO): 8.23; 36.26; 42.36; 62.00; 73.11; 78.65; 79.13; 79.25; 99.52; 122.36; 124.30; 127.67; 129.54; 129.55; 129.56; 140.11; 145.06; 148.07; 152.00; 155.79; 159.09; 171.89.

IR (KBr): 1649; 1751; 3404.

Preparation 19: 10-benzyloxy-5-ethyl-9-fluoro- 4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15 (4*H*,13*H*)-dione

The procedure exemplified in stage 4.i. is applied to 3-fluoro-4-methoxy-acetanilide in order to produce 2-chloro-7-fluoro-6-methoxy-quinoline-3-carbaldehyde which is treated with an excess of boron tribromide in dichloromethane at ambient temperature for 24 hours. 2-chloro-7-fluoro-6-hydroxy-quinoline-3-carbldehyde is obtained which is O-benzylated in dimethylformamide in the presence of benzyl bromide and potassium carbonate in order to produce 6-benzyloxy-2-chloro-7-fluoro-quinoline-3-carbaldehyde which is reduced with sodium borohydride in methanol in order to produce the corresponding quinolinemethanol. The latter is coupled with compound (M) as described in stage 4.j. of Preparation 4. The resultant coupled product is cyclized according to the procedure described in stage 4.k. A yellow solid is obtained, m.p. > 275°C.

NMR-^{1}H (DMSO) : 0.86 (t, 3H); 1.85 (q, 2H); 3.05 (d, 1H); 5.25 (s, 2H); 5.37 (s, 2H); 5.45 (dd, 2H); 6.05 (s, 1H); 7.4-7.6 (m, 5H); 7.88 (d, 1H); 7.95 (d, 1H); 8.56 (s, 1H).

Preparation 20: 5-ethyl-9-fluoro- 4,5-dihydro-5,10-dihydroxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15 (4*H*,13*H*)-dione

The compound of Preparation 19 (0.79 mmol) dissolved in trifluoroacetic acid (15 ml) is treated with hydrogen using 10% palladium on carbon (60 mg). A yellow solid is obtained, m.p. > 275°C.

NMR-^{1}H (DMSO) : 0.86 (t, 3H); 1.85 (q, 2H); 3.05 (d, 1H); 5.25 (s, 2H); 5.37 (s, 2H); 5.45 (dd, 2H); 6.05 (s, 1H); 7.8 (d, 1H); 7.90 (d, 1H); 8.56 (s, 1H).

The above preparations will serve as the basis for illustrating the invention by the examples which follow.

***EXAMPLE 1* :**

5-ethyl-9,10-difluoro- 4,5-dihydro-5-(2-amino-1-oxoethoxy)-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15 (4*H*,13*H*)-dione

a. **5-ethyl-9,10-difluoro- 4,5-dihydro-5-(2-(*t*-butyloxycarbonyl-amino)-1-oxoethoxy)-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15 (4*H*,13*H*)-dione, hydrochloride**

A mixture of 5-ethyl-9,10-difluoro-4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7] indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione (200 mg, 0.526 mmol, obtained according to Preparation 4), *N*-Boc-glycine (185 mg, 1.051 mmol) and a catalytic quantity of 4-dimethylaminopyridine (20 mg) in anhydrous pyridine (10 ml) is treated at 0°C and under argon with dicyclohexylcarbodiimide (239 mg, 1.16 mmol), then agitated at ambient temperature for 48 hours. The volatiles are driven off under vacuum and the residue is chromatographed (SiO_2, 1% methanol in chloroform) in order to produce the desired intermediate (40 mg, 14%), a yellow solid.

NMR-^{1}H ($CDCl_3$): 1.20 (t, 3H); 1.38 (s, 9H); 1.40-1.70 (m, 2H); 3.10 (d, 1H); 4.00 (d, 2H); 4.30 (d, 1H); 5.00 (t, 1H); 5.20 (s, 2H); 5.30-5.90 (dd, 2H); 7.20 (s, 1H); 7.50-8.10 (m, 2H); 8.30 (s, 1H).

b. 5-ethyl-9,10-difluoro- 4,5-dihydro-5-(2-amino-1-oxoethoxy)-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15 (4*H*,13*H*)-dione, hydrochloride

The intermediate obtained above (40 mg, 0.072 mmol) in solution in dichloromethane (10 ml) is maintained at 0°C and dioxan saturated with hydrogen chloride (8 ml) is added dropwise. The yellow suspension thus formed is maintained under agitation for 2 hours, then the volatiles are driven off under vacuum. The residue, taken up in water (5 ml), is washed with dichloromethane (3 x 30 ml). The aqueous phase is frozen and lyophilized in order to produce the expected salt, a hygroscopic yellow solid (20 mg, 50%).

NMR-^{1}H ($CDCl_3$): 1.00 (t, 3H); 2.15 (m, 1H); 2.30 (m, 1H); 3.60 (d, 1H); 3.90 (d, 1H); 4.15 (s, 2H); 5.10 (s, 2H); 5.40 (d, 1H); 5.70 (d, 2H); 7.40 (s, 1H); 7.80 (m, 2H); 8.50 (s, 1H).

***EXAMPLE 2*:**

5-ethyl-9,10-difluoro- 4,5-dihydro-5-(2-amino-1-oxopropoxy)-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15 (4*H*,13*H*)-dione

The procedure of Example 1 is applied to 5-ethyl-9,10-difluoro- 4,5-dihydro-5-hydroxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15 (4*H*,13*H*)-dione using *N*-Boc-*b*-alanine instead of *N*-Boc-glycine, then the Boc protector of the intermediate thus obtained is cleaved by treatment with trifluoroacetic acid in dichloromethane. The volatiles are evaporated off under vacuum and the residue is taken up in dichloromethane. The resultant solution is washed with dilute bicarbonate, dried and evaporated. A yellow solid is obtained.

By applying the method of Examples 1 and 2 to other compounds, similar results are obtained. In this way an entire class of campothecin analogues is accessible in "pro-drug" form.

EXAMPLE 3 **:**

1,8-diethyl-8,9-dihydro-8-hydroxy-2*H*,10*H*,12*H*-[1,3]oxazino[5,6-*f*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-10,13 (15*H*)-dione

A suspension of 5-ethyl-4,5-dihydro-5,10-dihydroxy-1*H*-oxepino [3',4':6,7]indolizino [1,2-b]quinoline-3,15 (4*H*,13*H*)-dione (84 mg obtained according to Preparation 5) in acetic acid (2.5 ml) is treated with 1,3,5-triethylhexahydrotriazine (0.5 ml). The reaction mixture is agitated at 70°C for 30 minutes, then evaporated under vacuum. The residue is taken up in ethanol, filtered and washed with ether. A solid is obtained, m.p. > 275°C.

NMR-^{1}H (DMSO) : 0.87 (t, 3H); 1.50 (t, 3H); 1.85 (q, 2H); 2.77 (q, 2H); 3.05 (d, 1H); 3.47 (d, 1H); 4.37 (s, 2H); 5.00 (s, 2H); 5.22 (s, 2H); 5.45 (dd, 2H); 6.00 (s, 1H); 7.34 (s, 1H); 7.36 (d, 1H); 7.93 (d, 1H); 8.53 (s, 1H).

NMR-^{13}C (DMSO) : 8.46; 13.48; 36.46; 42.49; 45.49; 46.44; 50.75; 61.43; 73.33; 82.06; 99.02; 112.90; 122.00; 122.98; 125.42; 127.04; 129.04; 130.20; 144.09; 144.97; 149.87; 152.92; 155.98; 172.07.

IR (KBr) : 1045; 1215; 1502; 1604; 1657, 1722.

EXAMPLE 4 **:**

8-ethyl-8,9-dihydro-8-hydroxy-1-methyl-2*H*,10*H*,12*H*-[1,3]oxazino[5,6-*f*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-10,13 (15*H*)-dione

A suspension of 5-ethyl-4,5-dihydro-5,10-dihydroxy-1*H*-oxepino [3',4':6,7]indolizino [1,2-b]quinoline-3,15 (4*H*,13*H*)-dione (200 mg obtained according to Preparation 5) in acetic acid (5 ml) is treated with hexahydro-1,3,5-trimethyltriazine (110 mg). The reaction mixture is agitated at 70°C for 30 minutes, then evaporated under vacuum. The residue is taken up in ethanol, filtered and washed with ether. A solid is obtained, m.p. > 275°C.

NMR-^{1}H (DMSO) : 0.87 (t, 3H); 1.85 (q, 2H); 3.04 (d, 1H); 3.48 (d, 1H); 4.33 (s, 2H); 4.93 (s, 2H); 5.28 (s, 2H); 5.45 (dd, 2H); 6.01 (s, 1H); 7.35 (s, 1H); 7.38 (d, 1H); 7.94 (d, 1H); 8.49 (s, 1H).

NMR-^{13}C (DMSO) : 8.46; 36.43; 37.85; 42.55; 48.68; 50.79; 61.43; 73.35; 83.82; 99.04; 112.49; 122.04; 123.00; 125.46; 127.14; 129.07; 130.27; 144.99; 149.95; 152.46; 155.99; 172.09

IR (KBr) : 1047; 1058; 1219; 1246; 1295, 1439; 1504; 1604, 1655, 1735.

EXAMPLE 5 :

8-ethyl-8,9-dihydro-8-hydroxy-1-benzyl-2*H*,10*H*,12*H*-[1,3]oxazino[5,6-*f*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-10,13 (15*H*)-dione

A suspension of 5-ethyl-4,5-dihydro-5,10-dihydroxy-1*H*-oxepino [3',4':6,7]indolizino [1,2-b]quinoline-3,15 (4*H*,13*H*)-dione (200 mg obtained according to Preparation 5) in acetic acid (5 ml) is treated with 1,3,5-tribenzylhexahydrotriazine (285 mg). The reaction mixture is agitated at 70°C for 30 minutes, then evaporated under vacuum. The residue is taken up in ethanol, filtered and washed with ether. A solid is obtained, m.p. > 275°C.

NMR-^{1}H (DMSO) : 0.85 (t, 3H); 1.85 (q, 2H); 3.05 (d, 1H); 3.47 (d, 1H); 3.96 (s, 2H); 4.33 (s, 2H); 5.04 (s, 2H); 5.17 (s, 2H); 5.44 (dd, 2H); 6.01 (s, 1H); 7.38 (m, 6H); 7.42 (d, 1H); 7.97 (d, 1H); 8.42 (s, 1H).

NMR-^{13}C (DMSO) : 8.42; 19.96; 36.45; 42.51; 46.36; 50.78; 55.38; 61.39; 73.31; 99.00; 112.55; 122.01; 123.08; 125.38; 127.09; 127.47; 128.70; 129.14; 130.35; 128.40; 139.19; 144.18; 149.99: 152.84; 155.92; 159.24; 172.05.

IR (KBr) : 1056; 1205; 1225; 1248; 1504; 1535; 1599; 1655; 1726.

EXAMPLE 6 :

8-ethyl-8,9-dihydro-4-fluoro-8-hydroxy-1-benzyl-2*H*,10*H*,12*H*-[1,3]oxazino[5,6-*f*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-10,13 (15*H*)-dione

A suspension of 5-ethyl-9-fluoro-4,5-dihydro-5,10-dihydroxy-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15 (4*H*,13*H*)-dione (200 mg obtained according to Preparation 20) in acetic acid (5 ml) is treated with 1,3,5-tribenzylhexahydrotriazine (285 mg). The reaction mixture is agitated at 70°C for 30 minutes, then evaporated under vacuum. The residue is taken up in ethanol, filtered and washed with ether. A solid is obtained, m.p. > 250°C.

NMR-^{1}H (DMSO) : 0.85 (t, 3H); 1.85 (q, 2H); 3.05 (d, 1H); 3.48 (d, 1H); 3.95 (s, 2H); 4.45 (s, 2H); 5.20 (s, 4H); 5.45 (dd, 2H); 6.05 (s, 1H); 7.40 (s, 7H); 7.90 (d, 1H); 8.45 (s, 1H).

IR (KBr) : 1248; 1451; 15001; 1598; 1657; 1727.

Pharmacological study of the products according to the invention

Relaxation activity test of DNA induced by topoisomerase 1.

All the reactions are carried out in a 20 µl reaction buffer constituted by 50 mM of Tris-HCl (pH 7.5), 50 mM of KCl, 0.5 mM of dithiothreitol, 10 mM of $MgCl_2$, 0.1 mM of ethyldiamine tetraacetic acid (EDTA), 30 µg/ml of bovine serum albumin and 300 ng of supercoiled pUC19 (Pharmacia Biotech, Orsay, France) with or without the compounds to be tested at defined concentrations. All the compounds to be tested are initially dissolved in dimethylsulphoxide (DMSO) or in water for the hydrosoluble compounds, the other dilutions being carried out with distilled water. The final concentration of DMSO does not exceed 1 % (v/v). The reaction is initiated by the addition of a unit of DNA topoisomerase 1 of purified calf thymus (Life Technologies/Gibco-BRL, Paisley, United Kingdom) such that the reaction is completed in 15 minutes at 37° C. The reactions are stopped by the addition of 3 µl of a mixture containing 1% dodecyl sodium sulphate at 1 %, 20 mM of EDTA and 500 µg/ml of K proteinase (Boehringer Mannheim, Meylan, France). After an additional incubation period of 30 minutes at 37° C, 2 µl of a loading buffer containing 10 mM of Na_2HPO_4, 0.3 % of bromophenol blue et 16 % Ficoll are added to samples which are subjected to electrophoresis in agarose gels at 1.2 % at 1 V/cm for 20 hours in a buffer containing 36 mM of Tris-HCl at pH 7.8, 30 mM of Na_2HPO_4, 1 mM of EDTA and 2 µg/ml of chloroquine. The gels are stained with 2 µg/ml of ethidium bromide, photographed under UV light at 312 nm with a charge-coupled device (ccd) camera and the fluorescent intensity is measured using a bioProfil image analyzer (Vilber Lourmat, Lyon, France) with a view to determining the percentage of relaxed DNA.

In each experiment, the supercoiled plasmid DNA is incubated alone or with topoisomerase 1. The reaction is completed within 15 minutes. For each compound to be tested or the control (the vehicle alone is called the control), the supercoiled plasmid DNA is incubated in the presence of the maximum concentration chosen for the experiment of the compound to be tested or the control without enzyme or in the presence of the compound to be tested, at concentrations ranging from 1 µM to 200 µM or of the control in the presence of enzymes. As indicated in Table I, Examples 3 to 6 inhibit the relaxation activity encouraged by topoisomerase 1 in a concentration-dependent manner.

TABLE I

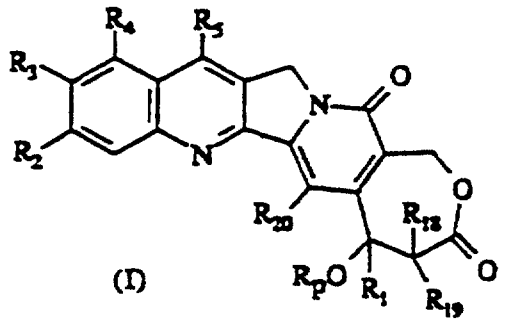
	Micromolar concentration			
	10	50	100	200
Examples				
Camptothecin	88.7	62.4	52.9	46.9
3	79.7	46.9	33.5	23.2
4	86.2	32.7	35.1	32.1
5	56.2	30.4	28.0	24.2
6	55.6	39.9	38.9	30.0

CLAIMS

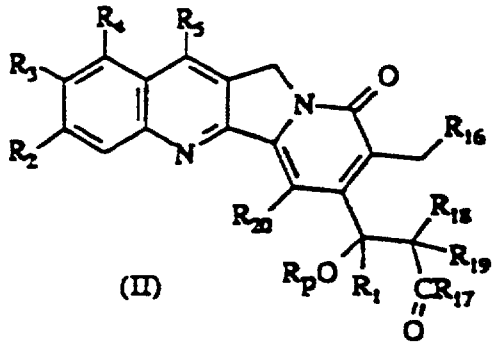
1. An analogue of camptothecin for which the hydroxy lactone of camptothecin is a β-hydroxy lactone or the corresponding β-hydroxy acid resulting from the opening of this lactone, characterized in that said analogue comprises an optionally substituted oxazine ring, grafted in positions 10 and 11 on ring A.

2. An analogue of camptothecin characterized in that the hydroxy lactone of camptothecin is replaced by a β-hydroxy lactone protected by an easily cleavable group or the corresponding β-hydroxy acid resulting from opening this lactone.

3. A compound characterized in that said compound is of formula (I) or formula (II),



(I)



(II)

in racemic or enantiomeric form or any combinations of these forms, in which

R_1 represents a lower alkyl, a lower alkenyl, a lower alkynyl, a lower haloalkyl, a lower alkoxy lower alkyl or lower alkylthio lower alkyl;

R_2, R_3 and R_4 represent, independently, H, halo, lower halo alkyl, lower alkyl, lower alkenyl, cyano, lower cyano alkyl, nitro, lower nitro alkyl, amido, lower amido alkyl, hydrazino, lower hydrazino alkyl, azido, lower azido alkyl, $(CH_2)_mNR_6R_7$, $(CH_2)_mOR_6$, $(CH_2)_mSR_6$, $(CH_2)_mCO_2R_6$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mC(O)R_8$, $(CH_2)_mOC(O)R_8$, $O(CH_2)_mNR_6R_7$, $OC(O)NR_6R_7$, $OC(O)(CH_2)_mCO_2R_6$ or $(CH_2)_n[N{\approx}X]$, $OC(O)[N{\approx}X]$, $(CH2)_mOC(O)[N{\approx}X]$, in which $[N{\approx}X]$, in this invention, represents a heterocyclic group with 4 to 7 members with the nitrogen atom N, which is a member of the heterocyclic group, and X represents the remaining members required to complete the heterocyclic group, selected from the group constituted by O, S, CH_2, CH, N, NR_9 and COR_{10}), substituted (i.e. substituted one to four times on the aryl group or the heterocycle) or non substituted aryl or lower aryl alkyl, in which

the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl or R_3 and R_4 form together a chain with 3 or 4 members in which the elements of the chain are selected from the group constituted by CH, CH_2, O, S, N or NR_9;

R_5 represents H, halo, lower halo alkyl, lower alkyl, lower alkoxy, lower alkoxy lower alkyl, lower alkylthio lower alkyl, cycloalkyl, lower cycloalkyl alkyl, cyano, cyano alkyl, lower alkyl sulphonyl lower alkyl, lower hydroxy alkyl, nitro, $(CH_2)_mC(O)R_8$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mNR_6R_7$, $(CH_2)_mN(CH_3)(CH_2)_nNR_6R_7$, $(CH_2)_mOC(O)R_8$, $(CH_2)_mOC(O)NR_6R_7$, $(CH_2)_mS(O)_qR_{11}$, $(CH_2)_mP(O)R_{12}R_{13}$ $(CH_2)_2P(S)R_{12}R_{13}$ or $(CH_2)_n[N\approx X]$, $OC(O)[N\approx X]$, $(CH_2)_mOC(O)[N\approx X]$, substituted (i.e. one to four times on the aryl or heteroaryl group) or non substituted aryl or lower aryl alkyl radical, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl;

R_6 and R_7 represent, independently, H, a lower alkyl, lower hydroxy alkyl, lower alkyl lower amino alkyl, lower amino alkyl, cycloalkyl, lower cycloalkyl alkyl, lower alkenyl, lower alkoxy lower alkyl, lower halo alkyl, or substituted (i.e. one to four times on the aryl group) or non substituted aryl or lower aryl alkyl, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl;

R_8 represents H, a lower alkyl, lower hydroxy alkyl, amino, lower alkyl amino, lower alkyl lower amino alkyl, lower amino alkyl, cycloalkyl, lower cycloalkyl alkyl, lower alkenyl, lower alkoxy, lower alkoxy lower alkyl, lower halo alkyl, or the substituted (i.e. one to four times on the aryl group) or non substituted aryl or lower aryl alkyl radical, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl;

R_9 represents H, a lower alkyl, lower halo alkyl, aryl, or aryl substituted by one or more groups chosen from the following radicals: lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl;

R_{10} represents H, a lower alkyl, lower halo alkyl, lower alkoxy, aryl or aryl substituted (i.e. having one to four substituents on the aryl group) by

one or more groups chosen from the following radicals: lower alkyl, lower halo alkyl, lower hydroxy alkyl or lower alkoxy lower alkyl;

R_{11} represents a lower alkyl, aryl, $(CH_2)_mOR_{14}$, $(CH_2)_mSR_{14}$, $(CH_2)_2NR_{14}R_{15}$ or $(CH_2)_m[N{\approx}X]$;

R_{12} and R_{13} represent, independently, a lower alkyl, aryl, lower alkoxy, aryloxy or amino;

R_{14} and R_{15} represent, independently, H, lower alkyl or aryl;

R_{16} represents H or OR_{21};

R_{17} represents OR_6 or NR_6R_7;

R_{18} and R_{19} represent, independently, H, halo, lower alkyl, lower alkoxy or hydroxy;

R_{20} represents H or halo;

R_{21} represents H, a lower alkyl, CHO or $C(O)(CH_2)_mCH_3$;

R_p represents H or an easily cleavable group preferably chosen from the groups corresponding to the formula -C(O)-A-$NR_{22}R_{23}$, in which A represents a linear or branched alkylene radical optionally substituted by a radical chosen from the free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino, mono or dialkylamino radicals, while R_{22} and R_{23}, independently, represent H, a lower alkyl, lower hydroxy alkyl, lower alkyl lower amino alkyl, lower amino alkyl, cycloalkyl, lower cycloalkyl alkyl, lower alkenyl, lower alkoxy lower alkyl, lower halo alkyl, or substituted (i.e., one to four times on the aryl group) or non-substituted aryl or lower aryl alkyl, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkyl amino, lower halo alkyl, lower hydroxy alkyl, lower alkoxy or lower alkoxy lower alkyl, or R_{22} and R_{23} together form a ring with 5, 6 or 7 members optionally substituted, optionally comprising another heteroatom chosen from O, N, S;

m is an integer comprised between 0 and 6;

n is 1 or 2; and

q represents an integer from 0 to 2; and [N≈X] represents a heterocyclic group with 4 to 7 members, X representing the chain necessary to complete said heterocyclic group and selected from the group constituted by O, S, CH_2, CH, N, NR_9 and COR_{10};

it being understood that when R_p is a hydrogen atom, R_3 and R_4 together form a chain with 3 or 4 members;

or a pharmaceutically acceptable salt of the latter.

4. A compound according to claim 3, characterized in that R_1 represents the ethyl group; or a pharmaceutically acceptable salt of the latter.

5. A compound according to claim 3, characterized in that R_5 represents H, a lower alkyl or $(CH_2)_mNR_6R_7$ or $(CH_2)_n[N\approx X]$ non substituted or substituted by a lower alkyl; or a pharmaceutically acceptable salt of the latter.

6. A compound according to claim 3, characterized in that R_3 and R_4 form an optionally substituted oxazine ring;

or a pharmaceutically acceptable salt of the latter.

7. A compound according to claim 3, characterized in that R_p is an easily cleavable group;
or a pharmaceutically acceptable salt of the latter.

8. A compound according to claim 7, characterized in that R_p represents the C(O)-(A_1)-N-R_{22}-R_{23} group in which A_1 represents CH_{2m} or a branched lower alkylene radical and m represents an integer between 0 and 6;

or a pharmaceutically acceptable salt of the latter.

9. A compound according to claim 6, characterized in that said compound is chosen from the compounds corresponding to the following formulae:

- 1,8-diethyl-8,9-dihydro-8-hydroxy-2*H*,10*H*,12*H*-[1,3]oxazino[5,6-*f*]oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-10,13(15*H*)-dione
- 8-ethyl-8,9-dihydro-8-hydroxy-1-methyl-2*H*,10*H*,12*H*-[1,3]oxazino[5,6-*f*]oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-10,13(15*H*)-dione
- 8-ethyl-8,9-dihydro-8-hydroxy-1-benzyl-2*H*,10*H*,12*H*-[1,3]oxazino[5,6-*f*]oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-10,13(15*H*)-dione
- 8-ethyl-8,9-dihydro-4-fluoro-8-hydroxy-1-benzyl-2*H*,10*H*,12*H*-[1,3]oxazino[5,6-*f*]oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-10,13(15*H*)-dione

or a pharmaceutically acceptable salt of the latter.

10. A compound according to claim 7, characterized in that said compound is chosen from the compounds corresponding to the following formulae:

- 5-ethyl-9,10-difluoro-4,5-dihydro-5-(2-amino-1-oxoethoxy)-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione;
- 5-ethyl-9,10-difluoro-4,5-dihydro-5-(2-amino-1-oxopropoxy)-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione;

or a pharmaceutically acceptable salt of the latter.

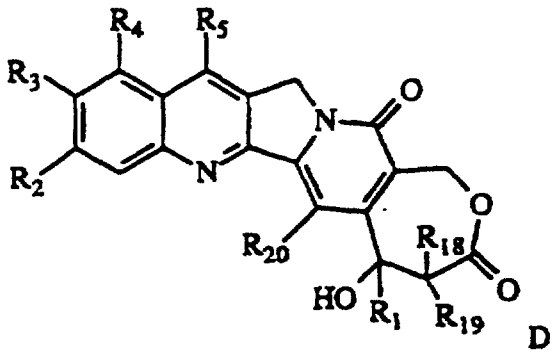
11. As a medicament, a compound according to any one of the previous claims or a pharmaceutically acceptable salt of the latter.

12. Pharmaceutical composition containing, as active ingredient, at least one of the compounds according to any one of claims 1 to 10.

13. Use of a compound according to any one of claims 1 to 10 for the preparation of antitumoral medicaments.

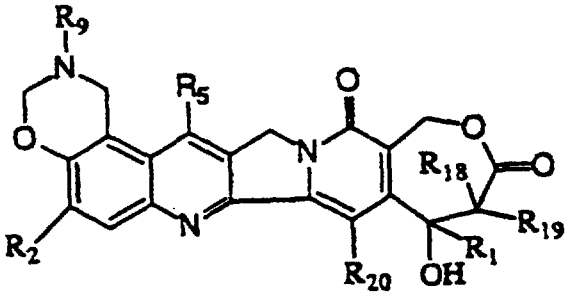
14. Process for the preparation of compounds of formula Ia corresponding to the products of formula I in which R_3 and R_4 form an oxazine ring according to any one of claims 1, 6 or 9, characterized in that:

- a β-hydroxylactonic compound of general formula D



D

in which R_3 is a hydroxyl radical, R_4 is H, and R_1, R_2, R_{18}, R_{19} and R_{20} have the meaning indicated above is treated with a primary amine, under Mannich's conditions, in order to obtain a β-hydroxylactonic compound of general formula Ia

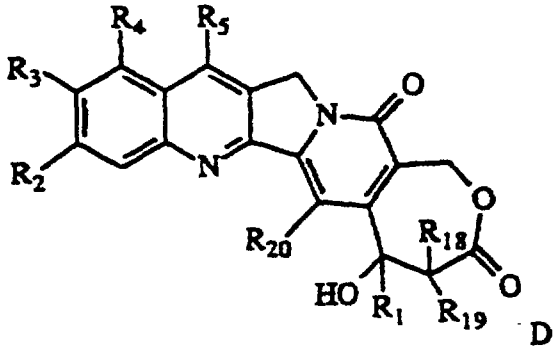


Ia

in which R_1, R_2, R_5, R_9, R_{18}, R_{19} and R_{20} have the meaning indicated above.

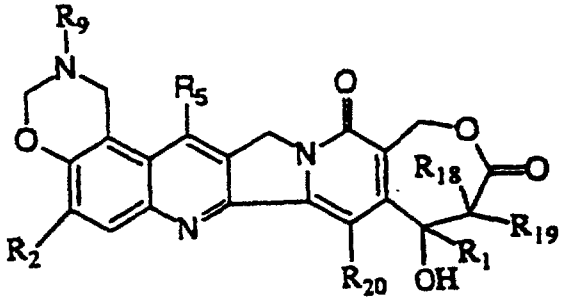
15. Process for the preparation of compounds of formula Ib corresponding to the products of formula I in which R_p is not a hydrogen atom, according to any one of claims 2 to 10, characterized in that:

- the compound of general formula D



D

or Ia

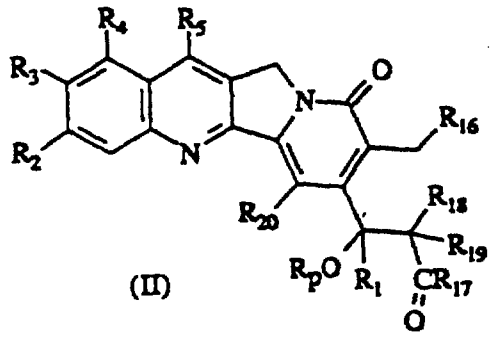


Ia

is actylated preferably with a derivative of the C(O)-A-N-$R_{22}R_{23}$ radical as defined in claim 3, in order to produce the β-hydroxylactonic compound of general formula I with R_p different from H.

16. Process for the preparation of compounds of formula II according to any one of claims 1 to 10, characterized in that:

- the lactone of general formula I is opened in a basic medium in order to produce after neutralization of the compound of formula II



(II)

in which R_1, R_2, R_5, R_9, R_{17}, R_{18}, R_{19}, and R_{20} have the meaning indicated above; R_{16} represents OR_{21} in which R_{21} represents H or a lower alkyl; and R_{17} represents OR_6 or NHR_6 and R_6 represents H, a lower alkyl, cyclocalkyl, lower cycloalkyl alkyl, lower alkenyl, lower alkoxy lower alkyl or aryl or lower aryl alkyl.